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PJHSL aims to advance scientific knowledge, promote evidence-based research, and facilitate the practical application of findings to improve health outcomes.

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Targeting the Substance P/Neurokinin-1 Receptor Axis: A Novel Avenue in Overcoming Cancer Resistance

Riffat Mehboob^{1,2*} and Miguel Munoz³¹Rotogen Biotech LLC, United States of America²Lahore Medical Research Center^{LLP}, Lahore, Pakistan³Research Laboratory on Neuropeptides, Institute of Biomedicine of Seville (IBIS), Spainmehboob.riffat@gmail.com

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The role of the Substance P (SP)/Neurokinin-1 Receptor (NK-1R) system in cancer biology has gained growing recognition. Recent literature consistently supports its implication in cancer promotion, progression, resistance, and inflammation [1]. SP is a peptide of the tachykinin family involved in multiple pathophysiological mechanisms, including nociception, inflammation, and immune modulation. However, its pathological role particularly through its preferred receptor, NK-1R has become increasingly evident in several malignancies [2].

Numerous studies have shown that SP and NK-1R is overexpressed in human cancer cells and NK-1R is essential for the viability of cancer cells. Activation of NK-1R, either constitutively or through SP binding, promotes cancer cell proliferation, antiapoptotic, survival, Warburg effect, angiogenesis, invasion and migration for metastasis [1]. Furthermore, this pathway contributes significantly to the establishment of a pro-inflammatory microenvironment, which sustains tumor progression. In head and neck cancers—especially laryngeal and oral squamous cell carcinomas the SP/NK-1R system has been implicated in the transition from chronic inflammation to preneoplastic and neoplastic lesions [3, 4]. Beyond its role in cancer progression, the SP/NK-1R axis is also associated with resistance to oncologic treatments. Overriding or malfunctioning NK-1R signaling appears to interfere with treatment response through modulation of signaling cascades and cross-talk with other receptor systems, potentially affecting immune escape and chemoresistance. This has opened the door to drug repurposing strategies involving NK-1R antagonists [5, 6].

Aprepitant, a well-known NK-1R antagonist currently approved for chemotherapy-induced nausea and vomiting, has shown potential in preclinical studies as an antitumor drug. It exhibits antiproliferative, pro-apoptotic, anti-Warburg effect, antiangiogenic, prevent invasion and migration, and has anti-inflammatory effects in cancer models [1, 6]. Importantly, aprepitant's established safety profile and widespread availability make it a promising candidate for repositioning in oncology [1, 6]. The current evidence suggests that combining NK-1R antagonists with existing therapies could improve treatment response and potentially overcome resistance in multiple cancer types [3, 6]. Despite this progress, more precise characterization of NK-1R's role across different tumors is needed. NK-1R signals through various pathways, and its full and truncated isoforms may exert distinct functions. Understanding these nuances will be critical for optimizing the clinical use of NK-1R-targeted therapies. Moreover, the availability of selective antagonists and the emerging potential for biased ligands based on receptor structural states present exciting research and therapeutic opportunities [6].

In conclusion, the SP/NK-1R system represents a multifaceted target in cancer biology. Its involvement in carcinogenesis, inflammation, and resistance mechanisms positions it as a valuable focus for novel cancer therapies. Future research should seek to translate these findings into clinical strategies, which could transform cancer care through these new drugs. In addition, the drug aprepitant and other similar drugs should be repurposed as antitumor drugs in cancer therapy.

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Review Article

Multi-Epigenetic Landscapes of Schizophrenia

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ABSTRACT

Schizophrenia is a debilitating neurodevelopmental disorder affecting approximately 1% of the global population. Traditional genetic models have provided limited insight into its complex etiology. This review synthesizes recent advances in epigenetic research related to schizophrenia, focusing on dynamic and reversible genome modifications. The study analyzed multi-omics and epigenomic profiling studies published between 2020 and 2025 that explore DNA methylation, histone modifications, non-coding RNAs and gene-environment interactions in schizophrenia. Epigenetic mechanisms, including DNA methylation, chromatin remodeling and non-coding RNAs, mediate environmental influences during critical neurodevelopmental periods, contributing to long-term gene expression changes associated with schizophrenia. These findings integrate genetic liability with environmental exposures and highlight potential biomarkers and therapeutic targets. Understanding schizophrenia through the lens of epigenetics may inform novel diagnostic and treatment approaches, advancing precision psychiatry.

INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by persistent cognitive, emotional and perceptual disturbances [1]. Despite extensive research, treatment resistance remains a significant challenge, especially regarding negative and cognitive symptoms [2]. Traditional models have primarily focused on dopaminergic dysfunction; however, these models do not fully explain the complex etiology or heterogeneity of schizophrenia symptoms. Emerging evidence suggests that epigenetics, the study of heritable and reversible modifications to gene expression without alterations in the DNA sequence. It offers a promising framework to bridge the gap between genetic predisposition and environmental influences [3]. Epigenetic mechanisms such as DNA methylation, histone modifications and non-coding RNAs regulate gene activity

and can mediate the effects of environmental stressors on gene expression [4]. This integrative approach may provide novel insights into schizophrenia pathophysiology. That may surpass the explanatory limits of dopaminergic hypotheses.

Although schizophrenia has traditionally been explored through genetic and neurotransmitter-based models, these frameworks inadequately explain the complex interaction between environmental exposures and disease manifestation. There remains a significant gap in integrating multi-epigenetic mechanisms—including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs—into a unified understanding of schizophrenia pathogenesis. This review aims to synthesize contemporary epigenetic evidence,



identify reversible molecular alterations linked to schizophrenia, and explore their potential as diagnostic biomarkers and precision-based therapeutic targets.

Factors Influencing Schizophrenia

Schizophrenia is a multifactorial disorder resulting from the complex interplay between genetic predispositions and environmental exposures. Advances in genomics and population studies have enhanced our understanding of how these factors interact to influence neuro-developmental trajectories, ultimately contributing to disease onset and progression [5].

Genetic and Environmental Contributions

The heritability of schizophrenia is estimated between 60% and 80%, as supported by large-scale twin and family studies [6]. Monozygotic (MZ) twins show approximately 50% concordance for schizophrenia, whereas dizygotic (DZ) twins exhibit around 15% concordance, underscoring a strong genetic component alongside critical environmental influences [6] (Table 1).

Table 1: Prevalence and Genetic Factors Associated with Schizophrenia

Metric	Value
Global Prevalence	~1%
Heritability	60–80%
MZ Twin Concordance	~50%
DZ Twin Concordance	~15%

Epigenetic Mechanisms in Schizophrenia

Epigenetic modifications regulate gene expression without altering the DNA sequence, playing a crucial role in the pathophysiology of schizophrenia. The principal epigenetic mechanisms implicated include DNA methylation, histone modifications, non-coding RNAs and chromatin remodeling complexes.

DNA Methylation

DNA methylation involves the addition of methyl groups to cytosine bases in CpG dinucleotides, mediated by DNA methyl-transferases (DNMTs). It includes DNMT1 (maintenance methylation) and DNMT3A/3B (de novo methylation). Aberrant methylation patterns have been repeatedly observed in schizophrenia-associated genes, including RELN, GAD1, and COMT in postmortem brain tissues [7]. Early-life adversity appears to induce persistent methylation changes that potentially increase long-term disease risk [8] (Table 2).

Table 2: Schizophrenia-Associated Genes, Their Functions, and Related Epigenetic Modifications

Gene	Function	Epigenetic Change
RELN	Neuronal migration	Promoter hypermethylation
GAD1	GABA synthesis	Downregulated by methylation
COMT	Dopamine metabolism	Methylation-sensitive allele

Histone Modifications

Histone modifications regulate chromatin structure, affecting DNA accessibility and gene transcription. Histone acetylation, catalyzed by histone acetyltransferases (HATs), generally promotes transcriptional activation by loosening chromatin. Conversely, histone deacetylases (HDACs) remove acetyl groups, leading to chromatin compaction and transcriptional repression [8]. In schizophrenia, increased expression of HDAC1 and HDAC2 has been observed in the prefrontal cortex and hippocampus of postmortem brains, potentially silencing genes crucial for synaptic plasticity and neuronal development [9]. Chromatin immunoprecipitation sequencing (ChIP-seq) studies have revealed enrichment of the repressive histone mark H3K27me3 in schizophrenia, particularly affecting genes involved in synaptic signaling and immune responses [10]. Additionally, reductions in the active mark H3K4me3 have been reported in genes related to GABAergic neurotransmission [11]. Histone deacetylase inhibitors (HDACi) such as valproic acid and vorinostat have demonstrated potential in preclinical models by partially restoring gene expression and synaptic function; however, their clinical efficacy remains under investigation [12–14].

Non-Coding RNAs and Chromatin Remodelers

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), contribute to epigenetic regulation by modulating gene expression at transcriptional and post-transcriptional levels [15]. MicroRNAs (miRNAs): MiR-137, identified through genome-wide association studies (GWAS), plays a central role in neurogenesis and synaptic plasticity. Dysregulation of miR-137 and other schizophrenia-related miRNAs, such as miR-132 and miR-219, affects neurotransmitter signaling and neuronal integrity [16, 17]. Long Non-Coding RNAs (lncRNAs): lncRNAs like NEAT1 and MALAT1 are implicated in chromatin remodeling and transcription regulation, with altered expression observed in schizophrenia. Chromatin remodeling complexes, including CHD8 and SWI/SNF (e.g., SMARCA2, SMARCB1), dynamically reposition nucleosomes to regulate DNA accessibility. Mutations or dysregulation of these remodelers have been linked to neurodevelopmental deficits relevant to schizophrenia [18, 19].

Interactions Between Gene and Environment

The pathogenesis of schizophrenia increasingly supports a gene-environment interaction (G×E) model, whereby environmental exposures modulate gene expression through epigenetic mechanisms, especially during sensitive developmental periods [20]. This framework integrates genetic susceptibility with environmental insults to explain the heterogeneous clinical presentation of schizophrenia. A seminal study by Kular and Kular, [21]

demonstrated that individuals carrying the COMT Val158 allele who used cannabis during adolescence had an elevated risk of psychotic symptoms compared to Met/Met carriers, providing early empirical support for G×E in psychiatry. Subsequent research has expanded this model to include other genes and environmental factors: BDNF (Brain-Derived Neurotrophic Factor): Early-life trauma and stress induce hypermethylation of the BDNF promoter, leading to reduced neurogenesis and impaired synaptic plasticity. NRG1 (Neuregulin 1): Prenatal immune activation affects NRG1 expression through methylation and histone modification, disrupting neural circuit formation [22]. Inflammatory Genes (e.g., IL-6, TNF- α): Maternal infection and perinatal immune challenges cause persistent epigenetic alterations in immune-related genes, contributing to neuro-inflammation and neuronal dysfunction [23] (Table 3).

Table 3: Genes, Environmental Triggers, Epigenetic Modifications and Impacts in Schizophrenia

Gene	Environmental Trigger	Epigenetic Effect	Impact
COMT	Cannabis (adolescence)	Altered enzymatic activity	Increased psychosis risk
BDNF	Early-life trauma	Promoter hypermethylation	Reduced neuroplasticity
NRG1	Prenatal immune activation	Histone modification	Disrupted neural development
IL-6	Maternal infection	Epigenetic priming	Chronic inflammation

Developmental Timing and Epigenetic Windows

Unlike static genetic mutations, epigenetic mechanisms are highly dynamic and responsive to environmental inputs during critical developmental windows. These sensitive periods, spanning prenatal, perinatal, and early childhood phases, coincide with intense neurogenesis, synaptogenesis and structural brain remodeling. Environmental factors such as maternal stress, malnutrition, infections and inadequate caregiving during these windows can induce long-lasting epigenetic alterations that disrupt neurodevelopmental trajectories. Animal studies have shown that prenatal stress increases DNA methylation at genes regulating the hypothalamic-pituitary-adrenal (HPA) axis, such as NR3C1 (encoding the glucocorticoid receptor), resulting in dysregulated stress responses, cognitive deficits and structural brain changes in offspring [24]. Importantly, epigenetic plasticity persists beyond early development. DNA methyltransferase (DNMT) activity and histone deacetylase (HDAC) expression remain active in adult neurons, particularly in brain regions involved in learning, memory and executive function, such as the prefrontal cortex and hippocampus [25]. This suggests that environmental insults during adolescence or adulthood, such as trauma or substance use, can continue to modify gene expression and contribute to disease onset

or relapse. Recent temporal epigenomic mapping studies indicate that schizophrenia-associated epigenetic alterations often emerge between mid-gestation and early adolescence, coinciding with established periods of heightened disease risk. These findings support a model in which schizophrenia results from the cumulative effect of epigenetic insults across developmental stages rather than from a singular event [26].

Transgenerational Epigenetics

Transgenerational epigenetics explores how environmentally induced epigenetic modifications can be inherited through the germline, potentially explaining the persistence of psychiatric risk across generations even in the absence of direct genetic mutations. This emerging field provides a novel perspective on familial vulnerability in schizophrenia. Animal models have demonstrated that maternal stress, malnutrition and substance exposure induce methylation changes in genes such as BDNF and NR3C1, which are transmitted to offspring via sperm or oocytes. These inherited epigenetic marks correlate with behavioural abnormalities, altered stress reactivity and disrupted neural circuitry [27]. In humans, preliminary studies on populations exposed to large-scale trauma, such as Holocaust survivors or victims of famine and war, suggest that descendants exhibit distinct methylation patterns in genes related to stress response and neuroplasticity, including FKBP5, SLC6A4 and OXTR, despite no direct trauma exposure [28]. Although the precise mechanisms and extent of transgenerational epigenetic inheritance in humans remain under investigation, these findings indicate that psychiatric vulnerability may be epigenetically primed by ancestral environmental experiences, contributing to the complex heritability of schizophrenia.

Clinical and Therapeutic Implications

Recognition of persistent and modifiable epigenetic changes in schizophrenia offers promising avenues for diagnosis and treatment, advancing the field toward precision psychiatry.

Epigenetic Therapies

Histone deacetylase inhibitors (HDACis) such as valproic acid and vorinostat have demonstrated efficacy in animal models by restoring the expression of key genes like RELN and GAD1, improving synaptic plasticity and cognitive functions [29, 30]. Early-phase clinical trials suggest potential benefits as adjunctive therapies; however, challenges regarding optimal dosing, safety and target specificity remain [31].

Targeted Epigenome Editing

Recent developments in CRISPR-dCas9-based epigenome editing allow precise targeting of gene promoters with modifiers such as DNA demethylases or HDAC inhibitors without altering DNA sequences [32]. Although still in

preclinical stages, these tools hold considerable promise for gene-specific reprogramming in psychiatric disorders, including schizophrenia.

Biomarkers for Diagnosis and Monitoring

Peripheral blood DNA methylation profiles are under investigation as diagnostic and prognostic biomarkers for schizophrenia. Candidate genes include SLC6A4 (serotonin transporter), which is linked to stress reactivity; NR3C1 (glucocorticoid receptor), reflecting hypothalamic-pituitary-adrenal axis sensitivity; and microRNAs such as miR-137 and miR-132, regulators of synaptic and neurodevelopmental pathways. Ongoing research aims to develop methylation panels to facilitate early detection, treatment stratification and relapse prediction [33].

Current epigenetic research in schizophrenia is limited by heterogeneity in study designs, reliance on peripheral biomarkers rather than brain-specific tissues, and insufficient longitudinal data to establish causality. Variability in environmental exposure assessment and the early-stage nature of epigenetic therapies further restrict clinical translation. Future studies should prioritize large-scale longitudinal multi-omics investigations, improve tissue-specific biomarker validation, and assess the long-term safety and efficacy of targeted epigenetic interventions to advance personalized psychiatry.

CONCLUSIONS

Epigenetic research has significantly advanced our understanding of schizophrenia, bridging the gap between genetic predisposition and environmental exposure. Unlike static genomic markers, epigenetic modifications are dynamic, reversible and influenced by developmental timing, offering a more nuanced model for disease pathogenesis. The integration of genome-wide methylation studies, transcriptomic analyses and multi-omic profiling has revealed that alterations in DNA methylation, histone modifications and non-coding RNAs are involved in synaptic regulation, neuro-inflammation, and stress responsiveness, all processes disrupted in schizophrenia. Emerging evidence of transgenerational epigenetic inheritance and gene-environment interactions suggest that psychiatric vulnerability is not solely determined by DNA sequence but also by inherited and acquired epigenetic states. These insights may provide new avenues for preventive interventions, diagnostic biomarkers, and therapeutic strategies. Nonetheless, significant challenges remain. Future studies must address the causal relevance of specific epigenetic marks, improve tissue specificity in peripheral biomarker studies, and evaluate long-term effects and safety of epigenetic therapies. With ongoing advancements, epigenetics may contribute meaningfully to a more personalized and mechanistically grounded

approach to the treatment and management of schizophrenia.

Authors' Contribution

Conceptualization: SBS

Methodology: SBS

Formal analysis: SBS

Writing and Drafting: SBS, SS, SA, MS

Review and Editing: SBS, SS, SA, MS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Review Article



Nutritional Knowledge and Health Behaviour Related to CVD, Narrative Review

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ABSTRACT

Cardiovascular disease is the leading cause of death worldwide. A person's diet plays a critical role in their cardiovascular health and is linked to the progression of heart-related diseases. Several scientific researchers have demonstrated an association between dietary habits, lifestyle, and Cardiac diseases. This narrative review aims to demonstrate the present state of scientific evidence on nutritional knowledge and health behaviour related to CVD (Cardiovascular Diseases). The review focuses on the impact of dietary patterns and lifestyle on the risk factors of CVD, summarizing facts from surveys, population-related scientific trials, observational research, and meta-analyses. Unhealthy dietary behaviours and lifestyle, for instance, high consumption of saturated fatty acids, red and processed meat, refined carbohydrates, sugar-sweetened beverages and excessive salt, have been related to an amplified possibility of CVD. On the contrary, increasing consumption of a plant-centred diet, such as food fiber, fruits, vegetables, and nuts, has been shown to reduce CVD risk-related factors. The Mediterranean diet is considered to be a well-supported dietary pattern for prevention. This review offers novel understandings into diet-related factors that are either harmful or beneficial in the context of CVD and suggests potential strategies for improving cardiovascular health. The implications of these findings put forward a need for healthcare providers to enhance their discussions with female patients about CHD, providing targeted education on its prevention.

INTRODUCTION

The most common kind of heart illness is coronary heart disease, and it is the consequence of atherosclerosis or the deposition of fatty plaques in arteries, leading to the arteries becoming narrow because of the thickening of artery walls. Atherosclerosis, coronary syndrome and other kinds of chronic ischemic diseases are included in the broad term coronary heart disease. These are responsible for a tremendous number of deaths. Shortness of breath, chest pain, and heart attack can happen because of the narrowed arteries due to the formation of blood clots or plaque, leading to a heart attack. The cardiovascular disease term comprises stroke, coronary heart disease, peripheral vascular disease and heart failure [1-3]. In a large population-based scientific research focusing on patients with cardiovascular ailments, researchers found that health knowledge is closely related to health

behaviour. This proposes that people with advanced levels of health knowledge may be more likely to engage in positive health behaviours and account for better overall health consequences [4]. Moreover, there is growing scientific evidence to suggest that socio-demographic features show a significant role in shaping how people perceive healthcare, make health-related choices, and adhere to medical recommendations. It is vital to understand women's understanding of heart ailments, their knowledge and awareness of risk features, and their knowledge of health-promoting strategies [5]. This understanding can offer valuable insights needed to create gender-specific health messages and is vital in the inhibition and treatment of heart ailments among women [6, 7]. Consequently, the purpose of this inclusive review was to analyze recently collected literature on women's



awareness and knowledge of threat-related factors associated with coronary heart disease (CHD), and to investigate how this awareness and knowledge influences their adoption of healthy lifestyle behaviours [2]. It is significant to understand that cardiac restoration programs, which conventionally have focused on secondary treatment and prevention, likewise emphasize the significance of constructing inclusive HL behaviour changes.

This study aims to discuss the significance of nutrition knowledge and health behaviours regarding CVD. The current study was based on a narrative review, which focused on demonstrating the nutrition knowledge and health behaviour regarding CVD. Different studies were evaluated using different sources, such as PubMed, Scopus, and Google Scholar. Different keywords were searched, such as healthy lifestyle, cardiovascular, risk factors, Mediterranean diet, balanced diet, and diseases, in different combinations. The studies that were included in elaborating the effect were mainly cross-sectional, descriptive, prospective, cohort, experimental, meta-analysis and case studies. Only studies published between 2015 and 2024 were included to ensure a comprehensive analysis of recent and relevant literature related to cardiovascular diseases. Studies from all geographical regions were considered to enhance the generalizability of findings across diverse populations and healthcare settings.

Prevalence of Coronary Heart Disease

There are 86% of cardiovascular patients in underdeveloped countries, and an 80% mortality rate because of this disease [2]. Women often believe that conditions such as osteoarthritis, arthritis, and cancer are more prevalent in women than coronary artery disorders (CAD). In reality, however, the foremost cause of death for women is heart disease. In Pakistan, 15.9% of the population has at minimum one risk factor for heart ailments, and women are found to have more risk factors than men. Notably, men commonly exhibit higher LDL and cholesterol levels, while women often experience lower HDL and higher triglyceride levels. Metabolic syndrome affects 49% of Pakistani women according to modified ATP criteria, and 30% of women with metabolic syndrome are also affected by coronary artery disease. The worldwide foremost cause of death is CHD. Although this is a disease of advanced age but it also attacks the people of middle-aged and a few young people too. The CHD occurred in all ages, and it was a renowned disease of the eighteenth and nineteenth centuries [3].

Cardiovascular Diseases

Cardiovascular diseases (CVD) include a variety of conditions that involve the cardiac system and blood vessels. This includes common types, for instance stroke,

cardiac failure, and coronary heart disease, in addition to less common types like congenital and rheumatic heart disease. The primary cause of CVD is a process called atherosclerosis, in which fatty deposits build up in the arteries, leading to narrowing and blockages [3]. This can result in various serious conditions, including heart attack, peripheral arterial disease, and stroke. There are numerous risk factors related to heart disease, several of which can be mitigated through the adoption of a healthy lifestyle. These risk factors include smoking, unhealthy eating habits, advancing age, diabetes, high blood cholesterol, kidney disease, high blood pressure, stress, depression, physical inactivity, family history of heart disease, and being overweight. To reduce the probabilities of cardiovascular disease healthy attitude should be adopted [4].

Risk Factors of Heart Disease

Despite advancements in treatment and diagnosis, cardiovascular disease has emerged as the predominant cause of illness and mortality globally. While the mortality rate associated with cardiovascular disease has demonstrated a downward trend, the incidence of CVD has shown an alarming increase. Notwithstanding the abundance of information available regarding the risk-related factors for coronary heart ailments, a significant proportion of women fail to perceive these risks as life-threatening. Remarkably, cardiovascular disease is viewed as the principal cause of death in women across numerous countries. Studies reveal that cardiovascular disease is responsible for over five hundred deaths annually, equating to an average of thirty women succumbing to heart disease each day. Regrettably, women's awareness of these issues is lacking, leading to an underestimation of the risks involved [5]. The risk factors of CVD are classified into two groups: modifiable (changeable) and non-modifiable risk-related factors. Risk factors that can be improved are the following: hypertension, diabetes, lack of exercise, elevated cholesterol level, obesity and smoking. Non-modifiable risk-related factors are family history, age and gender. The major possibilities of risk factors are as follows: elevated serum cholesterol, hypertension, reduced level of high-density lipoprotein, diabetes, smoking and high level of low-density [6].

Health Behaviors

The lifestyle behaviours that have placed the women at an increased risk of heart disease are as follows: sedentary lifestyle, obesity, diet and smoking. In light of the theoretical framework, notably the Health Belief Model, the study has been done on the perceived risk of heart disease by Rosen stock. According to the Health Belief Model, the suggested health action is taken by the individual if the individual perceives herself or himself susceptible to getting the disease, and the individual perceives that

getting heart disease is serious. The benefits of a suggested health action are more than the barriers. Firstly, the person must perceive themselves at risk of health threat, then they would take actions to decrease health risk behaviours or to engage in healthy behaviours [5]. In many studies, perception about vulnerability was considered as an indicator that shows the person's willingness to participate in behaviours that are risk-reducing of heart-

related diseases. The relationships between behaviours of adolescents and health beliefs have shown a correlation with the awakening of beliefs related to health, according to a ten-year study. The factors that lead to perception about health risk are very important to know to engage women in behaviour that decreases heart diseases [7] (Table 1).

Table 1: Displayed Studies Regarding CVD Risk Factors

Nutrients	Study	Research Object	Main Finding	References
Polyunsaturated and saturated fat	Meta-analysis research (RCT)	Research studied that randomized adults to amplified PUFA intake for at least 1 year and stated the occurrence of CHD	Taking PUFA instead of SFA can decrease the incidence of CHD risk factors	[8]
Saturated fat	Meta-analysis related to prospective (cohort studies)	Studied stroke and CHD risk factors in randomly selected patients	No substantial evidence supported the association between the ingestion of dietary saturated fat and the threat of CHD	[9]
Saturated fat	The Multi-Ethnic research	Selected randomly, Contributors who were 45–84 years old for CVD risk assessment	Saturated fats are certainly related to CHD risk-related factors; nevertheless dairy dairy-related fats are inversely related to risk factors	[10]
Dietary fat	PREDIMED study investigators	Selected randomly 7038 members with men and women (aged at high CVD risk	Saturated fatty acid and trans fat ingestion are associated with an increased hazard of cardiac problems; nevertheless, MUFA and PUFA ingestion are, contrarily, linked with CVD death	[11]
A Mediterranean dietary regime added with extra-virgin olive oil or nuts	The PREDIMED research	A multicenter experiment in Spain with 7447 members (55 to 80 years old, 57% female) at increased cardiac risk.	The Mediterranean diet efficiently inhibits the possibility of major cardiovascular events.	[12]
Diet with increased glycemic load and index	The study was a Meta-analysis of forthcoming cohort research	Studies displayed relations of glycemic index and load with the occurrence of CHD involving 240,936 participants.	Diet with increased glycemic index and load is ominously related to CVD in female mostly	[13]
Carbohydrate and saturated fat	Prospective- cohort study	9899 women (aged 50–55 years) were enrolled on the Longitudinal Study related to Women's Health.	A reasonable carbohydrate intake is related to reduced risk of heart disease and stroke.	[14]
Animal and plant protein	A prospective cohort study	The research encompassed 70,696 members in the Japan Public Health Centre-centred Prospective Cohort aged 45 to 74 years.	Higher plant protein consumption It is related to decreased CVD-related death, but animal-related protein ingestion is not related to death consequences.	[15]
Carbohydrate	A forthcoming (cohort research meta-analysis)	15,428 adults aged 45–64	Both an upsurge and a decrease in carbohydrate consumption are related to increased mortality rate.	[16]

CVD Risk Factors

In Pakistan, the incidence of CVD is more common among female compared to male. The ratio of male to female patients is 1:3. This is the misconception that CVD is more common among male compared to female and that arteriosclerosis is the least common problem to be worried about. The assertion that women are shielded from heart disease is not accurate, particularly in the case of post-menopausal women. After menopause, women experience a decrease in estrogen production, which in turn increases their susceptibility to heart attacks. However, arteriosclerosis manifests differently in women, leading to a higher propensity for blood clot formation due to increased coagulability in women's blood. In many women, endothelial dysfunction, diffuse arteriosclerosis, and smaller vessel size are the primary causes of ischemia even in the absence of significant blockage in the heart arteries. Furthermore, arteriosclerotic plaques in women are described by a lesser presence of fibrotic cells and an advanced density of foam cells filled with lipids, indicating an increased risk of thrombosis and plaque rupture [17]. Women have the same magnitude of arteriosclerosis, but it looks different because of genetic reasons and estrogen. In clinical manifestation of symptoms, women mostly have atypical angina as compared to classical angina. They experience symptoms like shortness of breath, non-coronary chest pain syndrome, fainting and weakness [18]. Physical inactivity is very common among Pakistani women because of our culture of keeping women in houses, especially during the menopausal age. This causes hypertension, obesity and diabetes mellitus, which are the major causes of heart ailments.

Women's Awareness About Heart Disease

Women's decision-making process is influenced by their perception of the risk factors of heart disease as compared to their decision-making regarding health care. Women do not understand the severity of heart disease, and they do not understand the importance of decreasing the risk factors to prevent heart disease [19]. Heart diseases are the main cause of mortality in women, specifically smoking, diabetes mellitus, hypertension, obesity and dyslipidemia. As most women do not have the perception of the risk factors of heart disease, they do not take any preventive measures, and their behaviours related to the reduction of risk are low. Even women with heart disease do not have any idea about the heart disease risk factors [20]. Those who want to have a healthy lifestyle respond positively to awareness programs about heart diseases. It is very significant to comprehend the association between the patient's attitudes, knowledge and behaviour. This should be taken into consideration when evolving any approach to decrease the chances of heart disease. People

lack information about the influence of CHD on women's health. More education about coronary heart disease is needed to increase knowledge about the disease, to reduce the mortality and morbidity of the disease [21].

Women's Knowledge regarding Risk Factors

Menopause and breast cancer were considered the most common health issues of women, which is why women now consider that heart disease is not a problem for them. Because of this, women are not aware of heart disease [22]. According to a study, even 45% patients had average knowledge about risk factors of disease, 35% of patients had below average knowledge, and only 20% had beyond average information about the risk-related factors of heart disease. The study shows that women know the overall harmful effects of smoking, but they fail to know that smoking is related to female illnesses, specifically among uneducated people and low levels of education [23]. According to the study, 68% population has poor awareness about cardiovascular disease and preventive methods. Most commonly mentioned by people, preventive methods are relaxing or decreasing stress, according to 52.1% of participants in the study. Poor knowledge about CVD prevention is low among people with elementary education, low income, poor self-health and people living in rural areas. There is a dire need for education in rural areas about CVD. The one explanation for the worst cardiovascular outcomes in women is the knowledge gap between actual disease risk and women's perceived risk. Historically, cardiovascular disease was considered a man's disease, and because of this perception, women were not incorporated into research programs related to cardiovascular disease [24].

Nutritional Knowledge

Many studies show that people with better nutrition knowledge have better nutrition intake. Adequate nutrition knowledge shows a vigorous role in decreasing the risk of heart disease and in improvement of nutritional status. Nutrition knowledge plays a very significant part in the promotion of health, and it has potential for improving dietary quality. Dietary fiber is the plant component that is not digestible by gastrointestinal enzymes. Functional fiber is the non-digestible kind of carbohydrate that has been extracted from or manufactured from sugars or starches. They have some benefits of natural fiber. Both of these fibers are beneficial in reducing risk factors of most diseases. Less soluble kinds of fibers are lignin and cellulose, and these are mostly in fruits, whole wheat and vegetables [25]. More soluble fiber is pectin, which is present in apples, carrots, strawberries, legumes and oats. Insoluble fiber modifies the concentration of serum lipid, and soluble fibers bind with the bile acid and increase the bile excretion. Fiber lowers the blood cholesterol level,

which is why it is considered beneficial for health. An increasing amount of vegetables, fruits and whole wheat products is beneficial in decreasing the possibility of heart ailments. Consumption of high fiber foods increases satiety, reduces cholesterol, and decreases the risk factors of heart disease and type 2 diabetes [26]. Antioxidants play a vital part in inhibiting oxidation, a chemical reaction that generates free radicals and initiates a chain of reactions, causing cellular damage. Notably, antioxidant vitamins, containing Vitamin C, E, and beta-carotene, elevate the plasma antioxidant level. Vitamin C, a water-soluble antioxidant, helps in the rejuvenation of oxidized vitamin E. These vital antioxidants are abundantly present in various foods such as carrots, blueberries, red kidney beans, strawberries, apples, oranges, plums, red grapes, spinach, beets, onions, corn, eggplants, and cabbage. Encouraging the ingestion of a diet rich in antioxidants is advised to decrease the risk factors related to heart ailments [27].

Impact of Various Dietary Components on CHD

Numerous management related to dietary habits can decrease the risk factors of heart disease. Intake of fat should be less than 30% of overall calorie consumption, ingestion of saturated fat and foods which contain trans-fat must be fewer and substituted with monounsaturated fat. Ingestion of salt ought to be less, and consumption of fruits and vegetables should be increased. Fish is good for the heart, so its consumption should be increased. Animal foods are the merely basis of saturated fat and cholesterol in the diet; nonetheless, they are high in protein. To get benefits from zinc, iron and vitamins B in meat, thin cuts of meat should be designated and skinless poultry because they are lower in saturated fat. Low-fat milk and its foodstuffs give protein of high quality, and they are low in saturated fat [28]. Oils of fish have anti-inflammatory potentials, preserve the nervous system, decrease clotting, decrease cholesterol level and triglycerides [29].

Healthy Food Consumption

The best preventive measure of cardio diseases is a healthy modified diet. Many types of foods have a direct effect on the contributors to cardio diseases such as atherosclerosis and hypertension. Without proper lifestyle and dietary habits, cardiovascular diseases are unavoidable. Canola oil, olive oil, tree nuts and peanut oil have monounsaturated fatty acids. According to healthy American dietary guidelines, saturated fatty acids must be substituted with polyunsaturated fatty acids and monounsaturated fatty acids, which leads to a decrease in the risk factors of cardiovascular diseases. Polyunsaturated fatty acids have more than two double bonds. The most important polysaturated fatty acids are linolenic acids (omega-3) and linoleic acids (omega-6). Omega-6 is present in canola oil, flaxseed, pumpkin seeds,

and sunflower seeds. Omega-3 is mostly present in nuts, oils and fish. Both omega-3 and omega-6 help in decreasing risk factors of heart disease. There is an inverse relationship between blood pressure and omega-3 [30]. Fiber also helps in decreasing the risk factors of heart diseases because of its action on lipoproteins, lipid, and glucose metabolism. Dietary fiber is found in vegetables, legumes, fruits and whole grains. Fiber also decreases insulin and glucose levels in patients. Fiber also lowers the cholesterol level in the body by binding with the bile acid. Bacteria ferment the fiber in the colon and produce the butyrate, acetate and propionate. In this way, it inhibits the synthesis of cholesterol [31].

Vegetables and Fruits

The food patterns which are high in vegetables and fruits are related to the reduction in the risk factors of the cardio ailments, which include high blood pressure, high lipid levels, weight control, endothelial function, insulin resistance, and inflammatory biomarkers. Plant-based diet gives us these benefits because of the following factors: a) fiber, micronutrients and phytochemicals existent in fruits and vegetables; b) increases the availability of these nutrients if they are consumed in their fresh state; c) the substitution of unhealthy foods in the diet by fruits and vegetables. There is the opposite relationship between fruits and vegetables and the possibility of heart disease [30].

Dietary Fiber and Whole Grain Consumption

Dietary fiber consumption has an inverse relationship to the risk factors of CVD. The American Heart Association (AHA) has established the description of whole grains centered on the fiber component of the whole grain. The whole grain term is mostly used for the germ, bran and endosperm. Whole grain products lower the absorption in the gastrointestinal tract and produce lower insulinemic and glycemic responses than refined grains. Bran is mostly high in the fiber, tocopherol, flavonoids, minerals and vitamins. These components of bran are important for health. Whole-grain consumption decreases the chances of heart disease. The dietary fiber component of the grains is mostly involved in lowering the risk factors of cardio diseases. The other characteristics of whole grains, including high minerals, fatty acids and phytochemicals, also have beneficial effects on health. The elimination of bran and germ, which mostly occur in refining processes, decreases the amount of dietary fiber, and that is why some of the significant benefits are gone, including a reduction in blood pressure and blood cholesterol level. Whole grains are important in reducing weight; improving homeostasis of insulin and glucose, and in biomarkers of inflammation [32].

Dairy Products

Dairy products are an important source of some nutrients

like potassium, magnesium, bioactive peptides and calcium. But the saturated fat is present in the dairy products, mostly palmitic acid is present which has bad effects on the lipid profile of blood. Low-fat dairy items are mostly recommended because they are low in calories, cholesterol and saturated fatty acids. Consumption of low-fat dairy items decreases blood pressure and reduces hypertension. The intake of little fat dairy products has an inverse relationship with blood pressure and hypertension [18]

Meat and Processed Meat

The patterns of foods which decrease the risk factors of heart diseases are the Mediterranean diet, the DASH diet, or the vegetarian diet. All of these diets include little consumption of red meat, especially processed red meat, because these components, saturated fatty acids, cholesterol, and heme iron, increase the risk of cardiovascular diseases. High levels of salt and preservatives present in treated meat also increase the risk factors of heart disease. Ingestion of red meat is connected with an increased risk of heart disease. Adverse preservative effects (eg phosphate, sodium and nitrites) present in meat which is processed and different methods of cooking like frying and high temperature cooking have bad effects on health [33].

Salt Ingestion

There is convincing proof that advanced consumption of sodium chloride (salt) is related to raised levels of BP. Over its impact on BP, a lessening in salt consumption will decrease stroke and CHD, as a meta-analysis of forthcoming observational studies has reinforced. Long-term follow-up of salt-reduction trials is also reliable, with a reduction in CVD rates after salt reduction. Foods in restaurants account for an extra 50% of sodium ingestion in Western countries. The rest is derived from naturally arising sources or added at home [34].

Prevention, Education and Treatments

Laws, treaties, policies and regulations have displayed significant roles in the avoidance and control of illnesses. Only governments can authorize health warnings on cigarettes, present obligatory food standards and labelling, set a "pro-health tax policy", or implement a national transport policy. Frequently, governments are the chief suppliers of health care; they choose how funding is apportioned, from prevention programs to treatment, research, and training [35].

Dietary Recommendation

Dietary reference for acute cardiovascular disease comprises caloric constraint, soft-texture foods, and small, recurrent meals to decrease the metabolic strains of digestion, absorption, and metabolism of foods and to attain ideal body weight; limit of fat and cholesterol

ingestion; and sodium. Chronic coronary heart disease and hypertension profit from sodium constraint to overcome oedema instigated by insufficient cardiac output and to aid in controlling the raised blood pressure [36].

As a narrative review, this study is limited by potential selection bias, variability in study designs, and the absence of standardized quantitative analysis, which may affect the generalizability of conclusions. Additionally, many included studies rely on self-reported behaviors, which can introduce reporting inaccuracies. Future research should prioritize large-scale, region-specific longitudinal studies and intervention-based trials to evaluate the effectiveness of nutrition education programs, especially among high-risk and underserved populations. Policymakers and healthcare systems should also develop culturally tailored, evidence-based educational initiatives to bridge knowledge gaps and promote sustainable cardiovascular health behaviors.

CONCLUSIONS

The content of this review points out that the solution to lowering the global epidemic burden of cardiovascular disease lies in enhancing health literacy and dietary health. Nevertheless, even with such limitations, a more plant-based, nutrient-dense diet, which is affordable and accessible, with equitable policies and evidence-based healthcare advice can make a world of difference in cardiovascular outcomes. It is imperative that the disparities in knowledge as well as access should be addressed. Education, an integrated approach of the healthcare systems, and policy will need to support the efforts of empowered individuals to realize enduring transformations to mitigate the risk of CVD.

Author's Contribution

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Formal analysis: AS

Writing and Drafting: AS

Review and Editing: AS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Original Article



The Role of Peer-Assisted Learning in Enhancing Medical Students' Academic Performance

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ABSTRACT

Peer-assisted learning (PAL) has gained recognition as an innovative and interactive educational strategy in medical education. **Objectives:** To evaluate the impact of PAL on the academic performance and satisfaction of undergraduate medical students. **Methods:** A comparative quasi-experimental study was conducted at Rawal Institute of Health Sciences, Islamabad, over six months. A total of 106 students participated, including 76 who attended PAL sessions and 30 who did not. Pre- and post-tests were administered to assess academic performance. PAL sessions were conducted twice weekly for four weeks and were led by trained senior students. Student satisfaction was measured using a structured questionnaire. Data were analyzed using SPSS version 25.0. Independent-samples and paired-samples t-tests were used to assess between-group and within-group differences. A p-value of less than 0.050 was considered statistically significant. **Results:** Pre-test scores were similar between groups. However, PAL participants achieved significantly higher post-test scores (Mean $\pm$ SD = 73.81 $\pm$ 9.00) and greater improvement (Mean = 18.95%) compared to non-participants (Mean = 6.82%, p = 0.001). Satisfaction levels were notably high among PAL participants, with over 90% reporting an enhanced understanding, increased exam preparedness, and increased academic confidence. **Conclusions:** It was concluded that PAL had a positive impact on both academic performance and student satisfaction. These findings support the integration of PAL as a complementary educational approach within medical curricula.

INTRODUCTION

Medical education is evolving rapidly to meet the demands of an increasingly complex healthcare system [1]. With the rise of competency-based curricula and the shift from passive knowledge acquisition to active learning, educational strategies must be restructured to foster deeper understanding, critical thinking, and collaboration among students. Traditional lecture-based methods, although still relevant, often fall short in addressing individual learning needs, particularly in settings where large class sizes and limited faculty availability hinder

personalized instruction. Consequently, there has been a growing emphasis on incorporating interactive, learner-centred approaches into undergraduate medical education [2, 3]. One such approach gaining global attention is peer-assisted learning (PAL), an educational model in which students support the learning of their peers, typically under the guidance of faculty. In PAL, senior or academically stronger students serve as peer tutors, facilitating discussions, clarifying difficult concepts, and creating a less intimidating learning



environment. Numerous studies have demonstrated that PAL enhances knowledge retention, boosts academic confidence, and improves examination performance [4]. It is also associated with improved communication skills, leadership development, and increased learner satisfaction. The horizontal relationship between peer tutors and learners often encourages more open discussions and the use of relatable language, making complex topics more accessible [5, 6]. Despite its well-documented benefits, PAL remains underutilized in many low- and middle-income countries, including Pakistan. In many institutions, didactic lectures continue to dominate the educational landscape, leaving limited space for structured peer-led teaching. Moreover, few medical colleges in the region have formally evaluated the academic impact of PAL or explored student perceptions in a structured format. Existing studies from South Asia are often limited by small sample sizes, unstructured PAL delivery, or a lack of objective performance evaluation [7, 8]. This lack of robust evidence creates uncertainty regarding the integration of PAL into mainstream medical curricula, particularly in resource-constrained environments where educational innovation is urgently needed. The rationale for this research lies in the need for locally relevant evidence to support educational reform. If proven effective, PAL could serve as a scalable, low-cost complement to traditional teaching, particularly beneficial in settings with limited faculty resources. By examining both objective academic outcomes and subjective student feedback, this study offers a comprehensive assessment of PAL's potential role in undergraduate medical education and provides a foundation for its broader adoption in similar institutions nationwide.

Medical education is increasingly shifting toward active and student-centred learning approaches to improve engagement and academic outcomes. Although peer-assisted learning (PAL) has demonstrated positive educational benefits in many international settings, its structured implementation and evaluation remain limited in many medical institutions in Pakistan. Existing regional studies often rely on small samples or lack objective comparisons of academic outcomes. Therefore, there is a need for locally generated evidence assessing the effectiveness of PAL on both academic performance and student perceptions in undergraduate medical education. This study aims to evaluate the academic outcomes of a structured PAL program implemented at the Rawal Institute of Health Sciences, Islamabad. Specifically, to assess the effectiveness of PAL in improving academic performance through standardized pre- and post-testing and to compare outcomes between students who did and did not participate in the intervention. Additionally, also to conduct a satisfaction survey to explore student

perceptions of PAL in terms of conceptual understanding, exam readiness, and overall academic experience.

METHODS

The quantitative, comparative quasi-experimental design was conducted at the Rawal Institute of Health Sciences, Islamabad, within the departments of basic medical sciences, over six months from December 2024 to May 2025. Ethical approval was taken from Rawal Institute of Health Sciences, Islamabad, with IRB no: RIHS/IRB/30/2024. This study evaluates the impact of peer-assisted learning (PAL) on the academic performance of undergraduate medical students. It compared pre- and post-test performance between students who participated in PAL sessions and those who did not. Additionally, student satisfaction with the PAL intervention was assessed through a structured questionnaire. PAL sessions were incorporated into the students' regular academic schedules under faculty supervision. The sample size was calculated using G*Power software for an independent two-sample t-test, assuming a two-tailed alpha of 0.05, 80% power, and an effect size of 0.7, based on findings from literature by Gros et al., who reported large gains in academic performance associated with peer-assisted interventions in healthcare students [9]. This yielded a minimum sample size of 98 students (49 per group). To accommodate potential dropouts, the final sample was increased to 106, with 76 students participating in PAL and 30 serving as the comparison group. Participants were selected using a non-probability purposive sampling technique. Inclusion criteria included MBBS students enrolled from the first to final year who consented to participate in both pre- and post-assessments. For inclusion in the PAL group, students had to attend at least one session. Students who had previously taken part in formal peer-teaching programs, were absent from both assessments, or withdrew consent were excluded. Participation was voluntary, and written informed consent was obtained from all participants after explaining the study objectives. Confidentiality was maintained throughout the process. Data were stratified based on academic year and gender to reduce potential confounding, but no randomization was employed. Before the PAL intervention, all participants completed a standardized pre-test comprising multiple-choice and case-based questions aligned with the ongoing module content. Over the following four weeks, PAL sessions were conducted twice weekly for 60–90 minutes. These sessions were facilitated by trained final-year medical students, who led small-group discussions, clarified key concepts, and supported clinical reasoning. All sessions followed a semi-structured format aligned with the formal curriculum and were conducted under faculty oversight.

After the intervention, a post-test mirroring the pre-test in structure and difficulty was administered. To minimize assessment bias, post-tests were anonymized and scored blindly. A structured satisfaction questionnaire was distributed to PAL participants, evaluating four domains: conceptual clarity, exam readiness, academic confidence, and willingness to recommend PAL. The questionnaire used Yes/No responses and was pilot-tested on a small group for clarity. All test items were reviewed by subject experts for content validity. Peer tutors were standardized through preparatory training. Internal consistency of the academic test was confirmed using Cronbach's alpha, which yielded a coefficient of 0.82. Data were analyzed using IBM SPSS Statistics version 25.0. Descriptive statistics were reported as means, standard deviations, frequencies, and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. As assumptions for parametric analysis were met, independent-samples t-tests were used to compare pre- and post-test scores between groups, and paired-samples t-tests were used for within-group comparisons. Satisfaction data were summarized using frequency distributions. A p-value of less than 0.050 was considered statistically significant.

RESULTS

A total of 106 undergraduate medical students participated in the study. Gender distribution was equal, with 53 male (50.0%) and 53 female (50.0%). Most students were aged 21-23 years (56; 52.8%), followed by those aged 18-20 years (47; 44.3%), and a smaller group aged ≥ 24 years (3; 2.8%). In terms of academic level, the majority were in their 3rd year (32; 30.2%) and final year (28; 26.4%), with others from 2nd year (26; 24.5%) and 1st year (20; 18.9%). Most participants were hostel residents (70; 66.0%), while the rest were day scholars (36; 34.0%) (Table 1).

Table 1: Demographic Characteristics of Participants (n=106)

Variables	Category	Frequency (%)
Gender	Male	53 (50.0%)
	Female	53 (50.0%)
Age Group	18-20 Years	47 (44.3%)
	21-23 Years	56 (52.8%)
	≥ 24 Years	3 (2.8%)
Year of Study	1 st Year	20 (18.9%)
	2 nd Year	26 (24.5%)
	3 rd Year	32 (30.2%)
	Final Year	28 (26.4%)
Living Status	Hostel Resident	70 (66.0%)
	Day Scholar	36 (34.0%)

Out of the total sample, 76 students (71.7%) reported attending PAL sessions, while 30 students (28.3%) did not. Among PAL attendees, 44 (57.9%) participated

occasionally (<75% attendance), and 32 (42.1%) attended regularly ($\geq 75\%$) (Table 2).

Table 2: Participation in PAL Sessions (n=106)

Variables	Category	Frequency (%)
Attended PAL Sessions	Yes	76 (71.7%)
	No	30 (28.3%)
Frequency of Attendance (n=76)	Occasional (<75%)	44 (57.9%)
	Regular ($\geq 75\%$)	32 (42.1%)

An analysis of academic performance showed no significant difference in pre-test scores between PAL participants (Mean = 62.16 ± 7.92) and non-participants (Mean = 61.24 ± 7.44 , $p = 0.587$), indicating a comparable starting level for both groups. However, post-test scores were significantly higher in the PAL group (Mean = 73.81 ± 9.00) than in the non-PAL group (Mean = 65.26 ± 6.83 , $p = 0.001$). Furthermore, the mean score improvement was markedly greater among PAL participants ($18.95\% \pm 5.25$) compared to non-participants ($6.82\% \pm 3.91$, $p = 0.001$), confirming a statistically significant academic benefit (Table 3).

Table 3: Comparison of Academic Performance (PAL vs Non-PAL)

Performance Metric	PAL Participants (n=76)	Non-PAL Participants (n=30)	p-Value
Mean Pre-Test Score	62.16 ± 7.92	61.24 ± 7.44	0.587
Mean Post-Test Score	73.81 ± 9.00	65.26 ± 6.83	0.001
Score Improvement (%)	18.95 ± 5.25	6.82 ± 3.91	0.001

Among PAL participants, satisfaction levels were high. A majority of students (70; 92.1%) reported improved conceptual understanding, (74; 97.4%) felt better prepared for exams, (72; 94.7%) experienced enhanced academic confidence, and (71; 93.4%) were willing to recommend PAL to peers (Table 4).

Table 4: Student Satisfaction with PAL Sessions (n=76)

Satisfaction Area	Agree, n (%)
Improved Understanding of Topics	70 (92.1%)
Boosted Exam Preparation	74 (97.4%)
Felt More Confident Academically	72 (94.7%)
Would Recommend PAL To Others	71 (93.4%)

The study presents a bar chart comparing the mean pre-test and post-test scores, as well as the percentage score improvement, between students who participated in PAL and those who did not. The data reveal that PAL participants had a significantly higher mean post-test score (73.81) compared to non-participants (65.26). Both groups began with comparable pre-test scores (62.16 vs. 61.24), suggesting similar academic baselines. However, the PAL group demonstrated a notably greater percentage improvement (18.95%) than the non-PAL group (6.82%), highlighting the effectiveness of PAL in enhancing academic performance (Figure 1).

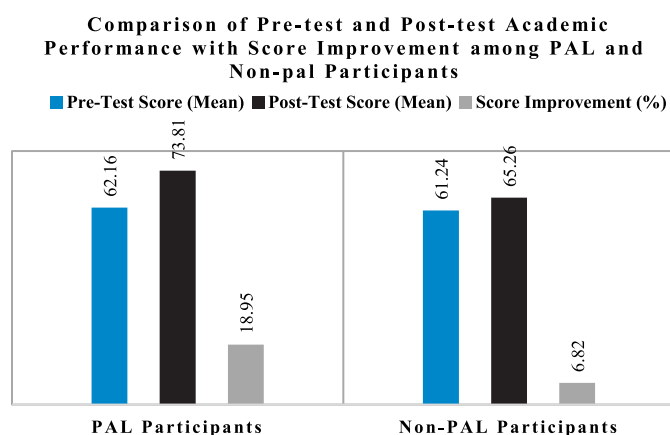


Figure 1: Comparison of Pre- and Post-Test Scores and Score Improvements Among PAL and Non-PAL Students

DISCUSSION

This study examined the impact of peer-assisted learning (PAL) on the academic performance and satisfaction of undergraduate medical students. The findings revealed that students who engaged in PAL demonstrated significantly higher post-test scores and greater overall improvement compared to their peers who did not participate. Both groups had similar pre-test scores, suggesting comparable baseline academic abilities. This supports the interpretation that the gains observed in the PAL group were attributable to the intervention itself, rather than to initial academic differences. These results align with existing literature on PAL's benefits in medical education. Studies by Amer *et al.*, and Williams *et al.*, found that PAL not only promotes engagement but also leads to better academic performance, particularly in the early clinical years [10, 11]. Similarly, Jawhari *et al.*, and Chan *et al.*, reported enhanced knowledge retention and assessment outcomes among students who received peer-led instruction [12, 13]. Current findings reinforce the evidence that PAL can serve as a valuable complement to traditional faculty-led teaching. Beyond academic scores, student satisfaction in this study highlighted the broader educational value of PAL. Most participants reported improved conceptual understanding, greater exam preparedness, and increased academic confidence. The majority also indicated a willingness to recommend PAL to their peers, demonstrating that the intervention was not only effective but also a well-received experience [14, 15]. The success of PAL may be explained through several well-established educational theories [16]. According to Vygotsky's Zone of Proximal Development (ZPD), learners benefit most when guided by individuals who are slightly more knowledgeable than themselves, exactly the dynamic created in PAL sessions. The peer tutors, being close in training level, help bridge the gap between what students can do independently and what they can achieve with support [17]. Furthermore, cognitive congruence, the idea

that peers explain concepts using language and frameworks more relatable than those used by faculty may make learning more accessible and less intimidating. Peer modelling, wherein students observe and emulate the strategies and attitudes of successful peers, also contributes to the motivational and behavioural benefits of PAL. Together, these mechanisms help foster an environment that encourages active learning, immediate feedback, and shared responsibility for academic progress. The informal, non-hierarchical structure of PAL sessions may also enhance their effectiveness. Students often feel more comfortable seeking clarification and expressing uncertainty in peer-led groups than in formal lectures. This sense of psychological safety supports deeper engagement and sustained attention, contributing to the improved outcomes observed. Previous studies by Slabbert and du Plessis, Khan *et al.*, and Zakaria *et al.*, emphasized that peer relatability enables explanations to be delivered at a level that resonates more clearly with learners [18-20]. Finally, the benefits of PAL extended beyond academic improvement. High satisfaction rates suggest that PAL may also offer psychosocial advantages, including reduced performance anxiety, increased motivation, and a greater sense of community. These multidimensional effects position PAL as a particularly valuable educational strategy in resource-constrained or high-stress academic environments.

This study has several limitations, including its single-institution setting and quasi-experimental design without randomization, which may limit the generalizability of the findings. The unequal group sizes and relatively short duration of the intervention may also have influenced the observed outcomes. Additionally, long-term knowledge retention and tutor training outcomes were not evaluated. Future multicenter studies with randomized designs, larger samples, and longitudinal follow-up are recommended to further validate the effectiveness and sustainability of PAL in medical education.

CONCLUSIONS

It was concluded that Peer-Assisted Learning (PAL) significantly improved medical students' academic outcomes, evident through higher post-test scores and notable gains in individual performance. Students also reported high satisfaction with the PAL experience, particularly appreciating its role in enhancing conceptual clarity, exam readiness, and self-confidence. Given its effectiveness and positive reception, integrating PAL into the formal medical curriculum could serve as a valuable adjunct to conventional teaching strategies. Moving forward, further research should explore the long-term retention of knowledge, evaluate the benefits of structured peer tutor training, and assess the adaptability of PAL

across various medical disciplines and academic years. Overall, PAL emerges as a practical, student-centred, and resource-efficient approach to medical education.

Authors' Contribution

Conceptualization: KA

Methodology: SS, SA, RS

Formal analysis: FP, SS, SA

Writing and Drafting: KA, FP, SS, HA, SA, RS

Review and Editing: KA, FP, SS, HA, SA, RS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Hematological and Biochemical Alterations in Patients with Recurrent Aphthous Stomatitis

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is a common oral mucosal disorder characterized by painful, recurring ulcers. Its etiology remains multifactorial, with potential links to hematological and biochemical imbalances. **Objectives:** To compare the hematological and biochemical profiles of adult patients with and without recurrent aphthous stomatitis (RAS) attending the outpatient department of a teaching hospital in Hyderabad, Pakistan. **Methods:** A comparative cross-sectional study was done. A total of 130 participants were enrolled using a non-probability convenience sampling method, with 65 individuals in the RAS group and 65 healthy controls. Standardized clinical oral examinations were conducted to evaluate the presence, number, and location of ulcers in RAS patients, while controls were examined to confirm the absence of oral mucosal lesions. Under sterile conditions, 6 mL of blood was collected from each participant for hematological and biochemical analyses, including serum levels of cortisol, ferritin, iron, folic acid, and vitamin B12, measured using an auto-analyzer. **Results:** Independent t-tests revealed significantly higher cortisol levels in RAS patients (459.2 ± 49.6 nmol/L) compared to controls (232.4 ± 119.4 nmol/L, $p=0.001$). Conversely, ferritin, iron, and folic acid levels were significantly lower in the RAS group ($p=0.001$). Hemoglobin (12.9 ± 2.1 g/dL vs 14.0 ± 1.4 g/dL, $p=0.001$) and hematocrit ($37.88 \pm 8.14\%$ vs $40.85 \pm 5.81\%$, $p=0.018$) were also significantly lower in RAS patients, while differences in RBC, WBC, and platelet counts were not statistically significant. **Conclusions:** These findings suggest potential connections between RAS and altered specific biochemical and hematological markers, including cortisol, ferritin, iron, folic acid, hemoglobin, and hematocrit.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most common inflammatory disorders of the oral mucosa, characterized by the repeated formation of painful, round or oval ulcers. It affects approximately 5–25% of the general population, with regional variation depending on age, diet, and socioeconomic conditions [1, 2]. While minor RAS accounts for nearly 80% of cases, typically presenting as shallow ulcers (<1 cm) on non-keratinized oral mucosa, major and herpetiform variants are more severe and often leave scars upon healing [3, 4]. Although RAS is clinically

well-recognized, its exact etiology remains unclear and is likely multifactorial. Contributing factors reported in literature include genetic predisposition, local trauma, stress, food allergies, hormonal imbalances, immune dysregulation, and nutritional deficiencies [5–7]. In particular, iron, folate, and vitamin B12 deficiencies have been frequently implicated in individuals with RAS, given their roles in maintaining epithelial integrity and hematopoiesis [8]. Vitamin B12 deficiency, for instance, has been associated with epithelial atrophy, megaloblastic



anemia, and oral mucosal changes, while folic acid is essential for DNA synthesis and repair of oral mucosa [9]. Iron deficiency, best assessed through serum ferritin, impairs epithelial regeneration and immune response, and is a recognized predisposing factor for oral ulcers [10, 11]. In addition to nutritional factors, psychological stress has also been linked to RAS in several studies, often assessed through serum cortisol levels. Elevated cortisol, a stress biomarker, may reflect underlying anxiety or emotional distress contributing to RAS recurrence. However, conflicting evidence exists, as some studies have failed to demonstrate a clear association between stress markers and RAS [12]. Despite extensive international research on recurrent aphthous stomatitis (RAS), there is limited context-specific data from South Asia, particularly Pakistan, examining the role of nutritional deficiencies, hematological profiles, and systemic inflammatory markers. Given regional dietary habits, healthcare access, and genetic variability, local investigation is crucial to identify relevant contributing factors and improve targeted management. Investigating hematological (e.g., anemia, leukocyte counts) and biochemical (e.g., vitamin B12, folate, iron) changes would provide insights into possible systemic causes, improve diagnostic accuracy, and guide more effective management strategies, ultimately enhancing patient outcomes.

Recurrent aphthous stomatitis (RAS) is a common oral mucosal disorder characterized by painful and recurrent ulcerations that significantly affect patients' quality of life. Although several studies have suggested associations between RAS and nutritional deficiencies, hematological abnormalities, and psychological stress, the exact mechanisms underlying these relationships remain unclear. Moreover, there is limited local evidence from Pakistan examining the combined role of biochemical markers such as cortisol and hematological parameters in patients with RAS. This lack of region-specific data highlights the need for studies investigating these potential systemic factors to improve understanding and management of the condition. This study aims to determine the hematological and biochemical changes among patients with and without RAS presented to the dental OPD at Liaquat University Hospital and the Diagnostic Research Laboratory, Hyderabad, Pakistan.

METHODS

This comparative cross-sectional study was done from April 2020 to May 2022 at the Dental Outpatient Department (OPD) of Liaquat University Hospital and the Diagnostic Research Laboratory, Hyderabad, Pakistan. The study was approved by the ERC committee of LUMHS vide letter no. LUMHS/REC/-818. Assuming a 10% prevalence of recurrent aphthous stomatitis [3], with a 5% margin of error and a 95% confidence interval for a target population

of 20,000, an equal allocation was made, with 69 individuals in the RAS group and 69 in the healthy control group. Following recruitment, eight participants withdrew, resulting in a final sample size of 130, with 65 participants in each of the two groups. A non-probability convenience sampling technique was employed due to the difficulty of obtaining a random sample of individuals with RAS from the general population. The inclusion criteria for the RAS group required patients to have a history of recurrent aphthous ulcers for at least six months, with a minimum of two ulcer episodes within the past year. The control group comprised healthy individuals with no history of recurrent oral ulcers or any other oral mucosal disease. Patients with pre-diagnosed or clinically confirmed iron deficiency anemia, vitamin B12 or folate deficiency anemia were excluded at the time of recruitment to avoid confounding pre-existing systemic causes of oral ulceration. Participants with chronic systemic diseases (e.g., diabetes, autoimmune disorders), pregnancy or lactation, tobacco or betel nut use, smoking history, or use of medications affecting oral ulcers or lab parameters were also excluded. All individuals who met the respective inclusion criteria, provided with informed consent before their enrollment in the study. Data and clinical findings were recorded for all participants. All participants underwent a standardized clinical oral examination conducted by two experienced clinicians with more than five years of experience in a filter clinic under adequate lighting conditions. In the RAS group, the presence, number, and location of ulcers were recorded, along with associated symptoms such as pain and discomfort. Active ulcers, if present at the time of examination, were documented in detail, including their morphological characteristics. Additionally, participants were asked about ulcer episodes. For the control group, a thorough oral examination was performed to confirm the absence of any active or past signs of recurrent aphthous ulcers or other oral mucosal lesions. The overall oral health status, including mucosal integrity, was assessed to rule out any conditions that could mimic RAS. 6 ml of Blood samples were collected between 8:00-10:00 AM, within 24 hours of clinical diagnosis of active RAS or 2 weeks of a recent episode, confirmed through oral examination. Hematological parameters (CBC, RBC indices, WBC count, platelets) were analyzed using the Sysmex XN-1000 hematology analyzer. Serum cortisol, ferritin, iron, folic acid, and vitamin B12 levels were measured using Electrochemiluminescence Immunoassay (ECLIA) on a Cobas e 601 auto-analyzer (Roche Diagnostics). Data were analyzed using SPSS version 25.0. Quantitative variables (e.g., cortisol, ferritin, iron, folic acid, vitamin B12, hemoglobin, hematocrit, RBC, WBC, and platelet count) were expressed as mean $\pm$ SD and tested for normality using the Shapiro-Wilk test. Qualitative variables (e.g.,

gender, age group, residence, education) were presented as frequencies and percentages. The primary outcomes were differences in biochemical and hematological parameters between the RAS and control groups. Independent Sample t-tests were applied to compare means of normally distributed quantitative variables between groups. A p -value <0.050 was considered significant.

RESULTS

A total of 130 participants were enrolled, with equal numbers in the RAS and control groups. Male predominated in both groups (72.3% in RAS, 70.8% in controls). Most participants were aged 18–30 years, followed by 31–45 years. Urban residents constituted the majority (63.1% in RAS, 60.0% in controls). Educational levels were comparable across groups, with roughly one-third having primary education or less, and around 30% being graduates or above (Table 1).

Table 1: Demographic Characteristics of Participants (n=130)

Demographic Variables	RAS Group (n=65)	Control Group (n=65)
Gender		
Male	47 (72.3%)	46 (70.8%)
Female	18 (27.7%)	19 (29.2%)
Age Group		
18–30 Years	29 (44.6%)	31 (47.7%)
31–45 Years	24 (36.9%)	23 (35.4%)
46–60 Years	12 (18.5%)	11 (16.9%)
Residence		
Urban	41 (63.1%)	39 (60.0%)
Rural	24 (36.9%)	26 (40.0%)
Education Level		
Primary or Less	18 (27.7%)	16 (24.6%)
Secondary	27 (41.5%)	29 (44.6%)
Graduate or Above	20 (30.8%)	20 (30.8%)

The results show significantly higher mean cortisol levels in the RAS group (459.2 ± 49.6 nmol/L) compared to the healthy controls (232.4 ± 119.4 nmol/L, $p=0.001$). Conversely, ferritin (58.9 ± 7.8 ng/mL vs 80.4 ± 9.7 ng/mL), iron (75.9 ± 13.1 ng/mL vs 85.1 ± 16.2 ng/mL), and folic acid (5.7 ± 3.5 ng/mL vs 8.7 ± 5.7 ng/mL) levels were significantly lower in the RAS group ($p=0.001$ for all). Vitamin B12 levels were slightly lower in the RAS group (262.0 ± 112.2 pg/mL) compared to healthy controls (279.3 ± 112.6 pg/mL), but the difference was not statistically significant ($p=0.079$). These findings indicate significant biochemical differences in RAS patients, except for vitamin B12 (Table 2).

Table 2: Comparison of Biochemical Parameters Between RAS and Healthy Control Groups Using Independent Sample t-Test

Variables	RAS Group (Mean $\pm$ SD)	Control Group (Mean $\pm$ SD)	95% CI	p-value
Cortisol (nmol/L)	459.2 $\pm$ 49.6	232.4 $\pm$ 119.4	(191.5, 266.7)	0.001

Ferritin (ng/mL)	58.9 $\pm$ 7.8	80.4 $\pm$ 9.7	(-24.7, -17.2)	0.001
Iron (ng/mL)	75.9 $\pm$ 13.1	85.1 $\pm$ 16.2	(-13.7, -5.9)	0.001
Folic Acid (ng/mL)	5.7 $\pm$ 3.5	8.7 $\pm$ 5.7	(-4.5, -1.5)	0.001
Vitamin B12 (pg/mL)	262.0 $\pm$ 112.2	279.3 $\pm$ 112.6	(-35.5, 0.8)	0.079

The hematocrit was significantly lower in the RAS group ($37.88 \pm 8.14\%$) compared to the control group ($40.85 \pm 5.81\%$, $p=0.018$). Red blood cell (RBC) count was lower in RAS patients ($4.90 \pm 0.76 \times 10^6/\mu\text{L}$) than in healthy controls ($5.21 \pm 1.02 \times 10^6/\mu\text{L}$). Conversely, WBC count was higher in the RAS group ($9.73 \pm 2.81 \times 10^3/\mu\text{L}$). Platelet counts were also slightly lower in the RAS group ($234.80 \pm 56.30 \times 10^3/\mu\text{L}$) compared to healthy controls ($250.84 \pm 105.54 \times 10^3/\mu\text{L}$). These findings suggest significant reductions in hemoglobin and hematocrit levels in RAS patients, while other hematological parameters showed trends toward variation without statistical significance (Table 3).

Table 3: Comparison of Hematological Parameters Between RAS and Healthy Control Groups Using Independent Sample t-Test

Variables	RAS Group (Mean $\pm$ SD)	Control Group (Mean $\pm$ SD)	95% CI	p-value
Hemoglobin (g/dL)	12.9 $\pm$ 2.1	14.0 $\pm$ 1.4	(-1.6, -0.5)	0.001
Hematocrit (%)	37.88 $\pm$ 8.14	40.85 $\pm$ 5.81	(-5.4, -0.5)	0.018
RBC Count ($\times 10^6/\mu\text{L}$)	4.90 $\pm$ 0.76	5.21 $\pm$ 1.02	(-0.6, 0.0)	0.054
WBC Count ($\times 10^3/\mu\text{L}$)	9.73 $\pm$ 2.81	7.38 $\pm$ 1.79	(-0.1, 4.7)	0.057
Platelet Count ($\times 10^3/\mu\text{L}$)	234.80 $\pm$ 56.30	250.84 $\pm$ 105.54	(-45.3, 12.1)	0.282

Among male, cortisol levels were significantly higher in the RAS group (469.2 ± 51.1 nmol/L) compared to healthy controls (240.8 ± 122.3 nmol/L, $p=0.037$). Ferritin, iron, folic acid, and vitamin B12 levels showed no statistically significant differences between RAS and control males. In females, folic acid levels were significantly lower in the RAS group (5.5 ± 3.7 ng/mL) than in healthy controls (8.5 ± 3.8 ng/mL, $p=0.023$), while other biochemical parameters showed no significant variations. Regarding hematological parameters, females with RAS had significantly lower hemoglobin (12.7 ± 2.2 g/dL) than their healthy counterparts (13.8 ± 1.3 g/dL, $p=0.001$), as well as significantly lower hematocrit levels ($37.2 \pm 3.8\%$ vs $40.5 \pm 3.4\%$, $p=0.004$). However, differences in red blood cell (RBC) count, white blood cell (WBC) count, and platelet count were not statistically significant in either gender. These findings highlight gender-specific variations in biochemical and hematological parameters between RAS patients and healthy controls, with significant differences in cortisol levels among males and folic acid, hemoglobin, and hematocrit levels among female (Table 4).

Table 4: Hematological and Biochemical Parameters Between RAS and Healthy Control Groups Stratified by Gender

Variables	Gender	RAS Group (Mean $\pm$ SD)	Control Group (Mean $\pm$ SD)	95% CI	p-value
Cortisol (nmol/L)	Male	469.2 $\pm$ 51.1	240.8 $\pm$ 122.3	(25.8, 442.6)	0.037
	Female	448.9 $\pm$ 48.5	223.4 $\pm$ 116.5	(21.4, 415.4)	0.023
Ferritin (ng/mL)	Male	60.2 $\pm$ 7.6	83.1 $\pm$ 10.3	(-1.2, 49.4)	0.091
	Female	57.6 $\pm$ 8.1	78.2 $\pm$ 9.2	(-0.9, 35.8)	0.001
Iron (ng/mL)	Male	77.1 $\pm$ 12.8	87.3 $\pm$ 17.2	(-1.0, 21.2)	0.065
	Female	74.4 $\pm$ 13.4	83.9 $\pm$ 15.8	(-0.8, 20.6)	0.078
Folic Acid (ng/mL)	Male	5.9 $\pm$ 3.4	9.0 $\pm$ 5.6	(-0.6, 6.4)	0.071
	Female	5.5 $\pm$ 3.7	8.5 $\pm$ 5.8	(-0.3, 5.9)	0.023
Vitamin B 12 (pg/mL)	Male	266.5 $\pm$ 110.8	281.9 $\pm$ 114.1	(-1.9, 31.5)	0.087
	Female	257.3 $\pm$ 113.4	276.4 $\pm$ 111.2	(-1.3, 37.4)	0.024

DISCUSSION

This study demonstrated that patients with recurrent aphthous stomatitis (RAS) had significantly elevated serum cortisol levels and reduced concentrations of ferritin, iron, folic acid, hemoglobin, and hematocrit compared to healthy controls. These findings suggest a multifactorial pathogenesis involving psychological stress, micronutrient deficiencies, and mild hematologic alterations. The most prominent biochemical finding was the elevated cortisol level in RAS patients, supporting the strong link between psychological stress and oral ulcer recurrence. Cortisol, a well-established biomarker of stress, is elevated in multiple studies involving RAS patients [13, 14]. Chronic stress may downregulate immune responses, delay epithelial healing, and increase susceptibility to mucosal breakdown [13]. Current results align with those of Vandana & Kavitha, and Aslam *et al.*, reinforcing the relevance of stress as a central trigger in RAS pathophysiology [14, 15]. Nutritional factors also appear to play a key role. The significantly lower levels of ferritin, serum iron, and folic acid in the RAS group are consistent with previous studies that identified hematinic deficiencies as common in RAS patients [16, 17]. Iron and folate are essential for epithelial regeneration, DNA synthesis, and immune function. Their deficiency may lead to delayed healing and recurrent mucosal injury. Furthermore, reduced hemoglobin and hematocrit levels indicate compromised oxygen transport and tissue repair capacity, potentially exacerbating ulcer formation [17, 18]. Although vitamin B12 levels were slightly lower in the RAS group, the difference was not statistically significant, suggesting a limited role in this population. Gender-specific analysis revealed that female with RAS had significantly lower folic acid, hemoglobin, and hematocrit levels compared to healthy female, potentially due to menstrual losses and hormonal influences. Conversely, male with RAS exhibited significantly elevated cortisol levels, suggesting a stronger stress-related physiological response [19]. These findings highlight the importance of considering gender-specific factors in RAS assessment

and management. From a clinical and public health perspective, these results underscore the need to integrate nutritional screening and stress evaluation into routine care for RAS patients. Dentists and primary care providers should be vigilant in identifying micronutrient deficiencies and stress-related triggers, particularly in low-resource settings where nutritional inadequacies are prevalent [20, 21]. Incorporating hematinic profiling and psychosocial assessments could guide more comprehensive and effective treatment strategies.

This study has certain limitations, including its relatively small sample size and the use of a non-probability convenience sampling technique, which may limit the generalizability of the findings. Additionally, the cross-sectional design does not allow for the establishment of causal relationships between hematological or biochemical alterations and the occurrence of RAS. Other potential contributing factors such as dietary habits, psychological stress assessments, and long-term follow-up were not comprehensively evaluated. Future large-scale longitudinal studies incorporating detailed nutritional and psychological assessments are recommended to better understand the pathophysiology of RAS and to develop targeted management strategies.

CONCLUSIONS

It was concluded that RAS exhibits distinct changes in hematological parameters, including stress hormone (cortisol), iron metabolism markers (ferritin, folic acid), and blood cell counts (WBC, RBC, Hb). Thus, thorough evaluations in RAS patients, encompassing blood tests and nutritional analyses, are crucial for uncovering contributing factors and tailoring management based on individual predispositions.

Authors' Contribution

Conceptualization: SB

Methodology: SB, AQKD, AN, MM

Formal analysis: MW, KS

Writing and Drafting: AQKD, AN

Review and Editing: AQKD, AN, MM, KS, SB

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



A Comparison of Urine Dipstick Test with Spot Urine Protein–Creatinine Ratio and 24-Hour Protein Excretion in Women with Pre-Eclampsia

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ABSTRACT

Pre-eclampsia is a major obstetric complication marked by hypertension and significant proteinuria after 20 weeks of gestation, posing serious maternal and fetal risks. Early and accurate detection is critical for effective management. **Objectives:** To assess the diagnostic accuracy, sensitivity, and specificity of the spot urine protein-creatinine ratio (UPCR) in detecting significant proteinuria in pre-eclamptic women, compared to 24-hour urine protein excretion. **Methods:** A cross-sectional study was conducted in the Department of Obstetrics and Gynaecology, Tertiary Care Hospital, Bahawalpur, from November 24, 2022, to May 23, 2023 (Approval No. 1516/Trg/2022). The study included 202 pregnant women diagnosed with pre-eclampsia. Spot UPCR and 24-hour urine protein were measured, and dipstick testing was performed. A UPCR cutoff of 0.3 was used to evaluate diagnostic accuracy. **Results:** The mean UPCR was 1.47 ± 1.05 mg/g, and the mean 24-hour urine protein excretion was 1475.35 ± 1099.87 mg. Spot UPCR showed a strong correlation with 24-hour urine protein ($r = 0.974$, $p < 0.001$). ROC analysis revealed an AUC of 0.971. At the 0.3 cutoff, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 84.2%, 83.3%, 98.8%, and 25.0%, respectively. **Conclusions:** It was concluded that spot UPCR is a reliable and efficient alternative to 24-hour urine collection for detecting significant proteinuria in pre-eclampsia. Its integration into routine antenatal care may enhance early diagnosis and improve maternal and fetal outcomes.

INTRODUCTION

Pre-eclampsia is an important obstetric complication associated with hypertension and proteinuria after 20th weeks of gestation, which threatens maternal and fetal health severely [1]. Early detection and management are essential in reducing the adverse consequences, such as maternal morbidity and mortality, fetal growth restriction (FGR) or spontaneous preterm birth [2, 3]. Precise and rapid assessment of proteinuria is crucial for diagnosis, severity classification, and risk evaluation associated with pre-eclampsia [4]. Traditionally, 24-hour urine collection has been used to quantify proteinuria in pre-eclampsia. Such an approach is, however, a 'gold standard' with many limitations, i.e. it's time-consuming, inconvenient for patients and susceptible to collection artefacts; hence,

such tests, e.g. are likely to give erroneous results [1]. Instead of a 24-hour measurement, the spot urine protein-creatinine ratio (PCR) is a good alternative to evaluate proteinuria and gives an easily obtained, rapid estimation of proteinuria [2]. Several studies have shown the spot urine PCR to correlate well with 24-H urine protein excretion [5–7]. Its accuracy and reliability in comparison to 24 h collection require full validation to be able to offer clinical utility in the management of pre-eclampsia. Proteinuria is defined as >300 mg/d in the 24-h urine collection; thus, it represents one of the hallmarks of pre-eclampsia [8]. However, a simple, quick, and most commonly used screening tool to detect proteinuria is the urine dipstick test [9]. However, the sensitivity and



specificity of the dipstick test are variable, and the test may be positive or negative in the presence of false positives or negatives for factors such as urine concentration and pH [1]. As such, more reliable diagnostic methods should be explored [10]. For pre-eclampsia pregnancies, there have been numerous studies evaluating the relationship between spot urine PCR and 24-hour urinary protein excretion in female with pre-eclamptic pregnancies [11, 12], but results are not conclusive [2]. For example, a study by Marshall et al., studied the proportion and protein content in patients having pregnancy-induced hypertension and suggested that spot urine PCR may appropriately reflect total proteinuria under specific circumstances [1]. Charles et al., analyzed renal function changes in women with pre-eclampsia in the Nigerian context, as well as stressing the need for accurate proteinuria measurement in determining disease severity. The findings also pointed out the feasibility of spot urine PCR for application in the clinical areas where timely early intervention is possible [4]. In addition, the study conducted by Walle et al., in Ethiopia, showed the value of biochemical tests for diagnosing preeclampsia by assessing proteinuria. According to them, spot urine PCR can be incorporated in the usual antenatal care to help in the early detection and management of the disease [5]. Hypertension and severe proteinuria together constitute a serious obstetric complication in the form of pre-eclampsia. Prompt diagnosis and treatment are vital to ensuring maternal and fetal safety. While the 24-hour urine collection is still considered the gold standard for quantifying proteinuria, it poses significant challenges in routine practice due to being time-consuming, inconvenient, and prone to collection errors. The spot urine protein–creatinine ratio (UPCR) offers a more practical alternative and has been widely studied internationally. However, there is limited data on its diagnostic performance in South Asian populations, particularly in low-resource, high-burden settings such as Pakistan, where factors like late antenatal presentation, variable nutritional status, and differing baseline renal profiles may influence test accuracy and utility. Furthermore, variations in laboratory practices, population demographics, and disease severity patterns necessitate local validation. In our study, significant proteinuria was defined as >300 mg/24 hours, and a UPCR cutoff of 0.3 was used for comparison.

Pre-eclampsia remains a major contributor to maternal and fetal morbidity and mortality worldwide, and accurate detection of proteinuria is essential for its diagnosis and management. Although the 24-hour urine protein test is considered the gold standard, it is time-consuming, inconvenient for patients, and prone to collection errors in routine clinical practice. The spot urine protein–creatinine ratio (UPCR) has emerged as a rapid alternative; however,

its diagnostic performance may vary across different populations and clinical settings. In Pakistan, particularly in resource-limited tertiary care hospitals, local evidence validating the reliability of spot UPCR compared with 24-hour urine protein estimation remains limited, highlighting the need for population-specific evaluation. This study aims to assess the diagnostic accuracy of spot UPCR specifically in our clinical population to determine whether it can serve as a reliable and efficient substitute for 24-hour urine testing in routine antenatal care.

METHODS

This cross-sectional study was conducted in the Department of Obstetrics and Gynaecology, Tertiary Care Hospital, Bahawalpur, from November 24, 2022, to May 23, 2023. It aimed to evaluate the diagnostic accuracy of the spot urine protein–creatinine ratio (UPCR) in detecting significant proteinuria among hypertensive pregnant women diagnosed with pre-eclampsia. Ethical approval was obtained from the Institutional Review Board of Tertiary Care Hospital, Bahawalpur, before initiation of the study (Approval No. 1516/Trg/2022). Written informed consent was obtained from all participants. Participants were assured of confidentiality, voluntary participation, and the right to withdraw. In cases of suspected false positives or false negatives in UPCR or dipstick results, participants were promptly re-evaluated clinically, and additional investigations were conducted to avoid mismanagement or inappropriate clinical decisions. A total of 202 pregnant women aged 18 years or older with a diagnosis of pre-eclampsia were enrolled. Exclusion criteria included women with chronic kidney disease, active urinary tract infection, or those who refused consent. Pre-eclampsia was diagnosed according to the criteria of the American College of Obstetricians and Gynaecologists (ACOG, 2020). Eligible participants had a new-onset systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg on two separate readings at least four hours apart after 20 weeks of gestation, along with proteinuria defined as ≥ 300 mg/24-hour urine protein, or a spot UPCR ≥ 0.3 , or a dipstick reading of $\geq 1+$ on two occasions. The sample size was calculated using the formula for estimating a proportion in diagnostic test accuracy studies: $n = (Z^2 \times P \times (1 - P)) / d^2$, where: n = required sample size, Z = Z-score for desired confidence level (1.645 for 90% confidence), P = expected sensitivity or specificity (taken as 88.1% or 98.1% from previous studies) and d = margin of error (set at 10%, or 0.10). The larger value derived from calculations based on sensitivity and specificity was selected as the final sample size. This formula was applied both manually and using Open Epi (Diagnostic Test Evaluation Sample Size Calculator, available at: <https://www.openepi.com/SampleSize/SSPropor.htm>),

an open-source statistical software recommended for epidemiological studies. Based on these calculations, a minimum sample size of 202 participants was determined to be statistically adequate for the study [13, 14]. Midstream clean-catch urine samples were collected using standard aseptic techniques. To minimize variability, all samples were obtained in the morning after confirming that participants had maintained adequate hydration and had not consumed excessive fluids. Spot UPCR was calculated using automated biochemical analyzers by measuring urine protein (mg/dL) and creatinine (mg/dL), and expressing the ratio in mg/g. The same samples were also tested using urine dipsticks (reagent strips) for qualitative proteinuria. A separate 24-hour urine collection was carried out for all participants following hospital protocol, and total protein excretion was measured using standard biochemical methods. Data were analyzed using SPSS version 25.0. Descriptive statistics were used to summarize demographic characteristics. Pearson's correlation was applied to assess the association between spot UPCR and 24-hour urine protein excretion. Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of spot UPCR. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated based on a UPCR cutoff of 0.3. A p-value < 0.050 was considered statistically significant.

RESULTS

This study evaluated 202 pregnant female with pre-eclampsia. On average, the participants of the study were 28.98 ± 2.37 years old and 34.48 ± 2.63 weeks' gestation. The mean proteinuria in spot urine samples calculated using the protein-creatinine ratio was 1.47 ± 1.05 mg/g, and the mean 24-H urine protein excretion was 1475.35 mg with a standard deviation of 1099.87. The variability in proteinuria levels as detected by the dipstick test among the study participants was significant. The results were distributed as follows: 17.8% negative, 18.3% trace, 22.3% 1+, 20.3% 2+, and 21.3% 3+. This variability underscores the dipstick test's utility for initial screening in clinical settings, reflecting a broad range of proteinuria among the participants (Table 1).

Table 1: Distribution of Urine Dipstick Test Results Among Pregnant Women with Pre-eclampsia

Urine Dipstick Results	Frequency (%)
Negative	36 (17.8%)
Trace	37 (18.3%)
1+	45 (22.3%)
2+	41 (20.3%)
3+	43 (21.3%)
Total	202

A substantial majority (94.1%) of the study participants

exhibited significant levels of proteinuria, while only a small fraction (5.9%) did not. This high prevalence highlights the critical need for effective proteinuria screening of pre-eclampsia patients and their treatment (Table 2).

Table 2: Prevalence of Significant Proteinuria

Significant Proteinuria	Frequency (%)
No	12 (5.9%)
Significant	190 (94.1%)
Total	202

Using a UPCR cutoff of 0.3 mg/g, the test showed a sensitivity of 92.6%, specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 46.2%. The overall diagnostic accuracy was 93.1%, indicating excellent agreement with 24-hour urine protein excretion. The association between spot UPCR and significant proteinuria was statistically significant ($\chi^2 = 86.36$, $p < 0.001$), confirming the high diagnostic utility of spot UPCR in detecting proteinuria among pre-eclamptic women (Table 3).

Table 3: Diagnostic Performance of Spot UPCR ≥ 0.3 Against 24-Hour Urine Protein Excretion in Women with Pre-eclampsia

Variables	UPCR Positive (≥ 0.3)	UPCR Negative (< 0.3)	Total
Significant Proteinuria (Yes)	176 (True Positives)	14 (False Negatives)	190
No Significant Proteinuria (No)	0 (False Positives)	12 (True Negatives)	12
Total	176	26	202

The Receiver Operating Characteristic (ROC) curve was used to examine the diagnostic performance of spot UPCR. The overall diagnostic accuracy of the AUC was 0.971 in differentiating patients with and without significant proteinuria. This high AUC is suggestive of its precision and hence suitability to serve as a clinical parameter (Figure 1).

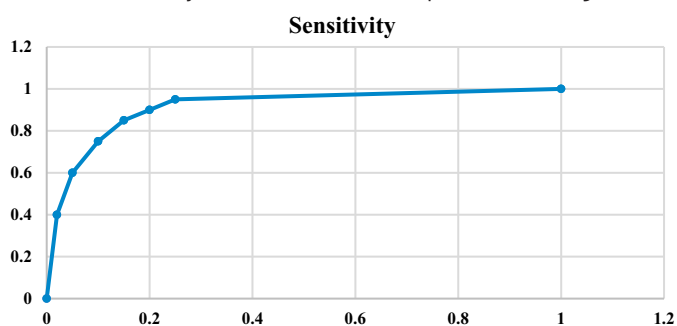


Figure 1: ROC Curve for Spot Urine Protein-Creatinine Ratio

Diagnostic Calculations: Sensitivity = $TP / (TP + FN) = 176 / (176 + 14) = 92.6\%$. Specificity = $TN / (TN + FP) = 12 / (12 + 0) = 100\%$. PPV (Positive Predictive Value) = $TP / (TP + FP) = 176 / (176 + 0) = 100\%$. NPV (Negative Predictive Value) = $TN / (TN + FN) = 12 / (12 + 14) = 46.2\%$. Diagnostic Accuracy = $(TP + TN) / \text{Total} = (176 + 12) / 202 = 188 / 202 = 93.1\%$. Chi-Square p-value = < 0.001 (significant).

DISCUSSION

The present study validates the use of spot urine protein-creatinine ratio (UPCR) as an effective diagnostic tool for identifying significant proteinuria in women with pre-eclampsia. When compared to the gold standard 24-hour urine protein measurement, spot UPCR demonstrated excellent diagnostic performance, with an area under the ROC curve (AUC) of 0.971, indicating a high level of precision in differentiating between women with and without clinically significant proteinuria. The sensitivity and specificity of spot UPCR were found to be 92.6% and 100%, respectively, reflecting its strong ability to accurately identify true positive cases without yielding any false positives. The positive predictive value (PPV) was also 100%, confirming that all positive results obtained through spot UPCR represented true cases of significant proteinuria. However, the negative predictive value (NPV) was lower at 46.2%, suggesting a limited ability of the test to confidently rule out disease in women who test negative. These findings are consistent with Olayinka et al., who reported lower sensitivity and specificity values of 74% and 69%, respectively [15], and support the observations of Shaikh et al., who noted improved sensitivity in cases with more severe proteinuria [16]. Given the relatively low NPV, reliance on a single negative spot UPCR result may risk underdiagnosing some cases. To mitigate this, combining UPCR testing with additional clinical indicators, such as escalating blood pressure, signs and symptoms of end-organ involvement (e.g., headache, epigastric pain, visual disturbances), and laboratory markers like elevated liver enzymes may improve diagnostic confidence. Serial measurements of UPCR may also be valuable, particularly in borderline or evolving clinical presentations. Moreover, establishing gestational age-specific cutoffs or developing predictive algorithms may further enhance the test's diagnostic utility in diverse populations. The current findings align with global literature, reinforcing the role of spot UPCR in various settings. Tian et al., reported slightly lower pooled diagnostic accuracy when compared to 12-hour collections, highlighting the influence of test timing and individual variability [17]. Pallavee also emphasized that although dipstick testing offers a convenient, rapid screening option, it lacks the diagnostic accuracy provided by UPCR, especially in resource-limited settings [18]. Other studies by Stefańska et al., and Shahbazian and Hosseini further support the use of spot UPCR while cautioning that factors like hydration status and renal function may affect protein excretion patterns [19, 20]. Similar conclusions were drawn by Park et al., [7], Mdunge and Baloyi and Shagufta et al., who endorsed the clinical reliability of UPCR as a practical and cost-effective alternative to 24-hour urine collection for the diagnosis and monitoring of pre-eclampsia [21, 22]. In conclusion, this study contributes important local data supporting the integration of spot UPCR into routine antenatal screening for pre-eclampsia.

Its high diagnostic accuracy, ease of administration, and time efficiency make it a practical alternative to the cumbersome 24-hour urine collection, particularly in high-burden, resource-limited clinical settings where rapid diagnosis is essential to guide timely management.

This study has certain limitations, including its single-center design and cross-sectional methodology, which may limit the generalizability of the findings to other populations. Additionally, the study did not evaluate longitudinal maternal or fetal outcomes associated with varying levels of proteinuria. Factors such as hydration status, renal function variations, and disease severity may also influence UPCR values and were not extensively analyzed. Future multicenter studies with larger sample sizes, longitudinal follow-up, and comprehensive clinical correlations are recommended to further validate the diagnostic and prognostic utility of spot UPCR in pre-eclampsia management.

CONCLUSIONS

It was concluded that the spot UPCR is an effective and reliable tool for detecting significant proteinuria in women with pre-eclampsia. It shows a strong correlation with the gold standard 24-hour urine protein measurement. With a sensitivity of 92.6% and specificity of 100%, spot UPCR offers a practical and time-efficient alternative to 24-hour urine collection. These findings support its incorporation into routine antenatal care to enable earlier identification and better management of pre-eclampsia, thereby enhancing maternal and fetal outcomes.

Authors' Contribution

Conceptualization: NS

Methodology: NS

Formal analysis: SU

Writing and Drafting: SZ, NH, AS

Review and Editing: SZ, NH, AS, SU, NS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Comparison of Alignment Efficiency of Steel Versus Elastomeric Ligatures in Lower Anterior Teeth: A Randomized Clinical Trial

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ABSTRACT

Ligature type influences orthodontic treatment speed, but conclusive evidence comparing alignment time between steel and elastomeric ligatures is limited. **Objective:** To compare the treatment time required by elastomeric ligatures and steel ligatures, in days, to achieve complete alignment of the lower anterior teeth. **Methods:** This randomized clinical trial was conducted at Khyber College of Dentistry, Peshawar, involving 180 participants (90 in each group: steel and elastomeric ligatures). The study included patients aged 12 to 18 years receiving permanent orthodontic treatment with lower premolar extractions and a Little's Irregularity Index of 7-9 mm. Exclusion criteria included systemic conditions, specific dental conditions, and poor periodontal health. Participants were randomly assigned to either the steel or elastomeric ligature group, and the time to reach alignment in the lower arch was recorded. A Student's t-test was used for comparison. **Results:** The age ($p = 0.860$), gender distribution ($p = 0.210$), and age groups ($p = 0.730$) were similar across both groups. The steel ligature group required less time (218.39 ± 10.02 days) compared to the elastomeric group (224.64 ± 9.39 days) ($p < 0.001$). This trend was consistent across gender, with both females and males demonstrating notable variations ($p < 0.001$ and $p = 0.004$, respectively). The 12-15 years age also showed a notable distinction ($p < 0.001$), while the 16-18 years group demonstrated a smaller but still significant difference ($p = 0.016$). **Conclusion:** Stainless steel ligatures required less time to achieve optimal alignment.

INTRODUCTION

It is important to have an efficient treatment approach that yields positive treatment outcomes while reducing the time spent in clinical settings and the overall duration of treatment [1]. The initial stage of fixed appliance therapy involves aligning the teeth, which can vary based on different factors. The biological condition of the tissues plays a crucial role in how orthodontic forces are applied to the periodontium, enabling tooth movement within the alveolar bone [2]. Numerous biological elements, including tooth vitality, cellular and connective tissue response, and periodontal health, are necessary for orthodontic tooth movement to be successful [3]. However, the choice of bracket system and archwire directly influences these biological factors [4]. An optimal ligation technique should

guarantee full bracket engagement with the arch wire and exhibit little friction between brackets and the arch wire in order to successfully resolve crowding in orthodontic treatment [5]. In orthodontic treatment, achieving proper alignment of anterior teeth is a key objective [6]. Different ligation methods, such as elastomeric and steel ligatures, have been employed to achieve alignment [7]. Elastomeric ligatures are preferred by orthodontists due to their ease of use and reduced chairside time, but the effectiveness is reduced overtime due to absorption and friction [8]. Steel ligatures on the other hand require manual twisting of wire thereby increasing chairside time but provide effective engagement of wire into bracket slot and provide low friction mechanics [9]. The duration of treatment is an



important factor for both patients and orthodontists, as it can impact overall treatment efficiency and patient satisfaction. In a study by A study reported the mean treatment time for alignment in elastomeric ligature was 224.95 ± 8.702 days while in steel ligature was 176.15 ± 9.81 days [10]. The purpose of this study is to compare the average amount of time needed to align anterior teeth with steel and elastomeric ligatures. By evaluating and analyzing these two commonly used ligation techniques can gain valuable insights into their respective effectiveness in facilitating the alignment of anterior teeth. Owing to the contradictory results of the aforementioned studies this study would put to rest the contradictions. Ultimately, the findings from this study may contribute to informed decision-making regarding ligation methods, optimizing treatment outcomes, and enhancing patient experiences in orthodontic practice. There is lack of research on this topic in Pakistan, so this study will provide local statistics. The results can be variable across different populations due to genetic, ethnic and environmental factors.

Efficient orthodontic treatment aims to achieve optimal tooth alignment within the shortest possible time while maintaining biological safety and patient comfort. Different ligation methods, particularly stainless steel and elastomeric ligatures, are widely used during fixed orthodontic therapy, yet their influence on alignment efficiency remains debated. Previous studies have reported inconsistent findings regarding treatment duration and frictional behavior between these ligation techniques. Moreover, limited clinical trials from Pakistan have evaluated their comparative efficiency, highlighting the need for locally generated evidence to guide orthodontic practice. The objective was to compare the treatment time required by elastomeric ligatures and steel ligatures, in days, to achieve complete alignment of the lower anterior teeth.

METHODS

180 patients (90 each group) participated in this randomised clinical trial, which was carried out at the Department of Orthodontics and Dentofacial Orthopaedics, Khyber College of Dentistry, Peshawar, from September 19, 2024, to May 10, 2025, using a sequential, non-probability sampling procedure. Using OpenEpi software and assuming a mean duration of 224.95 ± 8.7 days for the elastomeric ligature group and 219.95 ± 9.82 days for the steel ligature group, a sample size of 90 participants per group will detect a 5-day difference in mean duration with 95% power at a 5% significance level [10]. Patients aged 12 to 18 years, requiring fixed orthodontic treatment with premolar extractions in the lower jaw, having a Little's Irregularity Index score of 7-9

mm, and not undergoing any additional treatment with functional or orthopedic appliances were included. Patients with systemic conditions, those taking medications affecting tooth movement, and those with missing, impacted, unerupted, fractured, restored, carious, or enamel-defective lower front teeth, as well as those with poor periodontal health, were excluded. The study received ethical approval from the hospital's ethical council, notification number for which is 44/RRB/KCD. The trial was also registered on clinicaltrials.gov and was allotted a registration number: NCT07014332. Participants were recruited from Khyber College of Dentistry's Orthodontics Department if they satisfied the requirements for inclusion. Prior to their enrolment, all participants provided written informed permission after being fully told about the study's goals, methods, possible risks, and advantages. The subjects who fulfilled the inclusion criteria were assigned to one of two groups using the lottery method. Group A received steel ligatures, while Group B received elastomeric ligatures for wire engagement in the brackets. All participants were bonded with metal 0.022" slot MBT pre-adjusted appliances. The archwire order included 0.012 NiTi, 0.014 NiTi, 0.018 NiTi, and 0.019x0.025 NiTi until alignment was achieved. Adjustment appointments were scheduled at six-week intervals. Mandibular dental casts were taken on the day of appliance placement (T1) and again on the day when alignment was reached (T2). Using a Castroviejo calliper, Little's Irregularity Index was computed on the mandibular casts. The alignment time was recorded in days, starting on the day the appliance was placed and ending on the day alignment was attained (T2-T1). All of this information was documented in a predesigned proforma. Little's Irregularity Index was measured as the separation, in millimeters, of the total of horizontal shifts of the mandibular anterior teeth's anatomical points of contact, using a Castroviejo caliper. It was recorded as 0 (Perfect alignment), 1-3 (Minimal irregularity), 4-6 (Moderate irregularity), 7-9 (Severe irregularity), and 10 (Very severe irregularity) [11]. Alignment was defined as a Little's Irregularity Index score of zero, which was calculated by summing the distances (in millimeters) of the horizontal displacements of the anatomical contact mandibular anterior teeth points. Bias and confounders were controlled in the study by closely following to the inclusion/exclusion criteria and through randomization. Effect modifiers, including gender, age, and pre-treatment irregularity, were controlled by randomization. R software version 4.3.3 was used to analyse the data. The mean and standard deviation were calculated for numerical explanatory variables such as age and time to reach alignment. Frequency and percentage were calculated for qualitative explanatory variables like

gender. To compare the time to alignment (in days) for the steel and elastomeric groups at T2, an independent samples t-test was used. The Shapiro-Wilk test was used to evaluate the data's normality. Post-stratification independent samples t-test was used to control for confounders like age and gender. A p-value was deemed statistically significant if it was less than or equal to 0.050. Figure 1 shows the participant progression CONSORT flow diagram.

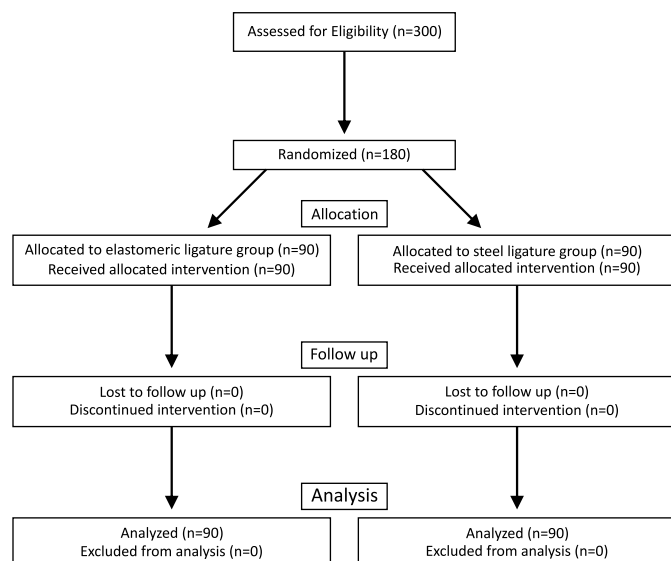


Figure 1: CONSORT Flow Diagram Depicting the Enrollment, Allocation, Follow-Up, and Analysis of Study Participants

RESULTS

The use of parametric analysis was supported by the data's approximate normal distribution (Shapiro-Wilk test: $W = 0.993$, $p = 0.512$). The demographic characteristics of the elastomeric group ($N = 90$) and steel ligature group ($N = 90$) were similar (Table 1). Mean age was 15.3 (SD 2.13) years for the elastomeric group and 15.2 (SD 2.04) years for the steel group ($p = 0.860$). Gender distribution did not differ significantly ($p = 0.210$), with 26.7% females in the elastomeric group and 35.6% in the steel group. Age groups (12–15 vs 16–18 years) were comparable ($p = 0.730$) (Table 1).

Table 1: Demographic Comparison of Both Groups ($n=180$)

Characteristics	Elastomeric Ligature Frequency (%)	Steel Ligature Frequency (%)	p-Value
Age	15.3 (2.13)	15.2 (2.04)	0.860*
Gender			
Female	24 (26.67)	32 (35.56)	0.210**
Male	66 (73.33)	58 (64.44)	
Age Groups			
12-15 years	44 (48.89)	47 (52.22)	0.730**
16- 18 years	46 (51.11)	43 (47.78)	

*Student t test; **Chi-square test

The comparison of alignment time (in days) between the

two groups revealed that the elastomeric ligature group took significantly longer (224.64 ± 9.39 days) than the steel ligature group (218.39 ± 10.02 days) ($p < 0.001$). Gender wise, among females, the elastomeric group required significantly more time (227.75 ± 9.54 days) compared to the steel group (218.19 ± 10.45 days), ($p < 0.001$). Similarly, males in the elastomeric group had a significantly longer alignment time (223.52 ± 9.14 days) compared to the steel group (218.50 ± 9.86 days), ($p = 0.004$). With respect to age groups, the 12–15 years age group showed a significant difference, with the elastomeric group taking longer (225.18 ± 10.22 days) than the steel group (217.77 ± 9.53 days), ($p < 0.001$), while the 16–18 years age group showed a smaller but still significant difference ($p = 0.016$) (Table 2).

Table 2: Time (Days) to Achieve Dental Alignment Overall, By Gender, And Across Age Groups ($n=180$)

Characteristics	Alignment time (Days)		p-Value*
	Elastomeric Ligature (Mean $\pm$ SD)	Steel Ligature (Mean $\pm$ SD)	
Overall	224.64 $\pm$ 9.39	218.39 $\pm$ 10.02	<0.001
Gender			
Female (N = 24 / 32)	227.75 $\pm$ 9.54	218.19 $\pm$ 10.45	<0.001
Male (N = 66 / 58)	223.52 $\pm$ 9.14	218.50 $\pm$ 9.86	<0.004
Age Group (years)			
12–15 (N = 44 / 47)	225.18 $\pm$ 10.22	217.77 $\pm$ 9.53	<0.001
16–18 (N = 46 / 43)	224.13 $\pm$ 8.59	219.07 $\pm$ 10.59	0.016

*p-values from independent t-tests or equivalent comparisons

DISCUSSION

The present study examined how efficiently teeth aligned when using either elastomeric or steel ligatures during fixed orthodontic treatment. The results showed a clear and alignment difference that is statistically significant time between the two approaches, both in the overall group and when looking at subgroups based on gender and age. These findings led to the rejection of the null hypothesis, which assumed that there would be no meaningful difference in alignment time between the two types of ligatures. The main finding of this study showed that patients who were treated with steel ligatures had their teeth aligned in significantly less time compared to those who received elastomeric ligatures, although the difference of 7 days is clinically insignificant. On average, the steel group completed alignment in about 218 days, while the elastomeric group took around 225 days, and this difference was statistically significant ($p < 0.001$). This shorter treatment time with steel ligatures is a clear advantage. When teeth move into position more quickly, patients may spend less time wearing fixed appliances overall, which could reduce the chances of developing problems like gingivitis, white spot lesions, or discomfort [12, 13]. A shorter treatment period can also make it easier for patients to stay motivated and follow their

orthodontists' instructions [14]. This finding aligns with the results of previous investigations which demonstrated that steel ligatures generate less friction at the bracket-wire interface compared to elastomeric modules [15]. Reduced friction facilitates more efficient transmission of orthodontic forces, thereby enhancing the rate of tooth alignment, particularly in cases of dental crowding [16, 17]. Furthermore, it is reported that elastomeric ligatures are prone to degradation over time due to exposure to saliva and masticatory forces, leading to a decline in their capacity to maintain consistent force levels. In contrast, steel ligatures exhibit superior mechanical stability and are capable of sustaining their force over prolonged periods, making them a more reliable choice in the early stages of orthodontic therapy [18]. In a randomized clinical trial, Soumya *et al.*, compared the efficiency of various ligation methods in aligning mandibular anterior teeth [10]. The study found that the mean time to alignment was significantly longer with elastomeric ligatures (224.95 ± 8.70 days) compared to stainless steel ligatures (176.15 ± 9.81 days). This considerable difference suggested that stainless steel ligatures are more effective in the early stages of orthodontic therapy. Their mechanical stability and resistance to force degradation enable more consistent tooth movement, whereas elastomeric ligatures tend to lose their elasticity over time, which can compromise the efficiency of alignment. In the research carried out by Reddy *et al.*, a direct comparison between different ligation systems revealed important information about the relative efficiency of stainless steel and elastomeric ligatures during the orthodontic treatment's initial alignment phase [19]. Among the five ligation systems evaluated, the study specifically reported that the mean treatment duration to achieve mandibular alignment was 176.3 ± 11.08 days for elastomeric ligatures and 175.56 ± 9.41 days for stainless steel ligatures. Although the difference between these two conventional systems was minimal and not statistically significant, the findings suggest that stainless steel ligatures may offer slightly more consistent performance in reducing friction and maintaining force over time. The subgroup analysis demonstrated that alignment was achieved over a shorter duration with steel ligatures across both genders and age groups, indicating that gender and age did not serve as a significant modifying factor. The effect of faster alignment with steel ligatures was more pronounced in the younger age group, likely due to enhanced tissue remodeling capacity during early adolescence [20]. Given that baseline characteristics such as age, gender distribution, and initial severity of malocclusion were comparable between groups, these findings can be attributed to the ligation method rather than confounding demographic variables. This study has certain limitations, including its single-

center design and the use of non-probability sampling, which may limit the generalizability of the findings. Additionally, only lower anterior alignment time was evaluated, while other treatment outcomes such as patient comfort, plaque accumulation, and long-term orthodontic stability were not assessed. The relatively short observation period also restricted evaluation of complete orthodontic treatment duration. Future multicenter randomized trials with longer follow-up and assessment of additional clinical parameters are recommended to provide more comprehensive evidence regarding the optimal ligation method in orthodontic therapy.

CONCLUSIONS

A significant difference in alignment time was observed between elastomeric and stainless steel ligatures. The findings shown that the type of ligature used can have a big impact on the alignment time. Compared to elastomeric ligatures, stainless steel ligatures take less time to attain ideal tooth alignment.

Authors' Contribution

Conceptualization: AJ, PG

Methodology: AJ, PG

Formal analysis: AJ, PG

Writing and Drafting: AJ, PG

Review and Editing: AJ, PG

All authors approved the final manuscript and take responsibility for the integrity of the work

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Original Article



Comparison of Frequency of Postpartum Haemorrhage in Augmented Versus Spontaneous Labour

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ABSTRACT

Postpartum haemorrhage (PPH) remains a major cause of maternal morbidity and mortality. Labour augmentation is commonly practiced but may increase the risk of excessive bleeding.

Objectives: To determine the frequency of PPH and compare its occurrence in spontaneous versus augmented labour. **Methods:** A descriptive cross-sectional study was conducted at the Department of Obstetrics and Gynaecology, Mardan Medical Complex, from August 2023 to January 2024. A total of 151 women aged 18–40 years with singleton pregnancies at ≥ 36 weeks were enrolled using non-probability consecutive sampling. Data on age, parity, gestational age, hypertension, socioeconomic and residential status, labour type, and PPH were collected through a structured proforma. PPH was defined as blood loss > 500 ml within 24 hours of vaginal delivery. Data were analyzed using SPSS version 25.0, and associations were tested using Chi-square and Fisher's exact tests. **Results:** The frequency of PPH was 13.2%. PPH occurred more frequently in spontaneous labour (15.7%) compared to augmented labour (10.3%), though this was not statistically significant ($p=0.333$). A significant association was found between hypertension and PPH ($p=0.017$), with hypertensive women showing a higher risk. **Conclusions:** It was concluded that Hypertension was significantly associated with postpartum haemorrhage, underscoring the importance of careful monitoring. Labour augmentation did not significantly increase PPH risk. Ongoing evaluation of maternal risk factors is crucial for improving outcomes.

INTRODUCTION

Postpartum haemorrhage (PPH) remains a major contributor to maternal morbidity and mortality worldwide [1]. Despite advances in obstetric care, excessive bleeding after childbirth continues to claim the lives of thousands of women each year, particularly in low- and middle-income countries. Defined clinically as a blood loss of more than 500 ml following vaginal delivery, or more than 1000 ml following caesarean section, PPH demands prompt recognition and effective intervention to prevent serious outcomes [2, 3]. Recent changes in obstetric practice and

variations in clinical definitions have made the true burden of PPH difficult to quantify [4]. While traditional estimates rely on visual assessment of blood loss, more accurate methods, such as weighing blood-soaked materials, have revealed that actual rates of PPH may be higher than previously documented. Moreover, symptoms such as hypotension and tachycardia may not manifest until a woman has lost a significant portion of her total blood volume, highlighting the danger of relying solely on clinical signs [5, 6]. Among the risk factors contributing to PPH,



labour induction and augmentation have drawn increasing attention. Induced or augmented labour, often necessary for medical or obstetric reasons is associated with a higher risk of uterine atony, a leading cause of PPH [7]. The use of oxytocin and prostaglandins, while effective for initiating or intensifying contractions, may also increase the likelihood of uterine muscle fatigue, thereby impairing postpartum contractility and elevating haemorrhage risk. With the growing trend of elective inductions, particularly for reasons such as post-term pregnancy or maternal preference, it is essential to examine whether these interventions contribute significantly to adverse maternal outcomes [8]. Evidence from local studies suggests a discrepancy in PPH rates between women undergoing spontaneous and augmented labour. For instance, research conducted in Pakistan has reported higher rates of haemorrhage among those whose labour was medically managed compared to those with spontaneous onset [9, 10]. However, these findings remain underexplored in many clinical settings, particularly in regional hospitals where resources may be limited and monitoring protocols variable. Given the clinical importance of timely recognition and management of postpartum haemorrhage, especially in induced or augmented labours, this study seeks to fill the gap by comparing the frequency of PPH in women who underwent spontaneous versus augmented labour. Findings from this research are expected to guide obstetric decision-making, improve maternal safety protocols, and contribute to broader public health efforts aimed at reducing preventable maternal deaths.

Postpartum haemorrhage (PPH) remains one of the leading causes of maternal morbidity and mortality worldwide, particularly in low- and middle-income countries. Labour augmentation using pharmacological agents such as oxytocin is widely practiced to manage slow labour progress; however, its potential association with increased risk of PPH remains debated. Although several international studies have examined this relationship, evidence from local clinical settings in Pakistan is still limited and inconsistent. Therefore, evaluating the frequency of PPH in spontaneous versus augmented labour in regional tertiary care hospitals is important to generate context-specific data and guide obstetric management strategies. This study aims to determine the frequency of PPH and compare its occurrence in spontaneous versus augmented labour.

METHODS

The descriptive cross-sectional study was conducted at the Department of Obstetrics and Gynaecology, Mardan Medical Complex, in collaboration with Bacha Khan Medical

College, Mardan. The duration of the study was six months, from August 2023 to January 2024. This study aimed to determine the frequency of postpartum haemorrhage (PPH) in women undergoing spontaneous versus augmented labour. Before the initiation of data collection, formal ethical approval was obtained from the Institutional Ethical Committee of Bacha Khan Medical College, Mardan (Approval No. 353/BKMC). Additionally, the synopsis was approved by the Research Evaluation Unit (REU) of the College of Physicians and Surgeons Pakistan (CPSP) under reference number CPSP/REU/OBG-2022-028-11418. Written informed consent was secured from all participants, ensuring confidentiality, voluntary participation, and the right to withdraw at any stage. A sample size of 151 participants was calculated using WHO sample size software, with a 95% confidence level and an expected postpartum haemorrhage rate of 11%. A non-probability consecutive sampling technique was used, enrolling all eligible women who met the inclusion criteria during the study period. Participants were eligible if they met the criteria like, aged between 18 and 40 years, singleton pregnancy confirmed on ultrasound, gestational age greater than 36 weeks (based on last menstrual period), any parity and undergoing vaginal delivery. Women were excluded if they had a known history of bleeding disorders such as disseminated intravascular coagulation (DIC), aplastic anaemia and thrombocytopenia. Participants were enrolled after verification of inclusion and exclusion criteria. A structured, pre-tested proforma was used to collect patient demographics, obstetric history, and clinical data, including maternal age, gestational age, parity, residential status (urban or rural), socioeconomic status (poor, middle, rich), hypertension status, labour type (spontaneous or augmented), and PPH outcome. Labour type was defined as follows: Spontaneous labour was determined by the presence of regular uterine contractions with progressive cervical dilation >3 cm without medical intervention. Augmented labour involved the use of intravenous oxytocin, starting at 12 ml/hour and increasing by 12 ml/hour every 30 minutes up to a maximum of >192 ml/hour. In some cases, prostaglandin E2 vaginal gel (1 gram) was administered, repeated at six-hour intervals up to three doses. Postpartum haemorrhage was identified based on a blood loss exceeding 500 ml within 24 hours after vaginal delivery. Blood loss was measured using soaked gauze, surgical pads, and visible clots, following a gravimetric method where a 1-gram weight difference equalled 1 ml of blood loss. To ensure consistency and accuracy, data collectors received uniform training on identifying labour types and estimating blood loss. Standard clinical definitions were strictly followed. The proforma was reviewed by obstetric consultants for face

and content validity. Daily cross-checking with patient files and labour ward registers was conducted to maintain data integrity. Data were entered and analyzed using IBM SPSS version 25.0. Descriptive statistics, including mean and standard deviation, were used for continuous variables like age, parity, and gestational age. Categorical variables hypertension status, labour type, parity, and residential status, were presented as frequencies and percentages. To compare the frequency of PPH across different categories, the Chi-square test or Fisher's exact test was applied where appropriate. A $p\text{-value} \leq 0.050$ was considered statistically significant. Post-stratification analysis was conducted for factors such as maternal age group, parity, gestational age, hypertension, socioeconomic status, and labour type to assess their association with PPH.

RESULTS

The study included a total of 151 participants. The mean maternal age was 28.29 ± 6.78 years, with a range between 18 and 40 years. The average gestational age at delivery was 39.31 ± 0.94 weeks, ranging from 37.08 to 41.48 weeks. The mean number of births (parity) was 1.40 ± 1.45 , with a range from 0 to 4. Most participants (40.4%) were between 26–35 years of age, while 38.4% were 18–25 years, and 21.2% were in the 36–40 age bracket. The majority (58.3%) were delivered between 39–40 weeks of gestation. A higher proportion of women were multiparous (58.3%) compared to primiparous (41.7%). Most resided in urban areas (64.2%), and the largest group belonged to the middle socioeconomic class (50.3%). Regarding comorbidities, 31.8% had hypertension. Spontaneous labour was observed in 55.0% of cases, while 45.0% underwent augmented labour. The overall frequency of postpartum haemorrhage (PPH) in this sample was 13.2% (Table 1).

Table 1: Demographic and Clinical Characteristics of Participants (n=151)

Categorical Variables	Categories	Frequency (%)
Age Group (Years)	Range: 18–40	28.29 ± 6.78
	18–25	58 (38.4%)
	26–35	61 (40.4%)
	36–40	32 (21.2%)
	Total	151
Gestational Age (Weeks)	Range: 37.08–41.48	39.31 ± 0.94
	37–38	41 (27.2%)
	39–40	88 (58.3%)
	>40	22 (14.6%)
	Total	151
Parity	Range: 0–4	1.40 ± 1.45
	Primiparous	63 (41.7%)
	Multiparous	88 (58.3%)
Residential Status	Urban	97 (64.2%)
	Rural	54 (35.8%)
Socioeconomic Status	Poor	52 (34.4%)
	Middle	76 (50.3%)

Hypertension	Rich	23 (15.2%)
	Yes	48 (31.8%)
Labour Type	No	103 (68.2%)
	Spontaneous	83 (55.0%)
Postpartum Haemorrhage	Augmented	68 (45.0%)
	Yes	20 (13.2%)
	No	131 (86.8%)

There was no statistically significant association between maternal age group and the occurrence of PPH ($\chi^2 = 1.080$, $df=2$, $p=0.583$). Although the highest rate of PPH (18.8%) was seen among women aged 36–40 years, the distribution across all age groups did not show meaningful differences. This suggests that maternal age alone may not be a strong predictor of postpartum bleeding in this sample. Gestational age at the time of delivery was not significantly associated with PPH ($\chi^2 = 2.989$, $df=2$, $p=0.224$). However, a trend was noted where the incidence of PPH increased with advancing gestational age, rising from 4.5% in post-term pregnancies (>40 weeks) to 17.0% in those delivering at 39–40 weeks. Despite this trend, the statistical analysis did not support a meaningful correlation. Parity did not show a significant association with the risk of PPH ($\chi^2 = 1.672$, $df=1$, $p=0.196$). However, primiparous women had a higher incidence of PPH (17.5%) compared to multiparous women (10.2%). Though not statistically significant, this pattern may reflect a clinical tendency for first-time mothers to be more vulnerable to labour complications, warranting further exploration (Table 2).

Table 2: Association Between Age Group, Gestational Age Parity and Postpartum Haemorrhage (n=151)

Variables	PPH Yes (n)	PPH No (n)	Total (n)	% with PPH	χ^2 (df), p-Value
Age Group (Years)					
18-25	7	51	58	12.1%	$\chi^2 = 1.080, (df=2)$ p=0.583
26-35	7	54	61	11.5%	
36-40	6	26	32	18.8%	
Total	20	131	151	13.2%	
Gestational Age (Weeks)					
>40	1	21	22	4.5%	$\chi^2 = 2.989, (df=2)$ p=0.224
37-38	4	37	41	9.8%	
39-40	15	73	88	17.0%	
Total	20	131	151	13.2%	
Parity					
Primiparous	11	52	63	17.5%	$\chi^2 = 1.672, (df = 1)$ p=0.196
Multiparous	9	79	88	10.2%	
Total	20	131	151	13.2%	

The relationship between place of residence and PPH was not statistically significant ($\chi^2 = 2.493$, $df=1$, $p=0.114$). Nevertheless, PPH was more frequently observed in urban residents (16.5%) than in rural counterparts (7.4%). While not statistically conclusive, the difference may reflect disparities in maternal care access, healthcare-seeking

behaviour, or obstetric interventions across settings. No significant association was identified between socioeconomic status and PPH ($\chi^2 = 4.380$, $df=2$, $p=0.112$). However, a notably higher rate of PPH (26.1%) was found among women in the high-income category. This could potentially be due to increased rates of elective interventions or underlying risk factors, although the finding did not reach statistical significance. Labour type was not significantly associated with PPH in this cohort ($\chi^2 = 0.938$, $df=1$, $p=0.333$). Interestingly, spontaneous labour had a slightly higher rate of PPH (15.7%) compared to augmented labour (10.3%), contrary to expected trends. However, due to the lack of statistical significance, this difference may be attributed to random variation rather than a causal link (Table 3).

Table 3: Association Between Residential Status, Socioeconomic Status, Labour Type and Postpartum Haemorrhage (n=151)

Variables	PPH Yes (n)	PPH No (n)	Total (n)	% with PPH	χ^2 (df), p-Value
Residential Status					
Rural	4	50	54	7.4%	$\chi^2 = 2.493$, (df=1), p=0.114
Urban	16	81	97	16.5%	
Total	20	131	151	13.2%	
Socioeconomic Status					
Poor	7	45	52	13.5%	$\chi^2 = 4.380$, (df=2), p=0.112
Middle	7	69	76	9.2%	
Rich	6	17	23	26.1%	
Total	20	131	151	13.2%	
Labour Types					
Augmented	7	61	68	10.3%	$\chi^2 = 0.938$, (df=1), p=0.333
Spontaneous	13	70	83	15.7%	
Total	20	131	151	13.2%	

Hypertension showed a statistically significant relationship with PPH ($\chi^2 = 5.728$, $df = 1$, $p=0.017$; Cramér's $V=0.195$). Women with hypertension experienced more than twice the rate of PPH (22.9%) compared to normotensive women (8.7%). This finding highlights hypertension as an important clinical risk factor for postpartum bleeding, underlining the need for close monitoring and preventive strategies in hypertensive pregnancies (Table 4).

Table 4: Association Between Hypertension and Postpartum Haemorrhage (n=151)

Hypertension	PPH Yes (n)	PPH No (n)	Total (n)	% with PPH	χ^2 (df), p-Value	Cramér's V
Yes	11	37	48	22.9%	$\chi^2 = 5.728$, (df=1), $p=0.017$	0.195
No	9	94	103	8.7%		
Total	20	131	151	13.2%		

The chart shows that the most represented age group was 26–35 years, followed closely by 18–25 years. A significant portion of deliveries occurred between 39–40 weeks of gestation. Multiparous women formed the majority, and

most participants lived in urban areas. Middle-income status was the most common socioeconomic group. From a clinical standpoint, a considerable proportion of the sample had hypertension (31.8%). Spontaneous labour was more frequent than augmented labour. Although only 13.2% of participants experienced postpartum haemorrhage (PPH), the graph emphasises that high-risk categories such as hypertensive patients, primiparous women, and urban residents showed a noticeable share of PPH cases. Visually, the gap between frequency and percentage bars also reflects distribution weight across categories, while “PPH No” cases dominate in count, the PPH Yes group still presents critical clinical implications in terms of relative proportion among certain subgroups.

DISCUSSION

This study explored the frequency of postpartum haemorrhage (PPH) in women undergoing spontaneous versus augmented labour at a tertiary care facility in Mardan. The overall frequency of PPH was 13.2%, which is slightly higher than the global average reported by the World Health Organization, where PPH complicates approximately 10% of vaginal deliveries. This variation could be attributed to local obstetric practices, population characteristics, or referral patterns. Our findings showed that maternal age did not significantly influence the likelihood of PPH, although the highest rate (18.8%) was observed in women aged 36–40 years. This was consistent with Rafiq et al., Bernitz et al., and Cheng et al., 2025 and suggests that advanced maternal age may be linked with reduced uterine contractility and vascular changes, but such associations may not always reach statistical significance in mid-sized samples [11–13]. Similarly, gestational age did not demonstrate a significant correlation with PPH. While a rising trend in PPH was seen with increasing gestational duration peaking at 17% in the 39–40-week group, this did not meet statistical criteria. Previous literature, like Kumar et al., Mentzoni et al., and Khurshid et al., indicates that prolonged gestation may increase uterine atony risk, though confounding factors such as induction method and birth weight may play a role, which were not the focus of this study [14–16]. Parity also failed to show a statistically significant association. However, primiparous women exhibited a higher incidence of PPH (17.5%) compared to multiparous women (10.2%). This aligns with previous reports like Zhu et al., Pettersen et al., and Girault et al., that suggest first-time mothers may be more prone to labour-related complications due to prolonged second-stage labour, ineffective uterine contractions, or lack of delivery experience among attending staff in certain settings [17–19]. Residential status and socioeconomic status, while not statistically significant, revealed notable trends. Urban residents and

women from higher-income groups experienced more PPH than their rural and lower-income counterparts. These findings were counterintuitive to the assumption that better-resourced populations have improved outcomes. However, elective labour interventions, stress, or delayed presentation in urban centres might contribute to this disparity [20, 21]. Importantly, hypertension emerged as a significant risk factor for PPH, with a rate of 22.9% among hypertensive women compared to 8.7% in normotensive patients ($p=0.017$). This finding echoes multiple studies where hypertensive disorders in pregnancy, preeclampsia, were linked with abnormal placentation, coagulopathy, and uterine atony, increasing bleeding risks post-delivery. Therefore, early detection and close management of hypertensive women during labour are essential to reduce maternal morbidity [22, 23]. Contrary to some expectations, the type of labour, spontaneous versus augmented, did not significantly impact the risk of PPH. Interestingly, PPH was slightly more common in spontaneous labour (15.7%) than in augmented cases (10.3%). This may suggest that with proper monitoring and protocol-driven augmentation using oxytocin and prostaglandins, blood loss can be controlled. Alternatively, it may reflect an underestimation of bleeding in spontaneous cases, where the anticipation of complications may be lower.

This study has certain limitations, including its single-center design and relatively small sample size, which may limit the generalizability of the findings to broader populations. Additionally, the cross-sectional nature of the study restricts the ability to establish causal relationships between labour type and postpartum haemorrhage. Other potential risk factors such as duration of labour stages, birth weight, and obstetric interventions were not extensively evaluated. Future multicenter studies with larger sample sizes and inclusion of additional clinical variables are recommended to better understand the determinants of PPH and improve maternal care outcomes.

CONCLUSIONS

The study highlights that postpartum haemorrhage remains a pressing concern in obstetric care, affecting over 13% of women delivering vaginally. While maternal age, parity, gestational age, labour type, and socioeconomic status did not show statistically significant associations, hypertension was identified as a major contributor to PPH. These findings underscore the need for vigilant monitoring of hypertensive patients and the development of standardized labour protocols irrespective of delivery method. Improving labour ward preparedness, ensuring active management of the third stage of labour, and early identification of high-risk pregnancies can

significantly reduce the burden of PPH. Future research with larger sample sizes and inclusion of factors such as birth weight, duration of labour stages, and care provider experience would provide a more comprehensive understanding of the determinants of postpartum haemorrhage in our setting.

Authors' Contribution

Conceptualization: MT

Methodology: MT, SR, SJ, CA, IR

Formal analysis: SR, CA, BSH, IR

Writing and Drafting: MT, CA, IR

Review and Editing: MT, CA, IR, SR, SJ, BSH

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Comparative Cardiovascular Impact of Early-Onset Type 1 and Type 2 Diabetes and Associated Risk Factors in Pediatric and Adult Patients

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ABSTRACT

Cardiovascular disease is a leading cause of morbidity and mortality among individuals with diabetes, with early-onset cases posing unique risks. **Objective:** To evaluate and compare the cardiovascular impact of early-onset type 1 and type 2 diabetes mellitus in paediatric versus adult patients and to identify associated clinical, biochemical, and sociodemographic risk factors in a low-resource Pakistani setting. **Methods:** This was an observational, comparative, cross-sectional study conducted at the Department of Paediatrics, Quaid-e-Azam Medical College, Bahawalpur, from March 2024 to March 2025. A total of 260 participants were enrolled using non-probability consecutive sampling, comprising 130 diabetic patients (aged 10-40 years) with early-onset diabetes mellitus (diagnosed ≤ 25 years) and 130 age- and gender-matched healthy controls. Data were collected through structured clinical examination, laboratory investigations (including HbA1c, lipid profile, serum creatinine, urinary albumin-creatinine ratio), electrocardiography, and echocardiography. Statistical analysis was performed using SPSS version 26.0. **Results:** Diabetic patients demonstrated significantly higher prevalence of left ventricular hypertrophy (36.9% vs. 10.8%; adjusted OR: 5.01; 95% CI: 2.51-9.99; $p=0.001$), CIMT ≥ 0.9 mm (44.6% vs. 16.2%; OR: 4.49; 95% CI: 2.44-8.26; $p=0.001$), and diastolic dysfunction (24.6% vs. 6.9%; OR: 4.25; 95% CI: 1.83-9.89; $p=0.003$). Significant associations were found between cardiovascular complications and poor glycaemic control (HbA1c $\geq 7\%$), LDL ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, low socioeconomic status, and sedentary lifestyle. **Conclusion:** Early-onset diabetes mellitus is strongly associated with adverse cardiovascular outcomes in young Pakistani patients.

INTRODUCTION

Because diabetes mellitus, including its early types, is so common around the world, it has become a significant public health problem linked to major heart problems [1]. Because resources for healthcare are lacking in Pakistan and many people cannot access preventive care easily, diabetes found in youth can be very serious [2]. Shockingly, nowadays, it is very common for these people to be diagnosed while young, influenced by new diets, less activity and more urbanization [3, 4]. Children or teenagers with Type 1 diabetes experience their pancreatic β -cells being destroyed by the immune system [5]. Meanwhile, type 2 diabetes in children is being observed more and

more, traditionally seen as a disorder found in Pakistan, it is clear from studies and data that type 2 diabetes in children and teens is rising, at the same time as obesity, hypertension and abnormal lipid levels are increasing [7]. In Pakistan, most studies have concentrated on measuring the number of people with diabetes and their blood sugar levels, but have not examined the relationships between the age at diagnosis, diabetes type and heart complications [8, 9]. The paucity of comprehensive, age-stratified cardiovascular profiling in diabetic patients from low-resource settings such as Pakistan represents a significant gap in the literature [10]. Moreover, the dual



burden of communicable and non-communicable diseases in Pakistan often relegates chronic conditions like diabetes to lower healthcare priorities [11]. This underscores the need for a focused analysis of early-onset diabetes in both children and adults, with an emphasis on cardiovascular implications, which could aid in refining screening protocols and guiding early interventions [12]. Rosengren and Dikaïou in 2023 also reviewed cardiovascular outcomes associated with type 1 and type 2 diabetes [13]. Early-onset diabetes mellitus has become an emerging public health concern due to its increasing prevalence and its strong association with premature cardiovascular complications. Although both type 1 and type 2 diabetes are known to elevate cardiovascular risk, limited evidence exists comparing their cardiovascular impact when diagnosed at a young age. In Pakistan, most studies have primarily focused on glycaemic control and prevalence of diabetes rather than comprehensive cardiovascular profiling across different age groups. This lack of comparative, age-stratified data highlights the need to evaluate cardiovascular outcomes and associated risk factors in patients with early-onset diabetes. This study addresses this critical gap by evaluating and comparing the cardiovascular effects of early-onset type 1 and type 2 diabetes in paediatric versus adult patients in a low-resource Pakistani setting.

METHODS

This observational, comparative cross-sectional study was conducted over a one-year period from March 2024 to March 2025 at the Department of Paediatrics, Quaid-e-Azam Medical College, Bahawalpur, Pakistan. The primary objective was to assess and compare the cardiovascular effects of early-onset type 1 and type 2 diabetes mellitus in paediatric and adult patients, and to identify relevant clinical, biochemical, and sociodemographic risk factors. A total of 260 participants were enrolled through non-probability consecutive sampling, comprising 130 diabetic patients and 130 age- and gender-matched healthy controls. The sample size was determined based on findings by Dabelea *et al.*, in a study entitled Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence with Complications During Teenage Years and Young Adulthood. Dart *et al.*, in 2014 found that youth with type 2 diabetes experience earlier onset of complications compared to typical adult-onset cases [8, 14]. JAMA, 2017, which reported a 33.5% prevalence of cardiovascular complications in youth with diabetes. With a 95% confidence interval, 6% margin of error, and 80% study power, a minimum of 130 diabetic participants was calculated. To enable meaningful subgroup comparisons by diabetes type and age category, the sample was increased to 260 individuals. Eligible participants were between 10 and 40 years of age,

diagnosed with either type 1 or type 2 diabetes mellitus, with disease onset at or before 25 years of age and a minimum disease duration of one year. All participants were required to be under regular follow-up at the study site and provide informed consent. Exclusion criteria included diabetes secondary to other medical conditions, congenital heart disease, chronic renal failure, autoimmune disorders other than type 1 diabetes, pregnancy, current use of statins or ACE inhibitors, and incomplete data records. Data collection involved comprehensive clinical evaluations, biochemical analyses, sociodemographic profiling, and cardiovascular assessments. Clinical variables included age, sex, Body Mass Index (BMI), duration of diabetes, and blood pressure, along with lifestyle history such as smoking status, level of physical activity, and dietary patterns. Additional clinical conditions considered included the presence of comorbidities such as hypertension and dyslipidaemia. Ethical approval for the study was obtained from the Institutional Review Board of Quaid-e-Azam Medical College, Bahawalpur (Ref. No. 2466/DME/QAMC). Informed consent was obtained from all participants or their legal guardians in the case of minors. Confidentiality of all patient information was ensured throughout the research process. Statistical analysis was performed using SPSS version 26.0.

RESULTS

A total of 260 participants were enrolled in the study, comprising 130 diabetic patients (65 type 1 and 65 type 2) and 130 age and gender matched controls. The present study has revealed a significantly higher burden of cardiovascular abnormalities in individuals with early-onset diabetes, compared to non-diabetic controls, in a low-resource Pakistani setting. This confirms existing global evidence suggesting accelerated vascular aging and atherosclerosis in early-onset diabetes but also adds region-specific data from a population where such comprehensive cardiovascular profiling has rarely been undertaken. Table 1 shows the distribution of demographic and socioeconomic characteristics between diabetic and control groups, including gender, residence, income level, and education. This table demonstrates that urban residence, low income, and lack of formal education were significantly more frequent among diabetic participants. These variables were independently associated with diabetes status after adjusting for confounders, suggesting socioeconomic disadvantage may contribute to disease burden.

Table 1: Demographic and Socioeconomic Characteristics of Diabetic and Control Participants(n=260)

Variables	Diabetic	Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-Value
Gender (Male)	76	72	1.13 (0.69-1.84)	1.08 (0.65-1.78)	0.610
Urban Residence	68	54	1.79 (1.05-3.06)	1.66 (0.92-3.00)	0.030
Income <20k PKR	50	28	2.56 (1.44-4.54)	2.34 (1.29-4.23)	0.001
Education (No formal)	36	22	2.11 (1.12-3.99)	1.98 (1.01-3.87)	0.020

Reference category used for each variable. All comparisons via Chi-square test. Adjusted ORs from multivariate logistic regression

Table 2 shows key clinical and biochemical categorical variables, including obesity, hypertension, LDL, and triglycerides. This table demonstrates that all four metabolic risk factors were significantly more prevalent in diabetic participants. Strong odds ratios highlight the magnitude of association, indicating that early-onset diabetes is strongly linked with metabolic syndrome components.

Table 2: Clinical and Biochemical Risk Factors in Diabetic and Control Groups(n=260)

Variable	Diabetic	Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-Value
BMI ≥30 (Obesity)	45	22	3.04 (1.72-5.38)	2.89 (1.56-5.34)	0.001
SBP ≥130 mmHg	58	24	4.27 (2.45-7.43)	4.01 (2.21-7.26)	0.001
LDL ≥100 mg/dL	76	38	3.86 (2.21-6.72)	3.70 (1.98-6.91)	0.001
Triglycerides ≥150 mg/dL	72	28	5.52 (3.10-9.84)	5.18 (2.86-9.38)	0.001

SBP – Systolic Blood Pressure; LDL – Low-Density Lipoprotein. Chi-square tests applied for all comparisons

Table 3 shows group-wise comparisons of continuous clinical and biochemical parameters using appropriate statistical tests based on normality assessment. This table demonstrates that diabetics had significantly higher systolic and diastolic blood pressure, HbA1c, LDL levels, and CIMT. These findings support the presence of early vascular damage and abnormal metabolic regulation in the diabetic group.

Table 3: Continuous Variables Comparison between Diabetics and Controls

Variable	Diabetic (Mean ± SD / Median)	Control (Mean ± SD / Median)	p-Value
Systolic BP* (mmHg)	132.4 ± 12.1	122.1 ± 10.3	0.003
Diastolic BP* (mmHg)	82.3 ± 9.6	76.2 ± 7.4	0.001
HbA1c (%)#	8.9 (7.4-10.2)	5.1 (4.9-5.7)	<0.001
LDL (mg/dL)*	116.2 ± 24.8	88.3 ± 19.5	<0.001
CIMT (mm)#	1.01 (0.87-1.15)	0.78 (0.64-0.89)	<0.001

(*)t-test, (#)Mann-Whitney U test

Table 4 shows the prevalence of cardiovascular complications between the diabetic and control groups. This table demonstrates that LV hypertrophy, elevated CIMT, diastolic dysfunction, and arrhythmias were all significantly more prevalent among diabetics. Adjusted ORs confirm strong and independent associations with early cardiovascular damage.

Table 4: Cardiovascular Complications in Diabetic vs. Control Groups(n=130)

Variable	Diabetic	Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-Value
LV Hypertrophy	48	14	5.36 (2.74-10.49)	5.01 (2.51-9.99)	0.001
CIMT ≥0.9 mm	58	21	4.75 (2.66-8.49)	4.49 (2.44-8.26)	0.001
Diastolic Dysfunction	32	9	4.68 (2.05-10.67)	4.25 (1.83-9.89)	0.003
Arrhythmias	38	14	4.07 (2.13-7.77)	3.91 (2.01-7.61)	0.005

All comparisons via Chi-square test. Adjusted ORs derived from multivariable logistic regression controlling for age, gender, and BMI

DISCUSSION

The results of this study revealed that individuals with early-onset diabetes mellitus in Pakistan exhibited a significantly higher burden of cardiovascular complications compared to age- and gender-matched non-diabetic controls. Key cardiovascular abnormalities observed in diabetic participants included a markedly greater prevalence of left ventricular hypertrophy, diastolic dysfunction, increased carotid intima-media thickness (CIMT), and arrhythmias [15]. These complications were particularly prominent among individuals with type 2 diabetes, poor glycaemic control, longer disease duration, elevated LDL and triglyceride levels, low socioeconomic status, limited educational attainment, and urban residency [16]. Larsson et al., in 2018 examined the association of type 1 and type 2 diabetes with the incidence of seven major cardiovascular diseases [17]. Another multicentre study conducted by Shah et al., reported that Evaluates the relationship between insulin sensitivity and arterial stiffness in youth with type 1 diabetes using data from the SEARCH CVD study [18]. Htay et al., in 2019 reviewed mortality and cardiovascular disease risks in individuals with type 1 and type 2 diabetes [19]. Lee et al., in 2019 conducted a nationwide study comparing early mortality and cardiovascular disease risk between type 1 and type 2 diabetes [20]. Several strengths of the study must be acknowledged. The use of both clinical and subclinical cardiovascular markers, including ECG, echocardiography, and CIMT, allowed for robust identification of early cardiovascular involvement.

This study has certain limitations, including its single-center design and the use of non-probability consecutive sampling, which may limit the generalizability of the

findings. Additionally, the cross-sectional nature of the study restricts the ability to determine causal relationships between early-onset diabetes and cardiovascular complications. Long-term cardiovascular outcomes and progression of complications were not assessed in this study. Future multicenter longitudinal studies with larger sample sizes and extended follow-up are recommended to better understand the progression of cardiovascular risk in patients with early-onset diabetes and to support early preventive strategies.

CONCLUSIONS

This study demonstrated a clear and concerning association between early-onset diabetes mellitus and increased cardiovascular risk in young individuals in Pakistan. Patients with early-onset type 1 and type 2 diabetes showed a significantly higher prevalence of left ventricular hypertrophy, increased carotid intima-media thickness, diastolic dysfunction, and arrhythmias compared to non-diabetic controls. These complications were strongly linked with poor glycaemic control (elevated HbA1c), high LDL and triglyceride levels, longer duration of diabetes, and low socioeconomic status. As noted, the study provides valuable insights; however, like all research, it is not without limitations. Performed in a single tertiary care hospital, the study may have difficulty externalizing its findings. Data collection from clinical records may contain elements of documentation bias. Evaluation of long-term outcomes after three months was not conducted.

Authors' Contribution

Conceptualization: UM, MN

Methodology: US

Formal analysis: IA, US

Writing and Drafting: AZ, FUR

Review and Editing: AZ, FUR, IA, US, UM, MN

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Hyperglycaemia and ABO Blood Groups: An Investigative Analysis among Young Adults of Hyderabad, Sindh, Pakistan

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ABSTRACT

Serious health problems include nerve damage, renal failure, and an increased risk of cardiovascular disease can result from chronic hyperglycemia. **Objective:** To investigate the relationship between hyperglycemia and ABO blood types in young adults from Hyderabad, Sindh. **Methods:** 582 randomly selected healthy individuals, 281 females and 301 males, aged 18 to 40, were recruited from various institutions for this cross-sectional study, which took place between January 2, 2021, and January 31, 2022. The data was gathered using the basic random approach. All participants gave their informed consent prior to recruitment. Descriptive statistics including mean, standard deviation, and frequency distributions were computed using the Chi-square test. Data collection was analyzed using SPSS version 20.0. **Results:** This study included 582 participants. In male individuals, the mean age was 27.83 ± 5.478 , and in females, 22.27 ± 4.730 . The mean BMI was 25.81 ± 5.08 in males and 24.00 ± 4.90 in females. The 207 B blood group individuals were found to be obese, comprising 112 males and 95 females, followed by 195 individuals with blood group O, 128 individuals with blood group A, and 52 individuals with blood group AB. People who are Rh-positive and have blood group B were shown to be more likely to experience elevated hyperglycemia. **Conclusion:** Blood group B and Rh-positive status may be linked to higher hyperglycemia risk in young adults from Hyderabad, suggesting blood typing as a potential screening tool.

INTRODUCTION

Hyperglycemia is a multifactorial metabolic syndrome characterized by an increased blood sugar concentration. Hyperglycemia results from the pancreas's inefficiency in secreting the required amount of insulin or the decreased capability of body cells to respond to insulin [1]. Management of hyperglycemia in hospitalized patients is essential due to its association with increased morbidity, including cases triggered by physiological stress [2, 3]. Approximately 10.5% of the global population, or 537 million adults, were diagnosed with diabetes in 2023 [4]. It is

projected that 783 million adults will have been diagnosed with diabetes in 2045, which is almost 46% more than the 2021 estimates [5]. The International Diabetes Federation (2023) report states that diabetes mellitus was the cause of 6.7 million fatalities in 2021. According to this, one person dies from diabetes mellitus every five seconds [6]. The ABO blood group system is the most commonly used blood group identification method in the world out of the 45 various blood group systems [7]. Based on the presence of specific antigens on the membrane of red blood cells, this



system divided people into four groups. Genetic inheritance governs the ABO blood group system, which is linked to a number of physiological and pathological conditions. Numerous studies concluded that certain blood groups may be linked with particular health problems, including malaria, multiple infections, obesity, cardiovascular disease, and even certain types of cancer [8]. Certain medications have been identified as contributing factors to elevated blood glucose levels, either by impairing insulin secretion or increasing insulin resistance. Drug-induced hyperglycemia is an important but often overlooked cause of metabolic disturbance, necessitating careful evaluation of patient medication history when assessing glycemic abnormalities [9]. Studies have identified genetic and molecular factors that may contribute to the relationship between ABO blood group and glucose metabolism. Furthermore, studies have also concluded that blood groups may influence inflammatory and vascular responses, both of which play a crucial role in regulating glucose and insulin levels. However, genetic loci that control the ABO blood group also influence glucose and lipid metabolism, suggesting a probable genetic linkage [10]. Few studies identified that individuals having the B blood group are more likely to develop hyperglycaemia [11]. Other studies have suggested that individuals with blood group O may be protected against hyperglycemia [12]. Apart from established routes like insulin resistance, β cell dysfunction, and dietary/lifestyle variables, genetic variation at the ABO locus (chromosome 9q34.2) may also affect coagulation, endothelial, and inflammatory pathways, which in turn may affect metabolic syndrome. Glycosyltransferases (A-, B-, or inactive O enzyme) are encoded by the ABO gene, and non-O alleles are connected to increased levels of markers like vWF, ICAM 1, and P selectin mediators linked to endothelial dysfunction and insulin resistance through SNPs like rs505922 and rs507666. This suggests that non-O alleles may influence the risk of hyperglycemia [13, 14]. The majority of previous research was done on diagnosed patients and older populations, where there is a strong correlation between diabetes and other metabolic diseases. However, because obesity, physical inactivity, and bad eating habits are more common in younger adults, hyperglycemia is becoming more common in this demographic. In addition, compared to older populations, young individuals have different lifestyle patterns in terms of stress levels, sleep patterns, physical activity levels, and eating habits. These elements could affect how glucose is metabolized. Specific studies on young adults are limited. Hyperglycemia is an increasing metabolic health concern among young adults and may lead to long-term complications such as cardiovascular disease and renal

dysfunction if not identified early. Although genetic and lifestyle factors contribute to glucose metabolism, the possible association between ABO blood groups and susceptibility to hyperglycemia remains unclear. Most previous studies have focused on diagnosed diabetic patients or older populations, with limited attention to apparently healthy young adults. Furthermore, region-specific evidence from Pakistan examining the relationship between ABO blood groups and hyperglycemia is scarce, highlighting the need for population-based investigations in younger age groups. Therefore, it was aimed to investigate the relationship between the ABO blood group and hyperglycemia in young adults from the Hyderabad district.

METHODS

This cross-sectional study was carried out with permission from the University of Sindh, Jamshoro's Research Ethics Committee, Letter No. ERC/1601, to look into the connection between ABO blood types and hyperglycemia in the young people living in District Hyderabad who are between the ages of 18 and 40. Every participant gave their informed consent. Participants were selected based on preset criteria to get the most accurate results. Participants included those who knew their blood types, did not have diabetes, were not pregnant, did not smoke, and did not have an addiction. This study excluded participants who did not live in the Hyderabad district, were over 40, had a diagnosis of diabetes, were pregnant, were active smokers, had a genetic disorder associated with obesity, had hypothyroidism, polycystic ovary syndrome, Cushing syndrome associated with obesity, or were drug addicts. Eight to twelve hours before to the test, participants were told to avoid eating or drinking anything other than water. This entails abstaining from coffee, tea, sugary drinks, and snacks. In order to avoid dehydration during the fasting period, drinking water is typically advised. The automatic capillary method was used to analyze blood sugar levels using a glucometer (Easy Max by Biotechnology Corp, Made in China). Reference range for fasting blood: normal 70–100 mg/dl; rise > 100 mg/dl. The Statistical Package for the Social Sciences (SPSS), Version 20.0, was used to analyze the data. To summarize the individuals' clinical and demographic traits, descriptive statistics such as mean, standard deviation, and frequency distributions were calculated. The relationship between high blood sugar and ABO blood groups was evaluated using the Chi-square test. Crude Odds Ratios (ORs) were calculated using logistic regression analysis to further assess the strength of this association. A statistically significant p-value was defined as less than 0.050.

RESULTS

Five health-related variables were compared between people with different ABO blood groups (A, B, AB, and O) in Table 1. These variables included age, Body Mass Index (BMI), Fasting Blood Sugar (FBS), Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP). The F-value represents the result of the ANOVA (Analysis of Variance) test, and the P-value indicates the statistical significance of the result. The mean ages across blood groups are similar, ranging from 24.56 ± 5.40 (O group) to 25.58 ± 6.13 (A group). The P-value (0.294) indicates no statistically significant difference in age among blood groups. An essential difference in BMI is observed across blood groups ($P = 0.003$). Individuals with blood group B had the highest

mean BMI (25.96 ± 5.66), suggesting a possible association between blood group B and higher Body Mass Index (BMI). A statistically significant difference was observed in fasting blood sugar levels ($P = 0.036$). Blood group B again showed the highest mean Fasting Blood Sugar (FBS) level (100.90 ± 31.01). In contrast, AB and O groups had lower values, indicating that individuals with blood group B may be at a higher risk for hyperglycaemia. Systolic Blood Pressure (SBP) varied significantly between blood groups ($P = 0.003$). The mean SBP was higher in blood group B (121.28 ± 13.52) than in blood group O (115.70 ± 15.55). A significant difference was also found in Diastolic Blood Pressure (DBP) ($P = 0.008$), with group B again having the highest value (81.41 ± 10.33) and group O having the lowest (78.20 ± 9.41).

Table 1: Basic Characteristics of Individuals According to ABO Blood Group System

Variables	A (130) Mean $\pm$ SD	B (205) Mean $\pm$ SD	AB (50) Mean $\pm$ SD	O (197) Mean $\pm$ SD	F	P
Age	25.58 ± 6.131	25.52 ± 6.210	24.82 ± 4.952	24.56 ± 5.402	1.241	0.294
BMI	24.813 ± 4.574	25.964 ± 5.66	24.230 ± 5.23	24.154 ± 4.52	4.798	0.003
Blood Sugar Fasting	100.28 ± 35.08	100.90 ± 31.01	92.64 ± 32.28	93.41 ± 24.79	2.877	0.036
Systolic Blood Pressure	117.16 ± 19.35	121.28 ± 13.52	116.64 ± 12.61	115.70 ± 15.55	4.693	0.003
Diastolic Blood Pressure	80.65 ± 9.54	81.41 ± 10.33	79.20 ± 8.41	78.20 ± 9.41	4.024	0.008

Table 2 presented the distribution of ABO and Rh blood groups among a total of 582 participants, divided by gender (301 males and 281 females). The frequencies (N) and percentages (%) for each blood group type are reported for the overall population, as well as for male and female subgroups. Blood group B is the most common overall (35.5%), and it is also the most common in both males (37.2%) and females (33.8%). Blood group O follows closely, accounting for 33.5% of the total, with a slightly higher percentage in females (35.5%) compared to males (31.5%). Blood group A accounts for 21.99% of the overall population, with a higher frequency in males (23.5%) compared to females (20.2%). Blood group AB is the least common overall (8.9%), with a slightly higher prevalence in females (10.3%) than in males (7.6%). The majority of the population is Rh positive (91.7%), with similar proportions in males (92.6%) and females (90.7%). Only 8.2% of participants are Rh negative, with a slightly higher percentage in females (9.3%) than males (7.3%).

Table 2: Distribution of Participants (n=1164)

Variable	Overall Frequency (%)	Male Frequency (%)	Female Frequency (%)
A	128 (21.99)	71 (23.5)	57 (20.2)
B	207 (35.5)	112 (37.2)	95 (33.8)
AB	52 (8.9)	23 (7.6)	29 (10.3)
O	195 (33.5)	95 (31.5)	100 (35.5)
Rh Positive	534 (91.7)	279 (92.6)	255 (90.7)
Rh Negative	48 (8.2)	22 (7.3)	26 (9.3)

The association between ABO and Rh blood types and FBG levels was shown in this table, which divided participants into two groups according to normal (<100 mg/dL) and

increased (>100 mg/dL) FBG levels. Using blood group O and Rh-positive as reference categories, the odds ratio (OR) with 95% CI and p-values are presented to show the strength and statistical significance of correlations. Blood Group O (Reference Group): 74.35% of individuals had normal FBG, and 25.64% had increased FBG. Compared to group O, blood group A displayed a greater percentage of elevated FBG (33.59%). A 46% increased risk was indicated by the OR = 1.46, but this difference was not statistically significant ($p = 0.214$). The largest percentage of elevated FBG was seen in blood group B (41.06%). With an OR = 2.20 (95% CI: 1.34–3.61), the risk of hyperglycemia is more than double that of the statistically significant group O ($p = <0.001$). Although it was not statistically significant ($p = 0.223$), Blood Group AB had the lowest percentage of elevated FBG (17.30%) and an OR of 0.47, suggesting a protective trend. 32.77% had elevated FBG and 67.22% had normal FBG in the Rh-Positive (Reference Group) group. Rh-Negative: 75.00% had normal FBG and 25.00% had elevated FBG; there was no discernible difference between Rh-negative and Rh-positive people ($p = 0.361$), with an OR of 0.90.

Table 3: The Association of ABO and Rh Blood Groups with Fasting Blood Sugar

Blood Group	Normal FBG <100 mg/dl Frequency (%)	Increased FBG >100 mg/dl Frequency (%)	OR (95% CI)	P-Value
O (n = 195)	145 (74.35)	50 (25.64)	Reference	—
A (n = 128)	85 (66.40)	43 (33.59)	1.46 (0.83–2.56)	0.214
B (n = 207)	122 (58.93)	85 (41.06)	2.20 (1.34–3.61)	<0.001
AB (n = 52)	43 (82.69)	9 (17.30)	0.47 (0.19–1.17)	0.223

Rh Factor	Normal FBG <100 mg/dl	Increased FBG >100 mg/dl	OR (95% CI)	p- Value
Rh-Positive (n = 534)	359 (67.22)	175 (32.77)	Reference	—
Rh-Negative (n = 48)	36 (75.00)	12 (25.00)	0.90 (0.41-2.01)	0.361

DISCUSSION

The goal of the current study was to look into any connections between young people's hyperglycemia and their ABO blood type. B blood group participants were more prevalent in this study, which is consistent with earlier reports [15]. 67.86% of people had normal fasting blood sugar, while 32.13% had elevated blood sugar. Individuals with the B blood group were more likely to develop hyperglycemia, followed by those with the A, O, and AB blood groups, and Rh-positive individuals were more prone to the condition than Rh-negative individuals. A cross-sectional comparative research of people with and without diabetes mellitus (D.M.) found that people with the B blood group are more likely to experience hyperglycemia. Additionally, it is proposed that blood group and hyperglycemia are related since both have a wide genetic and immunological foundation [16]. Sulaiman *et al.*, conducted a study in Mardan, Pakistan, which also agreed with these findings that the B blood group is more prone to develop hyperglycaemia; this study was conducted on students of Abdul Wali Khan University [17]. The findings of this investigation are also supported by another study carried out in Iraq by Pandey [18]. A study conducted at Karachi by Anwar *et al.*, revealed agreement with these findings that the B blood group was more prone, but disagreed with blood group AB, which was safer in this study [19]. Similarly, Gotawa agreed with these findings [10]. The findings of this study, which found a negative correlation between the ABO blood group and elevated FBS and diabetes, are in conflict with a Malaysian study by Kamil *et al.* Additionally, compared to healthy individuals, those with type 2 DM had a greater distribution of the B blood group; however, this difference did not reach statistical significance [20]. Hedge found that blood groups A and O were more likely to develop hyperglycemia than blood groups AB and B, in contrast to this finding [21]. The genetic expression of this disease may be influenced by geographical and ethnic characteristics, which could account for these inconsistent findings. Ewald D. *et al.*, found that the ABO blood group is one of the hereditary host variables that changes the intestinal microbiota's composition and affects metabolism by changing energy balance, glucose metabolism, and low-grade inflammation [22]. A potential genetic link between ABO blood groups and cardiovascular disease has been suggested because of the role played by the ATP-binding cassette transporter A2 (ABCA2) gene, which is crucial for controlling cholesterol, as well as the ABO blood type system [23]. The ABO gene is

located on chromosome 9 (locus 9p34). This proximity suggests that ABO blood types may have an impact on plasma lipid levels. (8). The involvement of ABO genotypes in regulating circulating levels of Total Cholesterol (TC) and Low-Density Lipoprotein (LDL), two known causative risk factors for atherosclerotic cardiovascular disease, is supported by evidence from Genome-Wide Association Studies (GWAS) and later meta-analyses [24]. Furthermore, a large meta-analysis involving 46 lipid-focused GWAS studies identified a significant relationship between ABO gene variants, specifically Single-Nucleotide Polymorphisms (SNPs), and lipid levels [25].

This study has several limitations, including its cross-sectional design, which limits the ability to establish a causal relationship between ABO blood groups and hyperglycemia. The sample was restricted to young adults from Hyderabad, Sindh, which may limit the generalizability of the findings to other populations. Additionally, important confounding factors such as dietary habits, physical activity, socioeconomic status, and family history of diabetes were not comprehensively assessed. Future multicenter longitudinal studies with larger and more diverse populations, along with genetic and metabolic analyses, are recommended to further clarify the potential role of ABO blood groups as a marker for hyperglycemia risk.

CONCLUSIONS

The results of this study show that among young individuals in Hyderabad, Sindh, there is a substantial correlation between fasting blood glucose levels and ABO blood classes. Individuals with blood group B demonstrated a notably higher risk of hyperglycaemia compared to other blood groups, particularly when contrasted with the reference group (blood group O). While blood groups A and AB showed non-significant trends toward increased and decreased risk, respectively, the Rh factor did not show any significant association with fasting blood glucose levels. These results suggest that blood group B may be a potential genetic marker for increased susceptibility to hyperglycaemia, warranting further investigation in larger, diverse populations. It is important to recognize the various limitations of this study. Because it is a cross-sectional study, it can only identify connections rather than causative relationships between ABO blood types and hyperglycemia. The results may not be as generalizable to other demographics because the sample was restricted to young adults in Hyderabad, Sindh. Additionally, critical confounding factors such as diet, physical activity, socioeconomic status, and family history of diabetes were not accounted for, which could influence fasting blood glucose levels. The study also lacked genetic analysis to explore underlying mechanisms linking ABO blood groups

to glucose metabolism. Furthermore, the relatively small number of participants with blood group AB and Rh-negative status may have limited the statistical power for detecting associations in these subgroups.

Authors' Contribution

Conceptualization: SA

Methodology: SA, AM, HL, NM

Formal analysis: SA, SFM, KRL

Writing and Drafting: SA, SFM, ZAL

Review and Editing: SA, SFM, ZAL, KRL, AM, HL, NM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Histopathological Diversity in Hysterectomy Specimens at Jinnah Sindh Medical University Lab

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ABSTRACT

Hysterectomy is common but often overused in Pakistan, with rising cases in cities like Dera Ghazi Khan. Fibroids and abnormal uterine bleeding are the top causes, though many effective non-surgical treatments exist. Experts urge prioritizing medical management and preserving fertility through alternatives like myomectomy before resorting to surgery. **Objective:** To determine the spectrum of hysterectomies' lesions in histopathological analysis at Jinnah Sindh Medical University Lab (JSMU lab). **Method:** This retrospective study was conducted in the setting of the JSMU diagnostic lab in Karachi, from January 2023 to December 2024. The sample size included the hysterectomy samples received during the two years mentioned before. The sampling technique was non-probability consecutive sampling. A proforma was designed to collect data from the records of the JSMU lab. This included the age of the patients, Indication of surgery, and outcome/diagnosis after histopathological examinations. **Results:** This study included 147 hysterectomies with a mean age of 44.11 years, and the Individuals aged between 40 and 49 years comprised the largest proportion, making up half of the total participants. Heavy menstrual bleeding was the most frequent clinical finding, present in 44% of cases. Histopathologically, 50% of cases showed leiomyoma, followed by adenomyosis, with almost all patients having chronic cervicitis and nabothian cysts. **Conclusions:** It was concluded that hysterectomy was most common in women aged 40–49 years, primarily for heavy menstrual bleeding. Leiomyoma was the leading histopathological finding, followed by adenomyosis, with chronic cervicitis and nabothian cysts in most cases.

INTRODUCTION

Hysterectomy remains a widely performed surgery across the United States. Hysterectomy in Pakistan, like in other parts of the world, is considered to be overused in several cases [1]. In a city of Pakistan, Dera Ghazi Khan, Hysterectomy cases grew from 7% of gynaecological admissions in 2013 to 17% by 2016 [1]. It is typically used as a last-line treatment when other methods fail. In nationwide study conducted in the United States identified the leading indications for hysterectomy as symptomatic uterine fibroids (51.4%), abnormal uterine bleeding (41.7%), endometriosis (30%), and uterine prolapse (18.2%) [2]. In a study of Karachi at Jinnah Postgraduate Medical Centre

(JPMC) in 2020, 260 hysterectomies were done in a single hospital in only one year [3]. The most common reason for hysterectomy in gynaecological cases was fibroids, followed by uterine prolapse. For obstetric cases, the main cause was a severely attached placenta. Experts believe that with better treatment options now available, the number of hysterectomies for non-cancerous reasons may decrease in the future [3]. Fibroid is the most common cause of hysterectomy. Evidence from recent analyses suggests that the location of uterine fibroids plays a critical role in fertility outcomes. Fibroids growing just below the uterine lining are most frequently linked to difficulties in



embryo implantation, whereas those embedded in the muscular wall or on the outer uterine surface tend to have less impact. Instead of giving hope, hysterectomies are usually done. However, Myomectomy appears to affect fertility improvement in different cases [4]. In a recent study, regarding fibroids treatment, there are many options for fibroid treatment, like surgical, medical and nonsurgical alternatives [5]. So there is a point to ponder if there are so many options apart from the last resort, why hysterectomies' frequency is increasing. On the other hand, if we take the second most common cause of hysterectomy which is abnormal uterine bleeding then there is a recommendation that women presenting with abnormal uterine bleeding require a comprehensive workup involving ultrasound examination, preferably supplemented by hysteroscopy, along with blood tests including platelet levels and coagulation profiles to rule out manageable sources of bleeding [6]. Typically, medical interventions are favoured as the primary approach for addressing abnormal uterine bleeding (AUB). When it comes to managing acute AUB, hormonal techniques stand as the initial choice in medical treatment. Options such as intravenous administration of combined oral contraceptive pills or oral progestins are effective therapeutic options. Surgery should be considered only in patients in whom medical treatment has failed, cannot be tolerated, or is contraindicated [7]. Although several regional and international studies have explored the histopathological spectrum of lesions found in hysterectomy specimens, there is limited data specific to the population served by Jinnah Sindh Medical University (JSMU). There is significant histopathological diversity in hysterectomy specimens at JSMU, with benign lesions being more prevalent than malignant ones, and their distribution varying with age and clinical presentation.

Hysterectomy remains one of the most frequently performed gynecological surgeries worldwide and is commonly indicated for conditions such as abnormal uterine bleeding, fibroids, and adenomyosis. However, the correlation between clinical indications and final histopathological findings is not always well established, which may lead to unnecessary surgical interventions. In Pakistan, limited local data are available describing the spectrum of histopathological lesions identified in hysterectomy specimens. Therefore, evaluating the histopathological diversity of hysterectomy specimens is essential to better understand disease patterns and to support evidence-based clinical decision-making. This study aims to evaluate the histopathological diversity in hysterectomy specimens at JSMU Lab, to categorize findings by type, correlate them with clinical indications and patient demographics, and assess the concordance between clinical and histological diagnoses.

METHODS

The retrospective descriptive study was conducted in the setting of Jinnah Sind Medical University (JSMU) Diagnostic Lab, Karachi. The study duration was between January 2023 and December 2024. Informed consent was obtained from all patients at the time of specimen submission through a standardized research consent form in Urdu and the English language provided by the Histopathology Department of Jinnah Sindh Medical University Laboratory. Patients were informed that their anonymized data may be used for academic and research purposes. Only those specimens for which written consent was provided were included in the study. Approval for the study was obtained from the Institutional Review Board (IRB) of Jinnah Sindh Medical University (JSMU/IRB/2024/871). Patient confidentiality and anonymity were strictly maintained throughout the study. The sampling technique was non-probability consecutive sampling, while the sample size type was complete enumeration of available cases (census of available data). After receiving the hysterectomy specimen, a general consent form for Specimen Collection and testing for research purposes was asked to be filled out by the patient. A proforma was designed to collect data from the records of the JSMU lab. This included the age of the patients, the Indication of surgery, and outcome/diagnosis after histopathological examination. All hysterectomy specimens received at the Histopathology Department of Jinnah Sindh Medical University Laboratory were included in this study. Each specimen was accompanied by a histopathology requisition proforma containing relevant clinical details such as patient age, presenting symptoms, provisional diagnosis, and type of surgical procedure performed. Inclusion criteria were such specimens that were adequately preserved and suitable for histopathological evaluation. Exclusion criteria included poorly preserved, damaged, or inadequate specimens that cannot be processed or yield conclusive histopathological results. Upon receipt, the specimens were labelled with unique identification numbers and fixed in 10% neutral buffered formalin for 24–48 hours. Gross examination was performed by a pathologist or trained technologist, and the following details were noted: size, weight, and appearance of the uterus, condition of endometrium, myometrium, and cervix, presence of any lesions, masses, polyps, fibroids, or adhesions, involvement of adnexal structures (if present). Representative tissue sections were taken from: endometrium, myometrium (including any fibroids or masses), cervix, ovaries and fallopian tubes (if included), and any abnormal or suspicious areas. The selected tissue samples were processed using an automatic tissue processor. The tissues underwent dehydration (using increasing grades of alcohol), clearing (in xylene), and impregnation with molten paraffin wax. Once embedded,

tissue blocks were prepared using paraffin embedding stations. Thin sections (4–5 microns) were cut from the paraffin blocks using a microtome. These sections were mounted on glass slides and allowed to dry. Slides were then stained using the routine Hematoxylin and Eosin (H and E) staining method. Special stains (e.g., PAS, Masson's Trichrome) were used when required for specific diagnostic purposes. The stained slides were examined under a light microscope, MAKE AND MODEL? by qualified histopathologists. Each case was evaluated for: type and nature of the lesion (inflammatory, benign, and malignant), presence of specific pathological features such as leiomyoma, adenomyosis, endometrial hyperplasia, carcinoma, polyps, or chronic cervicitis coexistence of multiple pathologies. The tabulated results underwent statistical analysis to determine the type of lesion, clinical findings and age group distribution for frequency /percentage. The data were compiled and processed using Microsoft Excel software for subsequent analysis.

RESULTS

This study comprised a total of 147 hysterectomy cases. The average age of participants was 44.11 years, with ages ranging broadly from 28 to 85 years. The largest proportion of cases, 73 (50%), fell within the 40–49-year age group. The most frequent clinical finding was heavy menstrual bleeding, which accounts for 44% of total cases (Table 1).

Table 1: Age and Clinical Features of the Total 147 Cases of Hysterectomies

Sr. No	Variables	Frequency (%)
Age (Years)		
1	20-29	02 (1%)
2	30-39	28 (19%)
3	40-49	73 (50%)
4	50-59	34 (23%)
5	60 and Above	10 (7%)
	Total	147 (100%)
Clinical Findings		
1	Heavy Menstrual Bleeding	65 (44%)
2	Irregular Bleeding	18 (12%)
3	Post- Menopausal Bleeding	13 (9%)
4	UV Prolapse	09 (6%)
5	Lower Abdomen: Heaviness or Pain	09 (6%)
6	Abdominal Distension	05 (3%)
7	Post Coital Bleeding	01 (0.5%)
8	Percutaneous Umbilical Blood	02 (1%)
9	History Not Provided	26 (17%)

The most common significant histopathological diagnosis is adenomyosis, followed by leiomyoma. The frequency of the coexisting and single diseases was analyzed (Table 2).

Table 2: Histopathological Diagnosis in 147 Cases, Most Cases Carries More Than One Diagnosis

Sr. No	Histopathological Diagnosis	Frequency
1	Adenomyosis	81
2	Leiomyoma	76
3	Endometritis	45
4	Endometrial Hyperplasia	35
5	Endometrial Atrophic Changes	19
6	Endometrial Polyp	7
7	Cervical Polyp	4
8	Ovarian Cyst	3
9	Endometrial Cancer	2
10	Leiomyosarcoma	2
11	Ovarian Cancer	2
12	Cin	1
13	Ovarian Endometriosis	1
14	Cervical Cancer	0
Single and Coexisting Diseases		
1	Coexisting Diseases	98
2	Single Diseases	49

The 30–40 age group demonstrated high rates of ovarian cysts (67%), chronic cervicitis (27%), and endometritis (42%), suggesting a predominance of inflammatory and functional disorders in early reproductive years. Adenomyosis (21%) and endometrial hyperplasia (29%) were also noted in this group, though less frequently than in the 40–50 range. ovarian cancer (figure 5) is solely seen in women the 40–50 years. of the age range. In the 50–60-year group, there was a marked reduction in overall pathology, although ovarian cysts (33%), endometrial polyps (43%), and cervical polyps (50%) persisted, potentially reflecting postmenopausal presentations or incidental findings during surgery. Patients over 60 showed minimal pathology, with isolated cases of chronic cervicitis, adenomyosis, and leiomyoma (all <5%). The <30 age group showed almost no significant pathology except minor percentages of chronic cervicitis (1%), endometritis (2%), and adenomyosis (1%), indicating a low burden of histopathological disease at younger reproductive ages. This distribution emphasizes that the most significant uterine and adnexal pathologies occur in the fourth and fifth decades, coinciding with perimenopausal hormonal changes. It also reinforces the need for heightened clinical surveillance and diagnostic evaluation in women aged 40–50, especially for conditions with malignant potential, such as CIN and cervical cancer (Table 3).

Table 3: Correlation of Histopathological Diagnosis with Age

Variables	Age (Years)				
	<30	30-40	40-50	50-60	60+
Chronic Cervicitis	1%	27%	52%	17%	4%
Nabothian Cyst	0%	33%	51%	15%	1%
Endometritis	2%	42%	40%	11%	4%
Ovarian Cyst	0%	67%	0%	33%	0%

Cervical Polyp	0%	0%	50%	50%	0%
Endometrial Atrophic Changes	0%	21%	37%	37%	5%
Ovarian Endometriosis	0%	0%	100%	0%	0%
Leiomyosarcoma	0%	50%	50%	0%	0%
Endometrial Hyperplasia	3%	29%	66%	3%	0%
Leiomyoma	1%	28%	49%	20%	3%
CIN	0%	100%	0%	0%	0%
Adenomyosis	1%	21%	56%	19%	4%
Endometrial Cancer	0%	0%	100%	0%	0%
Cervical Cancer	—	—	—	—	—
Endometrial Polyp	0%	14%	43%	43%	0%
Ovarian Cancer	0%	0%	100%	0%	0%

The cross-tabulated data revealed significant associations between clinical complaints and underlying histopathological findings in hysterectomy specimens. Heavy menstrual bleeding was most frequently associated with leiomyoma (62%), cervical intraepithelial neoplasia (CIN) (58%), adenomyosis (43%), and endometritis (31%). This indicates that heavy bleeding is a dominant clinical manifestation in patients with fibroids, precancerous cervical lesions, and adenomyosis. Irregular bleeding demonstrated a particularly strong association with CIN (100%), followed by endometritis (20%) and endometrial atrophic changes (12%), suggesting that irregular bleeding may serve as a clinical indicator of precancerous or atrophic endometrial changes. Postmenopausal bleeding

was commonly linked with endometrial atrophic changes (33%) and ovarian endometriosis (18%), emphasizing the need to investigate atrophic or ovarian pathology in postmenopausal women presenting with such symptoms. Cases clinically diagnosed as fibroid uterus frequently showed histological evidence of leiomyoma (5%) and adenomyosis (3%), confirming clinical suspicion but also indicating that adenomyosis may coexist and contribute to the symptomatology. Ovarian cysts and cervical polyps were found with high frequency (33%) across diverse complaints such as constipation and heavy bleeding, suggesting that these may often be incidental or coexisting findings rather than primary causes. Interestingly, uterovaginal prolapse showed a notable association with ovarian endometriosis (35%), possibly reflecting pelvic floor involvement or deep infiltrating disease. This analysis underscores that certain clinical presentations—particularly heavy and irregular bleeding correlate strongly with specific histopathological diagnoses such as leiomyoma, CIN, adenomyosis, and endometritis. Findings like CIN and leiomyoma appear to be complaint-linked rather than incidental, supporting their diagnostic significance. Such clinico-pathological correlations are valuable for enhancing clinical suspicion and guiding appropriate diagnostic and therapeutic strategies (Table 4).

Table 4: Correlation Between Clinical Complaints and Histopathological Findings in Hysterectomy Specimens

Variables	Column Labels Complain of Lower Abdominal Pain							
	Constipation	Fibroid Uterus	Heavy Menstrual Bleeding	Irregular Bleeding	Not Provided	Pain in Both Iliac Fossa	Post-Menopausal Bleeding	U/V Prolapse
Chronic Cervicitis	1%	3%	48%	9%	16%	2%	9%	12%
Nabothian Cyst	1%	1%	45%	13%	21%	3%	7%	7%
Endometritis	0%	3%	31%	20%	29%	3%	9%	6%
Ovarian Cyst	33%	0%	33%	33%	0%	0%	0%	0%
Cervical Polyp	33%	0%	33%	0%	0%	0%	33%	0%
Endometrial Atrophic Changes	0%	12%	18%	12%	6%	0%	18%	35%
Ovarian Endometriosis	0%	0%	0%	100%	0%	0%	0%	0%
Leiomyosarcoma	—	—	—	—	—	—	—	—
Endometrial Hyperplasia	0%	0%	58%	15%	12%	3%	6%	6%
Leiomyoma	0%	5%	62%	9%	14%	2%	6%	3%
CIN	—	—	—	—	—	—	—	—
Adenomyosis	1%	3%	43%	10%	19%	3%	10%	11%
Endometrial Cancer	0%	0%	100%	0%	0%	0%	0%	0%
Cervical Cancer	—	—	—	—	—	—	—	—
Endometrial Polyp	0%	0%	33%	17%	0%	0%	50%	0%
Ovarian Cancer	0%	0%	50%	0%	0%	0%	50%	0%

The age-stratified distribution of histopathological findings among hysterectomy specimens reveals distinct patterns across reproductive age groups. The 40–50-year age bracket showed the highest concentration of pathologies, with notable peaks in endometritis (40%), adenomyosis (56%), endometrial hyperplasia (66%), indicating this decade as the most clinically active period for uterine pathology (Figure 1).

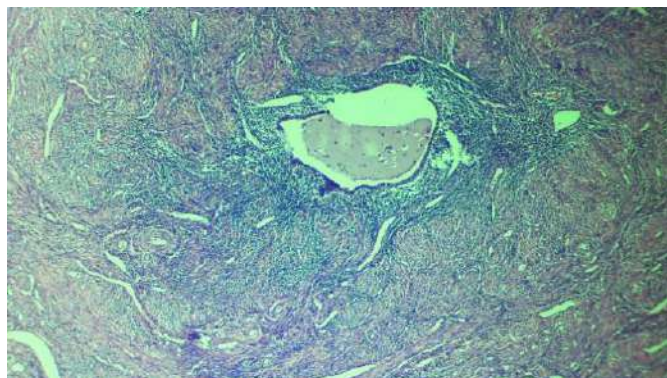


Figure 1: Adenomyosis(H and E Staining at Power of Scanner)

The 40–50-year age bracket showed the highest concentration of pathologies, with notable peaks in chronic cervicitis (52%) indicating this decade as the most clinically active period for uterine pathology(Figure 2).

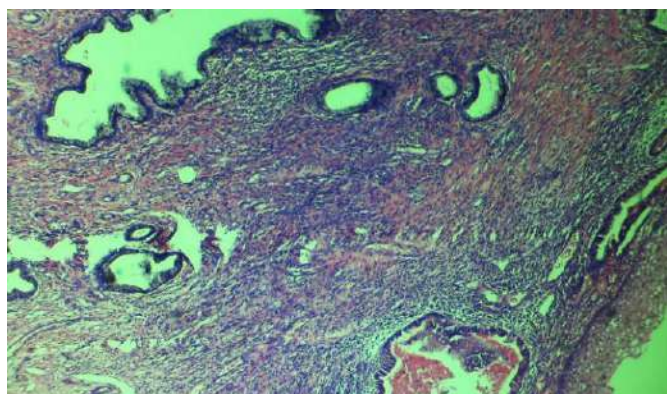


Figure 2: Chronic Cervicitis (H and E Staining at the Power of Scanner)

The 40–50-year age bracket showed the highest concentration of pathologies, with notable peaks in nabothian cysts (51%) indicating this decade as the most clinically active period for uterine pathology(Figure 3).

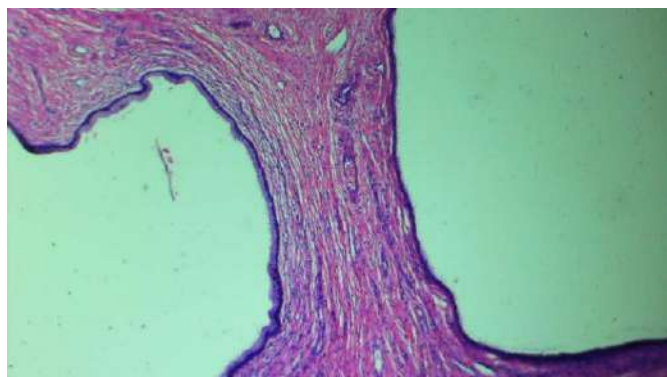


Figure 3: Nabothian Cyst(H and E Staining at Power of Scanner)

The 40–50-year age bracket showed the highest concentration of pathologies, with notable peaks in leiomyoma (49%), indicating this decade as the most clinically active period for uterine pathology(Figure 4).

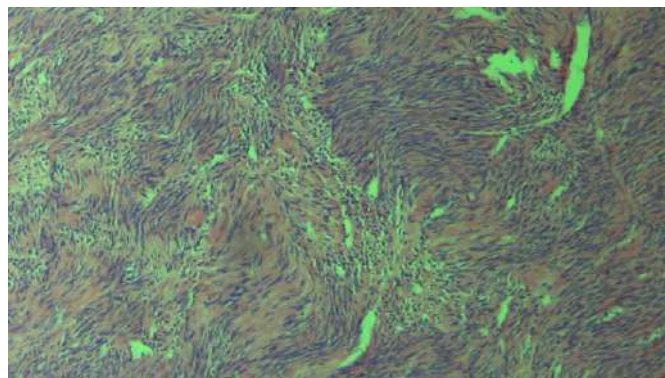


Figure 4: Leiomyoma(H and E Staining at Power of Scanner)

The 40–50-year age bracket showed the highest concentration of pathologies, with notable peaks in cervical polyps, (50%) indicating this decade as the most clinically active period for uterine pathology(Figure 5).

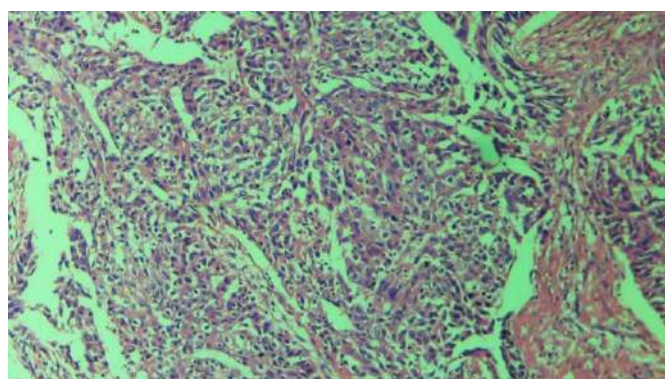


Figure 5: Ovarian Cancer(H and E Staining at Power of Scanner)

This age group also accounted for 100% of CIN, ovarian endometriosis, and cervical cancer, highlighting its critical role in both benign and premalignant or malignant conditions.

DISCUSSION

Removal of the uterus is likely a critical intervention in the presence of malignancies involving the uterus or ovaries, or in cases of severe uterine hemorrhage refractory to conservative management. In other clinical scenarios, the procedure is performed electively to alleviate symptoms and improve the patient's quality of life. When not performed as an emergent, life-saving measure, the surgery is classified as an elective hysterectomy. Hysterectomy is preferred for specific gynecologic conditions. However, the anticipated benefits must be carefully balanced against the potential risks of the procedure and other treatment options. For appropriately chosen patients, the surgery should lead to an improved quality of life. The cost of the procedure, both to the healthcare system and to the patient, should be considered concerning the expenses of leaving the condition untreated. Additionally, the method chosen for performing the hysterectomy will influence the overall cost of the surgery. Heavy menstrual bleeding (HMB) affects women's

health, daily life, and well-being. While medication is the first-line treatment, surgery is considered when it fails. Hysterectomy is the definitive solution, but it comes with major risks and costs. Less invasive options like endometrial resection and ablation offer effective symptom relief with fewer complications [8]. Hysterectomy can lead to physical and emotional challenges, including estrogen deficiency (if ovaries are removed) and health risks. Loss of femininity often contributes to anxiety and depression [9, 10]. The uterus symbolizes womanhood, pregnancy, and femininity for many. Its removal, even post-menopause, can impact self-image and identity. Abdominal hysterectomy may also affect sexual function; which estrogen therapy cannot fully restore [11]. Recent research suggests that declining estrogen levels may heighten vulnerability to mental health issues [12]. Hysterectomy should not be the only solution for adenomyosis. Emerging treatments like GnRH therapy, progestin IUDs, and ultrasound ablation offer promising alternatives. Levonorgestrel IUD stands out as a highly effective, non-invasive, and fertility-preserving option [13, 14]. Urgent research is needed to refine treatment strategies and establish definitive guidelines, ensuring patients have better choices beyond hysterectomy. Uterine fibroids can be treated by myomectomy, myolysis [15]. uterine fibroid volume decreases by an average of 57% over a six-month course of treatment by GnRH agonists [16], while Laparoscopic myolysis may be considered as an alternative to abdominal hysterectomy for women over 40 with large or multiple intramural fibroids who do not wish to have children but want to avoid undergoing a hysterectomy [17]. In certain situations, the decision to undergo a hysterectomy may be influenced or even unintentionally swayed by doctors. Several factors could contribute to this happening, like Pressure for Quick Solutions, Lack of Awareness of Alternatives or Financial and Institutional Pressures. The cost of a hysterectomy in Pakistan varies widely, typically ranging from 150,000 to 250,000 Pakistani Rupees (PKR). The final price depends on factors such as the hospital, location, surgeon's fees, and the type of procedure performed, whether laparoscopic, robotic-assisted, or abdominal [18]. In India, many women undergo hysterectomies without medical need due to a mix of misconceptions, economic hardship, and poor healthcare access. Some view the uterus as unnecessary after childbirth, while others see surgery as a one-time, cheaper alternative to ongoing treatment. Fear of cancer, misdiagnosis, and lack of contraception further fuel the trend [19]. So the solution to this is to improve reproductive health education, access to primary care, and promote non-surgical treatment options [20]. The increasing rate of hysterectomy, despite the availability of alternative treatments, is a complex issue influenced by a variety of factors, including lack of awareness, perceived simplicity of the procedure, and pressure from healthcare systems. To reverse this trend, it is crucial to provide better

education to both healthcare providers and patients about the range of available treatments, ensure that hysterectomy is only recommended when truly necessary, and encourage shared decision-making in treatment planning. By adopting these strategies, we can help ensure that women receive the most appropriate care and avoid unnecessary surgeries whenever possible.

This study has certain limitations, including its retrospective design and single-center setting, which may limit the generalizability of the findings. Additionally, the study relied on laboratory records and did not include detailed clinical follow-up or evaluation of alternative treatment approaches prior to hysterectomy. Variations in surgical indications and patient management could also influence the observed histopathological spectrum. Future multicenter studies with larger sample sizes and comprehensive clinicopathological correlation are recommended to better evaluate indications for hysterectomy and promote more conservative treatment strategies where appropriate.

CONCLUSIONS

This study analyzed the histopathological characteristics of lesions identified in hysterectomy specimens. The most common uterine pathologies encountered were leiomyoma and adenomyosis. Chronic cervicitis was the predominant cervical lesion observed, along with one case of cervical polyp and three cases of cervical intraepithelial neoplasia grade III (CIN III). Malignant tumors were identified in four specimens, including three cases of endometrial carcinoma and one case of ovarian carcinoma.

Authors' Contribution

Conceptualization: MA

Methodology: MA, YAZ, BAS, SP

Formal analysis: MA

Writing and Drafting: WH, YAZ, FZ

Review and Editing: WH, YAZ, FZ, MA, BAS, SP

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Assessment of Thickness of Macular Edema on Optical Coherence Tomography in Diabetic Patients Treated with Anti-Vascular Endothelial Growth Factor

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ABSTRACT

Diabetes is becoming more commonplace worldwide with potential causes. Diabetic retinopathy is a serious ocular complication that affects working-age adults and causes moderate to severe vision loss. **Objective:** To determine the outcome of anti-VEGF by optical coherence tomography (OCT) in DME thickness. **Methods:** A prospective (interventional) study was carried out at the Chandka Medical College Hospital's Department of Ophthalmology at SMBB Medical University, Larkana. The study included all individuals over the age of 15 who had diabetes mellitus of any kind. SPSS version 26 was used for data analysis. **Result:** Patients were 64.8 ± 14.2 years old on average, had a BMI of 33.56 ± 7.85 kg/m², and had been on DME for an average of 8.06 ± 4.23 years. There were 17(34%) female patients and 33(66%) male patients out of 50. The most common risk factor among 50 patients was hyperlipidemia, 45(90%) followed by hypertension 43(86%), anemia 42(84%), insulin dependent, 37(74%), obesity 31(62%), chronic renal failure, 28(56%) and smoking, 26(52%). **Conclusion:** OCT can be used to accurately measure retinal thickness brought on by DME. OCT can therefore be a helpful technique in predicting the functional outcome and assessing how well anti-VEGF medication works for individuals with DME. Anti-VEGF therapy results in rapid and sustained thickness reduction on OCT, generally correlating with improvements in visual acuity. The outcome of anti-VEGF therapy in diabetic macular edema (DME), as measured by OCT, typically shows a significant reduction in central retinal thickness(CRT) or central subfield thickness(CST).

INTRODUCTION

Diabetes is a public health crisis that is expanding at the fastest rate since it can have many serious health effects [1]. Diabetes is becoming more commonplace worldwide; potential causes include ageing, obesity, physical inactivity, urbanization, sedentary lifestyles, and unhealthy eating habits. As a developing nation, Diabetes prevalence is sharply increasing in Pakistan [2]. Diabetic retinopathy is a serious ocular complication that affects working-age adults and causes moderate to severe vision loss. Diabetic retinopathy patients often have visual loss due to diabetic macular oedema (DME), which affects around 21 million

individuals globally [3, 4]. Currently, intravitreal injections of various anti-vascular endothelial growth factor (anti-VEGF) medicines must be administered repeatedly to treat macular edema [5]. Other management techniques for DME comprise intravitreal steroid injections & macular laser photocoagulation [6]. VEGF has been linked to enhanced Vascular Permeability through the disruption of blood-retina barriers and its function in angiogenesis, both of which are pathophysiological factors for numerous retinal complications [7]. Additionally, VEGF regulates proper angiogenesis and vasculogenesis, among other



physiological processes, and during the formation of retinal blood vessels, it serves as a survival factor [8]. They have a neuroprotective function that lowers neuronal apoptosis and preserves the metabolism of choriocapillaris and photoreceptors. There have been questions raised about the safety of using these agents over an extended period since these physiological activities of VEGF may get disrupted through protracted management of retinal problems with frequent injections [9, 10]. Numerous investigations revealed harmful cellular consequences when VEGF was inhibited. Nevertheless, several previous investigations used fundus fluorescein angiography (FFA) and OCT to evaluate the effects on macular and retinal perfusion of repeated intravitreal injections of anti-VEGF drugs used for DME. When compared to FFA, the OCT offers high-resolution, three-dimensional pictures of each of the distinct retinal vascular layers, allowing for noninvasive, dye-free imaging of superficial and deep retinal vessels. OCT can reliably and precisely detect capillary drop-out zones and produce a picture of the foveal avascular zone (FAZ) without being obstructed by dyed leaking or macular xanthophyll pigmentation shadowing, unlike FFA [11, 12]. Retinal vascular density (VD) and fractional dimension (FD) may also be accurately measured quantitatively and automatically using OCT [13]. Numerous studies have reported the short-term efficacy of anti-VEGF agents in reducing central macular thickness and improving vision. Studies exist comparing different anti-VEGF agents regarding efficacy and safety.

Diabetic macular edema (DME) is a major cause of visual impairment among patients with diabetic retinopathy, particularly in developing countries where the burden of diabetes is rapidly increasing. Anti-vascular endothelial growth factor (anti-VEGF) therapy has emerged as a key treatment modality for reducing macular edema and improving visual outcomes. However, the effectiveness of this therapy and its anatomical response assessed through optical coherence tomography (OCT) has not been extensively studied in the local population. Moreover, limited regional data exist regarding changes in central subfield thickness following anti-VEGF treatment, highlighting the need for further clinical evaluation. This study aims to find out how anti-VEGF treatment using OCT affects the thickness of diabetic macular edema (DME). Owing to a lack of data, research on this topic would be beneficial as well.

METHODS

A prospective (interventional) study, using a random sampling approach was carried out at the Chandka Medical College Hospital Department of Ophthalmology at Shaheed Mohtarma Benazir Bhutto (SMBB) Medical University, Larkana (1-9-2024 to 28-2-2025). Data were collected after

getting approval from the research ethics committee of SMBBMU Larkana (NO.SMBBMU/IRB/06). To calculate sample size, an equation was used: Effect size (Δ): 40 μ m. Standard deviation (σ): 90 μ m. $\alpha = 0.05$, Power = 0.80. $n = (Z\alpha/2 + Z\beta) \cdot \sigma / \Delta)^2$. $n = (1.96 + 0.84) \cdot 90 / 40)^2$. $n = 40$ patients. To account for dropouts, the study has increased it to around 50 patients. Inclusion criteria was consisted on patients of any type of DME, having age above 15 years to 70 years, either gender, no history of Retinal by treatment by (focal/grid/scatter) laser or by intravitreal injections of anti-VEGF agents or steroids were included and patients of DME with intraocular inflammation or infection, uncontrolled glaucoma, previous retinal laser photocoagulation, Grid, Focal and Scatter, history of stroke and uncontrolled hypertension, intravitreal injections of anti VEGF/steroids were excluded from the study. Patients who satisfied the selection criteria were chosen from the ophthalmology department's retina clinic and given a thorough examination that included measurements of intraocular pressure, anterior and posterior segment investigations, and best-corrected visual acuity measurements (BCVA). All patients signed consent forms to confirm their enrollment in the study. Baseline data like age, gender, duration, type of DM, grading of DME, type of diabetes, diabetic retinopathy stage (Both proliferative and non-proliferative diabetic retinopathy are possible), risk factors of DME and central subfield thickness were recorded from patients' history on a pre-designed approved Performa. All patients underwent treatment with one injection of bevacizumab (1.25 mg/ 0.05 ml) for 3 months consecutively, as a similar drug was studied by Elnahry et al., [14]. The protocol of using optical coherence tomography was based on informed consent obtained from the patient. The procedure was explained for non-invasive imaging using light waves to take cross-sectional pictures of the retina. Remove contact lenses/glasses. Turn on the OCT machine and allow it to calibrate. Select appropriate scan protocol: (e.g., macular cube, optic disc cube, anterior segment). Check lens cleanliness and optical components. Adjust the chair and chin rest for proper alignment. Seat the patient comfortably at the machine. Instruct the patient to place the chin on the rest and the forehead against the bar. Select the eye to scan (right or left). Use auto-focus or manual focus to get a sharp image. Ensure the eye is centred in the scan window. Capture the scan: Confirm image quality: signal strength ≥ 6 -7/10 is generally acceptable. Check for segmentation errors or artefacts. Save images to the patient's electronic record. The patients were assessed for CST on an OCT investigation basis (Before and after 3 injections). The outcome variable, i.e. change in CST on OCT, was measured at 3 months. OCT made in Poland with model REVO 60 was used. SPSS software, version 26.0, was used to enter and analyze the data that were gathered. Mean $\pm$ SD was calculated for

quantitative data regarding the age, gender, duration/ type of DM, and CST before and after injections. Frequency and percentage were calculated for gender, diabetic retinopathy stage, grading, and risk factors of DME. T-tests were also applied, pie chart was constructed. Normality of data was checked by Shapiro-Wilk's test. A p -value < 0.050 was considered significant.

RESULTS

Fifty people participated in the current study. Findings display the patients' mean age, BMI and DME (64.8 ± 14.2 years), ($33.56 \pm 7.85 \text{ kg/m}^2$), (8.06 ± 4.23 years), respectively. According to gender distribution, 33 (66%) of the 50 patients were men and 17 (34%) were female. Regarding diabetes type status, most of the patients were type-II DM 42 (84%), and 8 (16%) were Type-I DM (Table 1).

Table 1: Demographic Information Related to Age, Gender, DME and Diabetes Status of Patients

Variables	Mean $\pm$ SD, Frequency (%)
Age	64.8 ± 14.2
BMI	33.56 ± 7.85
DME (Years)	8.06 ± 4.23
Gender	
Male	33 (66%)
Female	17 (34%)
Type of Diabetes	
Type I	8 (16%)
Type II	42 (84%)

Results demonstrate the risk factors of diabetic macular edema. The most common risk factor was hyperlipidemia 45 (90%), followed by hypertension 43 (86%), anemia 42 (84%), insulin dependent 37 (74%), obesity 31 (62%), chronic renal failure 28 (56%) and smoking 26 (52%) (Table 2).

Table 2: Risk Factors Associated with Progression of Diabetic Macular Edema

Risk Factors	Frequency (%)
Smoking	26 (52%)
Obesity	31 (62%)
Hyperlipidemia	45 (90%)
Insulin dependent	37 (74%)
Anemia	42 (84%)
Chronic Renal Failure	28 (56%)
Hypertension	43 (86%)

This study demonstrates that baseline CST was compared post-intervention of ANTI-VEGF at the 1st month, 2nd month, and 3rd months; a significant difference was observed (Table 3).

Table 3: Patients with Diabetes with Anti-Vascular Endothelial Growth Factor (ANTI-VEGF) Treatment Showed CST on OCT

Central Subfield Thickness				
Before Treatment	CST after 1 st Anti-VEGF (1 st Month)	CST after the 2 nd Anti-VEGF (2 nd Month)	CST After 3 rd Anti-VEGF (3 rd Month)	p-value
442.6 ± 117.0	375.2 ± 57.4	337.3 ± 62.9	323.0 ± 65.4	0.001

DISCUSSION

Clinical research has shown that a decline in visual acuity corresponds with an increase in central macular thickness in DME, and that vision is improved by treatments that lessen retinal thickening. Macular edema that is not clinically obvious can be detected by OCT, and number of biomarkers acquired from OCT can be used to predict the severity, course, and visual prognosis of the condition. In this work, we examined new measures to assess change in the Central subfield thickness on OCT in DME eyes receiving intravitreal treatment during 3 months. There was a considerable change in visual acuity related to any given central macular thickness. While eyes with moderate edema showed considerable reduction in vision, several eyes with severe macular edema had extremely strong visual acuity. It has also been observed that there is not always a consistent increase in central macular spot thickness accompanied by an improvement in visual acuity, nor is there a consistent decrease in central retina thickness accompanied by a decrease in visual acuity. This suggests that in cases with macular edema associated with diabetes, OCT assessment may serve as a reliable proxy for visual acuity. OCT measures DME, the main clinical factor affecting visual acuity in DR, to evaluate and assess therapeutic response. There exists a somewhat negative relationship between retinal thickness and visual acuity [15]. In comparison to baseline, our study found a statistically significant gain in visual acuity and a statistically significant decrease in CST at the end of a 3-month follow-up period. Following anti-VEGF medication therapy, our results were in line with earlier studies that showed a reduction in Central subfield thickness [16]. In their research, Zhang et al., studied variables influencing how individuals with DME responded to intravitreal anti-VEGF injections [17]. After three and six months of therapy, they saw improvements in BCVA from 4.78 and 5.52 letters and a decrease in central retinal thickness from 80.25 and 106.12 microns. Their response to the reduction in core retinal thickness led them to conclude that the most promising candidates for anti-VEGF therapy might be identified. This data could then be utilized to forecast a post-treatment improvement in BCVA. The effectiveness of bevacizumab as a single anti-VEGF injection as the main therapy for DME was established by Santos J et al., [18]. The study examined the effects of bevacizumab administered alone, in conjunction with intravitreal triamcinolone acetonide, and concerning macular laser photocoagulation. The outcome demonstrated that there

was no discernible difference between these two treatments in terms of improving visual acuity while lowering central macular thickness. In clinical studies and clinical practice, central subfield thickness is frequently used to evaluate the effectiveness of intravitreal treatment in patients with DME. Nevertheless, prior research has shown that in DME eyes, CST and BCVA may not exhibit a linear association. Specifically, a decrease in CST below normative healthy values does not always translate into an increase in BCVA [19]. These results appear to support the idea that visual improvement is linked to an initial drop in retinal thickness caused by fluid absorption, but visual deterioration relates to further retinal thinning caused by retinal neurodegeneration. According to recent research, anti-VEGF medications are astonishingly successful at treating macular edema owing to diabetes, are safe, affordable, and easily accepted in clinical settings. Patients also seem to handle these medications well. Researchers have shown that bevacizumab (1.25mg) is effective in treating DME patients [20]. When intravitreal bevacizumab (1.25 mg) was used as a single dosage to treat proliferative DR, the area of leaky vessels significantly decreased. It was linked to a notable increase in average visual acuity. According to these studies, bevacizumab frequently reduces the thickness of macular tissue in the non-injected partner eye in bilateral DME, and 40% of injected eyes show improved visual acuity. Prior research indicates that when bevacizumab is coupled with dexamethasone for DME, visual acuity is significantly improved compared to bevacizumab monotherapy [21]. The effectiveness of using injectable bevacizumab (anti-VEGF) to treat diabetic macular disease in people with diabetes was reported in this study. The established effectiveness metrics on OCT were the central subfield thickness. According to recent research, initiating anti-VEGF medication early in the course of the disease greatly improves visual results. [21, 22]. Six months following therapy, patients who had presented sooner and had a shorter history of symptoms showed higher improvement in visual acuity and persistent decrease in central retinal thickness. In individuals with an extended medical history, however, there would be little difference between baseline values at the start of therapy and core retinal thickness and visual acuity three and six months later [23]. Based on these findings, early macular edema therapy is recommended for better and longer-lasting morphological and visual outcomes. Therefore, early identification of decreased visual acuity is crucial for the management of recurrent ME. Further research demonstrated the relationship between baseline visual acuity and central subfield thickness following bevacizumab therapy. Younger individuals with DME were linked to considerably better visual acuities and decreased central retinal thickness after every six weeks of therapy, which is consistent with other research [24, 14]. Recurring intravitreal bevacizumab would not, however, result in

discernible improvement in vision if the course of therapy is postponed for longer than six weeks.

This study had several limitations, including a relatively small sample size and short follow-up duration, which may limit the generalizability of the findings. Additionally, the study was conducted at a single center and evaluated only one anti-VEGF agent, which may not reflect outcomes with other treatment regimens. Future studies with larger multicenter populations and longer follow-up periods are recommended to better understand long-term treatment efficacy and visual outcomes. Further research comparing different anti-VEGF agents and combination therapies may also provide more comprehensive insights into optimal management strategies for diabetic macular edema.

CONCLUSIONS

It was concluded that anti-VEGF therapy significantly reduces central macular thickness in patients with diabetic macular edema (DME), as assessed by OCT. This indicates a positive anatomical response to treatment, reinforcing the efficacy of anti-VEGF agents in managing DME. Continued monitoring with OCT remains essential for evaluating therapeutic outcomes and guiding treatment regimens. The reduction in CST after anti-VEGF (vascular endothelial growth factor) treatment plays a critical role in improving outcomes for patients with retinal vascular diseases such as diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), and retinal vein occlusion (RVO) and the reduction in CST helps patients in improved visual acuity, decreased retinal swelling, reduced risk of vision loss and better quality of life.

Authors' Contribution

Conceptualization: IMS

Methodology: IMS, IA, SAA

Formal analysis: IMS

Writing and Drafting: AAK, PAGK, ZG, SAA

Review and Editing: AAK, PAGK, ZG, SAA, IMS, IA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Original Article



Effect of Dexamethasone on Perioperative Lactate Levels in Donor Hepatectomy

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ABSTRACT

The use of intravenous dexamethasone intraoperatively has been advocated for analgesia, prevention of nausea and vomiting, post-operative sore throat and inflammation. Hyperlactinemia associated with dexamethasone is a concern in patients undergoing hepatectomy. There is limited evidence to support safety or adversity of dexamethasone in terms of hyperlactinemia. **Objective:** To evaluate the effect of dexamethasone administration on perioperative lactate levels in living related donors undergoing liver donor right hepatectomies. **Methods:** This quasi-experimental study, with a prospective design was conducted. The 60 patients who had donor hepatectomy appointments in total were divided into two groups at random. After the induction of anesthesia, Group B (n=30) got dexamethasone at a dose of 8 mg while Group A(n=30) received a placebo. Perioperative lactate levels were assessed at various time points, and statistical comparisons were made between the two groups' mean lactate levels. **Results:** The patients' mean age was 25.68 years, and their mean BMI was 21.48 kg/m². At every time point, Group B displayed significantly higher mean lactate levels than Group A (p<0.001). Additionally, there were statistically significant differences between the groups, an hour after drug administration, and after graft extraction (p<0.001). The perioperative mean glucose level climbed steadily in both groups. **Conclusion:** The administration of dexamethasone in patients undergoing right living related donor hepatectomy was associated with significantly higher perioperative lactate levels compared to patients receiving placebo.

INTRODUCTION

Living related donor hepatectomy is the surgical removal of right lobe of the liver for transplantation. This involves a number of physiological changes as well as the possibility of complications. Hemodynamic and metabolic alterations during the perioperative period can have a major impact on surgical outcomes [1]. Lactate is produced by most tissues in the human body, for example, in red blood cells, neurons, hepatocytes, and muscles. Muscles are primary site of lactate production. It is cleared by the liver, but the kidney also removes a small amount. Under conditions of cellular stress, glycolysis increases and results in increased lactate production [2, 3]. In anesthetized patients, lactic acidosis may occur due to an imbalance between lactate production and lactate utilization. It is frequently measured in critically

ill patients as a measure of tissue hypoxia and anaerobic metabolism. Blood lactate levels are extremely important in determining the patient's metabolic status as it signifies tissue hypoperfusion or decreased oxygen supply [2, 3]. Dexamethasone, a synthetic glucocorticoid, is used by anesthesiologist during surgery because of beneficial effects like analgesia and prevention of postoperative nausea and vomiting, suppression of inflammation, and reduction of the risk and severity of post-intubation sore throat [4]. However, dexamethasone also has some adverse effects, for example increasing blood glucose levels and type B hyperlactatemia [5]. The therapeutic benefit of perioperative dexamethasone treatment in hepatectomy has been evaluated [6, 7]. However, its effect



on perioperative lactate levels in living related donor hepatectomy patients remains unclear. Since liver is the primary organ for lactate clearance hence it is hypothesized that impairment of liver function as seen in patients undergoing hepatectomy may lead to lactic acidosis which may further be attenuated by intravenous dexamethasone administration [8]. Elevated lactate levels in perioperative period have been associated with worse clinical outcomes in terms of morbidity and mortality. [9, 10] In fact, lactate levels exceeding 3.8mmol/L have been linked to very high incidence of post hepatectomy liver failure and even death. [11,12] In majority of cases, lactic acidosis in perioperative period is a transient phenomenon that settles in most of the patients with conservative strategies yet some patients may need continuous renal replacement therapy for clearance of lactic acid. [13, 14]. Dexamethasone with all of its benefits in perioperative anesthetic management may be a factor contributing to lactate production. Usually cadaveric liver dissections are done in western world for liver transplantation where intravenous dexamethasone is omitted as all of its benefits are for living patient [15].

Living donor hepatectomy is a complex surgical procedure associated with significant metabolic and physiological alterations during the perioperative period. Dexamethasone is commonly administered intraoperatively for its anti-inflammatory and antiemetic effects; however, its potential role in increasing lactate levels and contributing to hyperlactatemia remains a concern, particularly in patients undergoing liver resection where lactate clearance may already be compromised. Although several studies have evaluated the benefits of dexamethasone in surgical settings, limited evidence exists regarding its specific impact on perioperative lactate levels in living liver donors. Therefore, further investigation is required to clarify its metabolic effects and safety in this population. Hence, its effect on lactate metabolism in said population is understudied and under reported. The aims and objective of this study was to evaluate the effect of dexamethasone administration on perioperative lactate levels in living related donors undergoing liver donor right hepatectomies.

METHODS

This quasi-experimental study, with a prospective design was conducted from October 2019 to March 2020 following approval from the Institutional Review Board and Ethics Committee of Shifa International Hospital (IRB # 078-568-2019). A pilot study was conducted to calculate the sample size, to determine the effect of dexamethasone in donor hepatectomy. The following calculations with level of significance were carried out with the aid of the WHO sample size calculator: In a pilot research done at SIH, Islamabad, the test's 5% power was 95%, the population's

standard deviation was 1.22, and the test value of the population mean was 3.64 (lactate levels in mmol/L in placebo group patients against predicted population mean:5.32 (lactate levels in mmol/L in dexamethasone group patients). Each group's sample size (n) is 30 patients, for a total of 60 patients. A total of 60 adult donors over the course of 4 years scheduled to have Right living related donor hepatectomy with American Society of Anesthesiology status I and II were recruited from the Liver Transplant operation rooms. All living donors were healthy individuals and are free from any co-morbidities who underwent Right Hepatectomy with or without Middle Hepatic Vein. Patients who had received corticosteroids within last two weeks of surgery, patients allergic to dexamethasone, and patients suffering from any illness that elevates blood lactate levels, such as G6-PD deficiency, were excluded from the study. For general anesthesia, the anesthesiologist had followed the standard protocol used in hospital. Induction was obtained using midazolam 0.3 mg/kg, buprenorphine 0.03mg/kg and propofol 2mg/kg. Neuromuscular blockade was obtained with atracurium 0.5mg/kg, a loading dose followed by maintenance intermittent dosage guided by monitoring with train of four. Anesthesia was maintained using the inhalational agent Isoflurane 1 MAC with oxygen and air. Intraoperative monitoring consisted of a continuous electrocardiogram, invasive blood pressures using arterial line, peripheral oxygen saturation, end-tidal carbon dioxide (ETCO₂), core temperature, urine output, and central venous pressure monitoring. The thoracic epidural catheter was inserted for pain control at T 7-8. The hospital protocol was used to strictly maintain mean arterial pressure above > 65 mm of Hg, CVP of < 5 mm of Hg, temperature above 36°C and urine output 0.5 ml/ hour. Patients were divided into two study groups using consecutive sampling technique. Group A: Conventional Care Patients in the control group received conventional care but did not get dexamethasone. Group B: Patients in the experimental group received 8 mg of intravenous dexamethasone after anesthesia induction, as per regular institutional policy. The primary outcome measure was perioperative lactate levels, assessed at predefined time points during perioperative period i.e., 1 hour after dexamethasone administration, lobe resection, graft extraction, incision closure and at PACU. Lactate levels were measured using arterial gas analysis. Data were collected and analyzed using the computer software SPSS version 21.0. Mean and calculated standard deviation of continuous variables, e.g. age, BMI, blood loss, blood sugar levels, and postoperative and perioperative lactate levels in all the patients. Categorical variables, i.e. gender, were presented as frequency and percentage. An independent sample t-test was applied to compare mean lactate levels in both groups. P-value < 0.050 was considered statistically significant.

RESULTS

Donors had an average age of 25.68 ± 6.43 years and a BMI of 21.48 ± 2.13 kg/m². There were 37 (61.7%) males and 23 (38.3%) females. Table 1 displayed descriptive statistics broken down by group which suggest that patients in both study groups were standardized in terms of hemodynamics and volume status in terms of central venous pressure. In table 1 comparisons between age, BMI, duration of surgery, MAP and CVP in Group A and Group B were described by using Mean (M) and Standard Deviations (SD) and its statistical significance was determined by student t Tests. A p value ≤ 0.050 was considered statistically significant (n=60).

Table 1: Comparison of Demographic and Hemodynamic Variables Between Groups

Variables	Group A Mean $\pm$ SD	Group B Mean $\pm$ SD	p-Value
Age (Years)	24.67 $\pm$ 6.08	26.70 $\pm$ 6.71	0.450
BMI (kg/m ²)	21.55 $\pm$ 2.20	21.41 $\pm$ 2.09	0.160
Duration of surgery (hours)	9.08 $\pm$ 1.33	9.32 $\pm$ 1.18	0.890
MAP before drug administration	79.98 $\pm$ 9.93	83.10 $\pm$ 9.96	0.120
MAP one hour after drug administration	86.30 $\pm$ 9.57	83.42 $\pm$ 9.44	0.210
MAP at lobe resection	82.60 $\pm$ 8.27	83.78 $\pm$ 8.27	0.470
MAP after graft extraction	81.66 $\pm$ 8.26	84.58 $\pm$ 9.06	0.100
MAP at incision closure	81.80 $\pm$ 9.70	81.94 $\pm$ 8.99	0.940
MAP in PACU	85.84 $\pm$ 11.36	85.12 $\pm$ 11.04	0.740
CVP before drug administration	5.94 $\pm$ 2.84	5.16 $\pm$ 2.41	0.140
CVP one hour after drug administration	5.28 $\pm$ 2.6	5.96 $\pm$ 3.34	0.540
CVP at lobe resection	4.60 $\pm$ 1.78	5.10 $\pm$ 1.45	0.140
CVP at graft extraction	5.84 $\pm$ 2.16	5.56 $\pm$ 1.47	0.360
CVP at incision closure	7.02 $\pm$ 2.22	6.46 $\pm$ 2.00	0.110
CVP in PACU	7.82 $\pm$ 1.88	8.30 $\pm$ 1.03	0.100

In group A, the mean blood loss was 470 ± 134.93 ml versus 480 ± 136.83 (p=0.73). The liver remnant in group A was 35.47 ± 3.81 , whereas in group B it was 33.77 ± 3.02 . The liver attenuation index was 9.94 ± 3.87 in group A versus 9.92 ± 3.07 in group B (p=0.970). It was observed that mean blood lactate levels in patients of Group B were higher as compared to group A at all intervals. The difference was very highly statistically significant (p<0.001). In table 2 comparisons between perioperative lactate levels in Group A and Group B were described by using Mean (M) and Standard Deviations (SD) and its statistical significance was determined by student t Tests. A p-value ≤ 0.050 was considered statistically significant (n=60).

Table 2: Effect of Intraoperative Dexamethasone on Perioperative Lactate Levels in Donor Hepatectomy

Lactate Levels (mmol/L)	Group A Mean $\pm$ SD	Group B Mean $\pm$ SD	p-Value
1 hour of drug administration	1.89 $\pm$ 0.41	2.36 $\pm$ 0.72	0.002
After lobe resection	1.94 $\pm$ 0.17	2.95 $\pm$ 0.80	<0.001
After graft extraction	2.15 $\pm$ 0.18	3.63 $\pm$ 1.05	<0.001

After incision closure	2.31 $\pm$ 0.18	4.46 $\pm$ 1.20	<0.001
In PACU	2.60 $\pm$ 0.18	5.71 $\pm$ 1.40	<0.001

The difference in mean blood glucose levels between the study groups was variable. Mean blood glucose levels were statistically higher in Group A at 1 hour of dexamethasone administration and after graft extraction. However, the difference between study groups in terms of blood glucose levels was comparable at all other stages of surgery as it is apparent in Table 3. Comparisons between perioperative sugar levels in Group A and Group B were described by using mean (M) and standard deviations (SD) and its statistical significance was determined by student t Tests. A p-value ≤ 0.050 was considered statistically significant (n=60).

Table 3: Comparison of Perioperative Blood Glucose Levels between Dexamethasone and Placebo Groups in Donor Hepatectomy

Sugar Level (mg/L)	Group A Mean $\pm$ SD	Group B Mean $\pm$ SD	p-Value
1 hour of drug administration	155.10 $\pm$ 21.62	129.07 $\pm$ 24.64	0.001
After lobe resection	146.73 $\pm$ 31.34	139.63 $\pm$ 25.52	0.340
After graft extraction	154.40 $\pm$ 33.39	133.40 $\pm$ 25.89	0.009
After incision closure	135.80 $\pm$ 21.78	143.33 $\pm$ 21.23	0.100
In PACU	142.30 $\pm$ 19.14	144.67 $\pm$ 17.12	0.610

DISCUSSION

According to the findings of this study, mean lactate levels were higher in the group of living related liver donor hepatectomies patients who got dexamethasone than in the group who did not. These findings were true across all time intervals studied, from medication delivery until the PACU. Dexamethasone may raise lactate levels by increasing gluconeogenesis, which is the process of turning non-carbohydrates into glucose. The metabolic pathway gluconeogenesis is frequently stimulated in response to low blood sugar levels during surgeries as patients are fasting for eight hours before surgery. It can, however, be activated in reaction to trauma, such as surgery. These effects are hypothesized to contribute to the stress response and subsequent increase in lactate levels [2]. Similarly, it was reported in a randomized controlled trial called Dexamethasone for Cardiac Surgery (DECS), in which one group of patients received a single intravenous (IV) bolus of Dexamethasone (20 mg/mL, 1 mg/kg, maximum 100 mg). Another group received a placebo (NaCl 0.9%) immediately after induction of general anesthesia. The effect of Dexamethasone on perioperative lactate levels was observed, and they found that the lactate levels were significantly higher in the dexamethasone group than in the placebo group, i.e. lactate levels 25.8 ± 13.1 versus 19.9 ± 11.2 mmol/L $\times$ hour, P < 0.001 [16]. In contrast to present study, a higher dose of Dexamethasone was used along with extracorporeal circulation. This was not the case in our study. DREAMS Trial advocates use of

intravenous dexamethasone for prevention of post-operative nausea and vomiting [17]. However, transient worsening of glycemic control has been reported by various studies which is incoherent with findings of present study which can be explained by difference in study population as patients with impaired glucose levels preoperatively or diabetics were excluded from the study [18]. Clinicians must weight benefits of dexamethasone in accentuation of systemic inflammatory response syndrome against potential of confounding rise in lactic acidosis [19, 20]. In addition, the rise in perioperative glucose levels found in both groups reflects a metabolic response to surgery, however there were no significant differences between groups except at certain time periods. Further research is needed to identify the clinical implications of these glucose level changes on patient outcomes. There are a few limitations of this study. First off, this study was performed in a single center, and the sample size was quite small. Therefore, the results of future studies with greater sample sizes and multi-center designs would be more generalizable. Despite the fact that none of the patients had serum lactate levels in the potentially harmful range, the study also did not evaluate the long-term clinical effects linked to the observed variations in lactate levels.

This study has certain limitations, including a relatively small sample size and its single-center design, which may limit the generalizability of the findings. Additionally, the study focused only on short-term perioperative lactate changes and did not assess long-term clinical outcomes related to hyperlactatemia. Variations in patient characteristics and perioperative management may also influence metabolic responses. Future multicenter studies with larger sample sizes and extended follow-up are recommended to better evaluate the long-term clinical implications of dexamethasone administration on metabolic parameters and postoperative outcomes in donor hepatectomy patients.

CONCLUSIONS

In conclusion, donor hepatectomy patients who received dexamethasone had significantly higher perioperative lactate levels than those who had not received it.

Authors' Contribution

Conceptualization: R

Methodology: R, MHF, MA, MZA

Formal analysis: ZAR

Writing and Drafting: MA, ZAR, MNAK, SAN

Review and Editing: MA, ZAR, MNAK, SAN, MZA, R

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Frequency of Hyperthyroidism in Patients Diagnosed with Atrial Fibrillation

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ABSTRACT

The global prevalence of hyperthyroidism in patients with atrial fibrillation (AF) ranges between 10% and 20%, with lower and higher rates in developed countries to regions with iodine deficiency and health care settings with limited resources, respectively. Demographic variations, such as age, the severity of hyperthyroidism, or differences in AF detection methods, may lead to additional disparities. Hence, the study was planned to help clarify these variations and facilitate more accurate global comparisons. **Objective:** To evaluate the prevalence of hyperthyroidism in patients diagnosed with AF. **Methods:** This cross-sectional study was conducted at Lady Reading Hospital, Peshawar, Department of Cardiology, from July 1, 2023, to December 31, 2023. 119 male and female participants in the age range of 30 to 60 years diagnosed with atrial fibrillation were enrolled. The patients were analyzed for hyperthyroidism. Serum TSH levels of blood test <0.1 mU/L and FT4 >1.5 ng/dL by laboratory were considered confirmatory for hyperthyroidism. **Results:** The Mean age of participants was 41.84 ± 8.376 years. Male participants were 79 (66.4%). Hyperthyroidism was found in 35 patients (29.4%). The p-value for the association between hyperthyroidism and hypertension was statistically significant (p-value=0.025). **Conclusions:** Our study revealed a higher frequency of hyperthyroidism-induced AF when compared to global reports. Iodine disorder, delayed diagnosis, multiple medical conditions, and economic inadequacies could be the underlying reasons. Female patients with atrial fibrillation, aged more than 45 years, with a history of hypertension, were more likely to have hyperthyroidism.

INTRODUCTION

Atrial fibrillation is a disorder of cardiac electrical activity characterized by excessive excitatory activity of the atria leading to uncontrolled rapid transmission of electrical impulses to the ventricles [1]. It is a supraventricular tachyarrhythmic disorder and constitutes the most common type of cardiac rhythm disorder [2]. Irregular and dysrhythmic cardiac activity leads to turbulence in the blood flow, which is a prothrombotic condition, rendering the patients at risk of emergencies such as cerebrovascular accidents [3]. Clinical spectrum of atrial fibrillation is very wide, ranging from symptom-free to chest pain, syncope, palpitations and potentially fatal emergent conditions such as acute ischemic stroke [4]. Treatment strategies have evolved drastically over the years and include management of the underlying cause as well as the associated sequelae [5]. Anticoagulants are

offered to patients with AF to prevent prothrombotic events while simultaneously controlling the rate and rhythm of the heart. Depending upon the clinical settings, management to control rate and rhythm may be conservative to medical cardioversion or ablation techniques [6]. Hyperthyroidism is a syndrome arising from excessive production of thyroxin. Thyroxin is produced by the thyroid gland under the control of the pituitary gland. Thyroxin promotes metabolic activity of the body [7]. Cardiac effects of thyroxin include increased heart rate and contractility, leading to increased cardiac output [8, 9]. Pathologic hyper-stimulation of the thyroid by pituitary, ectopic production of thyroxin or any exogenous intake of thyroxin leads to hyperthyroidism [10]. More than half were found to have atrial fibrillation, followed by dilated cardiomyopathy and heart failure in a



study [11]. A study by Ullah et al., has shown that the frequency of hyperthyroidism was 8.39% in patients with AF [12]. Hyperthyroidism-induced atrial fibrillation are seldom studied. International reports in this regard are variable which cannot be generalized.

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and is associated with significant morbidity and mortality. Thyroid dysfunction, particularly hyperthyroidism, is recognized as an important reversible cause of AF due to its stimulatory effects on cardiac rhythm and metabolism. However, the reported prevalence of hyperthyroidism among AF patients varies widely across different populations and healthcare settings. In Pakistan, limited local data are available regarding the burden of hyperthyroidism among patients diagnosed with AF, highlighting the need for further investigation to guide screening and management strategies. This study aims to provide valuable insights about the burden of thyroid derangements among patients with AF.

METHODS

A descriptive cross-sectional study was performed at Lady Reading Hospital, Peshawar, Department of Cardiology. Participants were enrolled during the period from 1st July 2023 to 31st December 2023. Approval for the conduct of the study was obtained vide no: 765/LRH/MTI. Patients aged 30 to 60 years labelled with the diagnosis of atrial fibrillation were recruited. Patients with a history of cardiac valvular disorder, smoking, severe cardiopulmonary compromised patients, prior history of cardiac interventions, ischemic heart disease and patients taking rate-enhancing medications were excluded. The total sample size was 119, calculated using the WHO sample size calculator, taking the expected frequency of hyperthyroidism as 8.39%, 5% margin of error and a 95% confidence level [12]. Participants were enrolled using a non-probability consecutive sample technique. Atrial fibrillation was diagnosed on ECG, revealing a lack of obvious P waves with irregular R-R intervals. Hyperthyroidism was diagnosed by blood thyroid function tests, taking the simultaneous presence of 1) TSH <0.1 mU/L and FT4 >1.5 ng/dL as a cut-off for hyperthyroidism. The study risks, benefits and purpose were explained to the patients, and informed consent was obtained. Baseline clinical and demographic data were gathered. 10cc blood samples were obtained from all participants and sent to the hospital laboratory for estimation of thyroid-stimulating hormone level and free thyroxine. All samples were processed and placed in a hormone analyzer for estimation of TSH and free T4 to record the presence or absence of hyperthyroidism. Data were analyzed using SPSS version 26.0. Categorical data were presented as frequencies and percentages, and continuous data as mean $\pm$ SD. Effect

modifiers were controlled through stratification. Test of statistical significance included a chi-square test, applied at 5% level of significance.

RESULTS

The mean age of the participants was 41.84 ± 8.376 years, the mean weight was 75.14 ± 5.874 kg, the mean height was 172.89 ± 6.493 cm, mean BMI was 25.204 ± 2.2996 kg/m² (Table 1).

Table 1: Patients According to Age, Weight, Height and BMI (n=119)

Demographics and Baseline Characteristics	Mean $\pm$ SD
Age (years)	41.84 ± 8.376
Weight (kg)	75.14 ± 5.874
Height (cm)	172.89 ± 6.493
BMI (kg/m ²)	24.29 ± 2.647

The majority of the participants were male (n=79, 66.4%), while the age group ≤ 45 years was most common (n=93, 78.2%). For comorbidities, diabetes was recorded in 40 patients (33.6%), and hypertension was observed in 31 (26.1%) patients. 71 patients (59.6%) belonged to rural areas, and 83 patients (69.7%) had a BMI within the healthy range (18.5 – 24.9 kg/m²) (Table 2).

Table 2: Frequency and Percentages of Patients According to Various Clinic-Demographic Parameters (n=119)

Parameters	Subgroups	n (%)
Gender	Male	79 (66.4%)
	Female	40 (33.6%)
Age	≤ 45 Years	93 (78.2%)
	> 45 Years	26 (21.8%)
Diabetes	Yes	40 (33.6%)
	No	79 (66.4%)
Hypertension	Yes	31 (26.1%)
	No	88 (73.9%)
Residence	Rural	71 (59.6%)
	Urban	48 (40.4%)
BMI (kg/m ²)	18.5–24.9	83 (69.7%)
	25.0–29.9	26 (21.8%)
	30.0 and Above	10 (8.4%)

It was recorded in 35 participants (29.4). 19 patients (15.9%) had overt hyperthyroidism and 16 (13.4%) had subclinical hyperthyroidism. AF was most frequently diagnosed incidentally (n = 53, 44.5%), and chest pain was the most frequent symptom (n=31, 26.0%) (Table 3).

Table 3: Frequency and Percentages of Patients According to Outcome Variable (n=119)

Outcome Variables	Subgroups	n (%)
Hyperthyroidism	Yes	35 (29.4%)
	No	84 (70.6%)
Presenting Complaints	Syncope	07 (5.8%)
	Chest Pain	31 (26.0%)
	Incidental AF	53 (44.5%)
	AF Related Complications	15 (12.6%)

	Overt Hyperthyroidism	19 (15.9%)
	Subclinical Hyperthyroidism	16 (13.4%)

Hyperthyroidism was more frequent in female (n=14, 35.0%) compared to male (n=21, 26.6%). P-value=0.341. Hyperthyroidism was recorded in 10 (38.5%) patients aged more than 45 years compared to 25 (26.9%) patients aged less than 45 years (p-value 0.252). The p-value for the distribution of hyperthyroidism for diabetes and hypertension was 0.109 and 0.025, respectively (Table 4).

Table 4: Subgroup Analysis of Hyperthyroidism with Various Parameters (n=119)

Variables		Hyperthyroidism		Total	Chi-square (p-Value)
		Yes (n=35)	No (n=84)		
Gender	Male	21 (26.6%)	58 (73.4%)	79 (100.0%)	0.341
	Female	14 (35.0%)	26 (65.0%)	40 (100.0%)	
Age (Years)	≤45	25 (26.9%)	68 (73.1%)	93 (100.0%)	0.252
	>45	10 (38.5%)	16 (61.5%)	26 (100.0%)	
Diabetes Mellitus	Yes	8 (20.0%)	32 (80.0%)	40 (100.0%)	0.109
	No	27 (34.2%)	52 (65.8%)	79 (100.0%)	
Hypertension	Yes	14 (45.2%)	17 (54.8%)	31 (100.0%)	0.025
	No	21 (23.9%)	67 (76.1%)	88 (100.0%)	

DISCUSSION

The cardiovascular milieu is maintained under tight hormonal control. Thyroxin plays an essential role in regulating this homeostasis. Intrinsic production or extrinsic intake of thyroxin leads to a clinical syndrome affecting various organs, including the heart. Bakarmom et al., reported 3.6% prevalence of hyperthyroidism among patients with AF [13]. Increased heart rate is a common manifestation of hyperthyroidism [14]. In this study, the frequency of hyperthyroidism in patients with AF was 35 (29.4%). Distribution of hyperthyroidism with various clinical and demographic parameters showed that hyperthyroidism was more frequently recorded in patients aged less than 45 years, 25 (26.9%) of patients, as compared to 10 (38.5%) patients in the age group more than 45 years. The p-value for the difference in distribution of hyperthyroidism for age was 0.341 (>0.050), hence statistically insignificant. Overall frequency of hyperthyroidism among patients with AF in a study by Ullah S and colleagues was 13 (8.39%) patients, which was much lower compared to our study [14]. Atrial fibrillation was reported in a higher proportion in a study (about 21%) in patients with Graves' disease. Similar to patients with Graves' disease and similar to our observation, age-wise distribution showed higher prevalence among patients aged more than 40 years (31% versus 0%) [15]. This inconsistency in the results may be attributed to variations in population factors, such as regional differences in thyroid disease, iodine intake, or genetic susceptibility. While other studies may have relied on clinical suspicion or symptomatic presentation, our study actively screened all

AF patients for thyroid dysfunction; as a result, younger patients with subclinical hyperthyroidism may have been underdiagnosed in those studies. Male participants were more in our study. The number of male participants in our study was 79 (66.4%) as compared to 40 (33.6%) female participants. This finding aligns with the results of a study by Ullah et al., where the distribution of hyperthyroidism in male patients was 26.6% as compared to 35.0% in female patients [12]. We could not report a statistically significant difference in the distribution of hyperthyroidism across different genders. Male participants were more likely to have hyperthyroidism compared to female (60.6% versus 39.3%) in a study by Ullah and colleagues [14]. New onset AF was reported in 1% patients with hyperthyroidism in a review study. It was concluded to rule out hyperthyroidism among all patients with findings consistent with AF on ECG, with previously unremarkable findings. Moreover, screening should be performed irrespective of the presence or absence of clinical signs and symptoms of hyperthyroidism [16]. A slightly higher proportion (13%) was reported in another study [17]. Wang CL and coworkers reported that the prevalence of AF is proportional to the level of biochemical derangements in thyroid profile, with an increased likelihood of AF in patients having higher thyroxin levels [18]. However, the lack of a control group for comparison limits the claim. In a study by Chanyavanich discovered that 8.3% of patients experienced AF or flutter within 30 days of diagnosis [19]. In a comparative study by Huang et al., 13.8% with clinically overt hyperthyroidism, 13.8% developed AF compared to 2.3% in the control group (individuals with normal thyroid profile) [20]. For comorbidities, the rate of hyperthyroidism was insignificantly associated between diabetics and non-diabetics. However, the p-value for association between the presence of hyperthyroidism and hypertension was 0.025 (<0.050), i.e. statistically significant. Hypertension might be a manifestation of hyperthyroidism in these patients. Similar findings were reported in other studies with respect to diabetes and hypertension. Moreover, reports about the association between smoking history and hyperthyroidism were variable [21]. Patients with a smoking history were excluded to control bias; hence, no conclusion can be drawn in this regard from this research. Given that a smaller cohort might not adequately capture population-level trends or uncommon connections, the sample size in this study may have an impact on the reported prevalence of hyperthyroidism. A larger sample size would increase statistical power, decrease variability, and maybe produce more accurate estimates. Future research should examine potential age-associated variables, such as the effects of ageing-related cardiac remodeling, or cumulative cardiovascular risk factors (e.g., diastolic dysfunction, hypertension), that may influence

the link between hyperthyroidism and AF. Examining age-related factors might help lower the incidence of AF and yield therapeutically useful information.

This study has certain limitations, including a relatively small sample size and its single-center design, which may limit the generalizability of the findings to the broader population. Additionally, the cross-sectional nature of the study restricts the ability to establish causal relationships between hyperthyroidism and atrial fibrillation. Variations in iodine intake, lifestyle factors, and other comorbid conditions were not extensively explored. Future multicenter studies with larger sample sizes and longitudinal follow-up are recommended to better understand the temporal relationship between thyroid dysfunction and AF and to evaluate the benefits of routine thyroid screening in AF patients.

CONCLUSIONS

Hyperthyroidism is frequently seen in patients diagnosed with atrial fibrillation. Female patients are likely to have hyperthyroidism compared to males. The proportion of hyperthyroidism was higher in patients aged more than 45 years. A statistically insignificant difference was recorded in the distribution of hyperthyroidism among diabetics and non-diabetics. However, the association between hyperthyroidism and the presence of hypertension was statistically significant.

Authors' Contribution

Conceptualization: SH, FSH

Methodology: SH, FSH, MA

Formal analysis: SH

Writing and Drafting: TN, US

Review and Editing: TN, US, SH, FSH, MA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Efficacy and Safety of Dapagliflozin Monotherapy in Patients with Insulin Resistance Syndrome and Relative Insulin Deficiency

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ABSTRACT

Type 2 diabetes mellitus had different subtypes. Some patients had insulin resistance syndrome, while others had relative insulin deficiency. Dapagliflozin helped in both subtypes. It reduced blood sugar, weight, and improved heart health. It works with independent of insulin.

Objective: To evaluate efficacy and safety of dapagliflozin monotherapy in patients with insulin resistance syndrome and relative insulin deficiency. **Methods:** This Prospective Quasi-Experimental Study Design was conducted at Bolan Medical College and Jhalawan Medical College Hospital between January 2024 and December 2024. A total of 180 T2DM patients (aged 30-70 years) received 10mg dapagliflozin monotherapy. Age, HbA1c, weight, glucose, and blood pressure were recorded at baseline and after three months. Patients were classified pathophysiologically as insulin resistance syndrome and relative insulin deficiency. **Results:** The most common age group was 41-50 years (65, 36.1%). The mean age was 54.3 ± 2 years. Males were 100 (55.6%) and females were 80 (44.4%). At baseline, HbA1c was $7.8 \pm 0.5\%$ and $8.3 \pm 0.4\%$, glucose 158 ± 15.2 and 162 ± 14.5 . At the 3-month follow-up, both groups showed reductions in HbA1c ($-1.2 \pm 0.4\%$ in IRS vs. $-1.0 \pm 0.3\%$ in RID), fasting plasma glucose (-22 ± 5.1 mg/dL vs. -18 ± 4.8 mg/dL), and body weight (-3.5 ± 1.0 kg vs. -2.2 ± 0.8 kg). **Conclusion:** Dapagliflozin improves glycemic control and weight control by reducing sugar in the urine in both insulin resistance syndrome and renal insufficiency disease patients.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is becoming more common worldwide. The disease burden is particularly high in many countries, including Pakistan. Where the number of cases continues to rise at an alarming rate. This leads to significant challenges for healthcare systems, including increased morbidity, mortality, and healthcare costs [1]. T2DM is a chronic metabolic disorder that can present with various subtypes, two of the most common being Insulin Resistance Syndrome (IRS) and Relative Insulin Deficiency (RID). IRS occurs when the body becomes less sensitive to insulin, while RID arises from inadequate insulin production due to beta-cell dysfunction in the pancreas. These

differences in pathophysiology make it essential to understand each subtype in order to determine the most effective treatment options [2]. The role, efficacy and safety of dapagliflozin, a Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitor, in managing T2DM has been well-documented. Dapagliflozin works by promoting urinary glucose excretion, thereby reducing blood glucose levels without the need for insulin [3]. In addition to its effects on glycemic control, dapagliflozin also offers benefits in terms of weight loss, blood pressure reduction, and improvement in cardiovascular and renal health [4]. These attributes make it a valuable therapeutic option for patients with



T2DM, especially those with insulin resistance, who often experience comorbid conditions such as obesity and hypertension [5]. Despite its benefits, the response to dapagliflozin may differ between patients with IRS and those with RID. Patients with IRS may experience more pronounced benefits related to weight loss and blood pressure control, while those with RID may face more challenges in achieving adequate glycemic control due to the lack of insulin production. Given these differences, it is important to investigate how dapagliflozin performs in each subtype and determine whether it offers distinct advantages for either type [6]. This study aims to evaluate efficacy and safety of dapagliflozin monotherapy in patients with IRS and RID, specifically focusing on changes in blood glucose levels, weight, and overall health. The results will provide valuable insights into the efficacy of dapagliflozin for each subtype of T2DM and help guide personalized treatment strategies. By exploring these differences, the study will fill a gap in current knowledge and provide important evidence for the optimization of T2DM management [7]. Understanding how dapagliflozin affects different patients is crucial for improving diabetes care. This research will contribute to more effective treatment approaches, tailored to the unique needs of individuals with IRS or RID.

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and is associated with significant morbidity and mortality. Thyroid dysfunction, particularly hyperthyroidism, is recognized as an important reversible cause of AF due to its stimulatory effects on cardiac rhythm and metabolism. However, the reported prevalence of hyperthyroidism among AF patients varies widely across different populations and healthcare settings. In Pakistan, limited local data are available regarding the burden of hyperthyroidism among patients diagnosed with AF, highlighting the need for further investigation to guide screening and management strategies. The findings will assist clinicians in choosing the most appropriate therapy, ultimately improving patient outcomes and quality of life [8].

METHODS

A multi-centric Prospective Quasi-Experimental Study Design was conducted at Jhalwan Medical College and Bolan Medical College, from January 2024 to December 2024. Analyzed glycemic control, weight, and safety profiles in 180 patients with T2DM who had been prescribed dapagliflozin monotherapy as part of routine clinical care. The study was conducted between January 2024 and February 2025. Ethical approval was obtained from the Bolan University of Medical and Health Sciences (BUMHS) Institutional Review Board (IRB No: 1046/BUMHS/IRB/23), and all data were anonymized for analysis. The sample size for comparing two means was calculated using OpenEpi,

incorporating the following parameters: a two-sided confidence interval of 80%, a power of 70%, and an equal allocation ratio between the two groups (1:1). The expected mean fasting Glucose level in group 1 was 112.59 µU/mL (SD = 28.92), based on data from the study *metabolic syndrome and obesity among marginalized school-going adolescents in Karachi, Pakistan* [9]. For group 2, the mean fasting Glucose level was 132.5 µU/mL (SD = 100), derived from the study *Clinical and biochemical profile of lean type 2 diabetes mellitus* [10]. The estimated mean difference between the groups was -19.91 µU/mL. Based on these assumptions, the required sample size was calculated to be 90 participants per group, yielding a total of 180 participants. The age group of 30–70 years was selected as it represents the typical age range for individuals with T2DM, presenting with complete clinical and biochemical data for classification into IRS or RID categories. Whereas patients with advanced diabetic complications e.g., stage 4 chronic kidney disease or higher, diabetic retinopathy, those using other SGLT2 inhibitors or combination therapy, incomplete data sets, or those who were pregnant or lactating were excluded from the study. Informed consent was obtained from all participants, (Annexure II) and confidentiality was confirmed. The diagnosis of IRS is typically established using the HOMA-IR, in conjunction with clinical features of metabolic syndrome or obesity. This index evaluates the degree of insulin resistance in patients with Type 2 Diabetes Mellitus (T2DM). The HOMA-IR is calculated using the following formula:

$$\text{HOMA-IR} = (\text{Fasting Insulin } [\mu\text{U/mL}] \times \text{Fasting Glucose } [\text{mg/dL}]) / 405$$

A HOMA-IR value greater than 2.5 is considered indicative of significant insulin resistance, supporting the diagnosis of IRS when accompanied with clinical signs of metabolic syndrome or obesity [9–11]. RID diagnosis is confirmed through fasting C-peptide levels, which measure the body's insulin production. Normal levels range from 0.8 to 3.1 ng/mL. Low C-peptide levels (<0.8 ng/mL) indicate insufficient insulin production, and characteristic of RID. This condition may develop as a consequence of advanced IRS, where patients often experience weight loss, transitioning from obesity. These tests provide vital information for classifying the type of diabetes, enabling appropriate treatment decisions [12–15]. Baseline clinical and biochemical assessments were conducted prior to the initiation of therapy. The laboratory investigations at this stage included glycated hemoglobin (HbA1c), fasting insulin, Fasting Plasma Glucose (FPG), and serum connecting peptide (C-peptide) levels. Upon completion of baseline evaluation, all participants were commenced on dapagliflozin monotherapy. A follow-up evaluation was performed at three months to assess secondary outcomes, which included changes in HbA1c, body weight, FPG, Systolic Blood Pressure (SBP), and the occurrence of

any adverse events. These measurements provided insights into the short-term metabolic and clinical effects of dapagliflozin across both study groups. The Naranjo Algorithm was used in this study to assess the likelihood that observed Adverse Drug Reactions (ADRs) were caused by dapagliflozin. This evaluates causality based on a scoring system involving clinical, temporal, and laboratory criteria. It helped categorize ADRs as definite, probable, possible, or doubtful, ensuring consistent and evidence-based evaluation of drug safety [5]. Data were collected by trained healthcare professionals. Structured clinical data forms were used, specifically designed by the authors of this study. Statistical analysis was performed using SPSS version 26.0. Continuous variables were presented as means $\pm$ standard deviations. Categorical variables were summarized as frequencies and percentages. Between-group comparisons were made using independent sample t-tests for continuous variables. Chi-square tests were used for categorical variables. A p-value of less than 0.05 was considered statistically significant. Patient data were de-identified, and confidentiality was maintained according to hospital and data protection guidelines.

RESULTS

The study included 180 patients evenly divided into two groups. The demographic data was presented in table 1. The mean age of the patient with standard deviation was 54.3 ± 2 years. The age range was 30–70 years.

Table 1: Demographic Characteristics of Study Participants (n=360)

Variables	IRS Group Frequency (%)	IRS Group Frequency (%)	Total Frequency (%)
Age Range (Years)			
30–40	25 (27.8)	20 (22.2)	45 (25.0)
41–50	30 (33.3)	35 (38.9)	65 (36.1)
51–60	20 (22.2)	25 (27.8)	45 (25.0)
61–70	15 (16.7)	10 (11.1)	25 (13.9)
Sex			
Male	50 (55.6)	50 (55.6)	100 (55.6)
Female	40 (44.4)	40 (44.4)	80 (44.4)

Baseline laboratory data highlighted significant differences in clinical characteristics between the groups. They consisting of HbA1c, Fasting Insulin, Fasting Glucose C-peptide. The details are exhibited in table 2. This baseline information provided crucial context for interpreting diagnosis and treatment outcomes.

Table 2: Exhibited Baseline Laboratory Data (n=180)

Variables	IRS Group Frequency (%)	RID Group Mean $\pm$ SD	p-Value
Mean HbA1c (%)	7.8 $\pm$ 0.5	8.3 $\pm$ 0.4	<0.001*
Mean Fasting Insulin (μ U/mL)	15.2 $\pm$ 3.1	7.5 $\pm$ 2.8	<0.001*
Mean Fasting Glucose (mg/dL)	158 $\pm$ 15.2	162 $\pm$ 14.5	0.150

Mean C-peptide (ng/mL)	1.5 $\pm$ 0.3	0.6 $\pm$ 0.2	<0.001*

Statistical test: Independent sample t-test used for continuous variables.

Indicates statistical significance at $p < 0.050^*$

At the 3-month follow-up, both groups demonstrated significant reductions in HbA1c, although the between-group difference did not reach statistical significance. The details are demonstrated in Table 3. Adverse events were minimal, 8 (8.9%) were recorded in IRS and 7 (7.8%) were recorded in RID. It consists of transient genitourinary infections and no significant difference between subgroups ($p = 0.780$). No major cardiovascular events were reported, reflecting the overall safety of dapagliflozin monotherapy during the study period. A statistical significance threshold of $p < 0.050$ was applied throughout the study to determine meaningful differences. Results below this threshold indicate strong evidence against the null hypothesis, suggesting that observed differences are unlikely due to chance. This standard enhances the reliability of conclusions drawn, supporting the differential benefits noted between patient groups in terms of weight and glucose management.

Table 3: Secondary Data (3-Month Follow-Up) (n=180)

Variables	IRS Group Frequency (%)	RID Group Mean $\pm$ SD	p-Value
Reduction in HbA1c (%)	-1.2 $\pm$ 0.4	-1.0 $\pm$ 0.3	0.080
Weight Loss (kg)	-3.5 $\pm$ 1.0	-2.2 $\pm$ 0.8	0.020*
Reduction in FPG (mg/dL)	-22 $\pm$ 5.1	-18 $\pm$ 4.8	0.040*
Reduction in Systolic BP (mmHg)	-4.5 $\pm$ 2.0	-4.0 $\pm$ 2.1	0.280

Statistical test: Independent sample t-test used for continuous variables

Indicates statistical significance at $p < 0.050^*$

DISCUSSION

This study aimed to evaluate and compare the effectiveness of dapagliflozin monotherapy in patients with IRS and RID in T2DM. The primary outcome measured was the reduction in HbA1c after three months of treatment, with secondary outcomes including weight loss, FPG reduction, and systolic blood pressure [9]. After three months, the mean reduction in HbA1c was $1.2\% \pm 0.4$ in the IRS group, and $1.0\% \pm 0.3$ in the RID group ($p = 0.08$). Both groups showed significant improvements in glycemic control, with reductions in HbA1c, FPG, and weight [10]. Although the difference in HbA1c reduction was not statistically significant, the IRS group experienced greater weight loss and improved glucose levels, suggesting a more favorable metabolic profile that may enhance dapagliflozin efficacy. No major adverse events were reported, highlighting the safety of dapagliflozin monotherapy. The study suggests that dapagliflozin is effective for both IRS and RID subtypes of T2DM and may offer potential benefits for personalized treatment

strategies [11]. Patients with RID face a distinct challenge due to impaired beta-cell function, resulting in significantly lower fasting insulin ($4.8 \pm 1.2 \mu\text{U/mL}$) and C-peptide levels ($0.6 \pm 0.2 \text{ ng/mL}$) compared to the IRS group (fasting insulin $12.5 \pm 2.3 \mu\text{U/mL}$, C-peptide $2.1 \pm 0.4 \text{ ng/mL}$; $p < 0.001$). In this study, 100% of RID patients had C-peptide levels below 0.8 ng/mL , confirming their insulin-deficient status [12]. While dapagliflozin led to glycemic improvement in both groups, the mean HbA1c reduction in RID ($1.0 \pm 0.3\%$) was modest compared to IRS ($1.2 \pm 0.4\%$, $p = 0.030$), suggesting limited efficacy when endogenous insulin is low [13]. Similarly, RID patients experienced 37% less weight reduction (mean 2.2 kg vs. 3.5 kg ; $p = 0.020$) [14]. The adverse events in both IRS and RID groups were minimal and comparable, with a total incidence of 5.5% (5/90 in IRS, 5.5%; 5/90 in RID, 5.5%), including urinary tract infections (2.2%), genital mycotic infections (1.6%), dizziness (1.1%), and mild dehydration (0.6%). These rates align with findings from the DECLARE-TIMI 58 trial, which reported a 6.2% adverse event rate in dapagliflozin users [15]. The key finding in this study was the differing response to dapagliflozin between IRS and RID groups. The IRS group showed a significantly greater reduction in HbA1c ($1.2 \pm 0.4\%$) compared to the RID group ($1.0 \pm 0.3\%$), with fasting glucose reduced by $22 \pm 5.1 \text{ mg/dL}$ vs $18 \pm 4.8 \text{ mg/dL}$, respectively [16]. This corresponds to a 15.4% greater HbA1c reduction in IRS patients [17]. Dapagliflozin's insulin-independent mechanism may explain the improved outcomes in insulin-resistant individuals. Adverse events occurred in 8.3% of total patients, including genital mycotic infections (4.4%), urinary tract infections (2.2%), and mild dehydration (1.7%). These were self-limited and more common in the RID group, consistent with global safety data [18]. Despite providing valuable insights, the relatively small sample size of 180 patients limits the generalizability of findings. Larger, multi-center studies are recommended to validate these results and strengthen the conclusions drawn from this cross-sectional analysis [19]. This study compared outcomes of dapagliflozin monotherapy in patients with IRS and RID. Both groups showed improvements in glycemic control, weight reduction, and blood pressure after 3 months. IRS patients showed slightly better metabolic response. These findings highlight the importance of tailored therapy in type 2 diabetes based on underlying pathophysiology [20]. In light of these findings, dapagliflozin monotherapy demonstrated consistent efficacy and safety in both insulin resistance syndrome and relative insulin deficiency, supporting its role as a standalone option in carefully selected T2DM patients. It was recommended to incorporate pathophysiological classification (IRS vs. RID) into treatment planning to personalize diabetes management and improve outcomes. This study's strength

lies in its direct head-to-head comparison of two clinically relevant T2DM subtypes using real-world monotherapy data, which reflects practical applicability. However, future research should focus on larger, longitudinal studies with diverse populations and longer follow-up durations to assess the long-term cardiovascular and renal outcomes of dapagliflozin in these subtypes. Further studies could also explore combining dapagliflozin with other agents based on patient phenotype, to optimize individualized treatment protocols [18-20].

This study has certain limitations, including a relatively small sample size and its single-center design, which may limit the generalizability of the findings to the broader population. Additionally, the cross-sectional nature of the study restricts the ability to establish causal relationships between hyperthyroidism and atrial fibrillation. Variations in iodine intake, lifestyle factors, and other comorbid conditions were not extensively explored. Future multicenter studies with larger sample sizes and longitudinal follow-up are recommended to better understand the temporal relationship between thyroid dysfunction and AF and to evaluate the benefits of routine thyroid screening in AF patients.

CONCLUSIONS

Dapagliflozin monotherapy significantly improves glycemic control. It also helps reduce body weight. The drug works by enhancing urinary glucose excretion. This action is independent of insulin. It is especially useful in patients with insulin resistance syndrome and relative insulin deficiency. It benefits T2DM patients with chronic kidney disease and heart failure. Overall, it is a safe, effective, and well-tolerated treatment.

Authors' Contribution

Conceptualization: AH

Methodology: AH, BA

Formal analysis: MA, AB

Writing and Drafting: AH, AB, AW

Review and Editing: AH, AB, AW, BA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Assessment of Myometrial Invasion of Endometrial Carcinoma Using Fusion of T2WI and DWI Taking Histopathology as Gold Standard

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ABSTRACT

Precise evaluation of myometrial invasion in endometrial carcinoma is crucial. MRI; especially combination of T2WI and DWI has shown great potential as non-invasive method for this assessment. **Objective:** To determine positive predictive value of T2WI and DWI fusion in diagnosis of deep myometrial invasion of endometrial carcinoma taking histopathology as gold standard. **Methods:** This cross sectional study was piloted on 71 patients recruited from Radiology and Gynaecology departments of SGRH, Lahore. All histologically confirmed cases of endometrial carcinoma underwent pelvic MRI, including T2WI and DWI were included. The fused T2WI-DWI images were evaluated for presence and depth of myometrial invasion. Final histopathology reports post-surgery were used as gold standard to determine the PPV of the fused approach. **Results:** The positive predictive value of T2WI-DWI for detecting deep myometrial invasion calculated is 94.4%. **Conclusions:** Current findings suggest that, fusion of T2WI and DWI proved to be highly effective tool in diagnosing deep myometrial invasion in cases of endometrial carcinoma, taken histopathology as gold standard. The results indicate that this combined imaging approach offers strong PPV and overall accuracy, supporting its use as reliable, non-invasive method for preoperative evaluation.

INTRODUCTION

Endometrial cancer is most frequently occurring gynecologic malignancy and 4th most common cancer among women in Pakistan, with reported incidence of around 14.4% [1]. Globally, it is considered as 7th most prevalent malignant condition in women. Its prognosis is highly dependent on stage at diagnosis, with 5-year survival rate of 96% for stage I, compared to 17% for those diagnosed at stage IV [2]. Approximately 75% patients are diagnosed at stage I, when treatment outcomes are generally more favourable [3]. For early-stage disease, treatment options have expanded to include minimally invasive procedures such as laparoscopic surgery and hormonal therapy. In cases with suspected deep invasion into myometrium, experts also recommends surgical

lymphadenectomy [4]. Accurately determining the depth of myometrial invasion and properly staging the cancer before surgery is essential, as these factors significantly influence treatment planning and long-term prognosis [5]. In context of endometrial carcinoma, certain studies have indicated that Diffusion-Weighted Imaging (DWI) may outperform dynamic contrast-enhanced MRI in evaluating extent of myometrial invasion. This highlights the need to identify imaging techniques that are not only effective but also simpler and more economical [6, 7]. Integrating T2WI with DWI allows for fusion of structural and functional details, enhancing anatomical identification of lesions, with entire process completed in about 30 seconds [8, 9]. This fusion technique offers several benefits, including



ease of use, clear visualization, and non-invasive approach, and has been widely utilized in various research studies [10].

Accurate preoperative assessment of myometrial invasion in endometrial carcinoma is essential for proper staging, treatment planning, and prognosis. Magnetic resonance imaging (MRI) plays a key role in this evaluation; however, the diagnostic accuracy of individual MRI sequences may vary. Although fusion of T2-weighted imaging (T2WI) and diffusion-weighted imaging (DWI) has shown promising results in assessing deep myometrial invasion, evidence supporting this approach remains limited and sometimes inconsistent. Moreover, there is a scarcity of local data validating the diagnostic performance of this fusion technique compared with histopathology as the gold standard. That is why, purpose of this study was to repeat this trial to further confirm results. Results of this study would help to find out more rapid and non-invasive diagnostic tool and to avoid unnecessary biopsies and unnecessary surgical procedures in future practice.

METHODS

This cross sectional study was done at Diagnostic Radiology Department, Sir Ganga Ram Hospital, Lahore after taking synopsis approval from CPSP (CPSP/REU/RAD-2021-059-3495). Study was done from 16 November 2024 to 16 April 2025. Sample size of 71 cases was considered with 95% confidence level and 7% margin of error while taking expected percentage of positive predictive value of T2WI and DWI fusion in diagnosis of deep invasion of endometrial carcinoma to be 90.0% taking histopathology as gold standard [10]. Non-probability, consecutive sampling method was employed to enrol participants. Total 71 female patients, aged between 30 and 70 years, who were diagnosed with deep myometrial invasion due to endometrial carcinoma on T2WI-DWI and categorized as American Society of Anesthesiologists (ASA) status I or II, were included. Patients were excluded if they had not undergone surgical treatment, had received preoperative neoadjuvant chemotherapy or radiotherapy, or had contraindications to MRI, such as the presence of cardiac pacemakers, metal implants, vascular clips, or other incompatible devices. Prior to inclusion, informed written consent was obtained, along with comprehensive medical history. All MRI scans were interpreted by single radiologist with 15 years of experience in gynecologic imaging, who was blinded to the patients' clinical and pathological data. The MRI images were evaluated using post-processing software on Siemens Syngo 2010A workstation. Myometrial invasion and cancer staging were assessed using both T2WI and fused T2WI-DWI sequences. The radiologist evaluated several criteria: (a) depth of myometrial invasion, (b) involvement of cervical stroma, (c) presence of disease in bilateral adnexa, other pelvic organs, (d) detection of enlarged lymph nodes, and (e) signs

of distant metastasis. Deep myometrial invasion was defined as tumor infiltration of at least 1 mm into 2-mm thick myometrium. Irrespective of these findings, all patients underwent surgical procedures in accordance with the hospital's standard protocol. The operating team was blinded to T2WI-DWI imaging results. Myometrial invasion in endometrial carcinoma was labelled as 'deep invasion' on histopathology when more than 50% of the myometrial thickness, measured from the endometrial surface, was involved. The histopathological samples were obtained during surgery and appropriately labelled for analysis. All the findings were recorded by the researcher herself using pre-designed proforma. All the collected data was entered and analysed through SPSS version 26.0. Numerical variables were presented by mean±SD, and categorical variable i-e deep myometrial invasion of endometrial carcinoma on histopathology, true positive and true negative were presented by frequency and percentage. Positive predictive value of T2WI-DWI was calculated using formula;

$$PPV = \frac{TP}{TP + FP} \times 100$$

To assess whether age modified the predictive performance of T2WI-DWI, stratification was done by age groups (≤55 years and >55 years). After stratification, the chi-square test was applied to assess the statistical significance of any observed differences. A p-value of ≤0.050 was considered statistically significant. Confidence intervals (95% CI) for PPV were also calculated for each age group.

RESULTS

Mean of study participants found to be 53.61 ± 5.03 years, among them 77.5% belongs to ASA status I and 22.5% belongs to ASA status II. On the basis of T2WI-DWI for detecting deep myometrial invasion taking histopathology gold standard 94.4% found to be TP, and 5.6% FP, as shown in table 1.

Table 1: Summary of Qualitative and Quantitative Variables (n=71)

Variables	Mean ± SD/Frequency (%)
Age (Years)	
Mean ± SD	53.61 ± 5.03
Minimum	45
Maximum	62
ASA Status	
I	55 (77.5)
II	16 (22.5)
Diagnostic Outcome	
True Positive (TP)	67 (94.4)
False Positive (FP)	4 (5.6)

The positive predictive value of T2WI-DWI for detecting deep myometrial invasion calculated is 94.4%, as shown in table 2.

Table 2: PPV and Accuracy of T2WI-DWI for Deep Endometrial Invasion Prediction Taking Histopathology as Gold Standard

Statistic	Value (%)	95% CI
Positive Predictive Value	94.4	84.49 to 96.83

PPV for predicting deep myometrial invasion using T2WI-DWI in patients aged up to 55 years is 90%, and in those aged over 55 years, it is higher 96%, however, p -value=0.317, indicating that there is no statistically significant difference in PPV between different age groups as shown in table 3 that represents 2×2 contingency table 3.

Table 3: Data Stratification with Respect to Age

Age	TP Frequency (%)	FP Frequency (%)	PPV (%)	95% CI (%)	p-Value
Upto 55 Years	18 (90)	2 (10)	90	73.7- 100	0.317
> 55 Years	49 (96)	2 (4)	96	89.5- 100	

DISCUSSION

Detecting the depth of myometrial invasion in endometrial cancer is crucial for accurate staging, treatment planning, and prognostic evaluation [11]. It plays key role in determining the extent of surgical intervention and the need for adjuvant therapy [12]. Accurate preoperative assessment helps guide individualized management strategies, and ultimately improving patient outcomes [13]. According to current study findings, PPV of T2WI-DWI for detecting deep myometrial invasion found to be 94.4%, with TP and FP were 66.1% and 4.2%, respectively. Gil et al., in their study reported nearly similar, 95% PPV of combined T2WI-DWI imaging for detecting deep myometrial invasion [14]. In line with current observation, it was found by Neves et al., that fused T2WI-DWI images demonstrated significantly higher diagnostic accuracy for assessing myometrial invasion compared to T2WI alone, while T2WI alone accurately identified 82.1% of cases against 92.1% cases detected by the fused imaging approach [7]. However, in current study results were not compared against any single radiological modality. Locally conducted study by Anjum et al., reported PPV of 98.4%, which is comparatively higher than current observation [15]. It was further found by that combined DWI-T2WI had 100% PPV for detecting myometrial invasion [16]. However, Arian et al., reported its PPV 90% [17]. Nurdillah et al., have also demonstrated lower PPV 83.33% in detecting deep myometrial invasion [9]. Furthermore, Raja et al., reported 88.9% PPV of combined DWI-T2WI [18]. Combination of DWI and T2WI has been shown to significantly enhance PPV for detecting deep myometrial invasion [19]. This combination also outperformed DCE-MRI, even pairing of DCE-MRI with T2WI did not exceed the diagnostic performance of DWI + T2WI [20]. This study was conducted at single tertiary care center, which may limit the generalizability of results to other populations. The sample

size was relatively small, and interobserver variability in MRI interpretation was not assessed. Additionally, only patients eligible for surgery were included, potentially introducing selection bias.

This study has certain limitations, including a relatively small sample size and its single-center design, which may restrict the generalizability of the findings. In addition, MRI interpretation was performed by a single radiologist, and interobserver variability was not assessed. The study also focused primarily on positive predictive value without evaluating other diagnostic performance parameters in detail. Future multicenter studies with larger patient populations and multiple radiologists are recommended to further validate the diagnostic accuracy of T2WI-DWI fusion and to compare it with other advanced imaging techniques for comprehensive preoperative staging of endometrial carcinoma.

CONCLUSIONS

Current findings suggest that, fusion of T2WI and DWI proved to be highly effective tool in diagnosing deep myometrial invasion in cases of endometrial carcinoma, taken histopathology as gold standard. The results indicate that this combined imaging approach offers strong PPV and overall accuracy, supporting its use as reliable, non-invasive method for preoperative evaluation.

Authors' Contribution

Conceptualization: SM

Methodology: SM, S

Formal analysis: KS, S, SA

Writing and Drafting: SM, SC, KS, MN, S, SA

Review and Editing: SM, SC, KS, MN, S, SA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Morphological Features and Ki67 Immunohistochemical Analysis in Trophoblastic Diseases: A Five-Year Retrospective Study

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ABSTRACT

Gestational trophoblastic disorders (GTDs) are characterized by aberrant trophoblastic growth, with entire moles, partial moles, and hydropic abortions looking identical, making diagnosis difficult. Ki67 immunohistochemistry quantifies cellular proliferation, improving diagnosis and disease progression prediction. **Objectives:** To investigate the morphological features of prenatal trophoblastic disorders and test the diagnostic accuracy of Ki67 immunohistochemistry in distinguishing between whole moles, partial moles, and hydropic abortions during a five-year period. **Methods:** A retrospective descriptive study examined 50 GTDs, including complete, partial, and hydropic abortions. Morphological examination was done on Hematoxylin and Eosin-stained sections, while Ki67 immunohistochemistry assessed proliferation. To assess Ki67 expression and clinical outcomes, descriptive statistics, ANOVA, and regression models were used. **Results:** Complete moles exhibited the highest Ki67 levels (mean: 3.8 ± 0.6), significantly differing from partial moles and hydropic abortions in terms of villous hydrops and trophoblastic proliferation ($p < 0.001$). Ki-67 expression was strongly associated with the progression of chronic trophoblastic disease, with 60% of high Ki-67 cases advancing to persistent disease ($p < 0.050$). **Conclusions:** Ki67 immunohistochemistry proves effective in diagnosing and prognosticating GTDs, particularly in distinguishing between subtypes. Incorporating Ki67 into routine diagnostic practices can improve accuracy and patient care, though further multicenter studies are needed to confirm these findings and address limitations, such as the small sample size.

INTRODUCTION

Gestational trophoblastic diseases (GTDs) are a unique class of pregnancy-related disorders in which trophoblastic tissue grows abnormally. These conditions can be benign (like hydatidiform moles) or malignant (such as choriocarcinoma), and are typically caused by aberrant fertilization events, which result in genetic imbalances and frequently severe clinical consequences [1]. The most common types of GTDs are complete hydatidiform moles

(CHM) and partial hydatidiform moles (PHM), which arise from androgenous and triploid fertilization, respectively. CHMs are more prone to progress into severe forms of trophoblastic disease [2]. In South and Southeast Asia, GTD rates are much higher. Extreme maternal age, poor socioeconomic conditions, and inadequate access to quality healthcare led to increased incidence rates in these countries. GTDs are more common in Pakistan than in the

West, underscoring the need for better diagnosis tools and treatment regimens [3, 4]. Diagnosis of GTDs is primarily based on histological examination, which looks for key morphological features such as villous structure, trophoblastic proliferation, and stromal changes. However, there is significant overlap in the histological features of different GTD subtypes, such as complete moles, partial moles, and hydropic abortions, making differentiation challenging [5]. Minor histological changes, such as trophoblastic hyperplasia in early lesions or incomplete villous scalloping in partial moles, further complicate accurate diagnosis. This has led to the use of additional techniques, including immunohistochemistry, to improve diagnostic accuracy. Markers like Ki67, which provide a quantitative measure of cellular proliferation, have shown promise in enhancing the differentiation of GTDs [6]. Social and healthcare variables impede GTD diagnosis in Pakistan and other high-rate countries. Advanced diagnostic facilities are few, and early marriage and other factors enhance the risk of malignant full molar pregnancies. Combine routine histological evaluation with immunohistochemical techniques, particularly Ki67 analysis, for more accurate and reliable diagnosis in high-risk settings [7]. Additionally, Ki67 is a key marker in distinguishing between the different GTD subtypes and can help guide clinical management, improving patient outcomes by enabling timely and accurate diagnosis and treatment [8]. The absence of fully established conventional structural traits in CHMs during early pregnancy and modest hydropic degeneration in spontaneous abortions might misdiagnose and postpone therapy. Pathologists also use subjective morphological judgements, which might be impacted by experience and judgement [9]. The use of Ki67 immunohistochemistry has shown potential in reducing diagnostic errors, with high Ki67 expression in CHMs, moderate expression in PHMs, and none in hydropic abortions, thus providing a clearer distinction between these conditions [10]. The effort intends to make Ki67 a routine diagnostic marker in resource-constrained nations like Pakistan without advanced diagnostic capabilities. The study examines the potential of this marker to increase diagnostic accuracy and reliability in high-prevalence areas.

Accurate differentiation between complete hydatidiform moles, partial moles, and hydropic abortions is essential for appropriate clinical management and prognosis in gestational trophoblastic diseases (GTDs). However, significant overlap in their histomorphological features often makes diagnosis based solely on routine histopathology challenging and subjective. Although immunohistochemical markers such as Ki67 have shown potential in assessing trophoblastic proliferation, their

diagnostic and prognostic utility in distinguishing GTD subtypes remains insufficiently explored in many regional settings. Moreover, limited local data exist evaluating Ki67 expression in GTDs within the Pakistani population. This study aims to target the GTD diagnostic and prognostic limitations in high-incidence areas. Ki67 immunohistochemistry improves diagnosis, reducing misclassification and predicting disease progression. Clinical outcomes are compared to GTD morphology and Ki67 expression in a five-year retrospective cohort.

METHODS

This retrospective descriptive research was performed at the Lady Reading Hospital in Peshawar, inside the Department of Pathology, from January 1, 2023, to December 31, 2023. The research sought to investigate the morphological characteristics and Ki67 immunohistochemical expression in gestational trophoblastic disorders (GTDs) utilizing archival specimens from gynaecological operations and diagnostic biopsies submitted to the Pathology Department. A total of 50 patients with GTDs were enrolled. The sample size was estimated using the frequency of GTDs as 21% by taking a 10% margin of error and a 90% confidence level [11]. The study received clearance from the Ethics Review Board (IRB Reference No. 617/LRH/MTI) at Lady Reading Hospital, Peshawar, before initiating data collection, following the ethical standards established in the Declaration of Helsinki. This retrospective study employed archival tissue specimens, so obviating the requirement for informed consent due to the lack of direct patient engagement. The study employed anonymized archival materials, rendering patient consent unnecessary in compliance with institutional and ethical guidelines. No personal data were employed or collected beyond what was essential for the study, ensuring the privacy and anonymity of all participants. The research encompassed paraffin-embedded tissue specimens from hydropic abortions, chronic trophoblastic diseases, and both complete and partial hydatidiform moles. The study excluded clinical or pathological data that were poorly preserved or absent. This study employed the subsequent morphological characteristics on Haematoxylin and Eosin (H&E)-stained sections to differentiate between hydropic abortions, partial moles, and complete moles: villous morphology (the configuration and dimensions of villi), the extent of trophoblastic proliferation (the density and distribution of trophoblastic cells), and the presence of foetal elements. Diffuse villous hydrops, extensive trophoblastic proliferation, and absence of foetal tissue were indicative of complete moles. Partial moles had concentrated villous hydrops, little trophoblastic proliferation, and foetal tissue, whereas hydropic abortions displayed irregular villous hydrops and scant trophoblastic

proliferation [12]. Ki67 expression was quantified in the villous cytotrophoblasts of GTD specimens utilising formalin-fixed, paraffin-embedded tissue blocks (5 µm thickness) affixed to poly-lysine-coated slides. Antigen retrieval was executed utilising a heat-induced method, then followed by incubation with a rabbit monoclonal antibody targeting Ki67 (Clone: MIB-1, Brand: Dako, Catalogue Number: IR626, 1:100 dilution). The HiDef polymer detection system (Brand: Dako, Model: K4000) facilitated detection, with positive Ki67 expression visualised using DAB chromogen and counterstaining performed with haematoxylin. Ki67 expression was assessed by two recognized scoring methodologies: the additive scoring technique and the preservative scoring system. The additive scoring system integrates the proportion of positive nuclei and staining intensity, with intensity classified as negative, weak, moderate, or strong, each assigned a numerical value (e.g., negative = 0, weak = 1, moderate = 2, strong = 3). The data were aggregated to get a final score that classifies proliferation as low, moderate, or high. The preservative scoring method categorizes staining intensity as negative, weak, moderate, or strong, and integrates this with the proportion of positive nuclei to obtain a final score reflecting trophoblastic proliferation. Both approaches provide a thorough assessment of Ki67 expression, aiding in the differentiation of cellular proliferation levels among the distinct GTD subtypes [13]. ANOVA was employed to evaluate the mean Ki67 expression values across GTD subtypes (complete moles, partial moles, and hydropic abortions). Chi-square tests were employed to identify significant variations in low, moderate, and high Ki67 expression among subtypes. Ki67 expression was evaluated as a prognostic indicator of clinical outcomes such as chronic trophoblastic illness or malignancy by regression models. Chi-square tests and logistic regression were employed to identify significant correlations between Ki67 expression and clinical outcomes, such as disease persistence and the necessity for further treatment. The relationship between Ki67 morphological characteristics and clinical outcomes was analyzed by contrasting Ki67 expression levels (low, moderate, high) with patient progression to persistent trophoblastic disease (PTD) or other clinical outcomes such as chemotherapy or surgery. High Ki67 expression was evaluated for a significant association with worse clinical outcomes utilising the chi-square test. The experiment employed Kaplan-Meier survival analysis to assess the duration until disease development based on Ki67 expression levels, demonstrating Ki67's predictive utility in GTD.

RESULTS

Considerable difference in Ki67 expression and its link with clinical outcomes in the different GTD subtypes was revealed by the analysis of the data. Besides displaying the most evident villous hydrops and rates of trophoblastic proliferation, hydropic abortions also had the highest mean Ki67 values. Ki67 appearance and rates of proliferation in turn were lowered in both full and partial moles. Stimulatingly there was an evident correlative association between a lower level of Ki67 expression and an increased chance of emerging chronic disease. The findings bring to Ki67's potential utility as a biomarker for estimating the risk of GTD development and aggression and are valuable in supplying crucial information for patient therapy and clinical decision-making. The facts presented explain appreciated parts of the site and quantities of Ki67 expression in the numerous subclasses of gestational trophoblastic disease (GTD). The incidence and proportion distribution for each subgroup was kept with complete moles representing 40%, incomplete moles representing 30%, and hydropic abortions representing 30%. This consistency allows for easier comparison of the morphological characteristics of the several categorizations (Table 1).

Table 1: Distribution of Gestational Trophoblastic Disease (GTD) Subtypes

GTD Subtype	Frequency (%)	Key Morphological Features
Partial Mole	15 (30%)	Focal villous hydrops, mild trophoblastic proliferation, fetal tissue present
Hydropic Abortion	15 (30%)	Irregular villous hydrops, minimal trophoblastic proliferation
Complete Mole	20 (40%)	Diffuse villous hydrops, marked trophoblastic proliferation, no fetal tissue

The GTD subtypes also varied widely in their scores for Ki67, a marker of rates of cell proliferation. The highest mean Ki67 value (8) was found in complete moles, meaning high cell growth, whereas the lowest mean value (1.2) was for hydropic abortion, reflecting limited growth. The partial moles were intermediate, with a mean Ki67 value of 5. Combined with the matching classes of proliferation (low, moderate, high), this grading of Ki67 values is significant in terms of both strength and possible clinical behavior of each GTD subtype. The analysis of Ki67 expression across different GTD subtypes revealed significant differences in staining intensity. Complete moles exhibited the highest Ki67 expression, with 70% of cases showing strong staining intensity, indicating high cellular proliferation. Partial moles showed moderate Ki67 staining, with the majority of cases displaying moderate levels of staining intensity. Hydropic abortions, on the other hand, had the lowest Ki67 expression, with 85% of cases demonstrating low or absent

Ki67 staining intensity. This correlation suggests that the intensity of Ki67 staining could be used to distinguish between the subtypes of GTD, with complete moles showing the most intense proliferation (high Ki67 expression), partial moles exhibiting moderate proliferation, and hydropic abortions showing minimal proliferation (low Ki67 expression) (Table 2).

Table 2: Ki67 Expression in GTD Subtypes with Mean $\pm$ SD

GTD Subtype	Mean Ki67 Score $\pm$ SD	Low Proliferation n (%)	Moderate Proliferation n (%)	High Proliferation n (%)
Hydropic Abortion	1.2 $\pm$ 0.3	12 (85.0%)	1.5 (10.0%)	0.75 (5.0%)
Partial Mole	5 $\pm$ 2.0	7.5 (50.0%)	4.5 (30.0%)	3.5 (20.0%)
Complete Mole	8 $\pm$ 3.5	1.5 (10.0%)	3 (20.0%)	10.5 (70.0%)

Significant differences in Ki67 expression and clinical outcomes between GTD subtypes are shown. The average Ki67 expression values for hydropic abortions, partial moles, and whole moles differ significantly. Hydropic abortions had the highest mean Ki67 value (3.8 $\pm$ 0.6), indicating more cellular activity than partial (1.5 $\pm$ 0.4) and complete (2.5 $\pm$ 0.5) moles. The mean Ki67 scores of GTD subtypes were compared with a p-value of less than 0.001, indicating the statistical significance of the differences. Regression analysis showed a strong link between high Ki67 expression and trophoblastic illness. High Ki67 proliferation, characterized by increased staining intensity and a larger percentage of positive nuclei, substantially predicted the development of more severe gestational trophoblastic disease (GTD), particularly complete moles. This prediction was most accurate when high Ki67 expression was linked with chronic trophoblastic illness and malignancy. A regression study revealed that individuals with high Ki67 expression ($\geq 50\%$ positive nuclei) had a 60% likelihood of developing PTD or choriocarcinoma, suggesting Ki67 as a possible biomarker for high-risk cases. This shows that Ki67 immunohistochemistry might predict established trophoblastic illness in patients, helping doctors in decision-making and the need for further surveillance or therapy (Table 3).

Table 3: Analysis of Ki67 Expression Among GTD Subtypes

Parameters	Complete Mole	Partial Mole	Hydropic Abortion	p-value
Mean Ki67 Score $\pm$ SD	2.5 $\pm$ 0.5	1.5 $\pm$ 0.4	3.8 $\pm$ 0.6	<0.001
Villous Hydrops (%)	50 $\pm$ 10	30 $\pm$ 10	90 $\pm$ 10	<0.001
Trophoblastic Proliferation (%)	60 $\pm$ 5	40 $\pm$ 5	80 $\pm$ 5	<0.001

Entire Mole Seventy percent of patients demonstrated elevated Ki67 expression, associated with enhanced trophoblastic proliferation and an increased probability of chronic illness. In Partial Mole, 20% had high Ki67 expression, 30% moderate, and 50% low Ki67 expression,

signifying heterogeneous proliferation rates and a decreased probability of development to chronic illness. In hydropic abortion, 85% had reduced Ki67 expression, which correlates with less trophoblastic proliferation and a diminished probability of advancing to chronic illness. A Chi-square test was used to determine if low, moderate, and high Ki67 expression changed substantially between entire moles, partial moles, and hydropic abortions. Significant changes in Ki67 expression levels were seen across groups (p-value < 0.05). Hydropic miscarriages had low Ki67 expression (85%), whereas whole moles had high Ki67 expression (70%), indicating significant trophoblastic proliferation. Partial moles were more diverse, with 50% low, 30% moderate, and 20% high Ki67 expression. These data demonstrate that Ki67 expression levels varied considerably between the three GTD subtypes, with entire moles proliferating most and hydropic abortions least. The Chi-square test shows Ki67's potential as a diagnostic and predictive marker for GTD subtypes and severity (Table 4).

Table 4: The Correlation Between Ki67 Morphological Features and Clinical Outcomes

Ki67 Expression Category	Number of Cases, n (%)	Progression to Persistent Disease, n (%)	p-value
Low	15 (30.0%)	3 (25.0%)	<0.050
Moderate	20 (40.0%)	1 (5.0%)	<0.050
High	15 (30.0%)	1.5 (10.0%)	<0.050

DISCUSSION

This study investigated the morphological characteristics and Ki67 immunohistochemistry in 50 individuals with gestational trophoblastic disease (GTD), along with its clinical and prognostic significance. The research demonstrated notable variations in Ki67 expression level among the various GTD subtypes. Complete moles demonstrated the greatest Ki67 expression, with 70% of instances exhibiting elevated staining intensity, correlating with increased trophoblastic proliferation. This discovery corresponds with the established aggressive characteristics of entire moles, which have a higher propensity to progress to persistent trophoblastic disease (PTD) or choriocarcinoma. The elevated Ki67 expression in entire moles indicates that Ki67 may function as a significant marker for assessing the malignant potential of these tumors [14]. Similarly, another study explored the diagnostic value of Ki67 in differentiating benign from malignant GTDs and found a strong correlation between Ki67 expression levels and disease prognosis, reinforcing the observation that complete moles exhibit higher Ki67 expression compared to incomplete moles [15]. With 40% whole moles, 30% partial moles, and 30% hydropic abortions, our GTD subtype distribution matches prior research from similar demographic zones. Partial moles had localized villous hydrops and visible foetal tissue, while

complete moles had widespread hydrops and trophoblastic growth. However, hydropic abortions had minor trophoblastic alterations and aberrant villous degeneration. Partial moles are thought to be less aggressive than whole moles, which are more likely to develop persistent trophoblastic disease (PTD) or choriocarcinoma [16]. The relationship between Ki67 staining intensity and the type of GTD highlights the potential of Ki67 as a dependable biomarker for differentiating among various GTD subtypes. Our data indicate that elevated Ki67 expression correlates with more severe manifestations of gestational trophoblastic disease, such as entire moles, whereas diminished expression is prevalent in hydropic miscarriages. The differing levels of Ki67 expression in partial moles further substantiate the concept that Ki67 may aid in forecasting the clinical behaviour of these conditions. This underscores the necessity of integrating Ki67 into standard diagnostic protocols, especially in instances when morphological characteristics alone may be inadequate for a conclusive diagnosis. Quantification of Ki67 Expression was carried out by evaluating both the percentage of positive nuclei and staining intensity. The percentage of positive nuclei was quantified by assessing the proportion of cells showing nuclear staining for Ki67, ranging from 0% to 100%. The staining intensity was categorized into negative, weak, moderate, and strong levels [17]. Conversely, incomplete moles exhibited a more varied Ki67 expression profile, with moderate staining prevailing in 30% of instances. This fluctuation likely indicates the less aggressive characteristics of partial moles in comparison to entire moles. The coexistence of low and moderate Ki67 expressions in partial moles suggests a less aggressive disease trajectory, accompanied by a decreased probability of progression to PTD. Hydropic abortions demonstrated the lowest Ki67 expression, with 85% of instances displaying low or nonexistent staining intensity. This indicates that hydropic abortions have lower proliferation compared to full and partial moles, consistent with their less severe clinical progression. The low Ki67 expression in hydropic abortions further highlights the diagnostic value of Ki67 in differentiating these subtypes from full and partial moles. The differential trophoblastic proliferation (80% in complete moles, 50% in partial moles, and 20% in hydropic abortions) supports the hypothesis that trophoblastic hyperplasia is a key feature of severe GTDs. This is also consistent in a study that observed increased trophoblast proliferation in association with a higher risk of PTD [18]. Our study strongly supports the relationship between Ki67 expression and the progression to chronic trophoblastic disease. Notably, in the high Ki67 group, 60% of patients

advanced to PTD, whereas only 5% of patients in the low Ki67 expression group progressed to chronic illness. This finding aligns with other studies, which found that increased Ki67 expression in GTDs correlates with a higher likelihood of malignant transformation [19]. Additionally, Ki67 could help clinicians identify patients who may need more intensive monitoring or treatment for the progression to choriocarcinoma [20, 21]. Future studies should address the limitations of this research by incorporating larger, multicenter cohorts to validate and expand the findings. Including additional biomarkers, such as p57 and P63, alongside Ki67, could provide a more comprehensive understanding of GTD biology and progression. These efforts will improve diagnostic methods and enhance patient outcomes in the treatment of Gtd.

This study has several limitations, including its retrospective design and relatively small sample size from a single institution, which may limit the generalizability of the findings. Additionally, only Ki67 was evaluated as a proliferation marker, while other useful immunohistochemical markers were not included. Variations in tissue preservation and archival sample quality may also influence immunohistochemical staining results. Future multicenter studies with larger cohorts and inclusion of additional biomarkers such as p57 and p63 are recommended to further validate the diagnostic and prognostic role of Ki67 in gestational trophoblastic diseases.

CONCLUSIONS

This study intended to assess the impact of Ki67 expression in diagnosing and predicting the course of gestational trophoblastic disorders (GTDs). Despite difficulties such as a smaller sample size of 50 cases (as opposed to the optimum 246), the data indicate Ki67 as a viable biomarker for discriminating between GTD subtypes and predicting disease progression, particularly in cases of full moles. The retrospective design and single-center setting limit the generalizability of the results and underscore the need for bigger, multicenter investigations to validate these findings. Future research should also explore Ki67 in comparison with other indicators to better clinical prognosis and treatment outcomes for GTD patients.

Authors' Contribution

Conceptualization: SUK, SN

Methodology: SUK, MSK, SN

Formal analysis: NK, HGS, MSK, SN

Writing and Drafting: SUK, HGS, MT

Review and Editing: SUK, HGS, MT, MSK, SN

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Genotypic Strain Determination of Multi-Drug Resistance (MDR) and Extended Drug Resistance (XDR) in *Acinetobacter Baumannii* from Tertiary Care Hospitals in Lahore

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ABSTRACT

Antibiotic resistance in *Acinetobacter baumannii* poses a major future challenge, with a sharp rise in drug-resistant infections significantly limiting treatment options. **Objectives:** To determine the frequency of multidrug-resistant (MDR) and extended drug-resistant (XDR) *Acinetobacter baumannii* and the frequency of blaOXA-23, blaOXA-24, blaOXA-51, and blaOXA-58 among all other resistance genes responsible for resistance in *Acinetobacter baumannii*. **Methods:** A descriptive cross-sectional study was conducted in the Department of Pathology, King Edward Medical University, Lahore. Specimens were collected from the (Neonatal ICU, ICU, CCU) of Mayo Hospital, Lahore, and were processed at the hospital laboratory. *Acinetobacter baumannii* was identified on CHROMagar based on colony morphology and growth conditions, confirmed by biochemical tests. Antimicrobial sensitivity was assessed using the disc diffusion method, and PCR was performed for genotypic identification, with primer details in the data collection procedure. **Results:** Out of 67 samples, 19 (23.36%) were positive for *Acinetobacter baumannii*. Among these, blaOXA-23 (57.89%) was the most common resistance gene, followed by blaOXA-51 (47.36%). All 19 had the OXA-58 strain. The isolates showed 100% resistance to Penicillin, Ceftazidime, Cefepime, Imipenem, Levofloxacin, Doxycycline, and Septran. The most effective antibiotics were Ampicillin + Sulbactam (42.11%) and Piperacillin + Tazobactam (26.32%). **Conclusions:** The frequency of *Acinetobacter baumannii* was 28.36%. according to the study results. Among these positive isolates, carbapenem-resistant genes blaOXA-23 (57.89%) and bla-OXA-58 (47.36%) were the most frequent drug-resistant genes which were isolated. Regarding antimicrobial susceptibility, very few drugs showed sensitivity for *Acinetobacter baumannii*, which poses a major challenge for clinicians.

INTRODUCTION

Morphology of *Acinetobacter baumannii* consists of the following characteristics: Gram-negative coccobacilli. It is immotile and has an aerobic nature. It can easily spread from one patient to another patient very easily especially in hospital settings. It can also persist in the environment for many days [1]. The intensive care units (ICUs) are the most common location for severe infections caused by *A. baumannii*. Ventilator-associated pneumonia (VAP), secondary meningitis, endocarditis, septicemia,

infections of the skin, soft tissues, urinary system, and infections resulting from prosthetic devices are among the many illnesses it causes [2]. *Acinetobacter baumannii* can enter the body through various routes as open wounds, mechanical ventilators and intravascular catheters [3]. *Acinetobacter baumannii* has become a major threat to intensive care units (ICUs) after *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). They are directly related to high morbidity and mortality as



well as long hospital stays [4]. *Acinetobacter baumannii* is now being considered an emerging threat of outbreaks in hospital settings throughout the world. The Infectious Diseases Society of America (IDSA) has included *Acinetobacter baumannii* among the six deadliest pathogens. Among all clinically isolated, aerobic, and facultative gram-negative pathogens, the overall percentage of *A. baumannii* varies by region; it ranges from 0.7% in North America to 4.6% in the Middle East, according to reports [5]. Pakistan is one of the most affected nations in South and Southeast Asia by carbapenem-resistant *A. baumannii*. More than 60% of *A. baumannii* isolates in Pakistan were found to be carbapenem-resistant [6]. A number of recent studies have shown that the prevalence of *A. baumannii* infections is rising in various parts of Pakistan. According to one study, *A. baumannii* is the most common bacterium responsible for bloodstream infections (54.2%) and ventilator-related pneumonia (30%) in Karachi [7]. A major worry related to the isolates of drug-resistant *A. baumannii* isolates is their direct relation with various nosocomial infections [8]. Nowadays, the most commonly isolated nosocomial pathogen in clinical laboratories is *A. baumannii*, with a mortality rate being about 41% [9]. Broad-spectrum antibiotics are becoming more and more resistant to *A. baumannii* day by day, even the carbapenems are showing resistance [10]. Carbapenem resistance is frequently initiated by serine oxacillinases (OXAs). Different genes encode these enzymes, the most important being blaOXA₋₂₃, blaOXA₋₄₀, blaOXA₋₅₈, and metallo- β -lactamases (MBLs) genes of the Vimentin (VIM) and Imipenemase (IMP). Clavulanic acid does not inhibit OXAs. While these genes are present in most parts of the world, MBLs exhibit resistance to carbapenems and every other β -lactamase except aztreonam [11]. Carbapenem resistance is thought to involve a list of various interlinked mechanisms: hydrolysis by various beta-lactamases, change in the permeability of the outer cell membrane, antibiotic affinity for proteins that bind penicillin, and elevated efflux pump activity [12]. Owing to the increasing importance of drug-resistant genes, my research aims to determine the frequency of drug-resistant genes in *Acinetobacter baumannii* in our population, namely blaOXA-51, blaOXA-23, blaOXA-24, and blaOXA-58.

The rising prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Acinetobacter baumannii* in tertiary care hospitals presents a major clinical and public health challenge due to limited therapeutic options and increased morbidity and mortality. Local data on the molecular resistance patterns, particularly carbapenemase-producing genes such as blaOXA-23, blaOXA-24, blaOXA-51, and blaOXA-58, remain insufficient in Pakistan. This study aimed to determine the frequency of

MDR/XDR *A. baumannii* isolates and identify the dominant resistance genes among hospitalized patients in Lahore. The research sought to provide region-specific genotypic and antimicrobial susceptibility data to support infection control strategies and guide evidence-based antibiotic stewardship.

METHODS

This descriptive cross-sectional study was conducted to assess the susceptibility to antibiotics and genotypic characterization of *Acinetobacter baumannii*. The samples were taken for six months, i.e. July 15, 2017, to January 15, 2018, following the approval of the research synopsis from the institutional review board (Ref # 464/RC/KEMU). Clinical specimens, including blood, sputum, urine, and pus, were obtained from the NICU, ICU, and CCU of tertiary care hospitals in Lahore. These were then processed at the Pathology Department of King Edward Medical University. The sample size was calculated by using the WHO calculator, taking a 95% confidence level, 8% margin of error, and a previously reported prevalence of 87.3% for the blaOXA-23-like gene [13]. A non-probability purposive sampling technique was employed. Informed consent was taken from patients whose specimens satisfied the inclusion criteria. Contaminated samples, defined by the growth of more than two organisms on culture plates, were excluded from the study. Collected clinical specimens were inoculated on Chromagar *Acinetobacter* for preliminary identification. Positive isolates were confirmed based on phenotypic characteristics such as colony morphology and growth patterns, followed by biochemical testing for oxidase, citrate utilization, motility, catalase, and oxidative carbohydrate utilization. Following the criteria of the Clinical and Laboratory Standards Institute (CLSI), isolates identified as *Acinetobacter baumannii* were tested for antibiotic susceptibility using the disc diffusion method. Seven classes of antibiotics were tested: carbapenems, aminoglycosides, fluoroquinolones, cephalosporins, penicillin, beta-lactamase inhibitors, and monobactams. A portion of each pure colony was reserved for molecular testing through PCR to detect specific genotypes. Genotypic analysis of *Acinetobacter baumannii* was conducted using PCR with specific primers targeting blaOXA-23, blaOXA-24, blaOXA-51, and blaOXA-58 genes. Primer sequences were selected to ensure specific amplification of each gene. Screening was performed following annexure 01, while antimicrobial susceptibility patterns were recorded following annexures 02 and 03. SPSS version 21.0 was used for data entry and statistical analysis. Qualitative variables like gender and resistance patterns were presented as frequencies and percentages, whereas quantitative data, like age, were represented as mean $\pm$ standard deviation.

RESULTS

A total of 67 patients were included in the study. The mean age of the patients was 41.98 ± 10.86 years, with the youngest patient being 25 years and the oldest 60 years. Of the total participants, 40 (59.70%) were male and 27 (40.30%) were female, indicating a male predominance in the study population. *Acinetobacter baumannii* was isolated from 19 (28.36%) of the 67 clinical samples (Table 1).

Table 1: Demographic Characteristics and *Acinetobacter baumannii* Frequency among Patients (n=67)

Parameters	Value
Age (Years)	
Mean $\pm$ SD	41.98 $\pm$ 10.86
Minimum – Maximum	25 – 60
Gender Distribution	
Male, n (%)	40 (59.70%)
Female, n (%)	27 (40.30%)
<i>Acinetobacter Baumannii</i> Positive Cases	
Number of positive samples, n (%)	19 (28.36%)

Molecular characterization of these 19 isolates revealed the presence of various carbapenemase-encoding genes. The blaOXA-23 gene was detected in 11 (57.89%) isolates, while bla OXA-51 was identified in 9 (47.36%) isolates. Importantly, all 19 isolates (100%) harbored the blaOXA-58 gene. The blaOXA-24 gene was not detected in any of the isolates (Table 2).

Table 2: Frequency of Strains of *Acinetobacter Baumannii*

Parameters	Frequency (%)
blaOXA-23	11 (57.89%)
blaOXA-24	0 (0%)
blaOXA-51	9 (47.36%)
blaOXA-58	19 (100%)

All 19 positive samples of *Acinetobacter baumannii* were tested for antimicrobial susceptibility, with the results summarized. Complete resistance (100%) was observed against Penicillin, Ceftazidime, Cefepime, Imipenem, Levofloxacin, Doxycycline, and Trimethoprim-Sulfamethoxazole (Septran). Among the remaining antibiotics, Ampicillin + Sulbactam showed the highest sensitivity, with 8 isolates (42.11%) being susceptible. Piperacillin + Tazobactam and Amikacin each demonstrated sensitivity in 5 (26.32%) isolates, while Tobramycin was effective in 3 (15.79%) cases. Tigecycline showed the lowest susceptibility, with only 2 (10.53%) isolates being sensitive.

Table 3: Antimicrobial Susceptibility of *Acinetobacter Baumannii* (n=100)

Positive Samples of <i>Acinetobacter Baumannii</i>	Sensitive	Inter-mediate	Resistant	Total
Penicillin	0 (0%)	0 (0%)	19 (100%)	19

Ampicillin + Sulbactam	8 (42.11%)	1 (5.26%)	10 (52.63%)	19
Piperacillin+ Tazobactam	5 (26.32%)	2 (10.53%)	12 (63.16%)	19
Amikacin	3 (15.79%)	1 (5.26%)	15 (78.95%)	19
Tobramycin	3 (15.79%)	3 (15.79%)	13 (68.42%)	19
Ceftazidime	0 (0%)	0 (0%)	19 (100%)	19
Cefipime	0 (0%)	0 (0%)	19 (100%)	19
Imipenem	0 (0%)	0 (0%)	19 (100%)	19
Levofloxacin	0 (0%)	0 (0%)	19 (100%)	19
Doxycycline	0 (0%)	0 (0%)	19 (100%)	19
Tigecycline	2 (10.53%)	1 (5.26%)	16 (84.21%)	19
Septran	0 (0%)	0 (0%)	19 (100%)	19

DISCUSSION

Recently, a sharp rise in the occurrence of MDR *A. baumannii* percentage contributing to nosocomial infections, has been demonstrated [12]. Especially during the last few decades, due to the combined effect of features of antibiotic resistance, ability to sustain environmental pressures, and easy transmission within health care facilities, MDR *A.baumannii* phenotypes are directly assigned to morbidity and mortality. Mortality rate of MDR *A. baumannii* bacteremia was 21.2% [14]. Contributions of general wards were 5% and of ICUs were 54% [15]. In present study, 19 (23.36%) samples were positive for *A. baumannii*. Among these positive samples, the frequency of resistance genes as highest for bla OXA-23 (57.89%) and bla OXA-51 (47.36%), respectively. Sepavand et al. did a study which showed that the most frequent resistant gene among multidrug resistance class was blaOXA-51 (48.38%), then bla-OXA-23 (46.31%) and bla-OXA-58 (5.31%) respectively [16]. These results are comparable to the findings of this study regarding the pattern of multidrug resistance genes. But in this study, no sample was positive for the blaOXA-24 and blaOXA-58 genes. Another study found blaOXA-23 and blaOXA-58 in bacterial chromosomes, but they did not identify patient strains of blaOXA-24 [17]. Four carbapenemases—blaOXA-23, blaOXA-24, blaOXA-51, and blaOXA-58 are responsible for *Acinetobacter baumannii* resistance. In contrast to other *Acinetobacter*, the OXA-51 is a naturally occurring organism [18]. One previous study reported that the main mechanisms of resistance to imipenem were due to blaOXA-51-like and blaOXA-23-like in *Acinetobacter baumannii* [1]. According to a different study conducted in an Indian community, the primary pathogens for carbapenem-resistant *Acinetobacter* are blaOXA51-like and blaOXA-23-like [5]. Nevertheless, other investigations did not present findings that were comparable to ours. All MDR *Acinetobacter baumannii* were found to have blaOXA-51-like and blaOXA58-like genes, according to a study conducted in a Spanish population [19]. Carbapenem-resistant *Acinetobacter baumannii* were shown to have an

abundance of blaOXA-23-like genes in another study conducted in a Chinese population; the genes blaOXA-24 and blaOXA-58 follow in order [20]. Disparity in various studies is likely to be due to various factors like different sample selection criteria, different sample sizes and genetic variations in different populations due to slight variation in genetic make-up. Our results propose that the CRAB resistance phenotype is mainly attributed to the blaOXA-23 gene, which is consistent with previous reports [21]. In current study, the resistance pattern showed that Penicillin, Ceftazidime, Cefipime, Imipenem, Levofloxacin, Doxycycline and Septran were the drugs who were showed 100% resistance for *Acinetobacter baumannii*. However, the most sensitive drugs for *Acinetobacter baumannii* was Ampicillin + Sulbactam (42.11%), followed by Piperacillin+ Tazobactam (26.32%), Amikacin (15.79%), Tobramycin (15.79%) and Tigecycline (10.53%). For *Acinetobacter baumannii*, all over the world, the pattern of drug resistance varies. Usually, the ability to tolerate various classes of antibiotics is related to the horizontal uptake of certain resistance genes. But the key mechanisms of tolerance to various disinfectants are not fully understood so far. Digging into the genetic traits as well as its morphological and physiological characteristics of *A. baumannii* clinical isolates will be an important starting point to explain the tactics of survival and tolerance of this opportunistic pathogen [22, 23]. Bahman Mirzaei's study reported that tobramycin, ceftazidime, ciprofloxacin, and imipenem were resistant [24]. Tobramycin and ceftazidime resistance was observed in 70% of *A. baumannii*, amikacin in 50% and imipenem in 80% of isolates, according to Kishk R's result [25]. 100% resistance for imipenem and 99.2% resistance for meropenem were noticed in all Dawiche F. isolates in another study [26]. In a cross-sectional study of Brazil in 2024, Freire MP, along with her colleagues, analyzed a steep rise in carbapenem-resistant *A. baumannii* from 30% to 70% [27]. Minocycline and tigecycline show sensitivity against all *A. baumannii* producing carbapenemases and metallo β -lactamases [28]. Comparable drug resistance patterns for *A. baumannii* isolates were found in another local study conducted in Pakistan. This multidrug resistance pattern exhibited the highest level of resistance to cephalosporins (98.75% for ceftazidime and cefepime, 97.5% for cefotaxime), 96.25% for trimethoprim-sulfamethoxazole, 88.75% for aztreonam, 86.25% for gentamicin, 77.5% for imipenem, 72.5% for piperacillin-tazobactam, and 72.05% for doxycycline [29]. Alamu J from Iran in his study showed that ciprofloxacin and imipenem were 100% resistant, piperacillin 99% and cefepime /levofloxacin/ ceftazidime were 97% resistant. Out of all isolates, complete resistance was noticed in 32% of isolates, while 91% were XDR. The prevailing resistance pattern was 32% with the sequence of resistance being

"ampicillin/sulbactam-ceftazidime-imipenem-gentamicin-tobramycin-doxycycline-ciprofloxacin-levofloxacin-cotrimoxazole piperacillin-cefepime [30].

The study was limited by its small sample size, single-city setting, and use of purposive sampling, which may restrict the generalizability of findings to broader populations. Additionally, only selected OXA resistance genes were investigated, potentially overlooking other important resistance mechanisms. Future studies should involve larger multicenter surveillance across diverse healthcare settings, include broader genomic profiling of resistance determinants, and assess clinical outcomes associated with MDR/XDR infections. Continuous molecular monitoring and stronger antibiotic stewardship programs are recommended to better control the spread of resistant *A. baumannii*.

CONCLUSIONS

The frequency of *Acinetobacter baumannii* was 28.36%, based to this study results. Among these positive isolates, the highest frequency of multidrug resistance was seen for blaOXA-23 (57.89%) and bla-OXA-58 (47.36%). Regarding antimicrobial susceptibility, very few drugs showed sensitivity for *Acinetobacter Baumannii*, which is posing a major challenge for the health care authorities as well as for MDR and XDRA. *baumannii*.

Authors' Contribution

Conceptualization: MS

Methodology: MS, QUAA, SFTZ

Formal analysis: SFTZ, JKK, ZM

Writing and Drafting: QUAA, ZM

Review and Editing: QUAA, ZM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Factors affecting Menstrual Hygiene Management Practices among Women Visiting a University Hospital of Lahore: A Cross-Sectional Study

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ABSTRACT

Menstrual practices are considered taboo in various spheres of our lives, serving as an impediment to the provision of adequate resources to women. **Objective:** To determine factors affecting menstrual hygiene practice (MHMP) in the population visiting a Tertiary Care Hospital. **Methods:** A Quantitative descriptive study was conducted at Lady Willingdon Hospital from July to December 2024. 382 female were included in the study after seeking informed consent and approval from ERB. The inclusion criteria for this study were female aged 18-45 years with regular menstrual cycles. Female who were pregnant or with irregular menstrual cycles were excluded. The data were analyzed by using SPSS version 21.0. **Results:** In this study age significantly influenced hygiene practices, with younger females (12-17 years) more likely to engage in unsafe practices ($p=0.005$). Maternal secondary education was a key factor in promoting safe hygiene practices ($p=0.009$). Awareness about menarches and the primary source of information were strongly associated with better hygiene practices ($p<0.001$). Sanitary pad usage was prevalent (99%) and linked to safer practices ($p=0.0032$), while access to water and sanitation facilities improved hygiene ($p=0.005$). **Conclusions:** This study highlights the crucial role of socio-demographic factors and access to sanitation facilities in influencing menstrual hygiene management practices. Promoting education, increasing awareness, and improving access to sanitary products and sanitation facilities are essential to enhance safe menstrual hygiene practices.

INTRODUCTION

Menarche is an important biological milestone in a woman's life as it marks the onset of the reproductive phase of her life. The average age at menarche is between 12 and 13 years of age [1, 2]. Despite its significance, societal taboos hinder appropriate education and awareness, highlighting menstrual health. This has led to growing distress and unease among the female population about the topic of menstruation [3, 4]. In various countries all over the world, including Pakistan, adolescent girls face obstacles in managing their menstruation effectively [5]. The United Nations defines adequate menstrual hygiene management as "women and adolescent girls using a clean menstrual

management material to absorb or collect blood that can be changed in privacy as often as necessary for the duration of the menstruation period, using soap and water for washing the body as required, and having access to facilities to dispose of used menstrual management materials [6, 7]. Particularly in poor countries, girls and women face substantial barriers to achieving adequate menstrual management, and add to that the limited research that exists on Menstrual Health Management Practices (MHMP), particularly in third-world countries such as Pakistan [8]. The decision-maker may have an impact on the overall menstrual hygiene practices as well



as the choice of menstrual products utilized. Mothers are essential in advising daughters on proper period hygiene habits and assisting them in selecting the appropriate menstruation products. Based on cultural or financial considerations, mothers may also opt to utilize conventional materials like rags or used clothing. Nonetheless, the usage of unsanitary materials should be avoided since it might result in major health issues [9]. Participants, on the other hand, are entitled to choose menstruation products of their preference, based on pricing and affordability. Menstrual hygiene habits can also be proportionally influenced by other decision-makers, including community leaders, lawmakers, and healthcare experts, amongst various others [10]. Health practitioners may educate and counsel women and girls about period hygiene habits, for instance, while lawmakers can adopt legislation to increase the affordability and accessibility of menstruation products [11]. By examining MHMP at Lady Willingdon Hospital, it serves as a contributing factor to evidence-based practices. Identifying factors affecting MHMP will inform targeted interventions and policy recommendations. Understanding MHMP can lead to better structured healthcare amenities, more awareness and enhanced well-being for women. The findings of this research will serve as the pedestal to future initiatives and promote sustainable menstrual hygiene practices.

Menstrual hygiene management remains a significant public health concern in Pakistan due to persistent social taboos, inadequate awareness, and unequal access to proper sanitation facilities, which negatively affect women's reproductive health and well-being. Limited local evidence exists regarding the socio-demographic, educational, and environmental factors influencing menstrual hygiene practices among women in tertiary healthcare settings. This study aimed to assess menstrual hygiene management practices and identify key factors such as age, maternal education, awareness, financial resources, and sanitation access that influence safe practices among women visiting a university hospital in Lahore. The research goal was to generate evidence for targeted interventions that can improve menstrual health education, product accessibility, and supportive healthcare policies. This study aimed to determine the menstrual hygiene practice (MHMP) in the population visiting a Tertiary Care Hospital so that an overview of existing practices can be made, and the associated factors assessed.

METHODS

This cross-sectional study was conducted for six months at the Department of Obstetrics and Gynaecology at Lady Willingdon Hospital in Lahore, Pakistan, from July 2024 to December 2024, after receiving approval from the

Institutional Review Board of King Edward Medical University, Lahore (216/RC/KEMU). A total of 382 female visiting the Outpatient Department (OPD) of Lady Willingdon Hospital participated in the study. Informed consent was obtained from all participants. The inclusion criteria for this study were female aged 18-45 years with regular menstrual cycles who visited the OPD of Lady Willingdon Hospital during the study period. Females who were pregnant or had health conditions that could affect their menstrual cycles, such as polycystic ovary syndrome or thyroid disorders, were excluded from the study. Sample size was calculated by using the following formula and the Epi Tools software. $n = Z^2 \times p(1-p) / d^2$ Where n = sample size, Z = Z statistics for a level of confidence = (1.96), P = Respondents reported good menstrual hygiene practices = (53.9% or 0.539), d = precision (if 5%, $d = 0.005$). Using the following numbers in the above-mentioned formula, the sample size for this work is 382 patients [12]. In this study, a structured questionnaire was used to assess menstrual hygiene practices among women, consisting of 16 multiple-choice and yes/no questions divided into four sections: demographics, menstrual health information, product use and awareness, and access to facilities and disposal practices. Menstrual hygiene practices were measured based on the type of material used, frequency of changing, access to water and sanitation, and disposal methods. These practices were categorized as safe (use of sanitary pads or clean cloth, changing every 4-6 hours, proper disposal, and access to water and private sanitation) or unsafe (use of old cloth, infrequent changing, improper disposal, or lack of facilities), following WHO guidelines and relevant literature. This questionnaire is mentioned in the supplementary data. The questionnaires underwent pilot testing and validation and were self-administered. Data entry and statistical analysis were performed using Excel and SPSS (version 21.0). For continuous variables, such as age, the mean and standard deviation were reported. For categorical variables, such as education, marital status, and occupation, frequency and percentage were calculated. The independent t-test was used to assess the mean difference in continuous variables concerning menstrual hygiene management practices (MHMP). Bivariate and multivariate logistic regression models were employed to identify independent risk factors associated with MHMP. A p-value of less than 0.050 was considered statistically significant.

RESULTS

The study found significant associations between socio-demographic factors and menstrual hygiene management practices. These findings highlight the importance of education, financial resources, and parental awareness in improving menstrual hygiene management (Table 1).

Table 1: Socio-Demographic Characteristics

Variables	Frequency (%)	p-Value
12-17	3.8 (0.8%)	0.005
18-23	201 (52.6%)	
24-29	172 (45%)	
>30	6 (1.6%)	
Education of Research Participants		
Primary	1 (0.26%)	0.005
Secondary	2 (0.52%)	
Higher Secondary	0 (0%)	
University	379 (99.3%)	
Education of Mothers		
Primary	121 (30%)	0.009
Secondary	150 (39%)	
Higher Secondary	81 (21%)	
University	30 (10%)	
Marital Status		
Married	34 (9%)	0.006
Unmarried	348 (91%)	
Income		
<2,00,000	281 (74%)	<0.001
>2,00,000	101 (26%)	
Financial Resources		
Housewife	203 (52%)	0.911
Unskilled Women	106 (28%)	
Skilled Women	59 (15%)	
Others	14 (4%)	

The study highlighted key factors affecting menstrual hygiene management practices (MHMP). These findings highlight the need for increased awareness, decision-making autonomy, and better sanitation facilities to improve MHMP (Table 2).

Table 2: Menstrual Knowledge of Respondents about Factors Affecting MHMP

Variables	Frequency (%)	p-Value
10-12	150 (39%)	0.008
13-15	218 (57%)	
>15	14 (3%)	
Yes	133 (35%)	0.024
No	249 (65%)	
Mother/Sister	340 (89%)	<0.001
Social Media	20 (6%)	
Friends	21 (5%)	
Sanitary pad	379 (99%)	0.032
Old Cloth	3 (1%)	
Others	0 (0%)	
Mother	307 (81%)	<0.001
Participant	75 (19%)	
Others	0 (0%)	
Yes	348 (91%)	<0.001
No	34 (9%)	
Yes	372 (97%)	0.005
No	10 (3%)	
Washing	122 (32%)	0.006
Burning	10 (3%)	
Throwing into Garbage	250 (66%)	

The multivariate and bivariate logistic regression analysis revealed several key factors influencing menstrual hygiene management practices among the respondents. These findings highlight the importance of maternal education, awareness, and access to sanitation in promoting safe menstrual hygiene practices among women (Table 3).

Table 3: Menstrual Knowledge of Respondents about Factors Affecting MHMP

Variables	Menstrual Hygiene Management Practices		AOR with 95% CI	COR with 95% CI	p-Value
	Safe	Unsafe			
Age					
12-17	132	160	0.213 (0.06, 0.67)	0.17 (0.054, 0.75)	0.005
>18	10	80	Ref.	Ref.	
Marital Status					
Unmarried	164	188	0.43 (0.11, 0.83)	0.33 (0.09, 1.18)	0.840
Married	25	5	Ref.	Ref.	
Mothers' Educational Status					
Primary	41	70	3.21 (1.13, 8.29)	1.48 (0.76, 5.30)	0.020
Secondary	67	85	3.65 (1.82, 5.82)	0.28 (0.15, 0.5)	0.040
Higher secondary	37	47	3.15 (1.76, 5.28)	1.64 (0.90, 3.01)	0.440
University	15	20	1.3 (0.7, 2.1)	1.58 (0.21, 1.90)	0.600
Awareness					
Awareness about menarche	140	242	0.56 (0.71, 0.13)	0.30 (1.02, 0.305)	0.001
Source of Information	80	61	3.2(1.5, 6.8)	0.46 (0.78, 0.10)	0.150
Mother/Sister	67	112	1.5 (0.8, 2.93)	0.28 (1.33, 0.15)	0.013
Social Media/Friends	43	19	Ref.	Ref.	—

Sanitary Material Used					
Pads	373	6	1.14 (5.31, 0.59)	1.77(4.14, 0.31)	0.560
Old clothes	3	—	1.5 (0.8, 2.93)	0.56 (0.71, 0.13)	1.001
Others	0	—	Ref.	Ref.	—
Decision maker					
Mother	180	127	1.5 (0.8, 2.93)	3.1(1.3, 5.8)	0.040
Participant/Others	30	45	Ref.	Ref.	
Knowledge About Commercially Existing Sanitary Pads					
Yes	348	—	0.213 (0.06, 0.67)	0.17 (0.054, 0.75)	0.050
No	—	34	Ref.	Ref.	
Access to Water and Sanitation Facilities					
Yes	372	—	1.27(2.28, 0.82)	1.47(5.18, 0.18)	0.050
No	—	10	Ref.	Ref.	

The study identified several key factors influencing menstrual hygiene management practices (MHMP). These findings highlight the need for increased awareness, affordable menstrual products, and improved sanitation facilities (Table 4).

Table 4: Factors Affecting Menstrual Hygiene Management Practices (MHMP) Among Women (n=382)

Factor	Category	Good MHMP (n, %)	Poor MHMP (n, %)	χ^2 (Chi-square Value)	p-Value
Age Group (Years)	≤18	95 (78.5%)	26 (21.5%)	7.91	0.005**
	>18	172 (60.8%)	89 (39.2%)		
Mother's Education	No Formal Education	48 (52.7%)	43 (47.3%)	4.10	0.040**
	Primary or Higher	219 (66.2%)	72 (33.8%)		
Awareness about Menarche	Yes	189 (70.7%)	78 (29.3%)	10.99	0.001**
	No	78 (52.7%)	70 (47.3%)		
Type of Menstrual Product Used	Sanitary Pads	221 (66.7%)	110 (33.3%)	3.83	0.050**
	Cloth/Reused Material	46 (55.4%)	37 (44.6%)		
Knowledge of Commercial Sanitary Pads	Yes	200 (68.5%)	92 (31.5%)	7.78	0.005**
	No	67 (54.2%)	57 (45.8%)		
Access to Water and Sanitation Facilities	Yes	215 (69.3%)	95 (30.7%)	7.81	0.005**
	No	52 (53.6%)	45 (46.4%)		

DISCUSSION

This study aimed to determine different factors affecting menstruation and the various practices acquired to deal with monthly menstrual cycles in all spheres of society. Our findings indicate that the mean age of first menstruation in the study was 14.5 years. These findings are consistent with similar studies [13, 14]. Menstrual knowledge is pivotal, specifically before reaching the age of menarche for pre-pubescent female. A cross-sectional study conducted in 2017 shows that 64% of girls did not know about menstruation before reaching menarche [15]. Like other

studies, this study also found that mothers and sisters together were the two primary sources of menstruation-related information. This indicates that poorly informed mothers hinder the appropriate transfer of knowledge regarding menstruation to their daughters [16]. Side by side, well-educated and literate mothers are well-equipped to dispense accurate menstrual information to their daughters having constructive impact on upcoming generations. The quality and fabric of the material used for the management of the period are also a concern in low-income areas [17]. The majority (99%) of the participants use pads instead of old clothes and other absorbents. UTIs and other reproductive tract infections may stem from improper hygiene management or use of low-quality products [18]. Menstrual waste disposal is also a subject of caution as subpar alternatives can lead to environment unfriendly effects and negatives effects of human health spheres as well. How these products are removed from the environment also affects the management of menstrual practices of women [19, 20]. Cultural ethics, insufficient information and infrastructural issues are a few factors that influence the process of disposal. Promoting women's menstrual hygiene management requires proper disposal of menstrual waste. More emphasis on this topic is quintessential. This study indicates that more than 66% of the participants disposed of their used sanitary materials in garbage, exposing the surrounding populace to fatal infectious diseases [21]. This study found that age, parental education, family income, perceived socioeconomic class, and age at first menstruation had a significant statistical association with menstrual hygiene management practices at the bivariate level, and these findings are like other studies [22].

The study was limited by its single-center cross-sectional design, self-reported data collection, and predominance of highly educated participants, which may reduce generalizability to broader or rural populations. Additionally, cultural sensitivity surrounding menstruation may have introduced reporting bias. Future research

should include multicenter and community-based studies with more diverse populations to better capture regional and socioeconomic disparities. Longitudinal studies and intervention-based programs focusing on menstrual education, sanitation infrastructure, and policy reforms are recommended to sustainably improve menstrual hygiene management practices.

CONCLUSIONS

It was concluded that the study highlights the crucial role of socio-demographic factors such as age, maternal education, awareness about menarche, and access to sanitation facilities in influencing menstrual hygiene management practices. Promoting education, increasing awareness, and improving access to sanitary products and sanitation facilities are essential to enhance safe menstrual hygiene practices.

Authors' Contribution

Conceptualization: MJ

Methodology: MJ, RW, SH, NA, KKM

Formal analysis: SS

Writing and Drafting: RW, SH, SS, NA, KKM

Review and Editing: RW, SH, SS, NA, KKM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Association of Chronic Psoriasis with Syndrome X

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ABSTRACT

Psoriasis is a chronic skin disorder and has been associated with a number of chronic inflammatory conditions. Syndrome X, which is commonly seen in our population and is responsible for major cardiovascular events, has been found to be linked with chronic skin disorders. **Objective:** To find out the link between Syndrome X and chronic plaque psoriasis in our population, to estimate the disease burden and plan the management strategies accordingly. **Methods:** This study included 130 participants selected through consecutive sampling including 65 patients as diagnosed cases of chronic plaque psoriasis and rest of 65 were controls. Data collection involved measuring body size, blood pressure, and lab investigations with lipids panel, complete blood counts and fasting sugar levels. For the diagnosis of Syndrome X, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria was applied. **Results:** The study results revealed that Syndrome X was common in the psoriasis patients (41.5%) than the other group (23.1%) with a p value of 0.035. The majority of psoriasis patients were obese, had hypertension, sugar levels were elevated, higher triglycerides, and low HDL cholesterol. The bivariate analysis indicated that psoriasis was associated with the high tendency of developing syndrome X (p value of 0.021). **Conclusion:** The study findings highlighted that appropriate treatment of syndrome X in patients with chronic psoriasis can reduce the cardiovascular complications.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder, mediated by autoimmunity and is demonstrated by characteristic skin lesions having papules and silvery plaques along with skin inflammation [1]. It mainly affects body areas like scalp, elbows and knees. The Global burden of disease survey 2019 showed approximately 4,622,594 new cases of psoriasis globally in the year 2019, majority of those patients had age of 60 or above and most of the cases were from countries with good socioeconomic status [2]. Psoriasis has been found to be linked with Syndrome X that comprises of components including diabetes mellitus, lipid abnormalities, high blood pressure and obesity. Evidence suggests that chronic psoriasis is linked to syndrome X and Hidradenitis suppurativa that emphasizes the necessity to diagnose and manage these co morbidities. As psoriasis is

interconnected with severe vascular events and syndrome X, therefore evaluation and screening for dyslipidemia and metabolic derangements should be done in these patients. The cardiovascular complications are more common in people with psoriasis hence timely diagnosis and management is essential to reduce the extra dermatological complications [3]. Apart from syndrome X, psoriasis has also been found to be associated with diabetes, fatty liver and chronic renal impairment [4]. Psoriasis is more commonly seen in people with abdominal obesity, elevated blood pressure, dyslipidemia, and abnormal glucose tolerance [4, 5]. Psoriasis has been found to be linked with the elevation of certain mediators and adipokines [6]. Psoriasis mediated inflammation is an important element for atherosclerosis, underscoring



clinical implications of addressing these co morbidities among psoriasis patients [7]. There was an increased prevalence of Syndrome X among those people who had psoriatic arthritis that highlights the negative effects of psoriatic disease on metabolic health [8]. Moreover, psoriasis has been associated with Non-Alcoholic Liver Disease (NALD), and also Polycystic Ovarian Syndrome (PCOS) [9]. This association of several metabolic co morbidities that are correlated with psoriasis emphasizes the need for metabolic assessment and management of psoriasis patients. The available evidence shows that most of the studies that have been carried out showed a higher occurrence of Syndrome X among those people who were suffering from psoriasis as compared to the general population. However, there is a dearth of data from the developing world, particularly from the Pakistani population. Since the syndrome X has been associated with significant cardiovascular morbidity and mortality, understanding its prevalence and association with psoriasis is important so as to devise screening and management strategies. In this research, we wanted to see the relationship between chronic plaque psoriasis and syndrome X.

Chronic plaque psoriasis is increasingly recognized as a systemic inflammatory disorder associated with metabolic syndrome (Syndrome X), which significantly raises cardiovascular morbidity and mortality. However, limited local evidence exists in the Pakistani population regarding the burden and strength of this association, creating a gap in early screening and preventive management strategies. The rationale of the study was to observe the relationship between chronic plaque Psoriasis and Syndrome X in this population and hence plan the management or preventive strategies accordingly, that would be helpful in reducing the morbidity and mortality associated with the extra dermatological manifestations of this disease. This study aimed to evaluate the relationship between chronic psoriasis and metabolic syndrome, identify the prevalence of metabolic abnormalities among psoriasis patients, and provide evidence for integrated clinical management to reduce long-term cardiovascular risks.

METHODS

This was a case-control research study conducted in the Dermatology Department of Farooq teaching hospital (Akhter Saeed Medical College, Islamabad Campus Pakistan after taking the ethical approval from the institutional ethical review board with approval number - IRB0413. This study included 130 participants calculated using WHO calculator for estimating a population proportion taking Confidence interval 95%, 80% power of study and 5% level of significance with 65 patients diagnosed with chronic plaque psoriasis (cases) and 65

individuals without psoriasis (controls). (The prevalence of metabolic syndrome is estimated to be 10% in general population and 29% in psoriatic patients [10, 11]. After taking informed consent, the participants were recruited through consecutive sampling from outpatient dermatology clinics. Patients with chronic plaque psoriasis of age between 20-60 years, and disease duration of at least 6 months were included in the study. Controls were selected from individuals visiting the hospital for routine health check-ups or non-dermatological conditions, with no history of psoriasis or other chronic inflammatory diseases. Exclusion criteria for both groups included current use of systemic steroids, cyclosporine, systemic retinoid, immunosuppressant, pregnancy. Demographic data, including gender, age, and medical history, were gathered through medical records and structured interviews. For all participants, the following measurements were recorded: we had included anthropometric measurements such as waist circumference. Body Mass Index (BMI) estimation was done using weight and height. Readings of blood pressure were taken for both systolic and diastolic pressure, recorded twice, with the average value noted after the participant had been sitting for at least 5 minutes. The biochemical tests involved taking 5 ml of blood from a vein after the person fasted for 12 hours overnight. Blood sugar levels were checked and the lipid profile including HDL cholesterol, total cholesterol, and triglycerides, was measured using enzyme-based tests. Syndrome X was diagnosed as per National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) criteria. A participant was considered to have Syndrome X if 3 of following were present including high blood pressure of 130/85 mm Hg or more or taking antihypertensive, abdominal obesity (waist size of at least 80 cm for women, at least 90 cm for men, high fasting blood sugar (at least 100 mg/dl) or using diabetes medication, high triglycerides of at least 150 mg/dl and above) or using lipid lowering medication, and low HDL cholesterol (50 mg/dl or lower for women and 40 mg/dl or lower for men). SPSS version 22.0 was employed for data analysis. Average values for continuous data have been described as mean $\pm$ standard deviation (SD), whereas the categorical data was shown as percentages and frequencies. The prevalence of metabolic syndrome among the cases and controls was examined using chi-square test for categorical data and t-test for continuous data. Bivariate analysis was used to see any link between chronic plaque psoriasis with metabolic syndrome and its component factors. A p-value of 0.050 or less was taken as statistically significant.

RESULTS

This study included 130 participants, comprising 65 psoriasis patients (cases) and 65 non-psoriatic individuals (controls). The mean age of cases and controls was 45.8 years and 44.9 years, respectively. Male participants constituted 64% of cases and 61% of controls. Comparison of metabolic parameters revealed that blood pressure, waist circumference, blood glucose, and triglyceride levels were higher in psoriasis patients compared to controls. In contrast, HDL cholesterol levels were lower in cases than in controls.

Table 1: Distribution of Characteristics

Variables	Cases Mean $\pm$ SD / Frequency (%)	Controls Mean $\pm$ SD / Frequency (%)	p-Value
Age (Years)	45.8 $\pm$ 11.6	44.9 $\pm$ 11.3	0.765
Gender			
Male	42 (64.6)	40 (61.5)	0.728
Female	23 (35.4)	25 (38.5)	
Waist Circumference (cm)	89.3 $\pm$ 12.4	84.7 $\pm$ 11.8	0.035
Blood Pressure (mmHg)			
Systolic	128.4 $\pm$ 16.7	122.1 $\pm$ 14.3	0.044
Diastolic	82.5 $\pm$ 10.2	78.6 $\pm$ 9.8	0.048
Fasting Glucose (mg/dl)	106.7 $\pm$ 20.1	98.4 $\pm$ 18.3	0.039
Serum Triglycerides (mg/dl)	168.9 $\pm$ 54.6	142.5 $\pm$ 49.8	0.033
HDL Cholesterol (mg/dl)	38.2 $\pm$ 11.4	45.6 $\pm$ 12.9	0.041
Duration of Psoriasis (Years)	10.2 $\pm$ 5.1	-	-

The study revealed high rate of metabolic syndrome was in the psoriasis patients as compared to the controls with 41.5% compared to 23.1% ($p = 0.035$). Table 1 provides details on the specific constituents of metabolic syndrome in both groups.

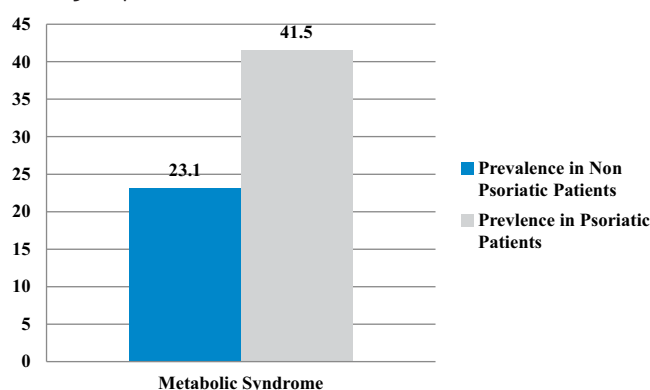


Figure 2: Prevalence of Metabolic Syndrome in Psoriatic Patients
The elements of metabolic syndrome were significantly high in patients with chronic psoriasis compared to controls. Abdominal obesity was observed in 46% (30/65) of cases and 29% (19/65) of controls ($p = 0.042$). Elevated

blood pressure was present in 52% (34/65) of cases compared to 35% (23/65) of controls ($p = 0.048$). Elevated fasting blood glucose levels were found in 38% (25/65) of cases and 22% (14/65) of controls ($p = 0.039$). Elevated serum triglycerides were noted in 44% (29/65) of cases and 27% (18/65) of controls ($p = 0.033$). Reduced HDL cholesterol levels were seen in 49% (32/65) of cases compared to 31% (20/65) of controls ($p = 0.041$).

Table 2: Prevalence of Metabolic Syndrome Elements in Cases and Controls ($n=130$)

Component	Cases Frequency (%)	Controls Frequency (%)	p-Value
Abdominal Obesity	30 (46)	19 (29)	0.042
Elevated Blood Pressure	34 (52)	23 (35)	0.048
Elevated Fasting Glucose	25 (38)	14 (22)	0.039
Elevated Triglycerides	29 (44)	18 (27)	0.033
Reduced HDL Cholesterol	32 (49)	20 (31)	0.041

When the data were separated by gender, 43% of male psoriasis patients had metabolic syndrome as compared with 25% male controls (p of 0.038). Among women, 39% of those with psoriasis had metabolic syndrome in contrast to 20% of female controls (p value 0.041). An analysis by age revealed that 39% of psoriasis patients aged 50 or younger had metabolic syndrome, while it was 22% in controls of the same age ($p = 0.032$). For those over 50, the prevalence was 44% in psoriasis patients versus 24% in controls ($p = 0.039$). The average duration of psoriasis among the cases was 10.2 years. Metabolic syndrome was more in patients with psoriasis disease duration of at least 10 years compared to those with the disease of less than 10 years duration. (50% vs. 31%, $p = 0.027$).

Table 3: Bivariate Analysis of different Parameters

Variables	Prevalence of Metabolic Syndrome		p-Value
	Cases (%)	Controls (%)	
Male	43	25	0.034
Female	39	20	0.041
Age less than 50	39	22	0.032
Age More than 50	44	24	0.039
Psoriasis More than 10 Years	50	Nil	0.027
Psoriasis Less than 10 Years	31	Nil	

The study also revealed that patients with chronic plaque psoriasis had a significantly increased rate of developing metabolic syndrome compared with people without psoriasis. The findings highlight the importance of routine screening for metabolic syndrome components in patients with psoriasis to facilitate timely diagnosis and management, thereby reducing the risk of cardiovascular and other related complications. Figure 2 showed the percentage distribution of patients with metabolic syndrome in each sub-group, emphasizing the disparities in prevalence according to age, gender, and the duration of psoriasis.

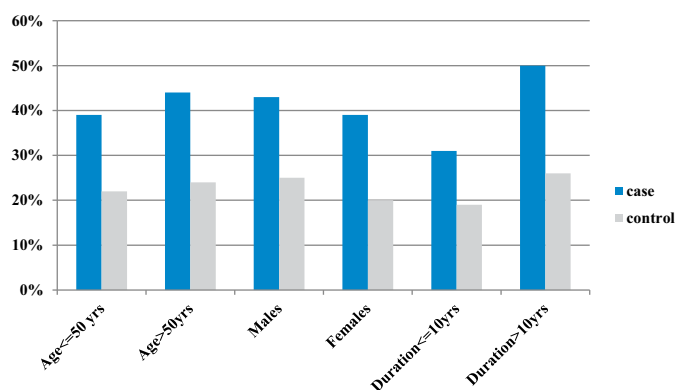


Figure 2: Prevalence of Metabolic Syndrome in different Groups

DISCUSSION

This case-control study found a strong connection between chronic plaque psoriasis and metabolic syndrome. The metabolic syndrome was much more common among psoriasis cases (41.5%) compared with control group (23.1%) supportive of the idea that psoriasis, as a chronic inflammatory condition, is linked to metabolic disorders. The study also showed that all aspects of metabolic syndrome were frequently observed in people with psoriasis compared with normal healthy individuals. These data are comparable to the results from few other studies showing the association between chronic systemic inflammation in psoriasis and metabolic syndrome [6, 7]. Significant gender and age differences in the frequency distribution of metabolic syndrome. People with psoriasis both male and female, showed a higher rate of metabolic syndrome than their control groups. Hormonal differences may affect fat distribution and metabolism, leading to this difference between genders [8, 9]. Literature also suggests that elevated cytokines like TNF- α and Interleukin-6 are crucial in psoriasis. However, published data also shows that this increased burden of inflammatory cytokines interfere with insulin signaling, and also promote fat accumulation therefore that results in dyslipidemia and hypertension [10, 11]. Older psoriasis patients over 50 had a higher rate of metabolic syndrome than younger ones. This suggests that metabolic risks increase with age [12]. It highlights the fact that close monitoring and timely management in older patients would be beneficial [13, 14]. Many studies have found that patients with psoriasis have more propensity to develop metabolic syndrome therefore evaluation of association between the two disorders is important [15, 16]. A study review also confirmed a strong link between psoriasis and metabolic syndrome [17]. This association could be because long-term inflammation affects both the skin and how the body manages metabolism [18]. Certain inflammatory proteins like TNF- α and IL-6 are out of balance in psoriasis. These proteins can cause insulin problems, weight gain, and bad cholesterol,

which are key parts of metabolic syndrome [19]. Another study investigated the association of palmoplantar plaque psoriasis with diabetes, hypertension, obesity, and metabolic syndrome [20]. People who have psoriasis for at least 10 years have high chances to develop metabolic syndrome than those with disease of short duration. This showed that psoriasis is a chronic disorder involving the whole body, with ongoing inflammation increasing the risk of metabolic issues over time. A growing evidence suggests that metabolic syndrome and psoriasis are strongly linked, their prevalence is increasing especially more in patients with psoriatic arthritis [21, 22]. They also found higher rates of high triglycerides and belly fat in psoriasis patients. However, Depression and mood related disorders are also more common in patients with Psoriasis and metabolic syndrome with inflammation as a likely precipitating factor [23, 24]. Research by Al-Hamad and Raman found that 41.5% of psoriasis patients had metabolic syndrome, compared to 23.1% of people without the disease [25]. Although current literature sheds light on the connection between chronic plaque psoriasis and metabolic syndrome, there are still many questions that need answering. No understanding regarding the biological mechanisms that drive this association. Future research should aim to uncover the pathways through which chronic inflammation in psoriasis leads to metabolic issues. Moreover, conducting more studies in diverse populations is crucial to see if these findings hold true across different ethnic and regional groups. This could help us better understand any potential variations in how psoriasis and metabolic syndrome are linked. This study had few limitations. The case-control design cannot establish causality between psoriasis and metabolic syndrome. The sample size, although adequate to show significant associations, might not be suitable to the broader population. Future longitudinal studies with bigger samples can be done to see the temporal relationship and underlying mechanisms between these conditions. Secondly, the study was conducted in one particular location hence results may show variation in other areas of this country therefore further studies preferably multi centric using larger sample would be appropriate.

The study was limited by its case-control design, which restricts causal inference, and its single-center setting with a relatively small sample size, reducing generalizability to the wider population. Additionally, regional and demographic variations may influence findings. Future multicenter longitudinal studies with larger and more diverse populations are recommended to better understand the temporal and biological mechanisms linking psoriasis with metabolic syndrome and to develop targeted prevention and treatment strategies.

CONCLUSIONS

This study highlighted the significant link between chronic plaque psoriasis and metabolic syndrome, therefore regular screening of patients with psoriasis for syndrome X along with comprehensive management strategies are important. Early intervention and lifestyle modifications can potentially reduce the chances of cardiovascular complications in these patients as usually the extra dermatological complications are often overlooked. Further research is warranted to explore the pathophysiological links and develop targeted therapeutic approaches that address both psoriasis and its metabolic comorbidities.

Authors' Contribution

Conceptualization: MFB, TMS

Methodology: ME, MN, JM

Formal analysis: ME, MN, JM

Writing and Drafting: MFB, ME, MN, TMS, JM, WSB

Review and Editing: MFB, ME, MN, TMS, JM, WSB

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Incidence of Fungal Pneumonia in Children with Acute Myeloid Leukemia Taking Oral Antifungal Prophylaxis

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ABSTRACT

Acute leukemia is common in children, with acute lymphoblastic leukemia (ALL) making up 80-85% and acute myeloid leukemia (AML) 10-15%. **Objective:** To determine the incidence of fungal pneumonia in children with acute myeloid leukemia taking oral antifungal prophylaxis. **Methods:** In this single-center retrospective study done in a tertiary care hospital, the study analyzed 276 pediatric AML cases from July 2022 to June 2024. The diagnosis of fungal pneumonia was made on the basis of CT scan findings. Demographic and AML subtype data were also analyzed. **Results:** Among the 276 AML patients enrolled in this study, the mean age of the patients was 8.4 years (range 1-16 years), and there was a male predominance (157 male vs. 119 female). The most common AML subtype was M2 (34.1%), followed by M4 (16.7%) and M5 (8.3%). Out of 276 patients with AML, 69 (25.0%) had CT findings suggestive of fungal pneumonia. M2 and M4 subtypes were the most commonly affected, accounting for about 50% of cases. **Conclusions:** Children with AML taking oral primary antifungal prophylaxis have a 25% incidence of fungal pneumonia. These findings highlight the importance of vigilant imaging surveillance and targeted interventions in high-risk subgroups (M2 and M4).

INTRODUCTION

Acute leukemia is common in children, with acute lymphoblastic leukemia (ALL) making up 80-85% and acute myeloid leukemia (AML) 10-15%. Childhood AML is the second most common hematological malignancy, arising from abnormal changes in stem cell precursors that typically mature into myeloid cells like white blood cells, red blood cells, and platelets [1, 2]. Etiological factors for childhood AML involve genetic syndromes (e.g., Down syndrome), hematological disorders (e.g., Fanconi anemia), and environmental factors (e.g., benzene exposure). High-risk factors include monosomy-7, alkylating agents, positive family history in identical twins, and Down

syndrome (risk increased by 200-400-fold) [3]. Children with AML typically show various symptoms such as fever, bone pains, lethargy, pallor, skin nodules, ocular proptosis, and bleeding tendencies like nose bleeds and gum bleeding. Treatment options encompass chemotherapy, immunotherapeutics (e.g., gemtuzumab ozogamicin), targeted therapy (e.g., FLT3 inhibitors), and supportive care [4, 5]. Children with AML undergoing intensive chemotherapy face high infection risks: 50-60% for severe bacterial infections and 5-15% for invasive fungal infections. Supportive care guidelines advocate prophylactic use of systemic antibiotics and antifungals,



granulocyte colony-stimulating factor (G-CSF), and mandatory hospitalization during severe neutropenia [6, 7]. Children with AML have increased infection risk from weakened immunity due to the disease and chemotherapy, which may be bacterial, viral, or fungal. Fungal infection is suspected with persistent fever during neutropenia despite broad-spectrum antibiotics [8]. In AML, myeloid cell dysfunction poses a higher risk of invasive fungal infections compared to lymphoid cell dysfunction in ALL. Additionally, profound neutropenia lasts longer after chemotherapy in AML (>10 days) than in ALL. Globally, fungal infection incidence in children with AML is 5% with oral antifungal prophylaxis and 20% without [9]. Yeasts (mainly candidemia and hepatosplenic candidiasis) and molds (mainly aspergillosis) are the main agents of invasive fungal infections affecting the lungs, sinuses, and brain [10]. Fungal pneumonia is a significant cause of morbidity and mortality, especially in acute myeloid leukemia, where around 90% of fungal infections occur. Patients typically show non-specific symptoms such as persistent fever, cough, vomiting, and respiratory difficulties. Chest HRCT is more sensitive and specific for diagnosis compared to chest radiograph, MRI, or PET scan [11, 12]. Radiographic findings indicate invasive fungal chest infection with pulmonary nodules and distinct signs like halo or ground glass appearance [13]. The current guidelines recommend mold-active antifungal prophylaxis for the incidence of IFD greater than 10% in conditions like AML, relapsed acute leukemia, allogeneic HCT, and high-risk ALL. Recommended options include voriconazole, posaconazole, or micafungin, available both orally and intravenously [14, 15]. Clinical approaches for treating invasive fungal infections include primary prophylaxis with antifungals throughout chemotherapy, empirical treatment for febrile neutropenia lasting 96 hours, and diagnostic-driven initiation of antifungals upon positive biomarkers or imaging. Pediatric patients with IFI often exhibit non-specific symptoms and imaging findings [16]. The rationale for this study is that invasive fungal infections usually remain undiagnosed and are a major cause of morbidity and mortality in children with hematological malignancy. In Pakistan, there is no data available on fungal pneumonia in children with acute myeloid leukemia. Children with acute myeloid leukemia (AML) are highly vulnerable to invasive fungal pneumonia due to prolonged neutropenia and intensive chemotherapy, even while receiving oral antifungal prophylaxis. Despite this serious clinical burden, local evidence from Pakistan regarding the incidence and subtype-specific risk of fungal pneumonia in pediatric AML patients is lacking. This study aimed to determine the incidence of fungal pneumonia in children with AML receiving oral antifungal prophylaxis and to identify high-risk subgroups for improved surveillance and preventive strategies.

METHODS

The single-center retrospective study was conducted at the Pediatric Oncology Department of the University of Child Health Sciences/The Children's Hospital Lahore, following Institutional Review Board approval (957/CH.UCHS). A single-center approach was adopted, building upon retrospective analysis of 276 pediatric AML cases from July 2022 to June 2024 using a non-probability consecutive sampling technique. A sample size of 276 was estimated by using a 95% confidence level, 4.34% margin of error and an expected percentage of fungal infections as 16.1% in children with AML [17]. The study enrolled children under 16 years of age diagnosed with acute myeloid leukemia who presented to the Outpatient Department and emergency room during the study period. Only those receiving oral antifungal prophylaxis while undergoing chemotherapy were included. Both genders were represented in the study population, while children over 16 years of age and those without evidence of invasive fungal infection were excluded. Eligible patients received oral antifungal prophylaxis consisting of either Tablet Voriconazole at 4 to 6 mg/kg/day or Tablet Posaconazole at a dose of 100 mg orally twice daily on the first day, followed by 100 mg once daily for 13 days. Fungal pneumonia was classified into three categories. Suspected fungal pneumonia included patients with one host factor, prolonged neutropenia with fever lasting more than 96 hours unresponsive to broad-spectrum systemic antibiotics, and respiratory symptoms, potentially requiring empirical antifungal therapy. Probable fungal pneumonia was defined by the presence of one host factor, a clinical or radiological parameter, and non-culture-based mycological evidence such as fungal antigen or β -D-glucan, necessitating pre-emptive antifungal therapy. Proven fungal pneumonia was diagnosed when a patient had one host factor, relevant clinical or radiological features, and either a positive fungal culture or histopathological evidence, justifying specific antifungal therapy. Host factors included hematological malignancy, receipt of stem cell or organ transplant, inherited immunodeficiency, prolonged use of immunosuppressive therapy, or acute graft-versus-host disease. Radiological indicators of fungal pneumonia, as observed on high-resolution chest CT (128 slice CT scan), comprised pulmonary nodules, halo sign, air crescent sign, ground-glass opacification, or cavitation, suggesting pneumonitis, pneumonic consolidation, or fungal cavitations. Each patient's age, sex, presenting complaints, and HRCT (HRCT chest interpretations were standardized using predefined radiological criteria for fungal pneumonia features. Two experienced pediatric radiologists independently reviewed all scans, with disagreements resolved through consensus

discussion. A standardized reporting template was used to document specific findings (ground glass appearance, pulmonary nodules, halo sign, cavitation, consolidation). Chest findings were recorded. A structured proforma was used to document all relevant clinical and radiological details. Patients were followed throughout the study duration to monitor the development and classification of fungal pneumonia. The diagnosis of AML was confirmed on flow cytometry, identifying AML-specific markers including CD11b, CD13, CD14, CD15, CD33, CD36, and CD41 (also referred to as platelet antigen glycoprotein IIb/IIIa), CD42 (glycoprotein Ib), CD61 (glycoprotein IIIa), CD64, CD117 (cKIT), CD163, lysozyme, and MPO. FAB M1 and M2 subtypes have high levels of CD13, CD15, CD33, CD117, MPO, and often the stem cell marker CD34. FAB M3 has decreased to absent expression of HLA-DR (class II), CD11b and CD11c antigens. FAB M4 subtype has CD14, CD36, CD64, CD68, CD163, and lysozyme, all monocyte lineage-associated antigens, along with more typical myeloid markers, CD13, CD15, and CD33. FAB M4 AML also tends to express CD11b and CD11c antigens. FAB M5 subtype typically shows a decrease or loss of expression of CD13 but retains expression of CD14, CD15, and CD33, as well as CD36, CD11b, CD11c, CD64, and CD68, often on a single population of leukemic blasts. FAB M6 characteristically express the erythroid marker glycophorin A on the erythroblasts. FAB M7 typically expresses platelet glycoproteins, such as CD41, CD42, and CD61, along with CD13, CD33, and often CD36. Adherence was monitored through: (1) Weekly medication reconciliation during hospital visits, (2) Patient/caregiver medication diaries, (3) Pill counts at each visit, (4) Therapeutic drug monitoring when clinically indicated, (5) Documentation of missed doses and reasons. Patients with <80% adherence were excluded from analysis to ensure the prophylaxis effectiveness evaluation. Data completeness was ensured through: (1) Prospective data collection using standardized case report forms, (2) Weekly database monitoring for missing values, (3) Regular follow-up calls for missed appointments, (4) Electronic medical record integration for automatic data capture, and (5) Data verification by two independent research coordinators. For statistical analysis, SPSS version 24 was used. Quantitative variables were expressed as means with standard deviations, while qualitative variables were presented as frequencies and percentages. The Chi-square test was applied to evaluate associations between age, gender, and the occurrence of fungal pneumonia to determine statistical significance.

RESULTS

The study examined 276 AML patients with a mean age of 8.4 ± 2.65 years (range 1-16 years) with male predominance (56.9%). Patients were almost equally distributed between

age groups 1-8 years (51.1%) and 9-16 years (48.9%). The most frequent AML subtype was M2 (34.1%), followed by M4 (16.7%), M5 (8.3%), and others (40.9%). Laboratory assessments revealed a mean hemoglobin of 8.41 ± 2.65 g/dL, mean total leukocyte count of $29.90 \pm 1.34 \times 10^9/L$, mean platelet count of $41.94 \pm 1.54 \times 10^9/L$, and mean blast percentage of 38.8%. Fungal pneumonia was identified in 69 patients (25.0%), predominantly affecting M2 and M4 subtypes (approximately 50% of cases). The most common CT findings were Ground Glass Appearance (20.7%) and Pulmonary Nodule (20.3%), followed by Consolidation (9.4%), Cavitation (5.1%), and Halo Sign (4.7%).

Table 1: Demographic, Clinical Characteristics, Laboratory Parameters, Fungal Pneumonia Characteristics and CT Findings of AML Patients

Variables	Mean $\pm$ SD/ n (%)
Clinical Characteristics	
Mean Age (Range)	1-16 Years: 8.4 ± 2.65
Gender Distribution	Males: 157 (56.9%)
	Females: 119 (43.1%)
Age Groups	1-8 Years: 141 (51.1%)
	9-16 Years: 135 (48.9%)
AML Subtypes	M2: 94 (34.1%)
	M4: 46 (16.7%)
	M5: 23 (8.3%)
	Others: 113 (40.9%)
Laboratory Parameters of AML Patients	
Hemoglobin	8.41 ± 2.65 g/dL
Total Leukocyte Count	$29.90 \pm 1.34 \times 10^9/L$
Platelet Count	$41.94 \pm 1.54 \times 10^9/L$
Blast Percentage	38.8%
Fungal Pneumonia Characteristics in AML Patients	
Total Patients with Fungal Pneumonia	69 (25.0%)
Most Common AML Subtypes	M2 and M4 (Approximately 50% of Cases)
CT Findings in AML Patients with Fungal Pneumonia	
Ground Glass Appearance	57 (20.7%)
Pulmonary Nodule	56 (20.3%)
Halo Sign	13 (4.7%)
Cavitation	14 (5.1%)
Consolidation	26 (9.4%)

When stratified by gender, fungal pneumonia affected 21.0% of male versus 30.3% of female ($p=0.079$), suggesting a non-significant trend toward higher female prevalence. Age-based stratification showed similar rates between younger (26.2%) and older children (23.7%) with $p=0.627$. The distribution of fungal pneumonia varied significantly across AML subtypes ($p=0.009$), with the highest rates in M5 (39.1%) and M2 (31.9%) subtypes, followed by other subtypes (23.0%), while M4 had the lowest incidence (8.7%) (Table 2).

Table 2: Stratification of Fungal Pneumonia in Patients with AML Concerning Different Variables

Variables		Fungal Pneumonia		p-Value
		Yes	No	
Gender	Male	33 (21.0%)	124 (79.0%)	0.079
	Female	36 (30.3%)	83 (69.7%)	
Age Groups	1-8 Years	37 (26.2%)	104 (73.8%)	0.627
	9-16 Years	32 (23.7%)	103 (76.3%)	
AML Subtype	M2	30 (31.9%)	64 (68.1%)	0.009
	M4	4 (8.7%)	42 (91.3%)	
	M5	9 (39.1%)	14 (60.9%)	
	Others	26 (23.0%)	87 (77.0%)	

DISCUSSION

This retrospective study found that 25.0% of pediatric AML patients developed fungal pneumonia despite receiving oral antifungal prophylaxis. The mean age of our cohort was 8.4 ± 2.65 years with male predominance (56.9%), consistent with typical demographic patterns in pediatric AML. Our findings reveal important insights regarding fungal pneumonia in this high-risk population. The 25.0% incidence of fungal pneumonia observed in our study aligns with rates reported by Kobayashi *et al.* who documented invasive fungal infections in 21-30% of pediatric patients with hematologic malignancies [18]. Similarly, Fisher *et al.* reported cumulative incidence of invasive fungal disease ranging from 7.2% to 27.4% in children with AML despite prophylaxis, suggesting variable effectiveness of preventive strategies across different clinical settings [19]. Present study demonstrated significant variation in fungal pneumonia rates across AML subtypes ($p=0.009$), with M5 (39.1%) and M2 (31.9%) showing the highest prevalence compared to other subtypes (23.0%), while M4 had substantially lower rates (8.7%). This heterogeneity supports observations by Sung *et al.* who found that infection susceptibility differs across AML subtypes, potentially due to subtype-specific impacts on neutrophil function and immunological defenses [20]. The particularly high risk in M5 subtypes may reflect the profound monocytopenia and dysfunctional granulocyte responses characteristic of this subtype, as previously documented by Lehrnbecher *et al.* [21]. Radiologically, ground glass appearance (20.7%) and pulmonary nodules (20.3%) predominated in our cohort, followed by consolidation (9.4%), cavitation (5.1%), and halo sign (4.7%). These patterns are consistent with Greene *et al.*, comprehensive analysis of radiographic manifestations of invasive pulmonary aspergillosis, though current observed frequency of halo sign was lower than the 60-80% reported in some adult series. This discrepancy may reflect age-related differences in radiological presentation or variations in pathogen epidemiology [22]. Regarding gender distribution, we noted a trend toward higher fungal

pneumonia rates in female (30.3%) compared to male (21.0%), though this did not reach statistical significance ($p=0.079$). This finding contrasts with most published literature, which has not identified significant gender disparities in fungal infection susceptibility among pediatric AML patients. Castagnola *et al.* reported no gender-based differences in invasive fungal infection rates in their multicenter study of pediatric hematology patients [23]. Current age-stratified analysis showed comparable fungal pneumonia rates between younger (1-8 years: 26.2%) and older children (9-16 years: 23.7%) ($p=0.627$). This contrasts with Hovi *et al.* who reported higher infection risks in younger children due to immature immune systems and treatment-related factors. The absence of age-related differences in our cohort may reflect uniform application of prophylactic strategies across age groups [24]. The 25% incidence of fungal pneumonia despite prophylaxis highlights important limitations in current preventive approaches. The breakthrough infections observed in our study align with findings from a multicenter trial by Maertens *et al.* which demonstrated that even with posaconazole prophylaxis, approximately 20% of high-risk patients still developed invasive fungal disease. This underscores the need for improved preventive strategies, particularly for high-risk AML subtypes [25].

This study was limited by its retrospective single-center design, which may reduce generalizability and restrict causal interpretation. Diagnosis relied mainly on CT imaging, which may not capture all confirmed fungal infections without microbiological correlation. Future multicenter prospective studies with larger populations, advanced fungal diagnostics, and comparative evaluation of different prophylactic regimens are recommended to optimize prevention and management of fungal pneumonia in pediatric AML patients.

CONCLUSIONS

It was concluded that children with AML taking oral primary antifungal prophylaxis have a 25% incidence of fungal pneumonia. These findings highlight the importance of vigilant imaging surveillance and targeted interventions in high-risk subgroups (M2 and M4).

Authors' Contribution

Conceptualization: LI

Methodology: LI, SR, SG, II, AG, TA

Formal analysis: LI

Writing and Drafting: LI, SG, II, AG, TA

Review and Editing: LI, SG, II, AG, TA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Treatment-Related Mortality in Pediatric Acute-Lymphoblastic and Myeloid Leukemia: Experience from A Low- and Middle-Income Setting

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ABSTRACT

Treatment-induced complications are challenging to manage in low-middle-income country (LMIC) settings, leading to higher mortality rates. **Objectives:** To ascertain the frequency, causes, and risk factors leading to treatment-related mortality (TRM) in children with acute leukemia (ALL and AML) in our setup. **Methods:** A Retrospective descriptive cohort study was done at the Hematology Oncology Department of the Children's Hospital, Lahore. Using non-probability consecutive sampling, data of pediatric acute leukemia patients (<16 years of age) who experienced TRM during the study period were recorded. **Results:** Among TRM 136 (75%) had Acute-Lymphoblastic-Leukemia, and 45 (25%) had Acute-Myeloid-Leukemia. Median age of expiry 7.0 years (1-15 years) with a Male-to-Female ratio 1.5:1. Underlying causes of TRM were Infection-related mortality in 168 (93%), Hemorrhage in 10 (5.5%), and Drug toxicity in 3 (1.5%). Under-nutrition (<10th centile) was found in 111 (61%) and 120 (67.4%) patients who were on active chemotherapy. Median hospital stays 10 days (1-45 days) and median distance of residence to medical facility 222 km (41-995 km). Median values of hematological parameters at death: hemoglobin 8.0 g/dl (2.6-14.7 g/dl), WBC 0.57x10³/mm³ (0.0-500), platelets 15x10³/mm³ (0-503), and CRP 149 mg/L (0.1-193 mg/L). Significant factors associated were platelet counts (p=0.009), hemoglobin (p=0.001), and CRP (p=0.017). **Conclusions:** The Major cause of TRM in children with acute leukemia is infection. Noteworthy factors were male gender, residents of rural areas, cytopenia, high CRP, under-nutrition, and ongoing chemotherapy sessions. The majority of deaths occurred during Induction chemotherapy. Infection prevention/control and enhanced supportive care can result in decreasing TRM in acute leukemia.

INTRODUCTION

Despite significant progress in pediatric oncology, cancer remains the leading cause of death among children globally and the second most common cause in high-income countries (HICs) [1]. Approximately 90% of the 400,000 annual pediatric cancer cases occur in low- and middle-income countries (LMICs), where five-year survival rates are markedly lower as compared to more developed areas or the world, estimating it less than 10% in low-income countries and around 50-60% in upper-middle-income countries (UMICs) [2-5]. In contrast, survival rates in HICs exceed 80% [2]. This striking disparity in outcomes can be attributed to numerous factors, including limited access to

specialized pediatric oncology centers, inadequate diagnostic services, insufficient availability of essential medicines and treatment supplies, a shortage of trained healthcare professionals, weak social support systems, delayed presentation, and high rates of treatment abandonment in LMICs [6]. As a result, the burden of pediatric cancer is disproportionately borne by resource-limited countries, which face significant challenges in providing optimal supportive care [7]. Many pediatric cancer units in LMICs lack the infrastructure and supportive care available in HICs, affecting outcomes when applying standardized/high-intensity regimens developed



in high-resource settings. As a result, the risks and benefits of these treatments often differ significantly between the two settings and are often associated with increased treatment-related toxicity and mortality in LMICs due to a lack of required supportive care [8]. Infections, particularly sepsis, remain a leading cause of death among children undergoing cancer treatment in these regions [9, 10]. Although treatment-related mortality (TRM) has declined over time in some UMICs, it continues to be a major contributor to poor outcomes in many LMICs. Enhancing the quality of care for pediatric cancer patients in these settings is essential to address the global survival gap [7]. However, a major barrier to progress is the lack of robust data on the causes and risk factors for TRM in LMICs, limiting the development of targeted, context-specific interventions.

Treatment-related mortality (TRM) remains a major barrier to improving survival in children with acute leukemia in low- and middle-income countries, where limited supportive care and high infection burden contribute substantially to poor outcomes. Despite advances in chemotherapy protocols, there is insufficient local evidence from Pakistan regarding the frequency, major causes, and contributing risk factors of TRM in pediatric ALL and AML patients. This study addresses this critical gap by evaluating the burden of TRM, identifying predominant causes such as infection and sepsis, and assessing demographic, nutritional, and clinical factors associated with mortality. This study aims to determine the rate and underlying causes of treatment-related mortality in pediatric patients with acute leukemia and to explore associated demographic and disease-related factors.

METHODS

This retrospective descriptive study was conducted in the Pediatric Hematology-Oncology and Bone Marrow Transplant Department at The Children's Hospital Lahore, Pakistan. The study duration was one year, and the data were collected from 1st January 2023 to 30th December 2023 after taking an Institutional Review Board approval (IRB No. 818/CH-UCHS). All pediatric acute leukemia patients who expired during the treatment and the study period and fulfilled the criteria of the study were recorded. The Non-probability consecutive sampling technique was used for the recruitment of the sample. Previous literature from similar low- and middle-income settings has reported TRM rates between 15–30%, particularly during induction chemotherapy [7]. Based on a total of 706 new leukemia cases in the study period, the observed TRM frequency of 181 (25.6%) was consistent with this expected range, supporting the relevance and adequacy of the sample size for descriptive analysis. The clinical course of the patient in each group was recorded on a pre-designed proforma. The

data obtained included demographic information (name, age, sex, and address), complete history, physical examination, subtype, laboratory, and radiological investigation that were done during hospital stay to determine the cause of the presenting illness and death. Patients were put in groups according to the type of leukemia. Inclusion criteria: All children diagnosed as having pediatric acute leukemia (ALL and AML) with an age range of 01 to 16 years, who were started on treatment and died before completing treatment due to any treatment-related complications. Exclusion criteria were children less than one year and more than 16 years of age, relapsed disease, expired before treatment started, treatment started/taken at other hospitals, malignancies other than acute leukemia, on Palliative treatment, and any cause of death other than treatment-related. All patients of ALL were treated according to the UKALL 2011 Interim Guidelines [11], and all patients of AML were treated according to the COG AAML 0531 protocol [12]. For the current study, operational definitions were formulated as follows: TRM was defined as any death during remission induction chemotherapy or any death occurring on treatment after remission induction chemotherapy with documented complete remission [13]. Under-nutrition was defined as less than the 10th centile weight-for-age (WFA) plotted on the CDC WFA centile growth charts. Death due to haemorrhage was defined as death due to intracranial bleeding or cerebral thrombosis evident on neuroimaging, viz, CT or magnetic resonance imaging (MRI). Death due to drug toxicity was defined as any drug-related complication suggested by the laboratory and/ or radiological findings. Sepsis was defined as clinical or laboratory evidence of infection with multiple organ dysfunction syndrome (MODS). The principal outcome measure of my study was to determine the causes of TRM. Further, they were divided into sepsis, drug toxicity, and hemorrhagic complications. The data were analyzed using SPSS version 24.0. Quantitative variables such as age, duration of illness, duration of treatment after diagnosis of malignancy, and hospital stay were summarized using medians and ranges due to non-normal distribution, as confirmed by the Shapiro-Wilk test. Categorical variables such as gender, clinical symptoms, and signs were described using frequencies and percentages. The Mann-Whitney U test was used to compare continuous variables between two independent groups, while the Pearson Chi-square test was applied to compare categorical variables. A p-value of <0.050 was considered statistically significant. Effect modifiers were controlled through stratification.

RESULTS

The total number of newly registered cases of acute leukemia in the duration of study period was 706, while the

total number of TRM of acute leukemia was 181 (25.6%) (Figure 1).

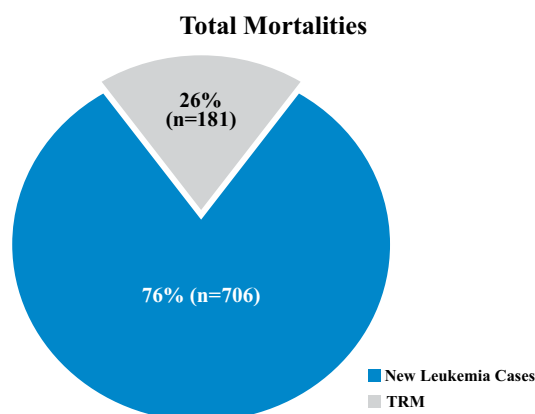


Figure 1: Total New Acute Leukemia Cases Vs TRM

Among the patients with TRM, 136 (75%) had Acute Lymphoblastic Leukemia, and 45 (25%) had Acute Myeloid Leukemia. Median age at expiry 7.0 years (1.0-15.0 years) with a Male-to-Female ratio of 1.5:1. The underlying causes of TRM were Infection-related mortality in 168 (93%), Hemorrhage in 10 (5.5%), and Drug toxicity in 3 (1.5%) (Table 1).

Table 1: Causes of Treatment-Related Mortality (TRM) (n=181)

Causes of TRM	Types	n (%)
Infection Related	Total	168 (92.8%)
	Sepsis	94 (51.4%)
	Fungal Pneumonia	34 (18.5%)
	Lower Respiratory Tract Infection	19 (10.5%)
	Central Nervous System (CNS) Infection	21 (11.6%)
Haemorrhagic	Intra-Cranial Bleed	10 (5.5%)
Drug Toxicity	Total	03 (1.7%)
	Peg Asparaginase-Associated Pancreatitis	01 (0.6%)
	Hepatic Failure	02 (1.1%)

The Mann-Whitney U test revealed significant differences in key hematological and inflammatory parameters at death. Platelet counts had a median of $15 \times 10^3/\text{mm}^3$ (range: 0-503; $p=0.009$) indicating a statistically significant reduction. Hemoglobin levels were also significantly low, with a median of 8.0 g/dL (range: 2.6-14.7; $p=0.001$). While WBC counts had a wide range (0-500 $\times 10^3/\text{mm}^3$) and a median of 0.57, the difference was not statistically significant ($p=0.096$). C-reactive protein (CRP) levels were markedly elevated median 149 mg/L (range: 0.1-193) showing a significant inflammatory response ($p=0.017$) (Table 2).

Table 2: Hematological Parameters Studied for Treatment-Related Mortality (TRM)

Factors	Parameter	Median (Range)	p-value (Mann-Whitney U test)
Hematological Parameters	Platelets ($\times 10^3/\text{mm}^3$)	15 (0-503)	0.009
	Hemoglobin (g/dL)	8.0 (2.6-14.7)	0.001
	WBC ($\times 10^3/\text{mm}^3$)	0.57 (0-500)	0.096
Inflammatory Marker	CRP (mg/L)	149 (0.1-193)	0.017

Undernutrition (<10th centile) was found in 111 (61%). Median stay at the hospital was 10 days (1-45 days), and median distance to travel to the medical facility was 222 km (41-995 km). Factors were studied concerning the cause of death (TRM), but no factor was found significant (Table 3).

Table 3: Factor Studied for Treatment-Related Mortality (TRM)

Factors	Groups	n (%)	p-Value
Age Groups	<1	0	0.190
	1-5	78 (43%)	
	5-10	62 (34.3%)	
	>10	41 (22.7%)	
Gender	Male	107 (59%)	0.530
	Female	74 (41%)	
Under-Nutrition	Yes	111 (61.3%)	0.740
	No	70 (38.7%)	
WFA (Centile)	<3	83 (45.9%)	0.930
	3-10	31 (17.1%)	
	11-25	23 (27.7%)	
	26-50	19 (10.5%)	
	51-75	13 (7.5%)	
	76-90	5 (2.8%)	
	91-97	1 (0.6%)	
	>97	6 (3.3%)	
Leukemia Type	ALL	136 (75%)	0.480
	Pre B	50 (27.6%)	
	Pre T	21 (11.6%)	
	Philadelphia +ve	5 (2.7%)	
	AML	45 (25%)	
ALL Risk Category	HR	65 (36%)	0.090
	SR	16 (8.8%)	
Last Chemo (Weeks Before Expiry)	<1	120 (66.3%)	0.820
	1-2	40 (22.1%)	
	>2	21 (11.6%)	
Expire During Chemo Session	Yes	122 (67.4%)	0.460
	No	59 (32.6%)	
Residence	Rural	135 (74.6%)	0.992
	Urban	40 (22%)	
	Afghanistan	6 (3.4%)	

(Data analysed using the Pearson chi-square test)

Blood culture results were available in only 14 (10.3%) cases of infection-related mortality with Pseudomonas (n=2), Klebsiella (n=1), MRSA (n=1), and no growth in 10 cases. Among the 168 infection-related treatment-related mortality (TRM) cases, 4 were culture-positive and 10

culture-negative. Median age was similar in both groups (7.5 vs. 6.5 years; $p=0.780$), with a comparable male predominance (75% vs. 60%; $p=0.620$). Rates of under-nutrition (75% vs. 70%), elevated CRP (median 162 vs. 141 mg/L), low platelets (median 12 vs. $16 \times 10^3/\text{mm}^3$), and anemia (median Hb 7.2 vs. 8.5 g/dL) were not significantly different (all $p>0.050$). Recent chemotherapy (<1 week) was more common in culture-positive cases (100% vs. 60%), though not statistically significant ($p=0.110$) (Table 4).

Table 4: Association of Culture Status with Clinical Variables among Infection-Related TRM Cases ($n=168$)

Variables	Culture-Positive (n=4)	Culture-Negative (n=10)	p-Value
Median Age (Years)	7.5 (3-12)	6.5 (1-14)	0.780
Gender (Male)	3 (75%)	6 (60%)	0.620
Under-nutrition (<10th centile)	3 (75%)	7 (70%)	0.840
Median CRP (mg/L)	162 (134-193)	141 (119-185)	0.210
Median Platelets ($\times 10^3/\text{mm}^3$)	12 (8-18)	16 (5-41)	0.390
Median Hemoglobin (g/dL)	7.2 (5.6-9.0)	8.5 (6.4-11.2)	0.160
Chemotherapy within <1 Week	4 (100%)	6 (60%)	0.110
Expired During Induction Phase	3 (75%)	6 (60%)	0.620

(Data analysed using the Pearson chi-square test)

Out of the total 181 TRMs, 118 (65%) were deaths during induction remission, and 17 (9.4%) during maintenance.

DISCUSSION

Roughly one in 15 children who are on active cancer treatment in LMICs die of treatment-related complications [7]. Chemotherapy-related febrile neutropenia (FN) exposes cancer patients to several treatment-related toxicities, making Infectious complications the major cause of mortality among pediatric oncology patients [10]. Specific cancers have concomitant immune deficiencies, e.g., lymphocytic leukemia patients commonly have hypogammaglobulinemia, which predisposes them to an increased possibility of encapsulated organisms. They might have repeated chest infections and bacteremia [14]. Children with cancer also have an increased risk of opportunistic viral-like fungal and protozoal infections, which are otherwise mild and rare in healthy people, but may lead to life-threatening complications in cancer patients [15]. Acute lymphoblastic leukemia ranks number one among childhood cancers having approximately 30% rate of incidence worldwide [16]. The overall 5-year survival of acute leukemia patients in High-income countries (HIC) like Sweden improved from 5% to more than 90% over the past 30 years [17]. But there is a significant disparity in the survival rate of childhood cancers in HICs and LMICs, attributed to several factors, including huge differences in the economy and infrastructure of health in these

countries [18]. Because there is scarce quality supportive care in LMIC, even more crucial than recurrence in cancer is treatment-related mortality [19]. Moreover, malnutrition always poses challenges in pediatric oncological patients with concurrent chemotherapy-related complications. This is a known fact that malnutrition has a noteworthy impact in multiple ways on the management of patients with pediatric acute leukemia [13]. A study conducted by Farrag et al. on pediatric cancer mortality in 2024 showed that the primary cause of mortality among hematological malignancies was TRM (66% of all cancer deaths), and among TRM main causes of death were infection-related (60%), hemorrhage (7.1%), and chemotherapy-toxicity (4.2%) [20]. Another study conducted by Rahat-Ul-Ain et al. on TRM in children with Acute lymphoblastic leukemia showed sepsis (87.5%) as a major cause of TRM, with malnutrition ($p\text{-value}=0.007$), reason for admission ($p\text{-value}<0.001$), immunophenotype ($p\text{-value}=0.032$) and ANC on death ($p\text{-value}<0.001$) being the significant factors associated with TRM [13]. This study identified sepsis and infection-related complications (93%) as the leading causes of treatment-related mortality (TRM). Additional factors significantly associated with TRM included thrombocytopenia, anemia, and elevated CRP levels at the time of death ($p\text{-value}=0.009, 0.001$ and 0.017 , respectively). A considerable proportion of TRM cases were also found to have underlying undernutrition (61%), and a notable percentage of deaths occurred during the induction phase of remission (65%). Importantly, these contributing factors are largely preventable. Although statistically non-significant, a large proportion of deaths occurred during induction and within one week of the last chemotherapy session, highlighting a clinically relevant trend. This suggests the induction phase is a high-risk period, warranting enhanced supportive care and close monitoring to prevent TRM. Therefore, TRM can potentially be reduced through improved supportive care, like strengthening infection control, prophylactic antibiotics use, nutritional support, and the use of appropriate chemotherapy protocols. Enhancing these aspects could significantly improve outcomes for pediatric oncology patients in low- and lower-middle-income countries. The Children's Hospital, University of Child Health Sciences Lahore, is the largest public sector pediatric hematology-oncology center in Pakistan, serving around 150 inpatients daily. This is the first study conducted from our center on factors associated with TRM in all types of acute leukemia. As the study highlights infection-related deaths as a major cause of death so it may serve as baseline assessment data for quality improvement projects in the future.

This study was limited by its retrospective single-center design, which may reduce generalizability to other

healthcare settings, and incomplete microbiological data, particularly low blood culture availability, which restricted detailed pathogen-specific analysis. The use of non-probability sampling and reliance on medical records may also introduce selection and documentation bias. Future multicenter prospective studies are recommended to validate these findings, improve infection surveillance, and evaluate the effectiveness of enhanced supportive care measures such as nutritional rehabilitation, early sepsis management, and strengthened infection prevention protocols to reduce TRM in pediatric leukemia patients.

CONCLUSIONS

The major reason for TRM in childhood acute leukemia cases in our resource-limited setting is infection. Noteworthy factors seem to be related to TRM were male sex, residents of rural areas, cytopenia, high CRP, under-nutrition, and ongoing chemotherapy sessions. The majority of the deaths due to treatment occurred during the Induction phase of chemotherapy in all types of acute leukemia. Infection prevention and control, and the provision of enhanced supportive care, can result in decreasing TRM in all types of childhood acute leukemia cases.

Authors' Contribution

Conceptualization: SG

Methodology: SG, AA, LI, RUA

Formal analysis: LI, RUA

Writing and Drafting: SG, WM, MF, AA, LI, RUA

Review and Editing: SG, WM, MF, AA, LI, RUA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Recurrence Rates and Postoperative Complications Following Colorectal Cancer Surgery: A 5-Year Study at a Tertiary Care Hospital in Peshawar

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ABSTRACT

Colorectal Cancer (CRC) is a leading cause of cancer related morbidity and mortality in the world. In low- and middle-income countries like Pakistan, delayed diagnosis, lack of access to specialist care, and irregular post-operative surveillance make things worse for a successful outcome. **Objective:** To evaluate the five-year recurrence rates and postoperative complications among patients undergoing colorectal cancer surgery at a tertiary care center in Peshawar, KPK, Pakistan. **Methods:** This retrospective cohort study was carried out in the department of General Surgery, Hayatabad Medical Complex, Peshawar, from March 2020 to February 2025. Patients presenting with metastatic disease at the time of surgery, palliative or bypass procedures, patients with missing follow-up data and patients lost to follow-up within 12 month following surgery were excluded from the study. **Results:** In terms of tumor stage, 14.4% had stage I, 28.5% had stage II, 46.8% had stage III, and 10.3% had stage IV. The majority of the patients (61.5%) underwent open surgery, while 38.5% underwent laparoscopic surgery. Postoperative complications were recorded in 122(39.1%) patients. Anastomotic leakage occurred in 6.7%, while surgical site infections (SSI) were observed in 12.2% of cases. **Conclusions:** A 26.9% recurrence rate and a high burden of postoperative complications were observed among colorectal cancer patients. Advanced stage, open surgery, anastomotic leaks, and older age were significantly associated with increased recurrence risk.

INTRODUCTION

As the third most common cancer (9.7% of all diagnosed cancers) and the second leading cause of cancer-related deaths globally, Colorectal Cancer (CRC) remains one of the most prevalent and fatal tumors [1]. For CRC, especially localized or locally advanced tumor stages, surgery is the cornerstone of curative therapy [2]. Despite significant advancements in surgical technique, perioperative care, and adjuvant medication, postoperative complications and relapse remained a significant therapeutic problem [3]. Depending on the tumor stage, surgical margins, and whether lymph nodes are involved, the 5-year recurrence rate for colorectal cancer following surgical resection has

been reported to range from 20-40% globally [4]. The liver and lungs are the most common sites for metastases, and recurrence might be local, regional, or distant [5]. Tumor biology, microsatellite instability, preoperative CEA levels, and the degree of lymphadenectomy are some of the several factors that influence recurrence [6]. In addition to contributing to poor patient outcomes, surgical complications such as anastomotic leak, wound infection, and ileus may further raise the chance of recurrence and death [7]. Pakistan has an increasing trend of CRC with scarce local surgical outcome data, particularly from under developed regions including Khyber Pakhtunkhwa



(KPK) [8]. Some reasons for the poor outcome in this group of patients include sociocultural determinants, and presentation at a late stage, lack of proper screening program, and access to oncology services. National studies have reported variable outcomes, with considerable heterogeneity in recurrence and complication rates, likely attributable to differences in postoperative protocols, patient adherence, and surgical expertise [9, 10]. International guidelines serve as standards for surgical quality and follow-up, but locally-derived data for assessment and improvement for CRC treatment in Pakistan are urgently needed. Few studies have systematically investigated the long-term prognosis of surgically treated colorectal cancer cases in Peshawar KPK. It is important to understand the pattern of relapse and the profile of postoperative adverse events for surgical planning, resource allotment and long-term monitoring. Colorectal cancer outcomes in Pakistan, particularly in underdeveloped regions like Khyber Pakhtunkhwa, remain poorly documented despite rising disease burden, delayed diagnosis, and inconsistent postoperative surveillance. Limited local evidence on recurrence rates, surgical complications, and long-term survival restricts the development of region-specific management strategies. This study aimed to evaluate five-year recurrence rates, postoperative complications, and survival outcomes following curative colorectal cancer surgery at a tertiary care hospital in Peshawar while identifying key predictors associated with recurrence and poor surgical outcomes.

METHODS

This retrospective cohort study was carried out in the Department of General Surgery, Hayatabad Medical Complex, Peshawar, from March 2020 to February 2025. Patients who were at least 18 years old who underwent curative-intent surgery for histologically certified colorectal adenocarcinoma during the study period were enrolled. Patients presenting with metastatic disease at the time of surgery, palliative or bypass procedures, patients with missing follow-up data and patients lost to follow-up within 12 month following surgery were excluded from the study. Patients who had systemic or metachronous cancer were also excluded. The sample size was calculated using the standard formula for estimating proportions in cohort studies: Assuming a 95% confidence level ($Z = 1.96$), and an expected recurrence rate (P) of 25%, and a 5% margin of error ($d = 0.05$), the minimum required sample size was 288 patients [11]. To account for potential exclusions, incomplete records, and loss to follow-up, a slightly larger sample of 312 patient were included. All data were obtained retrospectively from medical records, operation notes, and follow-up clinic visits. Demographic and clinical information (age, sex,

tumor location, TNM staging, histopathological grade and surgical related factors (type of resection, surgical approach and operation time, etc.) were collected. Postoperative morbidity was classified using the Clavien-Dindo classification system, where:

- Grade I-II were considered minor complications,
- Grade III-V were considered major complications.

Complications which were specifically analyzed included anastomotic leaks, Surgical Site Infection (SSI), wound dehiscence, postoperative ileus, intra-abdominal abscess and thromboembolic events. Tumor recurrence was defined as radiologically or histologically confirmed local, regional, or distant disease occurring after initial curative surgery. Diagnosis was confirmed either clinically or by imaging and/or biopsy. Imaging was conducted through contrast enhanced CT (Siemens SOMATOM Definition Flash) or MRI (GE Signa Explorer 1.5T). Biopsy was performed in certain patients to confirm recurrence histologically. Type of recurrences were noted in forms of presence/absence, time to recurrence (months to month since surgery) and site of recurrence. The follow-up time for the individual patients was 57 months or until the first event (recurrence or death) was observed. Surveillance was according to institutional guidelines by protocol; it included regular clinical review and regular CEA testing. CEA levels were measured using the Roche Cobas e411 analyzer, via Electrochemiluminescence Immunoassay (ECLIA) method. Serial CEA monitoring was performed every 3 to 6 months as per institutional follow-up protocols. Data were entered and analyzed using SPSS version 25.0. Continuous variables were expressed as means $\pm$ standard deviation or medians with interquartile ranges, depending on distribution, while categorical variables were presented as frequencies and percentages. Comparison with categorical variables were analyzed with chi-square, and with continuous variables by independent t-test. Recurrence-free survival was analyzed using Kaplan-Meier survival curves, and predictors of recurrence were identified by Cox proportional hazards regression. Recurrence-Free Survival (RFS) was defined as the time from surgery to the first documented recurrence or death. Overall Survival (OS) was defined as the time from surgery to death from any cause. Patients without recurrence or death were censored at the last known follow-up date. $P \leq 0.05$ was considered to be statistically significant. Ethical approval was obtained from Institutional Review Board before data collection (reference # 1217). As this was a retrospective study, the requirement for individual informed consent was formally waived by the IRB.

RESULTS

The participants' average age was 57.6 years, while 41.7% of the subjects were female and 58.3% were male. The tumors were distributed as follows: rectal tumors (40.7%) and colon cancers (59.3%). In terms of tumor stage, 14.4% had stage I, 28.5% had stage II, 46.8% had stage III, and 10.3% had stage IV. The majority of the patients (61.5%) underwent open surgery, while 38.5% underwent laparoscopic surgery. A total of 122 (39.1%) patients experienced at least one postoperative complication following colorectal cancer surgery. The total number of complication events recorded was 141, indicating that some patients experienced more than one type of complication. This results in an event-based complication frequency of 45.2%. The breakdown of individual complications is shown in table-1

Table 1: Demographic, Tumor, Surgical, and Postoperative characteristics of the study population

Variables	Frequency (%)
Mean Age (Years)	57.6
Gender	
Male	182 (58.3)
Female	130 (41.7)
Tumor Location	
Colon	185 (59.3)
Rectum	127 (40.7)
Tumor Stage	
Stage I	45 (14.4)
Stage II	89 (28.5)
Stage III	146 (46.8)
Stage IV	32 (10.3)
Surgical Approach	
Open Surgery	192 (61.5)
Laparoscopic Surgery	120 (38.5)
Postoperative Complications	
Anastomotic Leak	21 (6.7)
Surgical Site Infection (SSI)	38 (12.2)
Postoperative Ileus	34 (10.9)
Wound Dehiscence	19 (6.1)
Intra-abdominal Abscess	17 (5.4)
DVT/PE	12 (3.8)
Recurrence	
Recurrence Rate	84 (26.9)
Mean Time to Recurrence (months)	18.4

The Kaplan-Meier curve demonstrated a 12-month Recurrence-Free Survival (RFS) of 91.2%, 24-month RFS of 78.5%, 36-month RFS of 65.3%, and a 60-month RFS of 51.8%. The Overall Survival (OS) rates at 12, 24, 36, and 60 months were 95.6%, 86.7%, 74.9%, and 62.4% respectively. The median overall survival was estimated at approximately 57 months. The overall mortality rate was 69 (22.1%). The predominant cause of death was cancer

recurrence, 50 (72.5%) patients. Mortality due to surgical complications was observed in 10 (14.5%) patients, while unrelated medical causes were responsible for 9 deaths (13%) table 2.

Table 2: Oncologic outcomes and survival metrics (n = 312)

Variables	Frequency (%)
Recurrence-Free Survival (RFS)	
12-month RFS	285 (91.2)
24-month RFS	245 (78.5)
36-month RFS	204 (65.3)
60-month RFS	162 (51.8)
Overall Survival (OS)	
12-month OS	298 (95.6)
24-month OS	270 (86.7)
36-month OS	234 (74.9)
48-month OS	195 (62.4)
Median Overall Survival	47 months
Overall Mortality	69 (22.1)
Cause of Mortality	
Cancer recurrence	50 (72.5)
Surgical complications	10 (14.5)
Other causes	9 (13.0)

Tumor recurrence was identified in 84 patients, yielding an overall recurrence rate of 26.9%. The mean time to recurrence was 18.4 months (range: 4 to 49 months). Among those with recurrence, Stage III patients had the highest frequency (44 cases), followed by Stage II (18 cases), Stage IV (17 cases), and Stage I (5 cases), as illustrated in the figure below figure 1.

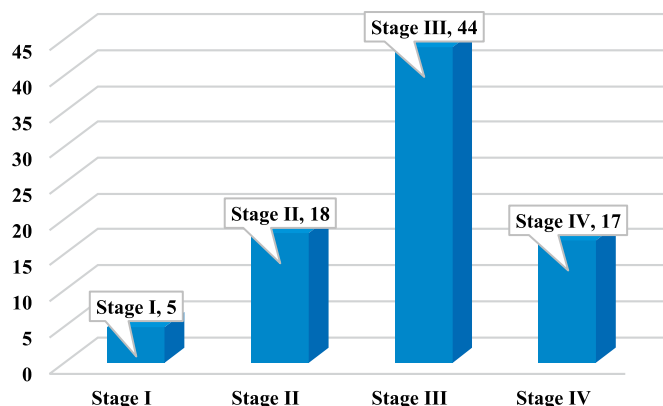


Figure 1: Recurrence Stage Frequency by TNM

Statistical analysis showed a significant association between higher tumor stage and recurrence ($p < 0.001$), and patients with recurrence were notably older than those without ($p = 0.012$). No significant links were found between recurrence and gender or tumor location. Open surgery was associated with higher complication rates ($p = 0.022$). A weak but significant positive correlation was observed between age and time to recurrence ($p = 0.035$), and recurrence-free survival varied significantly across tumor stages ($p < 0.001$) table 3.

Table 3: Association between Clinical Variables and Tumor Recurrence

Variables	Test Used	Test Statistic	p-Value
Age (recurrence vs no recurrence)	t-test	t = 2.52	0.012
Gender vs. Recurrence	Chi-square	$\chi^2 = 1.24$	0.260
Tumor Stage vs. Recurrence	Chi-square	$\chi^2 = 24.8$	<0.001
Tumor Location vs. Recurrence	Chi-square	$\chi^2 = 2.06$	0.150
Surgical Approach vs. Complication	Chi-square	$\chi^2 = 5.23$	0.022
Anastomotic Leak vs. Recurrence	Chi-square	$\chi^2 = 2.23$	0.140
Age and Time to Recurrence	Pearson Correlation	r = 0.21	0.035
Tumor Stage and RFS	Log-rank test	$\chi^2 = 29.6$	<0.001

Cox regression analysis identified tumor stage, surgical approach, anastomotic leak, and age as independent predictors of recurrence. Advanced-stage disease (Stage III-IV), open surgery, and anastomotic leaks were significantly associated with higher recurrence risk. Additionally, increasing age modestly raised the recurrence risk table 4.

Table 4: Multivariate Cox Proportional Hazards Regression for Predictors of Recurrence

Predictor	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-Value
Stage III-IV (vs I-II)	2.78	1.92 – 4.01	<0.001
Anastomotic Leak	1.89	1.15 – 3.10	0.012
Open Surgery (vs Laparoscopy)	1.52	1.01 – 2.30	0.045
Age (per year increase)	1.03	1.01 – 1.06	0.008

DISCUSSION

These average age of patients was 57.6 years, which is comparable to the average age of Western communities; yet, Oh B, found that the great majority of CRC cases in Western populations occur in people over 65 years of age [12]. With a significant percentage of Pakistani CRC patients under 60 years in over study, Bhurgri and Samiullah, had previously reported this trend of younger age of onset in populations of South Asian heritage [13]. Genetic predisposition, eating habits, and the region's underutilization of screening colonoscopies are some of the factors that could be responsible for this situation. Older age was significantly associated with recurrence ($p = 0.012$), and a weak but statistically significant positive correlation was noted between age and time to recurrence ($r = 0.21$, $p = 0.035$), implying that while recurrence risk increases with age, it may occur slightly later in older individuals. In terms of gender, 58.3% of research participants were men, which is consistent with statistics published by Al Rashid F et al., who similarly discovered a male prevalence among CRC patients in Lahore [14]. Higher exposure to possible risk factors, such as smoking, eating red meat, and engaging in sedentary behavior, may contribute to the rise in prevalence among men. In this study, colon cancer was more common (63.4%) than rectal

cancer (36.6%), which is also consistent with a global incidence analysis. However, when compared to the study of Hemminki et al., which exhibited higher incidence of rectal cancer, this might be explained by changes in distribution, most likely as a result of different environmental exposures or referral patterns [15]. Despite this variation, tumor location was not significantly associated with recurrence in the cohort ($p = 0.15$), suggesting that anatomical site alone may not independently predict oncologic outcomes. This staging data showed that the majority of patients received a diagnosis at Stage III (46.8%), followed by Stage II (28.5%). This end-stage illness resembles those reported by Ahmad R et al., and points to systemic issues with delayed detection, low public awareness, and the absence of structured screening programs in Pakistan [16]. It was found that anastomotic leakage rates of 6.7%, SSIs of 12.2%, and postoperative ileus of 10.9% in this sample. These rates are similar to the 5–8% reported by Abbasi H et al., who examined complications after colorectal surgery in Rawalpindi [17]. The series' recurrence rate of 26.9% was in line with rates reported in long-term follow-up studies 20–35% [18]. Anastomotic leak emerged as a significant independent risk factor ($p = 0.012$). These findings highlight the importance of surgical approach and perioperative care in influencing long-term oncologic outcomes. Stage III patients had the highest recurrence rate (52.3% of all recurrences), supporting the literature's earlier reports on the predictive significance of tumor stage Detering et al [19]. Just a small percentage of recurrences occur more than two years after surgery, and the mean time to recurrence in these series (18.4 months) is comparable to the data of Doah K et al., demonstrating the importance of careful follow-up shortly after surgery [20]. Tumor stage was strongly associated with recurrence in the analysis ($p < 0.001$), indicating its prognostic value. Patients with Stage III-IV disease had significantly higher recurrence rates than those with early-stage disease. This Kaplan-Meier analysis in this series demonstrated a gradual decrease in recurrence-free survival, with a considerable decrease in the first 30 months. These findings are consistent with those of Uehara et al., who highlighted the requirement to front load surveillance protocols in the first two to three years to detect early recurrences potentially still salvageable [21]. The study strength lies in its relatively large sample size and long follow-up that enabled meaningful assessment of patterns of recurrence and complications after the procedure.

Furthermore, the adoption of the standard data collection procedure, along with the survival analysis, helped to ensure the soundness of the findings. However the study is not without limitations. First, it is a single-center retrospective study, which may susceptible to various

biases such as selection bias and incomplete documentation. Additionally, detailed adjuvant treatment, molecular tumor features, and socioeconomic data were not available, which further restricted the depth of multivariate analyses. Prospective, multi-center studies with comprehensive molecular profiling and follow-up data are needed in the future to develop region-specific evidence-based approaches to management.

CONCLUSIONS

This study found that a significant proportion of colorectal cancer cases were diagnosed at an advanced stage, with an overall recurrence rate of 26.9% and a 60-month recurrence-free survival of 51.8%. Postoperative complications were observed in 39.1% of patients, with surgical site infections and postoperative ileus being the most common. Advanced tumor stage, anastomotic leak, open surgical approach, and increasing age were independently associated with higher recurrence risk.

Authors' Contribution

Conceptualization: TAR, FOS

Methodology: HJA, HI

Formal analysis: HAJ, HI

Writing and Drafting: TAR, FOS

Review and Editing: TAR, FOS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Adjunctive Brivaracetam Therapy in Epilepsy: A Prospective Clinical Study

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ABSTRACT

Epilepsy is one of those primary illnesses that affect the brain, and the population is estimated to be around 50 million people. **Objective:** To evaluate the efficacy and safety of adjunctive Brivaracetam therapy in adult patients with epilepsy. **Methods:** This observational, non-interventional, single-center study assessed the use of adjunctive Brivaracetam (BRV) in patients aged ≥ 16 years over six months (October 2023–March 2024). Eligible participants had stable antiepileptic drug (AED) regimens for at least one month before BRV initiation. Demographic data, seizure type, frequency, and intensity were documented at baseline, 3 months, and 6 months. The primary endpoint was the change in seizure frequency. Secondary outcomes included $\geq 50\%$ seizure reduction, seizure freedom, and adverse events. Data were analyzed using SPSS version 23.0. **Results:** A total of 168 patients (mean age: 25.1 ± 12.9 years) received adjunctive BRV therapy. Partial seizures and comorbid depression were the most common indications for BRV use. Mean seizure frequency decreased from 5.26 ± 0.29 at baseline to 2.41 ± 0.24 at 3 months. All patients achieved seizure freedom by 6 months. Reported adverse effects were generally mild: somnolence 12 (7%), headache 10 (6%), and dizziness 9 (5%). **Conclusions:** Adjunctive BRV therapy demonstrated significant efficacy in reducing seizure frequency and achieving seizure freedom, with a favourable safety profile. These findings support BRV as a promising treatment option for patients with epilepsy unresponsive to conventional AEDs.

INTRODUCTION

Epilepsy is one of those primary illnesses that affect the brain, and the population is estimated to be around 50 million people. Epilepsy is a neurological disorder that is marked by recurrent seizures, which in many ways affect the subject's quality of life, social standing, cognitive abilities, as well as physical wellbeing due to the possibility of the subject experiencing a fit at any given time [1]. It is important to state that the epilepsy disease burden is not evenly spread across the world; however, LMICs seem to be further burdened with this disease by factors such as

limited health care access, high perinatal brain damage incidence, and neuro-infection [2]. In Pakistan, the treatment deficit for epilepsy has been reported to be over 70%, which is due to social factors, inadequate knowledge about epilepsy, and the availability of neurological services [3]. Despite the use of first-line Anti-epileptic drugs (AEDs)-carbamazepine, sodium valproate and lamotrigine, many patients are still poorly controlled or experience side effects that are not tolerable, warranting the introduction of Brivaracetam as an added third-generation AED [4].



Anti-epileptic treatment is most commonly a lifelong process that involves administering AEDs to prevent seizures while limiting side effects in patients with epilepsy [5]. New AEDs have increased the availability of drugs for the treatment of epilepsy, and the situation when patients cannot tolerate conventional treatment or suffer from its side effects. Out of these, Brivaracetam, a drug that binds to the SV2A protein, has been found useful in treating focal seizures as an adjunct therapy to primary treatment in adults with epilepsy [6, 7]. Brivaracetam has been described to act through the SV2A protein as its binding partner in the synaptic vesicle and the course of synaptic transmitter release or recycling. This high selectivity of the drug to SV2A, as earlier pointed out, helps explain the drug's anticonvulsant efficacy, particularly in the focal seizures [8, 9]. As for its pharmacokinetics and anti-seizure mechanism, Brivaracetam has been discovered to be useful in patients with refractory focal seizures that are not effectively controlled with first-line AEDs [10]. Several papers and primary source articles were used for the literature review on randomized controlled trials and observational treatments with Brivaracetam (BRV) as an adjunct therapy for focal seizures. In a phase III study by Biton et al., Brivaracetam was proved to be effective in treating patients with refractory focal epilepsy, with seizure frequency reduction rates of 50% of range from 34–38% [11]. In the 2-year, open-label extension study, Klein et al., proved the long-term efficacy and safety with brivaracetam treatment, which includes the AE like dizziness, somnolence, and fatigue [12]. The BRIVAFIRST study is very beneficial in establishing the effectiveness of Brivaracetam (BRV) in actual focal epilepsy circumstances. That is 16.4% of the patients reported having no seizures at all within the 12 months, and 37.2% reported that at least their seizures were reduced by 50% from the baseline. These results provide evidence of BRV's ability to provide substantial seizure control to different patient groups and shed further light on the drug's role as a viable treatment in epilepsy [13]. An additional interventional study is an international, multicenter, non-interventional post-marketing individual patient data meta-analysis by The EXPERIENCE/EPD332 study, entailing epilepsy patients initiating the treatment with brivaracetam (BRV) in Spain, Germany, Australia, United States. This study included various clinical settings and patient categories. It was established that BRV was safe in the general clinical use and proved to be efficient as well [14]. Altogether, there is a growing epilepsy burden in Pakistan, and a large proportion of the population remains untreated; therefore, there is importance in the identification of well-tolerated AEDs for long-term management of epilepsy. However, there is little information on the efficacy and safety of brivaracetam with

lamotrigine in the local population.

Epilepsy remains a major neurological disorder in Pakistan, where many patients continue to experience uncontrolled seizures or intolerable side effects despite conventional antiepileptic drugs, creating a substantial treatment gap. Although Brivaracetam has shown promising efficacy internationally, there is limited local evidence regarding its real-world effectiveness and safety as adjunctive therapy in Pakistani adults with refractory epilepsy. This study aimed to evaluate the clinical efficacy, seizure reduction potential, and tolerability of adjunctive Brivaracetam therapy in adult epilepsy patients, addressing the lack of region-specific data for improved long-term management.

METHODS

An observational, non-interventional study was conducted in a real-world clinical setting from October 2023 to March 2024. The study did not involve any experimental or investigational use of Brivaracetam (Brivera; Helix Pharma Pvt Ltd, Sindh, Pakistan). The study was conducted by the principles of the Declaration of Helsinki and received ethical approval from the research ethics committee, Liaquat University of Medical and Health Sciences (LUMHS/REC/168). Informed consent was obtained from the patients, and patients' confidentiality was strictly maintained. All patients received Brivaracetam (Brivera manufactured by Helix Pharma) solely as part of their routine medical care, with treatment decisions made independently by their respective physicians, without any influence from the study investigators. A total of 168 patients were included, based on consecutive patient availability during the study period. In line with real-world evidence methodologies, no formal sample size calculation was performed, as the study design did not involve randomization, controlled interventions, or experimental protocols. The objective was to document treatment patterns and clinical outcomes as they occurred naturally in practice. Patients aged 16 years or older with a confirmed diagnosis of epilepsy were included if they had been on a stable dose of other antiepileptic drugs (AEDs) for at least one month before initiating adjunctive Brivaracetam (BRV) and had completed at least one follow-up after BRV titration. Patients were excluded if they had incomplete medical records, discontinued BRV before the first follow-up, had a known allergy to BRV, or had severe comorbidities that could interfere with follow-up visits. Patient characteristics, including age, sex, epilepsy type and origin, baseline seizure frequency, comorbidities, and prior antiepileptic drug (AED) use, such as the number, type, and duration of AEDs, were obtained from clinical records. Information gathered at 3 and 6 months after the beginning of BRV comprised information on the frequency of seizures and any associated adverse consequences. Seizure

reduction was defined as at least a 50% reduction of seizures from the baseline [15]. Seizure frequency was assessed based on clinical follow-up evaluations and patient-maintained seizure diaries, reviewed at each scheduled visit (baseline, 3 months, and 6 months). Seizure freedom was defined as the complete absence of seizures during the entire 6-month treatment period, as confirmed by patient/caregiver reports and medical record documentation [15]. Safety was supported by the low incidence of mild adverse events and the absence of serious drug-related complications. Brivaracetam (50–200 mg/day) was prescribed as adjunctive therapy, with dose adjustments based on clinical response and tolerability. It was administered alongside other antiepileptic drugs (AEDs), including lamotrigine, sodium valproate, carbamazepine, oxcarbazepine, phenobarbitone, and topiramate. Data were collected using a structured clinical assessment form adapted from a previously published phase III clinical trial on adjunctive brivaracetam therapy in adult Asian patients with focal-onset seizures [16]. Data were anonymized and stored securely, with access limited to authorized personnel only. Adverse drug reactions (ADRs) were monitored throughout the study. All reported adverse events were assessed for causality using the WHO-UMC causality assessment system [17]. Descriptive statistics were used to summarize the study variables. Categorical variables, such as gender, education level, seizure type, EEG findings, neuroimaging results, and antiepileptic drug combinations, were presented as frequencies and percentages. Continuous variables, including age, frequency of seizure and duration of epilepsy, were expressed as mean $\pm$ standard deviation (SD). Seizure frequency, measured at baseline, 3 months, and 6 months, was analyzed using non-parametric methods due to non-normal data distribution and lack of variance at the final time point. For repeated measurements of seizure frequency over time (Baseline, 3 Months, and 6 Months), the Friedman test was applied, as it is the non-parametric equivalent of repeated measures ANOVA. Pairwise comparisons between time points (Baseline vs. 3 Months, Baseline vs. 6 Months, 3 Months vs. 6 Months) were conducted using the Wilcoxon signed-rank test. A p -value < 0.050 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The study included 168 participants with a mean age of 25.1 ± 6.9 years (19–65 years). Among the participants, 79 (47%) were male, and 89 (53%) were female. Education levels showed notable variation among the 95 participants who provided their educational background, with 15 (8.9%)

being graduates, 22 (13.1%) having completed intermediate education, 36 (21.4%) completing matriculation, 48 (28.6%) with primary education, and 47 (28%) being uneducated. In terms of seizure types, 76 (45.2%) participants had focal onset seizures, 57 (33.9%) had focal onset with secondary generalization, 27 (16.1%) had generalized onset seizures, and 8 (4.8%) had unknown onset seizures. Brain imaging results were normal in 113 (67.3%) participants, while 12 (6.9%) had right MCA infarcts, 7 (4.2%) had mesial temporal sclerosis, 7 (4.2%) had CVST, 5 (2.9%) had encephalomalacia, and 24 (14.5%) had other abnormalities. EEG results showed normal findings in 115 (68.5%) participants and abnormal findings in 53 (31.5%). Sodium valproate was the most commonly used monotherapy, prescribed to 39 (23.2%) patients, followed by carbamazepine in 35 (20.8%) patients, oxcarbazepine in 29 (17.3%) patients, lamotrigine in 27 (16.1%) patients, phenobarbitone in 24 (14.3%) patients, and topiramate in 14 (8.3%) patients.

Table 1: Demographic Characteristics of Participants (n=106)

Demographics Variables	n (%)
Age (Years)	
Mean $\pm$ SD	25.1 $\pm$ 6.9
Min, Max	19, 65
Gender	
Male	79 (47%)
Female	89 (53%)
Education (n=95)	
Graduate	15 (8.9%)
Intermediate	22 (13.1%)
Matric	36 (21.4%)
Primary	48 (28.6%)
Uneducated	47 (28%)
Duration of Epilepsy	
Mean $\pm$ SD	7.57 $\pm$ 6.4
Min, Max	2 Months, 35 Years
Type of Seizures	
Focal Onset	76 (45.2%)
Focal Onset with Secondary Generalization	57 (33.9%)
Generalized Onset	27 (16.1%)
Unknown Onset	8 (4.8%)
Findings on Brain Imaging	
Normal	113 (67.3%)
Right MCA Infarct	12 (6.9%)
Mesial Temporal Sclerosis	7 (4.2%)
CVST	7 (4.2%)
Encephalomalacia	5 (2.9%)
Others (Encephalitis, Fungal Mass, Left MCA Infarct, Left Temporal Contusion, Leukoencephalopathy, Trauma)	24 (14.5%)
EEG Findings	
Normal	115 (68.5%)
Abnormal	53 (31.5%)

The most common reason for initiating adjunctive brivaracetam therapy was inadequate seizure control, reported in 75 (44.6%) of patients. Other prominent reasons included depression associated with prior antiepileptic drugs (AEDs) in 43 (25.6%) of cases and adverse drug reactions to previously administered AEDs in 42 (25.0%). A smaller proportion of patients 8 (4.8%), were switched to brivaracetam due to the use of an inappropriate drug as monotherapy (Figure 1).

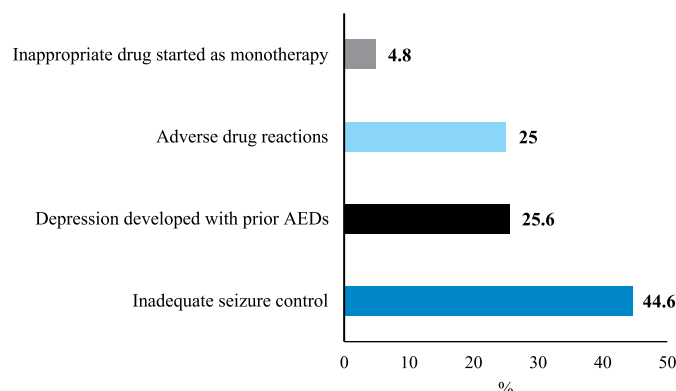


Figure 1: Reason to Start Adjunctive Brivaracetam (n=168)

Seizure frequency showed a significant reduction over time during adjunctive Brivaracetam therapy. The mean seizure frequency at baseline was 5.26 ± 0.29 , which decreased to 2.41 ± 0.24 at 3 months and reached 0.00 at 6 months. At the 6-month mark, all participants were seizure-free, resulting in a seizure frequency of 0.00 with no variability (SEM=0). The overall comparison using the Friedman test indicated a statistically significant difference across the three time points ($p < 0.001$). Post hoc pairwise comparisons using the Wilcoxon signed-rank test revealed that seizure frequency significantly decreased from baseline to 3 months ($p < 0.001$), from baseline to 6 months ($p < 0.001$), and from 3 months to 6 months ($p < 0.001$), confirming a consistent and progressive reduction in seizure burden throughout the follow-up period (Table 2).

Table 2: Comparisons of Seizure Frequency over Time and Across Time Points (Baseline, 3 Months, and 6 Months)

Time Point	Mean Seizures (Mean $\pm$ SEM)	p-Value**	Comparison	p-Value***
Baseline	5.26 ± 0.29	<0.001	Baseline vs. 3 Months	<0.001
3 Months	2.41 ± 0.24		Baseline vs. 6 Months	<0.001
6 Months	0*		3 Months vs. 6 Months	<0.001

*At 6 months, all participants were seizure-free. Seizure frequency was recorded as 0.00 with no variability (SEM=0);

Friedman Test; *Wilcoxon signed-rank test

A progressive and clinically meaningful reduction in seizure frequency was observed over the 6 months of adjunctive Brivaracetam therapy. Compared to baseline, seizure frequency decreased by 54% at 3 months, indicating a substantial early treatment response. By 6 months, all participants were seizure-free, reflecting a complete 100%

reduction in seizure frequency from baseline. This consistent downward trend underscores the effectiveness of Brivaracetam in sustained seizure control. The magnitude of reduction depicts the percentage change over time. The highest 50% responder rate defined as a $\geq 50\%$ reduction in seizure frequency was observed with BRV combined with sodium valproate, significantly outperforming combinations with oxcarbazepine (15.1%), carbamazepine (14.6%), and lamotrigine (12%). However, the 100% responder rate (complete seizure freedom) was comparable across all combinations, suggesting that while initial response rates varied by adjunctive therapy, BRV was broadly effective in achieving seizure freedom irrespective of the background AED regimen (Figure 2).

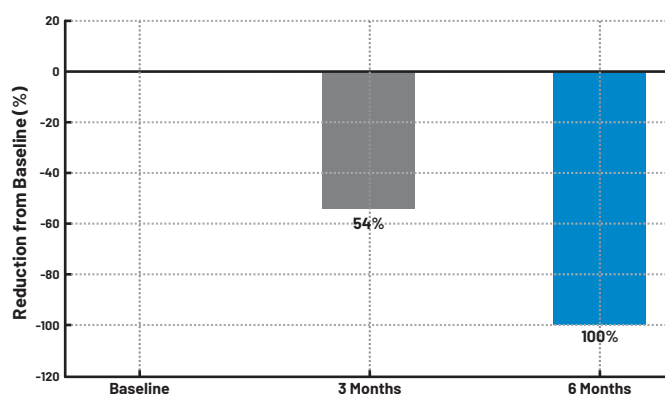


Figure 2: Percentage Reduction in Seizure Frequency at 3 and 6 Months Compared to Baseline during Adjunctive Brivaracetam Therapy

The most common treatment-emergent adverse events (TEAEs) observed in our study were somnolence 12 (7.1%), headache 10 (6.0%), 8 (4.8%), fatigue 5 (3.0%), and irritability 5 (3.0%). Less frequently reported TEAEs included insomnia and anxiety 3 (1.8%), and depression 2 (1.2%)

DISCUSSION

Brivaracetam (BRV) is approved in over 50 countries for treating focal-onset (also known as partial-onset) seizures, whether or not they evolve into secondary generalized seizures [14]. In our study Sodium valproate emerged as the most frequently prescribed monotherapy among patients, with carbamazepine following closely. Oxcarbazepine and lamotrigine were also common choices, while phenobarbitone and topiramate were prescribed less frequently. In a study conducted by Siddiqui et al., in Pakistan, the greatest reductions in seizures were observed when BRV was combined with sodium valproate, followed closely by its combination with carbamazepine. BRV paired with oxcarbazepine and lamotrigine also led to notable reductions in seizures, while combinations with phenobarbitone and topiramate resulted in smaller reductions [18]. Current study demonstrated a marked improvement in seizure control over the 6-month treatment period. Initially, patients exhibited frequent

seizures, which substantially decreased within the first 3 months of treatment, indicating a positive early response. By the end of the 6 months, all patients achieved seizure freedom, illustrating the sustained efficacy of the treatment in preventing seizures over time. This significant reduction suggests that the therapy not only addresses immediate seizure frequency but also supports long-term control, which is essential for improving patients' quality of life and stability. Previous analyses have demonstrated that brivaracetam (BRV), administered at doses of 50–200 mg per day, is effective in patients concurrently taking carbamazepine, lamotrigine, or topiramate [19, 20]. Inoue et al. found that adjunctive BRV was effective in patients taking concurrent valproate (VPA), carbamazepine (CBZ), or lamotrigine (LTG), the most commonly prescribed antiepileptic drugs (ASMs) in their study, aligning with standard clinical practice [16]. These findings are in line with the Ryvlin study, which also demonstrated BRV's efficacy and tolerability across different types and numbers of concomitant ASMs [21]. Adverse events (AEs) are a significant contributor to treatment failure with antiepileptic drugs (ASMs), often leading to early discontinuation, poor adherence, and preventing patients from reaching optimal therapeutic doses [22]. The most common treatment-emergent adverse events (TEAEs) observed in our study were somnolence 12 (7.1%), headache 10 (6.0%), dizziness 8 (4.8%), fatigue 5 (3.0%), and irritability 5 (3.0%). Less frequently reported TEAEs included insomnia and anxiety 3 (1.8%), and depression 2 (1.2%). Current findings align with several pivotal studies that have established the safety and tolerability of adjunctive brivaracetam therapy. Biton et al., and Ryvlin et al., reported low rates of adverse drug reactions (ADRs), with somnolence, headache, and dizziness being the most common, which is consistent with our findings, reinforcing its suitability for sustained use in epilepsy management due to generally well-tolerated side effects, as also noted in larger meta-analyses on BRV's tolerability [11, 21]. A systematic review and network meta-analysis on short-term tolerability found that brivaracetam (BRV) is associated with a lower risk of intolerable AEs and has a low rate of treatment withdrawal due to AEs [23]. Additional reviews indicate that BRV may be one of the most well-tolerated third-generation ASMs for focal seizures in adults [24, 25]. Despite the strengths of our methodology and findings, several limitations must be acknowledged. First, its single-center, observational design without a control group limits the ability to establish causal relationships and generalize findings to broader populations. Second, the relatively small sample size and short follow-up duration (6 months) may not fully capture long-term efficacy and safety outcomes. Third, reliance on patient-reported seizure diaries may introduce recall bias [26, 27].

Despite the strengths of our methodology and findings, several limitations must be acknowledged. First, its single-center, observational design without a control group limits the ability to establish causal relationships and generalize findings to broader populations. Second, the relatively small sample size and short follow-up duration (6 months) may not fully capture long-term efficacy and safety outcomes. Third, reliance on patient-reported seizure diaries may introduce recall bias [26, 27]. Future research should involve large-scale, multicenter randomized controlled trials with longer follow-up durations to validate efficacy, assess long-term safety, and compare Brivaracetam directly with other adjunctive therapies in diverse patient populations.

CONCLUSIONS

It was concluded that this study adds to the evidence supporting adjunctive BRV therapy's efficacy and safety for epilepsy management, underscoring its potential as an alternative for patients with inadequate response to other AEDs.

Authors' Contribution

Conceptualization: AHB

Methodology: AHB, MAL, SHS, NNS, NM, MIS, MAK

Formal analysis: ANB, MIA, MAK

Writing and Drafting: ANB, SHS, NNS, NM, MIS, MAK

Review and Editing: ANB, SHS, NNS, NM, MIS, MAK

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Innovative Pedagogies: Exploring Effective Teaching and Learning Methodology from Students' Perspective

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ABSTRACT

In recent years, educational institutions have integrated innovative methods such as interactive learning, digital tools, and student-centered approaches into traditional teaching to enhance understanding and engagement. Evaluating their effectiveness requires insight into students' perceptions is crucial. **Objectives:** To evaluate innovations in traditional teaching and learning methodology from the students' perspective of a public institution. **Methods:** A cross-sectional study was conducted at a Public Sector College, with a sample size of 282 students recruited through non-probability convenience sampling. Medical and dental undergraduates aged 18-24 years from both genders were included, while graduates and faculty members were excluded. Data collection involved a questionnaire filled out by undergraduate students using "Google Forms." Data were analyzed on SPSS version 25.0. **Results:** Among 82 participants, 41.8% were MBBS students and 58.2% were BDS students. Most students (37.6%) had limited knowledge of non-traditional teaching methods, yet 86.9% believed that specific learning outcomes should be included for each topic. Interactive lectures were favoured over traditional ones (46.8%), and students preferred 45-minute lectures followed by 15 minutes of revision. Nearly half (49.3%) favoured audiovisual learning over rote textbook study. Additionally, 42.2% felt the grading system needs improvement, and 64.5% highlighted the importance of interactive student-teacher strategies. Many preferred knowledge-based activities and e-learning, with 47.9% favouring e-learning over textbooks. **Conclusions:** It was concluded that transforming learned concepts into applied knowledge is more beneficial for students. Therefore, enhancing medical education is crucial for developing more competent and skilled physicians in the future.

INTRODUCTION

In medical and dental schools, teaching and learning have always been difficult since these fields require a precise and in-depth understanding of human anatomy, Physiology and other complex structures. No one can dispute that, in the twenty-first century, when everything has entered an advanced phase, medical research will probably evolve rapidly to keep up with the most recent technological developments. Information and communication

technology advancements will significantly impact the nature of medicine in the future, and it appears that the existing classroom model will not adequately prepare students for this future. Computer-aided education, virtual patients, augmented reality, human patient simulations, and virtual reality for competence evaluation are some new developments in teaching and assessment techniques [1]. Similarly, the field of teaching and learning itself has also



revised over the years in correlation to the introduction of newer techniques. Medical and dental educators are becoming more concerned that the traditional lecture-based curriculum used to teach medical and dental students does not spark students' interest or instill a lifelong appreciation of learning. As a result, adjustments must be made to the traditional teaching and learning methods. Traditionally, the main teaching method in medical school has been traditional didactic lecture-based learning (LBL). Fundamentally, LBL is a teacher-centred method that depends on the educator passively imparting knowledge to the student. This kind of instruction rewards memorization of data without requiring students to comprehend the material, and it frequently employs evaluation techniques that encourage surface learning [2]. The most prestigious medical and dentistry institutions in the world regularly implement innovative teaching techniques. This has increased students' attention and comprehension level in addition to aiding lecturers in expanding the topics. Measurable variations have been reported in the ways that students like to absorb, process, and remember new information [3]. Teachers need to be extremely skilled and informed in order to optimize student learning. Instead of depending just on conventional techniques, clinical education should use contemporary e-learning resources, including interactive platforms and asynchronous films. Online collaboration, virtual settings, and blended learning all improve student engagement, particularly in intricate domains like dental education. To increase the efficacy and efficiency of this resource-intensive teaching process, it is essential to comprehend the learning preferences of dental students [4]. The way a person interacts with knowledge and their personal learning preferences determine their learning style. It has been proposed that by being aware of these differences in learning styles, teachers can adapt their methods to better fit the preferences of their students, increasing the effectiveness and efficiency of their lessons. Determining one's preferred learning style can assist students in making choices that will improve their academic performance and increase their degree of pleasure with their educational journey [5]. Studies on students' preferred learning styles have been conducted for years, and it has been acknowledged that improving teaching strategies is necessary to increase knowledge comprehension and application. This study employs a Google questionnaire to collect opinions on traditional lecture-based instruction and ideas for improvement from medical and dental students at a single college in Karachi, Pakistan. By highlighting individual variances in attention span, expectations, and self-confidence, it challenges the antiquated idea of uniform learners. To address this variance, a customized teaching strategy is needed.

Multiple teaching modalities can better fulfil a range of learning demands, according to research [6, 7], which helps teachers combine old and modern approaches to create a more productive learning environment. The purpose of this study is to assess new developments in conventional teaching and learning approaches from the viewpoint of Karachi students. It is crucial to comprehend how students, who are the main stakeholders in the educational process, view the growing use of interactive tactics, digital tools, and student-centred approaches by educational institutions to improve engagement and learning results.

Traditional lecture-based teaching in medical and dental education often limits student engagement, critical thinking, and practical application of knowledge, while awareness of innovative teaching methodologies remains inadequate among many students. In Pakistan, limited local evidence exists regarding students' perspectives on integrating modern educational strategies such as interactive learning, e-learning, and outcome-based approaches into conventional systems. This study aimed to explore students' perceptions of current teaching practices, identify gaps in existing methodologies, and evaluate the effectiveness of innovative pedagogical approaches in improving learning experiences within public-sector medical and dental institutions.

METHODS

This descriptive cross-sectional study was conducted at a public sector institute in Karachi. The undergraduate student population of the first to final professional year of medicine and dentistry were included in the study. The study duration was 8 months from January 2024 to August 2024. Sample size determination was performed using "Raosoft Sample Size Calculator", which calculated a sample size of 282 with a 95% confidence level, a 5% margin of error, and a 50% response distribution based on a population size of 1050. A total of 282 students from both genders participated voluntarily. The sampling technique was non-probability convenience sampling. The ethical approval was taken by the institutional ethical committee of the institute (Ref. no: 049/23). The anonymity and patient details were kept confidential. Medical and Dental undergraduates whose age was between 18-24 years, both genders and students who consented to the study were included. Graduates, post-graduates, faculty members, non-teaching staff and Dental personnel were excluded from this study. The participants provided their verbal informed consent before completing a predesigned questionnaire validated from existing sources and reviewed by subject experts. The data were gathered using two-part Google questionnaire forms. The first section asked for demographic data, including branch (either

medicine or dentistry), professional year, and roll numbers. Students' knowledge of the traditional didactic lecture-based teaching style, student learning outcomes, their opinions on the length of each lecture, the quality of the evaluation standards, and the necessary adjustments and modifications to make learning sessions more engaging were all examined in the second part of the questionnaire, and recorded using Likert's scale. Data were analyzed using SPSS version 25.0. Descriptive statistics were computed through frequency and percentage distributions. Comparative analyses were conducted using the chi-square test, with statistical significance set at $p < 0.05$. This analytical approach allowed for the detection of significant differences in awareness levels across the various groups examined.

RESULTS

Out of the 282 participants, 118 students, or 41.8% of the total, were from BDS, while 164 students, or 58.2%, were from MBBS (Figure 1).

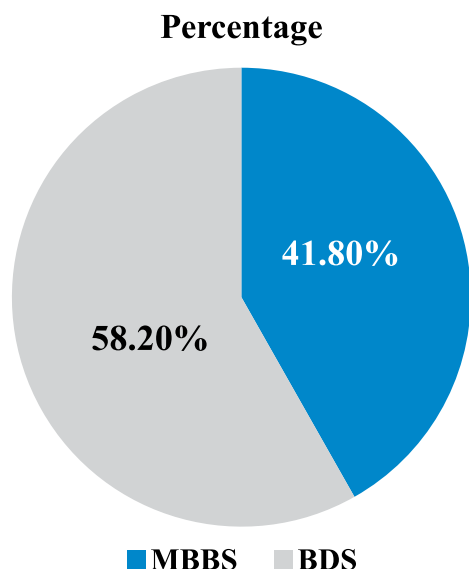


Figure 1: Population Size of MBBS and BDS in the Study

The third-year students responded at the highest rate from the first to the last year, or 27% ($n=78$) (Figure 2).

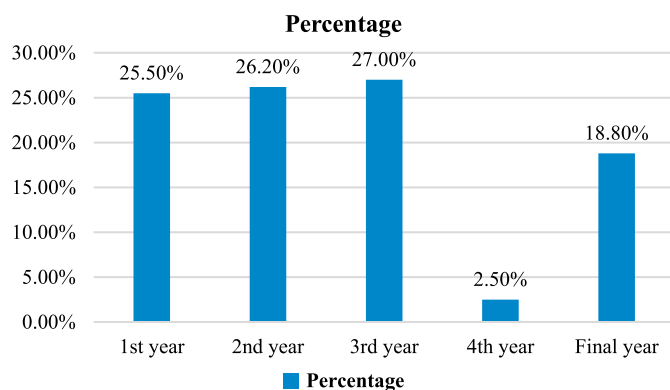


Figure 2: Percentage of Population from First to Final Year

Different questions were asked through a questionnaire to know about students' opinions on different teaching and learning methodologies and evaluation standards. A total of 245 (86.9%) students agreed that learning outcomes (SLOs) must be present with every topic. Approximately 106 (37.6%) population has little to no knowledge about teaching and learning methodologies other than the traditional one. A comparison between traditional and interactive teaching styles showed that most students, 132 (46.8%), prefer interactive lectures compared to the traditional chalk/duster method. A major study population of around 139 (49.3%) thinks that simply using audio-visual has better results than rote learning from textbooks. 119 (42.2%) of students agree that the grading system should be upgraded. Chi-square test was used in order to assess the association among variables ($p < 0.050$), but no statistical association was observed (Table 1).

Table 1: Response of Participants to Different Questions

Questions	Options	n (%)	P-Value
Using Student Learning Outcomes (SLO) Before Each Topic	Do Not Consider It Important for Each Topic	21 (7.4%)	1.066
	No Need for SLOS	12 (4.3%)	
	Must Be Present for Every Topic	245 (86.9%)	
	Only for Clinical Subjects	4 (1.4%)	
Awareness of Teaching / Learning Methods Other Than Conventional	Little Knowledge About Other Methods	106 (37.6%)	1.210
	Yes	100 (35.5%)	
	No	76 (27.0%)	
Preference for Traditional or Interactive Method	A New Method Should Be Introduced	36 (12.8%)	1.649
	Both Are Equally Effective	102 (36.2%)	
	Interactive Session	132 (46.8%)	
	Traditional Method	12 (4.3%)	
Ideal Time for Each Lecture	1 Hour with 15 Minutes of Revision	25 (8.9%)	1.385
	45 Minutes with 15 Minutes Revision	151 (53.5%)	
	30 Minutes with Revision in the Next Lecture	36 (12.8%)	
	45 Minutes With Revision in the Next Lecture	70 (24.8%)	
Question / Quizzes Involving Critical Thinking Should Be Added to the Module or Not	No	8 (2.8%)	0.907
	Yes	212 (75.2%)	
	Non-Clinical Subjects Should Include These	13 (4.6%)	
	Only Include in the Clinical Subject	49 (17.4%)	
Use of Audio / Visual and Chalk Duster Method Have The Same Result	Both Should Be Used Together	110 (39.0%)	1.463
	Audiovisual Is Better of Visual Presentation	139 (49.3%)	
	Traditional Is Better	14 (5.0%)	
	Level of Understanding Same	19 (6.7%)	
Need for Further Enhancement in the Evaluation Standard	Grading on Yearly Performance	63 (22.3%)	1.478
	Newer Grading Method for Viva/ Theory Evaluation	59 (20.9%)	
	The Current Method Is Sufficient	41 (14.5%)	
	The Grading System Should Be Upgraded	119 (42.2%)	

Preference in Teaching / Learning Methodology	Chalk And Talk with the Professor	48 (17.0%)	1.314
	Interactive Session	182 (64.5%)	
	Overhead Presentation by the Teacher and the Students	23 (8.2%)	
	PowerPoint Presentation by the Teacher	29 (10.3%)	
Need for Change in the Environment of Study	Introduce A Clinical Environment for Students	98 (34.8%)	1.232
	Environment Is Acceptable	7 (2.5%)	
	Upgradation with Advancement in the Field	54 (19.1%)	
	Activities with Application of Knowledge	123 (43.6%)	
E-Learning Tool Or books?	Books Require Revision E Learning Is Self-Modifying	75 (26.6%)	0.616
	Both Are Equally Effective Methods	55 (19.5%)	
	E Learning Is Preferred in This Era	135 (47.9%)	
	Books Are an Authentic Source	17 (6.0%)	

Duration of lecture plays a vital role in learning factor, and whatever the method is, once a saturation level of understanding is reached, students tend to lose interest. The most highly favoured duration of lecture was 45 minutes' lecture with 15 minutes of revision, opted by the student population of 159 (56.4%). Critical thinking and intellectual study are very important in every field to understand and excel in it. Approximately 212 (75.2%) agreed that questions involving critical thinking should be added in quizzes and monthly tests. Advancement in technology has provided new insight into learning style, using audio/ visual aids in addition to textbook learning helps enhance the concepts and solidify the fundamentals. However, a major study population of around 139 (49.3%) thinks that simply using audiovisual aids has better results than rote learning from textbooks. The grading system is very crucial to check a student's ability to grasp concepts and implement whatever is learned in the correct way. Over the years, there has been no significant change in grading and evaluation standards. 119 (42.2%) of students agree that the grading system should be upgraded. Different teaching methods have been introduced to make the process of learning more interesting and encouraging for students. Different options like (traditional chalk and duster method, interactive students' /teacher method, overhead presentation by teacher and students or simply lecture presentation only by teacher) are more or less different approaches converging towards the same method. In our study, about 182 (64.5%) emphasized more towards interactive student/teacher method. Over the years, a primitive environment for study has been a major reason for hindrance to quality learning. 123 (43.6%) populace for research corresponds by opting that activities that centers on the application of knowledge should be incorporated into this setting, similarly, in this era, E-Learning is navigating its way and proving to be more

beneficial for students in terms of gathering more erudition and skill set. 135 (47.9%) medical and dental students favoured E-learning over textbooks (Table 2).

Table 2: Response of Participants Concerning Year of Study

Questions	Most Chosen Option	1 st Year	2 nd Year	3 rd Year	4 th Year	Final Year	Total
Incorporation of student learning outcomes (SLO) before each topic	Must be present for every topic.	66	57	68	7	47	245
Awareness of Teaching / Learning Methods Other Than Conventional	Little knowledge about other methods.	24	33	34	3	12	106
Preference for traditional or interactive method	Interactive session	34	34	37	4	23	132
Ideal time for each lecture	45 minutes with 15 minutes revision	44	38	40	4	25	151
Question / quizzes involving critical thinking should be added to the module or not	Yes	57	51	56	5	43	212
The use of audio / visual and chalk duster methods has the same result	Both should be used together	35	33	43	2	26	139
Need for further enhancement in the evaluation standard.	The grading system should be upgraded.	34	32	32	2	19	119
Preference in teaching/learning methodology	Interactive session	41	49	45	5	42	182
Need for change in the environment of study	Activities with application of knowledge.	28	33	35	4	24	123
E-learning tool or books?	E learning is preferred in this era	33	33	41	4	24	135

DISCUSSION

The research paper evaluates innovations in traditional teaching and learning methodology from the perspective of students in a Medical and Dental College in Karachi. Dental students participated more than medical students, and the specific year of study in which they participated more was from third professional year. In a recent study, the third professional year contributed the most responses, and dentistry students participated at a higher rate than medical students. This tendency might be a result of students' heightened clinical and academic demands at this point, which encourages them to investigate effective learning resources like e-learning [8]. Research indicates that as students' progress in their education, their use of digital resources rises, underscoring the changing requirements of students during their clinical years. There are many methods to summarize the topics for studying

and deeply understanding the concept, and one of the very effective ways is the incorporation of student learning outcomes (SLOs) in students' yearly curriculum. About 86.9% students comment that SLOs must be present for every topic. According to a recent survey, 86.9% of students stressed that each topic should have its Specific Learning Outcomes (SLOs). SLOs aid in defining learning objectives, directing study activities, and improving academic achievement. According to research, having well-defined goals enhances student participation [9]. An organized and outcome-based approach to medical and dental education is ensured by including SLOs in curriculum preparation. The finding that 37.6% of students lacked awareness of alternative teaching styles highlights a significant gap in their educational experience. This suggests a continued reliance on traditional methods, limiting exposure to modern strategies such as problem-based learning, flipped classrooms, and digital tools. Without awareness, students cannot fully benefit from active learning techniques that enhance engagement and understanding. Institutions should conduct orientations or workshops to introduce these methods and encourage student involvement. Creating awareness can improve academic outcomes and make learning more effective and meaningful [10]. According to our research, more than half of the study population thought that the duration of class should be about 45 minutes of lecture with 15 minutes of revision. This result is consistent with educational research that indicates shorter, more concentrated sessions are more beneficial because students' attention spans tend to decrease beyond 45 minutes [11]. A revision period improves retention, promotes active recall, and serves to reinforce important ideas. A high percentage of our study population understands and agrees that questions involving critical thinking and intellect should routinely be a part of basic quizzes and assessments to change their pattern of study and learning. After examination comes the evaluation of students, which is equally important to know the academic standing of each student within the class [12]. The most commonly used method is examinations in the form of theory. OSCE and Viva are taken annually or biannually. Use of audio/visual and chalk duster methods has the same result. Digital technology has been incorporated into medical and dental education through the use of Google Forms for response collection, live streaming on YouTube, video lectures, problem-based and clinical-based learning, and more. Digital technological advancements will pave the path for a revolution in dentistry and medical education by enabling personalized, interactive, and effective learning [13]. Due to a lack of application of newer techniques to deep-rooted

methods, many students of our study population showed that they have little to no knowledge about different teaching and learning styles. There is a growing need to enhance evaluation standards in medical and dental education. Exams, whether theory or viva, are essential to assess a student's knowledge and capabilities. Clinical reasoning, especially in fields like physical therapy, involves critical thinking and self-reflection, making it challenging to teach and evaluate [14]. As examination patterns evolve, Pakistani medical institutions should focus more on critical thinking and problem-based questions. A curriculum that promotes clinical problem-solving, scientific reasoning, and communication skills is vital for lifelong learning [15]. A similar percentage of students highlighted the importance of having a clinical environment to apply theoretical knowledge for a deeper understanding. Effective blended learning or e-learning depends on accessible online platforms for both educators and students [16]. Traditionally, medical education relied on in-person lectures and printed materials. However, with the rise of the internet, modern curricula have expanded to include digital, online-supported teaching methods, enhancing the learning experience through e-learning [17]. Medical and dental students are encouraged to shift from traditional classroom methods to e-learning due to several advantages. E-learning increases accessibility by removing geographic barriers and offers flexible, self-paced learning tailored to individual styles [18]. It also reduces costs by minimizing the need for physical infrastructure and printed materials [19]. Additionally, interactive multimedia and simulations enhance engagement and retention, while global collaboration exposes students to diverse perspectives. Overall, e-learning supports adaptability to evolving educational and technological needs. A change in educational patterns is shown in medical and dentistry students' increasing preference for e-learning resources. A total of 135 (47.9%) of students in a recent research study preferred online learning to traditional textbooks, underscoring the need for learning systems that are flexible, interactive, and easily available [20]. Digital resources improve engagement and information retention by providing self-paced modules, multimedia content, and instant feedback. Research showed that the COVID-19 pandemic hastened this change even more [21]. While textbooks remain important, a blended learning approach may offer optimal outcomes. The teaching of untouched aspects of dentistry, like forensic odontology, also adds an interesting domain for the students [22]. Since each Chi-square value is less than the critical threshold for its degree of freedom, none of the questions exhibit statistically significant differences at the

$p < 0.05$ level. A comparatively homogeneous group in terms of educational exposure, experience, or institutional practices may be reflected in the consistency of the responses. Several patterns are noteworthy for their instructional value, even though the results were not statistically significant. There is substantial support for outcome-based education, as seen by the great majority of respondents (86.9%) who agreed that SLOs must be included for every topic. In the same way, 46.8% of respondents preferred interactive sessions over standard lectures, which is consistent with contemporary pedagogical trends that prioritize active learning. Approximately 53.5% of respondents preferred a 45-minute lecture with 15 minutes for revision after being asked how long they thought lectures should last. This distribution may help with curriculum preparation by pointing out a realistic time frame that promotes student attention spans [23] and information reinforcement, even if it is statistically non-significant. Despite the lack of significant diversity in responses, an adequate number of respondents (75.2%) supported the inclusion of critical thinking-based exams in all topics, demonstrating a broad appreciation of their function in cultivating analytical skills. The question of learning materials (e-learning vs. books) showed a preference for self-modifying resources (26.6%) and e-learning tools (47.9%), indicating an increasing trend toward adaptable, technologically enhanced learning environments [24, 25]. However, only 6% of respondents still valued traditional textbooks, highlighting the importance of using resources in a balanced manner. Overall, the patterns suggest a continuing shift in educational preferences toward interactive, learner-centred, and technologically integrated approaches, although no statistically significant differences were found. Even in the absence of statistically significant answer groups, these findings can help educators and curriculum creators match instructional tactics to student expectations.

The study was limited by its single-center design, convenience sampling method, and reliance on self-reported questionnaire responses, which may reduce generalizability and introduce response bias. Additionally, the cross-sectional nature restricted assessment of long-term educational outcomes. Future research should include multicenter studies with larger, diverse populations and longitudinal designs to evaluate the sustained impact of innovative teaching methods. Incorporating objective academic performance measures alongside student perceptions would further strengthen evidence for curriculum reform.

CONCLUSIONS

It was concluded that utilizing the learned concepts and converting them into applied knowledge is more beneficial for students; thus, refinement in medical education is key to producing more skillful and accomplished doctors more quickly.

Authors' Contribution

Conceptualization: MK, MM, MAK, FT, AS, ABKK

Methodology: MK, MM, MAK, FT, AS, ABKK

Formal analysis: MK, MM, MAK

Writing and Drafting: MK, FT, AS, ABKK

Review and Editing: MK, FT, AS, ABKK

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Role of Corticosteroid in Treatment of Bronchiolitis Presented to Qazi Hussain Ahmad Medical Complex

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ABSTRACT

Acute bronchiolitis is a major cause of hospitalization in infants and young children, most commonly caused by respiratory syncytial virus (RSV). Despite high spontaneous recovery rates, corticosteroids are frequently used, though their efficacy remains uncertain. **Objective:** To assess the short-term clinical efficacy of oral corticosteroids compared to placebo in infants with acute bronchiolitis. **Methods:** This quasi-experimental study was conducted at the Department of Pediatrics, Qazi Hussain Ahmad Medical Complex, Nowshera. A total of 234 children aged 3 months to 2 years with clinically diagnosed bronchiolitis were enrolled. Participants were allocated to receive either oral prednisolone (1 mg/kg/dose) or placebo twice daily for three days, alongside standard supportive care, including inhaled salbutamol. A blinded examiner assessed treatment response on day 3 using a validated respiratory distress score. Clinical improvement was defined as a reduction of more than two points in the score. **Results:** Clinical improvement was observed in 97.4% of the corticosteroid group and 94.9% of the placebo group. The difference was not statistically significant ($p=0.308$). Subgroup analyses based on gender, maternal education, socioeconomic status, and maternal occupation showed no significant impact on treatment outcomes. **Conclusions:** Oral corticosteroids did not significantly improve clinical outcomes compared to placebo in infants with mild to moderate bronchiolitis. Given the high rate of natural recovery and the potential for adverse effects, routine corticosteroid use is not recommended. Further research is needed to identify specific subgroups that may benefit from targeted steroid therapy.

INTRODUCTION

Acute bronchiolitis is a leading cause of lower respiratory tract infections in infants and young children, primarily resulting from inflammation and obstruction of the bronchioles. It most commonly affects children under two years of age and remains a major cause of pediatric hospitalization worldwide [1]. The disease typically presents with cough, wheezing, tachypnea (rapid breathing), and chest retractions (inward movement of chest muscles during breathing), which may progress to

respiratory distress in severe cases. While many children recover spontaneously with supportive care, a subset may require hospitalization and even intensive care support in resource-limited settings [2, 3]. Respiratory syncytial virus (RSV) is the most frequently implicated pathogen, accounting for approximately 30-70% of bronchiolitis cases [4]. Other causative agents include parainfluenza viruses, influenza A and B, adenovirus, rhinovirus, coronavirus, and human metapneumovirus. These



infections typically peak in colder seasons, placing a significant burden on healthcare systems, especially during winter months [5]. Inflammation in bronchiolitis is predominantly neutrophilic and can lead to epithelial damage and airway hyper-responsiveness, predisposing some infants to chronic wheezing and asthma later in life [6, 7]. The mainstay of bronchiolitis management remains supportive care, including hydration, oxygen therapy, and monitoring. However, interventions such as bronchodilators and corticosteroids have been frequently used in practice due to their effectiveness in conditions like asthma and croup [1]. Corticosteroids, in particular, are known for their anti-inflammatory effects, including the ability to reduce mucosal edema and limit immune-mediated tissue injury [8]. Despite widespread use, the clinical efficacy of corticosteroids in bronchiolitis remains controversial. While some randomized trials and observational studies have reported modest improvements in respiratory symptoms and hospital stay duration, many others have failed to demonstrate any significant difference when compared with placebo. This inconsistency in outcomes may reflect the heterogeneity of bronchiolitis in terms of viral etiology, host immune response, and disease severity. Consequently, international guidelines, including those from the American Academy of Pediatrics, advise against routine corticosteroid use in typical bronchiolitis cases [9]. In the South Asian region, and particularly within Pakistan, the existing evidence base on this subject remains limited [10]. Although corticosteroids continue to be prescribed for bronchiolitis in many local hospitals, robust local data evaluating their impact are scarce. A study from Pakistan by Ameen, Salahuddin, and Irfan (2025) found no clinical benefit from steroid use in bronchiolitis, highlighting the need for context-specific studies in neighboring populations [11]. To the best of our knowledge, no quasi-experimental study in Pakistan has directly compared oral corticosteroids with placebo in infants diagnosed with bronchiolitis, making this investigation both novel and necessary.

Acute bronchiolitis is a common cause of hospitalization in infants, yet oral corticosteroids continue to be widely prescribed despite inconsistent evidence regarding their effectiveness. In Pakistan, there is limited local research directly comparing corticosteroid therapy with placebo in bronchiolitis management, creating uncertainty in evidence-based pediatric practice. This study aimed to evaluate the short-term clinical efficacy of oral corticosteroids (prednisolone) in infants with mild to moderate bronchiolitis, using a standardized respiratory distress score to assess treatment response. Also, to examine whether demographic or socioeconomic factors

influenced treatment outcomes. In addition, to generate local data that could inform pediatric treatment practices in Pakistan, especially in resource-constrained settings, where corticosteroids are often used without definitive guidance.

METHODS

This quasi-experimental study was conducted in the Department of Pediatrics at Qazi Hussain Ahmad Medical Complex (QHMC), Nowshera, from October 2024 to March 2025. The study aimed to evaluate and compare the clinical efficacy of oral corticosteroids versus placebo in children diagnosed with acute bronchiolitis. The study was approved by the Institutional Ethical Review Board (IERB) of QHMC (Ref. No. 473/IERB/NMC) and by the Research Evaluation Unit (REU) of the College of Physicians and Surgeons Pakistan (Ref. No. CPSP/REU/PED-2022-305-6857). Informed, written consent was obtained from parents or legal guardians of all participants before enrolment. The study was conducted in full accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision), ensuring the rights, safety, and well-being of the Pediatric participants. Using non-probability consecutive sampling, 234 children aged 3 months to 2 years with clinical features of acute bronchiolitis were enrolled. Patients were non-randomly assigned to two groups based on a predefined allocation protocol maintained by the attending clinical team. The steroid group received oral prednisolone (1 mg/kg/dose) twice daily for 3 days. Placebo group: received a matched placebo solution with the same schedule. Both groups also received standard supportive care, including nebulized salbutamol, hydration, and oxygen therapy if required. Clinical efficacy was defined as a reduction of more than two points in the standardized Respiratory Distress Score after three days of treatment. This composite score (0-9) assessed three parameters: respiratory rate, wheezing, and use of accessory muscles. A reduction of ≤ 2 points was classified as no improvement. Inclusion Criteria were age 3 months to 2 years. Clinical diagnosis of bronchiolitis (cough, tachypnea, wheezing or crackles, chest retractions). Respiratory rate $>60/\text{min}$ (for <12 months) or $>50/\text{min}$ (for >12 months) and $\text{SpO}_2 <90\%$ on room air. Exclusion Criteria were suspected or confirmed asthma. Bacterial pneumonia. Illness duration >7 days. Requirement for ICU or ventilatory support. Prematurity or chronic cardiopulmonary/neurological disorders and corticosteroid contraindications. At baseline, demographic details and clinical parameters were recorded. A single, trained pediatrician blinded to treatment allocation assessed respiratory scores on Day 1 and Day 3 to reduce inter-observer variability and bias. Sample size was estimated using an online calculator (UBC

Statistics). Based on prior data showing clinical improvement of 99% in the steroid and 91% in the placebo groups [12], at a 95% confidence level, 80% power, and 5% margin of error, the required sample was 234 (117 in each group). The following formula was used: $n = [(Z\alpha/2 + Z\beta)^2 \times (p_1(1-p_1) + p_2(1-p_2))] / (p_1 - p_2)^2$. Where: n = required sample size per group, $Z\alpha/2$ = Z-value for desired confidence level (e.g., 1.96 for 95%), $Z\beta$ = Z-value for desired power (e.g., 0.84 for 80%), p_1 = expected proportion in group 1 (e.g., steroid group), p_2 = expected proportion in group 2 (e.g., placebo group) and $(p_1 - p_2)$ = effect size (difference between two proportions). $p_1 = 0.99$ and $p_2 = 0.91$, $Z\alpha/2 = 1.96$, $Z\beta = 0.84$. $n = [(1.96 + 0.84)^2 \times (0.99 \times 0.01 + 0.91 \times 0.09)] / (0.99 - 0.91)^2$ n = required sample size per group = 117. Total sample = 234 participants. All data were analyzed using SPSS version 25.0. The Shapiro-Wilk test was used to assess normality for quantitative variables (age, weight, hospital stay). As the data were not normally distributed, results were reported as medians (IQRs) and analyzed using non-parametric tests. Descriptive statistics were applied to demographic data. Clinical efficacy (primary outcome) was compared between groups using the Chi-square test, and Fisher's Exact Test was used when expected counts were <5 . Cramer's V was calculated for the effect size. A p-value <0.050 was considered statistically significant.

RESULTS

A total of 234 children aged 3 months to 2 years with clinically diagnosed bronchiolitis were included in this quasi-experimental study. Participants were equally assigned to either the corticosteroid group ($n=117$) or the placebo group ($n=117$). The overall cohort included slightly more female (53%) than male (47%). Most mothers had either an elementary (27.8%) or a graduate (25.6%) education. Regarding economic status, 36.3% were classified as well-off, 35.9% as middle-income, and 27.8% as poor. The majority of participants lived in rural areas (53.8%). In terms of maternal occupation, 35.5% were housewives, 34.6% manual workers, and 29.9% were employed in executive roles (Table 1).

Table 1: Descriptive Statistics of Categorical Variables ($n=234$)

Variables	Category	n (%)
Study Group	Corticosteroid	117 (50.0%)
	Placebo	117 (50.0%)
Gender	Female	124 (53.0%)
	Male	110 (47.0%)
Mother's Education	Elementary	65 (27.8%)
	Graduate	60 (25.6%)
	Highly Educated	55 (23.5%)
	Uneducated	54 (23.1%)
Economic Status	Well-off	85 (36.3%)

	Middle-income	84 (35.9%)
	Poor	65 (27.8%)
Living Area	Rural	126 (53.8%)
	Urban	108 (46.2%)
Maternal Profession	Housewife	83 (35.5%)
	Manual Worker	81 (34.6%)
	Executive	70 (29.9%)
Treatment Outcome	Improved	225 (96.2%)
	Not Improved	9 (3.8%)

The median age of participants was 12 months (IQR=11), and mean age was 12.43 ± 6.22 months. Median weight was 9.8 kg (IQR=4.9) and mean weight was 9.94 ± 2.88 kg. Median duration of hospital stay was 2 days (IQR=0.0), with a mean of 2.09 ± 0.46 days. All variables were non-normally distributed based on the Shapiro-Wilk test (Table 2).

Table 2: Descriptive Statistics of Quantitative Variables ($n=234$)

Variable	Median (IQR)	Mean $\pm$ SD
Age (Months)	12 (11)	12.43 ± 6.22
Weight (kg)	9.8 (4.9)	9.94 ± 2.88
Hospital Stay (Days)	2.0 (0.0)	2.09 ± 0.46

Clinical improvement was defined as a >2 -point reduction in the standardized respiratory distress score by Day 3. A total of 225 children (96.2%) met this criterion. The corticosteroid group showed an improvement rate of 97.4%, compared to 94.9% in the placebo group. However, this difference was not statistically significant ($\chi^2 = 1.04$, $p=0.308$). Fisher's Exact Test confirmed the non-significance due to small cell counts, and the effect size (Cramer's $V=0.067$) indicated a very weak association between treatment and outcome. Subgroup comparisons were conducted across gender, maternal education, economic status, residence, and maternal occupation. While some numeric differences were noted, none were statistically significant (Table 3).

Table 3: Subgroup Comparison of Treatment Efficacy ($n=234$)

Subgroups	Category	Improved n (%)	Not Improved n (%)	Chi-square (p-value)
Overall	Corticosteroid	114 (97.4%)	3 (2.6%)	1.04 (p=0.308)
	Placebo	111 (94.9%)	6 (5.1%)	
Female	Corticosteroid	58 (96.7%)	2 (3.3%)	0.004 (p=0.948)
	Placebo	62 (96.9%)	2 (3.1%)	
Male	Corticosteroid	56 (98.2%)	1 (1.8%)	2.124 (p=0.145)
	Placebo	49 (92.5%)	4 (7.5%)	
Mother's Education: Elementary	Corticosteroid	32 (100.0%)	0 (0.0%)	3.050 (p=0.081)
	Placebo	30 (90.9%)	3 (9.1%)	
Graduate	Corticosteroid	32 (97.0%)	1 (3.0%)	0.021 (p=0.885)
	Placebo	26 (96.3%)	1 (3.7%)	
Highly Educated	Corticosteroid	23 (92.0%)	2 (8.0%)	0.576 (p=0.448)
	Placebo	29 (96.7%)	1 (3.3%)	

Uneducated	Corticosteroid	27(100.0%)	0(0.0%)	1.019 (p=0.313)
	Placebo	26(96.3%)	1(3.7%)	
Economic Status: Poor	Corticosteroid	43(97.7%)	1(2.3%)	0.485 (p=0.486)
	Placebo	21(100.0%)	0(0.0%)	
Middle-income	Corticosteroid	28(100.0%)	0(0.0%)	1.024 (p=0.311)
	Placebo	54(96.4%)	2(3.6%)	
Well-off	Corticosteroid	43(95.6%)	2(4.4%)	0.996 (p=0.318)
	Placebo	36(90.0%)	4(10.0%)	
Living Area: Rural	Corticosteroid	66(98.5%)	1(1.5%)	1.317 (p=0.251)
	Placebo	56(94.9%)	3(5.1%)	
Urban	Corticosteroid	48(96.0%)	2(4.0%)	0.084 (p=0.772)
	Placebo	55(94.8%)	3(5.2%)	
Maternal Profession: Executive	Corticosteroid	43(97.7%)	1(2.3%)	1.170 (p=0.279)
	Placebo	24(92.3%)	2(7.7%)	
Housewife	Corticosteroid	34(97.1%)	1(2.9%)	0.508 (p=0.476)
	Placebo	45(93.8%)	3(6.3%)	
Manual Worker	Corticosteroid	37(97.4%)	1(2.6%)	0.008 (p=0.929)
	Placebo	42(97.7%)	1(2.3%)	

The finding illustrates the proportion of children who improved in both groups. While both arms demonstrated high efficacy, the steroid group had fewer non-responders (2.6%) than the placebo group (5.1%). Though not statistically significant, this trend suggests a possible clinical benefit in some subgroups. The majority in both groups improved, with a slightly higher number of non-improved cases in the Placebo group (Figure 1).

Treatment Efficacy by Intervention Group

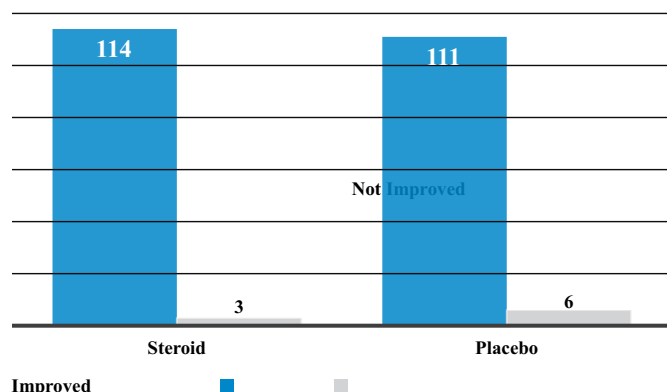


Figure 1: Improvement Versus No Improvement Across the Steroid and Placebo Groups

DISCUSSION

This quasi-experimental study evaluated the short-term clinical efficacy of oral corticosteroids in infants with acute bronchiolitis. Among the 234 enrolled participants, both treatment groups showed high rates of clinical improvement by Day 3, with no statistically significant difference between the corticosteroid (97.4%) and placebo (94.9%) groups ($p=0.308$). Subgroup analyses across gender, maternal education, economic status, residential status, and maternal profession similarly showed no significant variation in outcomes. These findings were

consistent with international clinical guidelines, such as those of the American Academy of Pediatrics, which recommend against the routine use of corticosteroids in bronchiolitis due to lack of proven benefit in most cases [12]. Multicenter trials and meta-analyses support this recommendation, highlighting the self-limiting nature of bronchiolitis and the high rate of spontaneous clinical resolution without pharmacological intervention [13-15]. Regionally, there was a noticeable scarcity of robust clinical studies on this topic in the Pakistani setting. However, limited data from tertiary care centers in South Asia mirror our results. For instance, Hasan et al. from Bangladesh observed widespread steroid use in pediatric bronchiolitis with no significant clinical advantage [16]. To our knowledge, this was among the first quasi-experimental studies in Pakistan specifically comparing oral corticosteroids and placebo for bronchiolitis in a controlled setting, thereby contributing much-needed local evidence. Internationally, some studies have suggested that corticosteroids may have a selective benefit in particular patient subgroups. Gelbart et al. found that in children with severe bronchiolitis requiring ventilation, corticosteroids may reduce the duration of respiratory support [17]. Others suggest a possible benefit in children with rhinovirus-associated bronchiolitis or first-time wheezers older than six months [18, 19]. However, these findings are not universally applicable and require more precise patient stratification. Our study reinforces the understanding that bronchiolitis is a clinically heterogeneous illness. Unlike asthma or croup, which respond predictably to anti-inflammatory therapy, bronchiolitis may involve variable viral triggers, age-related immune responses, and differing inflammatory profiles [20, 21]. Therefore, a uniform corticosteroid approach may not be justified for the general pediatric population. Importantly, the safety profile of corticosteroids must be carefully considered. Even short-term use may increase the risk of hyperglycemia, secondary infection, or other adverse effects [22]. Although our study did not record significant adverse events, the absence of added benefit makes such risks less acceptable in routine practice. Strengths of this study include a relatively large sample size, clear inclusion/exclusion criteria, blinded outcome assessment, and the use of a standardized clinical scoring system. This enhances the reliability and reproducibility of findings. The study was limited by its quasi-experimental design, non-randomized participant allocation, short follow-up duration, and focus on mild to moderate cases from a single medical center, which may reduce generalizability. Additionally, long-term respiratory outcomes and potential adverse effects of corticosteroids were not fully explored. Future research should involve multicenter randomized

controlled trials with larger diverse populations, longer follow-up periods, and subgroup analyses to identify specific patient groups that may benefit from corticosteroid therapy. This would strengthen treatment guidelines and optimize bronchiolitis management practices.

CONCLUSIONS

Oral corticosteroids showed no statistically significant benefit over placebo in infants with mild to moderate bronchiolitis over a short-term period. While both treatment groups demonstrated high rates of clinical improvement, the findings suggest that routine corticosteroid use offers limited additional advantage and should be approached cautiously. Given the self-limiting nature of bronchiolitis and the potential for adverse effects, corticosteroids should not be routinely prescribed in such cases.

Authors' Contribution

Conceptualization: AR

Methodology: MUS, GMZ, AS

Formal analysis: AR, IK, SN

Writing and Drafting: AR, IK, GMZ, AS

Review and Editing: AR, IK, GMZ, AS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

Fetomaternal Outcome of Pregnant Women with Malaria
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ABSTRACT

Malaria during pregnancy is a major public health concern, with devastating implications for both the mother and the unborn child. **Objectives:** To evaluate the maternal and fetal outcomes in pregnant women infected with *Plasmodium falciparum* and *Plasmodium ovale/vivax*. **Methods:** This descriptive cross-sectional study was carried out in Obstetrics and Gynecology Ward II using non-probability convenience sampling. It included 110 pregnant women diagnosed with malaria, excluding those with underlying health conditions. Data were gathered through interviews, medical records, and laboratory tests. Various maternal and neonatal factors, including hemoglobin levels and birth weight, were recorded. The chi-square test was performed to evaluate the relationship between malaria and fetal outcomes, with p-values < 0.05 considered statistically significant. **Results:** Among 110 pregnant women, 58 (52.7%) were aged 21-30 years. The majority, 69 (62.7%), had 2-5 pregnancies, while 25 (22.7%) were primigravida. Preterm birth and full-term deliveries were equally distributed, 55 (50.0%), while anemia was prevalent in 82 (74.5%) of cases. Low birth weight was observed in 35 (31.8%) of neonates. Among 71 women with *P. falciparum* infection, 63 (88.7%) developed anemia, which was significantly higher than in the *P. ovale/vivax* group, where only 19 out of 39 (48.7%) were anemic (p < 0.001). Preterm birth, 45 (63.4%) and low birth weight, 34 (47.9%), were significantly greater in *falciparum* cases (p < 0.001). **Conclusions:** It was concluded that *Plasmodium falciparum* infection poses a higher frequency of adverse fetomaternal outcomes compared to *Plasmodium ovale/vivax*, characterized by noticeably greater incidences of hypoglycemia, low weight at birth weight, premature birth, and anemia.

INTRODUCTION

Malaria in pregnancy is a well-documented worldwide health concern [1, 2], posing hazards to maternal, fetal, and newborn health, as well as impacting the wider community [2, 3]. From an epidemiological aspect, Pakistan is categorized as a country with a relatively high prevalence of malaria. Of the 217.1 million people living there, around 98% (212.6 million) are at risk of contracting malaria, with 54% having a high risk of infection [4]. *Plasmodium* parasite infections cause malaria, with *Plasmodium falciparum* (*P. falciparum*) and *Plasmodium vivax* (*P. vivax*) posing the greatest threat to humans [5]. When an infected female *Anopheles* mosquito bites a human, the disease is spread, causing a range of clinical signs from minor

discomfort to serious sickness and even death [6]. In Pakistan, *Plasmodium vivax* is the predominant cause of malaria, while *P. falciparum* accounts for approximately 15% of cases [7]. Worldwide, *P. falciparum* is the primary cause of malaria, frequently resulting in severe complications, especially among expectant mothers [8]. For many reasons, pregnant women are more vulnerable to malaria [9, 10], such as impaired immunity, which permits elevated parasitemia levels, and parasite accumulation in the placenta [11]. Furthermore, socioeconomic status and cultural variables may enhance experience or limit access to preventive interventions [12]. Pregnant women from lower SES backgrounds are more susceptible to

contracting malaria, insufficient prenatal care, improper health status, and adverse fetomaternal outcomes owing to limited access to healthcare resources and poor living situations [13]. The negative consequences of malaria during pregnancy are numerous and varied, with placental malaria being a frequent pathological consequence. Plasmodium-infected red blood cells becoming trapped inside the placenta's intervillous gaps is a defining feature of this disorder [14]. This can cause placental inflammation and impair the exchange of nutrients and gases, leading to unfavorable consequences such as low birth weight (LBW), premature birth, fetal mortality, and neonatal death [15]. Furthermore, malaria during pregnancy can cause maternal anemia, thus raising the risk of maternal death and further complicating pregnancy and childbirth, especially in malaria-endemic countries [16]. Early diagnosis of malaria is crucial for preventing complications, but it remains challenging. Many women harbor parasites with minimal or no symptoms due to immunity developed from repeated contact. The microscopic analysis of blood smears is the most often utilized approach for detecting placental malaria because of its long-term clinical use. Though this approach repeatedly fails to detect parasites in peripheral blood, even when they are abundantly sequestered in the placenta [17]. Because of this, those who have placental malaria can get false-negative test results, which would keep them untreated and unidentified. For pregnant women, rapid diagnostic tests (RDTs) offer an option, with reported sensitivity surpassing 90%, making them potentially more effective than traditional microscopy or clinical evaluation [18]. Pregnancy-related malaria remains a serious public health concern, particularly in endemic areas, contributing to severe maternal and neonatal complications. *P. falciparum* infection is known to cause more severe adverse outcomes, including anemia, preterm birth, LBW, and hypoglycemia, compared to *P. ovale/vivax*. Socioeconomic factors, residency, and access to healthcare further influence disease burden and outcomes. Understanding the differential impact of malaria parasite species on pregnancy outcomes is essential for emerging targeted prevention and management strategies.

Malaria during pregnancy remains a major public health challenge in Pakistan, particularly in resource-limited and endemic regions, where it contributes significantly to maternal anemia, preterm birth, low birth weight, and neonatal complications. Despite the high burden, limited local comparative data exist on the differential fetomaternal effects of *Plasmodium falciparum* versus *P. ovale/vivax* infections, especially among vulnerable rural and low socioeconomic populations. This study aims to analyze and contrast the fetomaternal outcomes of pregnant women infected with *P. falciparum* and *P.*

ovale/vivax, focusing on parameters such as maternal anemia, preterm birth, low birth weight, and hypoglycemia.

METHODS

This descriptive cross-sectional study was carried out in Obstetrics and Gynaecology Ward II at Peoples University of Medical and Health Sciences, Nawab Shah, utilizing a non-probability convenience sampling method. The study was performed for almost six months, from 26th June 2024 to 24th December 2024. This study was approved by the Ethical Review Committee with the reference # PUMHSW/SBA/PVC/ERC/44/2024. Using the open size Epi program for sample size calculation, the prevalence of malaria was 9.3%, as previously published study margin of error is 6%, interval 95% and 10% non-response rate. [19]. A total of 110 pregnant women in their third trimester who were diagnosed with malaria, based on specific criteria, such as age, gestational age, and severity of the infection, were included in the study. Women with underlying health disorders, such as sickle cell disease or psychological issues, who may have an impact on the study's outcomes, were excluded. All participants provided informed consent before data collection. Structured interviews, inspections of medical records, and laboratory testing were used to gather data. Plasmodium species were found on blood slides, and a Rapid Diagnostic Test (RDT) was used to confirm the diagnosis of malaria. The RDT used in this study was the SD BIOLINE Malaria Ag P.f/Pan (Standard Diagnostics, Republic of Korea; Catalogue No: 05FK60), which is commonly available. A small volume of capillary blood was obtained using a sterile lancet and added to the test cassette, followed by buffer solution as per the manufacturer's instructions. The presence of a colored test line along with a control line indicated a positive result. A pre-designed questionnaire was utilized to collect various data, including sociodemographic information, obstetric history, malaria status, laboratory findings (serum calcium and hemoglobin levels), and fetal outcomes such as preterm delivery (delivery of a baby before 37 weeks of gestation) [20], low birth weight (birth weight of less than 2500 grams (2.5 kg) [21], and neonatal birth weight. Every pregnant woman who was recruited was monitored until her hospital discharge following delivery. Laboratory testing, such as hemoglobin and blood glucose levels, was used to diagnose maternal anemia and neonatal hypoglycemia. Anemia was defined as hemoglobin levels less than 11 g/dL [22], and neonatal birth weight was measured shortly after delivery. Maternal Hypoglycemia was also monitored, which is a condition where blood glucose concentrations are low, defined as less than 2.2 mmol/L (40 mg/dL) [23]. Data were analyzed using SPSS version 23.0, with descriptive statistics used to summarize categorical variables as frequencies and percentages.

Fetomaternal outcomes and sociodemographic factors were compared between two malarial cases using the Chi-square test; a p-value of ≤ 0.050 was considered statistically significant.

RESULTS

There are 110 expectant mothers in all, with most of them, 58 (52.7%), aged between 21 and 30 years, followed by 35 (31.8%) in the 31 to 40 years' age group, and 17 (15.5%) under 20 years. In terms of parity, 69 (62.7%) of patients had between 2 to 5 pregnancies, while 25 (22.7%) were primigravida, and 16 (14.5%) had more than five pregnancies. Socioeconomic status was predominantly lower class 60 (54.5%), with 34 (30.9%) belonging to the middle class and 16 (14.5%) to the upper class. Regarding education, 45 (40.9%) of patients were uneducated, while 14 (12.7%) had primary education, 28 (25.5%) had secondary education, 16 (14.5%) had matric, and only 7 (6.4%) had studied up to the intermediate level. Most patients, 71 (64.5%), resided in rural areas, while 39 (35.5%) were from urban settings. A significant proportion, 104 (94.5%), were unemployed. The majority, 91 (82.7%), lived in a joint family system, while 19 (17.3%) lived in nuclear families. Malarial prophylaxis was taken by only 10 (9.1%) of patients, while 100 (90.9%) did not receive any prophylactic treatment. The incidence of preterm birth was 55 (50.0%), indicating an equal distribution between preterm and full-term births. Anemia was prevalent in 82 (74.5%) of patients, while 28 (25.5%) were non-anemic. Low birth weight was reported in 35 (31.8%) of newborns, whereas 75 (68.2%) had normal birth weight. Regarding the type of malaria parasite, *P. falciparum* was the most common, found in 71 (64.5%) of cases, while 39 (35.5%) were infected with *P. oval/vivax*. Hypoglycemia was observed in 18 (16.4%) of patients, whereas 92 (83.6%) had normal blood glucose levels, as depicted in table 1.

Table 1: Demographic Details of Pregnant Women with Malaria (n=110)

Variables	n (%)
Age of Patient (Years)	<20 17 (15.5%)
	21 to 30 58 (52.7%)
	31 to 40 35 (31.8%)
Parity of Patient	Primigravida 25 (22.7%)
	2-5 69 (62.7%)
	>5 16 (14.5%)
Socio Economic Condition	Lower Class 60 (54.5%)
	Middle Class 34 (30.9%)
	Upper Class 16 (14.5%)
Education Status	Uneducated 45 (40.9%)
	Primary 14 (12.7%)
	Secondary 28 (25.5%)
	Matric 16 (14.5%)
	Inter 7 (6.4%)
Residency of Patient	Rural 71 (64.5%)

	Urban	39 (35.5%)
Occupation of Patient	Unemployed	104 (94.5%)
	Employed	6 (5.5%)
Living Status of Patient	Joint Family	91 (82.7%)
	Nuclear Family	19 (17.3%)
Malarial Prophylaxis	Yes	10 (9.1%)
	No	100 (90.9%)
Preterm Birth	Yes	55 (50.0%)
	No	55 (50.0%)
Anemia	Yes	82 (74.5%)
	No	28 (25.5%)
Low Birth Weight	Yes	35 (31.8%)
	No	75 (68.2%)
Plasmodium Type	Falciparum	71 (64.5%)
	Oval/vivax	39 (35.5%)
Hypoglycemia During the Third Trimester of Pregnancy	Yes	18 (16.4%)
	No	92 (83.6%)

Pregnant mothers infected with *P. falciparum* and *P. ovale/vivax* had significantly different fetal outcomes. Women <20 years of age and primigravida cases were significantly greater in the *oval/vivax* group ($p < 0.001$). Socioeconomic and educational status also showed notable variations, with *falciparum* cases being more prevalent among the lower class 42 (59.2%) and uneducated women 30 (42.3%), whereas *oval/vivax* cases were more common in the upper class 15 (38.5%) and among those with higher education levels ($p < 0.001$). Residency and occupation further highlighted disparities, as *falciparum* cases were more frequent in rural areas 53 (74.6%) and among unemployed women 70 (98.6%), while *oval/vivax* cases were relatively more urban-based and included a higher proportion of employed women ($p = 0.003$, $p = 0.012$, respectively). Maternal health outcomes varied significantly between the two groups. Anemia was markedly higher in *falciparum* cases, 63 (88.7%), compared to *oval/vivax* 19 (48.7%) ($p < 0.001$). Similarly, preterm birth 45 (63.4%), low birth weight 34 (47.9%), and hypoglycemia 17 (23.9%) were significantly more frequent in *falciparum* infections ($p < 0.001$ and $p = 0.004$). Interestingly, a higher percentage of women in the *oval/vivax* group had received malarial prophylaxis 9 (23.1%) ($p < 0.001$), as depicted in Table 2.

Table 2: Fetomaternal Outcome of Pregnant Women for the Type of Malaria Parasite

Variables	Falciparum n (%)	Oval/Vivax n (%)	p-Value
Age of Patient (Years)	<20 3 (4.2%)	14 (35.9%)	<0.001
	21 to 30 46 (64.8%)	12 (30.8%)	
	31 to 40 22 (31.0%)	13 (33.3%)	
Parity of Patient	Primigravida 5 (7.0%)	20 (51.3%)	<0.001
	2-5 50 (70.4%)	19 (48.7%)	
	>5 16 (22.5%)	0 (0.0%)	
Socio Economic status	Lower Class 42 (59.2%)	18 (46.2%)	<0.001
	Middle Class 28 (39.4%)	6 (15.4%)	

	Upper Class	1(1.4%)	15(38.5%)	
Education Status	Uneducated	30(42.3%)	15(38.5%)	<0.001
	Primary	11(15.5%)	3(7.7%)	
	Secondary	27(38.0%)	1(2.6%)	
	Matric	2(2.8%)	14(35.9%)	
	Inter	1(1.4%)	6(15.4%)	
Residency of Patient	Rural	53(74.6%)	18(46.2%)	0.003
	Urban	18(25.4%)	21(53.8%)	
Occupation of Patient	Unemployed	70(98.6%)	34(87.2%)	0.012
	Employed	1(1.4%)	5(12.8%)	
Living Status of Patient	Joint Family	64(90.1%)	27(69.2%)	0.006
	Nuclear Family	7(9.9%)	12(30.8%)	
Malarial Prophylaxis	Yes	1(1.4%)	9(23.1%)	<0.001
	No	70(98.6%)	30(76.9%)	
Preterm Birth	Yes	45(63.4%)	10(25.6%)	<0.001
	No	26(36.6%)	29(74.4%)	
Anemia	Yes	63(88.7%)	19(48.7%)	<0.001
	No	8(11.3%)	20(51.3%)	
Low Birth Weight	Yes	34(47.9%)	1(2.6%)	<0.001
	No	37(52.1%)	38(97.4%)	
Hypoglycemia	Yes	17(23.9%)	1(2.6%)	0.004
	No	54(76.1%)	38(97.4%)	

DISCUSSION

Several negative outcomes, including LBW, preterm birth, and small-for-gestational-age (SGA) newborns, have been linked to malaria during pregnancy. The fetomaternal outcomes of pregnant women infected with *P. falciparum* and *P. ovale/vivax* were illustrated in this study. In the present study, pregnant women infected with *P. falciparum* experienced a significantly higher incidence of anemia 63 (88.7%), preterm birth 45 (63.4%), low birth weight 34 (47.9%), and hypoglycemia 17(23.9%) compared to those with *P. ovale/vivax* infections ($p < 0.001$, $p = 0.004$). These findings align with a meta-analysis that reported elevated risks of low birth weight (LBW), preterm birth (PTB), and small-for-gestational-age (SGA) infants among malaria-infected mothers, estimating a 75.5% increase in LBW, a 48.4% increase in PTB, and 55.4% increase in SGA births [24]. Similarly, other systematic reviews have observed a 63% higher risk of LBW and a 23% increase in PTB among infected women [25], as well as a notable association between malaria and stillbirths [26]. Another meta-analysis highlighted the predominance of *P. falciparum* in pregnant women (22.1%), followed by *P. vivax* (3%), *P. malariae* (0.8%), and *P. ovale* (0.2%) [27]. Interestingly, the present study showed a higher percentage of malaria prophylaxis usage among women infected with *P. ovale/vivax* 9 (23.1%) ($p < 0.001$). Previous studies have also shown that malaria prophylaxis can reduce the risk of anemia, LBW, and preterm labor [28], indicating that prophylactic treatment may contribute to the relatively better outcomes seen in the *P. ovale/vivax* group. Another research showed that post-delivery anemia 47.2%) and LBW 36.7% were among the most common maternal and

fetal complications in malaria-infected pregnancies. That study also reported that age, parity, socioeconomic status, and lack of malaria prophylaxis were significantly associated with adverse outcomes ($p \leq 0.05$) [28]. Likewise, anemia was found to be nearly twice as common among malaria-infected pregnant women in multiple studies [29–31], which is in agreement with the present study, showing that post-delivery anemia 63(88.7%) and LBW 34 (47.9%) were among the most common maternal and fetal complications in *P. falciparum* malaria-infected pregnancies. Socioeconomic status, education, and place of residence were significantly associated with malaria type and fetomaternal outcomes. *P. falciparum* was more frequent among women from lower socioeconomic backgrounds, 42(59.2%), rural areas, 53(74.6%), and those who were uneducated, 30 (42.3%) or unemployed, 70 (98.6%). These results support previous research indicating that low socioeconomic and educational status, as well as rural residence, are strong predictors of adverse pregnancy outcomes among malaria-infected women [28, 32]. Lufele et al., also found that rural women had a higher likelihood of delivering LBW infants and experiencing preterm birth [32]. The present study demonstrated that the adverse effects of malaria are also influenced by the timing and frequency of infection during pregnancy. Malaria during the first trimester has been associated with increased risk of LBW and PTB, as observed in studies from Congo, Kenya, and Zambia [33]. Some studies report conflicting findings, while Moeller et al. demonstrated that infection before 15 weeks significantly reduced birth weight in Tanzanian women [34]. Likewise, a study by Accrombessi et al., found no such effect in Beninese women [35]. These inconsistencies may relate to differences in transmission intensity, host immunity, and access to prenatal care.

The study was limited by its cross-sectional design, single-center setting, convenience sampling, and relatively small sample size, which may affect causal interpretation and generalizability. Exclusion of women with comorbidities and reliance on hospital-based data may also underestimate the broader community burden. Future large-scale prospective multicenter studies are recommended to assess long-term maternal and neonatal outcomes, incorporate broader demographic variables, and evaluate the effectiveness of preventive strategies such as early screening, malaria prophylaxis, and improved antenatal care in high-risk populations.

CONCLUSIONS

It was concluded that Plasmodium falciparum infection increases the risk of unfavourable fetomaternal outcomes as compared to Plasmodium ovale/vivax infection, with significantly higher rates of anemia, preterm birth, reduced birth weight, and hypoglycemia. Rural, lower-class, and uneducated women are more likely to be affected by socioeconomic and demographic differences, which also

affect the severity of the condition. The results emphasize the value of early detection, malaria prevention, and focused prenatal care in lowering the risks of malaria-related pregnancy problems for both mothers and newborns.

Authors' Contribution

Conceptualization: M

Methodology: M, MM, BS, E, R, F, T, NM

Formal analysis: M, MM, BS, E, R, F, T, NM

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Original Article



Clinical and Radiological Outcomes of Anterior Column Reconstruction Using Titanium Mesh Cage for Dorsolumbar Spine Pathologies

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ABSTRACT

Pathological fractures in the spine, often caused by cancer, infection, or aging, can lead to vertebral compression fractures, resulting in pain, deformity, and neural compromise. Anterior cervical corpectomy with titanium mesh cages is effective for decompression, stabilization, and spinal column restoration in trauma and tumor cases. **Objective:** To evaluate clinical and radiological outcomes of anterior column reconstruction using cylindrical titanium mesh cage for Dorsolumbar spine pathologies. **Methods:** A Descriptive Case Series was conducted at the department of Neurosurgery, Fatima Jinnah Medical University/Sir Ganga Ram Hospital. 60 Patients of either gender, aged 12 to 50 years, presenting with dorsolumbar spine pathologies were included. Pre-operative and post-operative plain X-ray, MRI plain film of Spine and CT Spine (wherever required) was All surgeries were performed by a single surgeon having 10 years of post-fellowship experience. Clinical and Radiological outcomes were assessed after 3 months. The data were analyzed using SPSS version 25.0. **Results:** Total of 60 patients, 36.6% were in age group of 12-30 years and 63.4% were in age group of 31-50 years. There were 60% were male whereas 40% were females. Clinical outcome was excellent in 28.3%, good in 45%, fair in 23.3% and poor in 3.3%. Mean change in intervertebral space height was 1.52 ± 0.19 and mean change in segmental angle was 0.490 ± 0.060 . **Conclusion:** In the current investigation it was concluded that the use of titanium mesh cages in patients with spinal disorders is safe and offering significant improvements in both clinical outcomes and radiological parameters.

INTRODUCTION

Dorsolumbar spine pathologies, including infective, traumatic, and neoplastic conditions, can lead to spinal instability, resulting in compression of the nervous elements and subsequent neurological impairments. The primary goal in managing an unstable dorsolumbar spine is to preserve remaining spinal cord function, restore spinal alignment, optimize neurological recovery, and facilitate early rehabilitation [1, 2]. Optimizing neuronal decompression and maintaining a stable internal fixation are two ways to achieve this [3]. Fixation with allograft and autograft bones with anterior and posterior fixation was a

common practice before the use of titanium implants [4]. Cylindrical titanium mesh cages, FDA-approved in 1990, are used for osseous reinforcement and reconstruction, initially proving effective for large segmental long bone defects when combined with bone grafts [5]. Biologically, they support cancellous bone grafts, maintain graft continuity, and enable circumferential reconstitution, while mechanically providing strength with minimal metal, reducing stress shielding. Functionally, they offer immediate limb stability, enabling early weight-bearing. However, their theoretical advantages remain unvalidated



in standardized experimental models [3, 6]. Titanium mesh cages of different sizes and shapes are now being used successfully to reconstruct spine after corpectomy providing an effective method of treating spine pathologies [7, 8]. Two approaches can be opted for stabilization and fixation of Dorsolumbar spine with having their own merits and demerits. Anterolateral and posterior approaches. While using anterior approach, decompression is done by removing the affected vertebral body and reconstructing the spine using titanium mesh cages. The device often needs to be positioned two levels above and below the lesion site to achieve posterior stability. It is still controversial which of the anterior, posterior and mixed techniques the best is [9, 10]. In extremely unstable thoracolumbar spines, it is generally recognized that anterior decompression and reconstruction with instruments is preferable to fixation with posterior pedicle screws [11]. The Anterior column reconstruction with titanium mesh cages restores spinal stability, relieves neural compression, and facilitates early mobilization.

Anterior column reconstruction for dorsolumbar spine pathologies remains surgically challenging due to the need for adequate decompression, restoration of spinal alignment, and durable stabilization. Although titanium mesh cages are increasingly used for vertebral body replacement, most available evidence is derived from heterogeneous populations, spinal tuberculosis studies, or comparative implant analyses rather than focused outcome evaluations in dorsolumbar trauma and infective cases. Furthermore, local data assessing short-term clinical and radiological outcomes following cylindrical titanium mesh cage reconstruction remain limited. Therefore, a structured evaluation of its effectiveness in dorsolumbar spine pathologies is necessary to guide evidence-based surgical practice. Therefore, the present study was conducted to evaluate clinical and radiological outcomes of anterior column reconstruction using cylindrical titanium mesh cage for Dorsolumbar spine pathologies.

METHODS

A Descriptive Case Series was conducted at the department of Neurosurgery, Fatima Jinnah Medical University/Sir Ganga Ram Hospital Lahore over a period of six months from 08-01-2023 to 08-07-2023 after ethical approval (34-MS-Neurosurgery/ERC). The sample size of 60 was estimated by confidence level of 95% with 9% margin of error and taking and expected percentage of excellent clinical outcome as 95.3% using following formula [12].

$$n = \frac{z^2 - \frac{a}{2} p(1-p)}{d^2}$$

Where:

p = Expected proportion of excellent clinical outcomes (95.3%)

d = Margin of error (9%)

q = 1 - p (4.7%)

Participants of either gender, aged 12 to 50 years, presenting with dorsolumbar spine pathologies were included in the study. Exclusion criteria include patients with American Society of Anesthesiologists (ASA) with grade 3 or above. Impairment Scale grades A and E, as well as those with comorbid conditions such as diabetes mellitus (blood sugar levels exceeding 200 mg/dL) and hypertension (diastolic blood pressure over 100 mmHg). Data were collected from patients meeting the inclusion criteria. 60 Patients were admitted to Neurosurgery department at SGRH after taking written consent for the treatment and surgical procedure. All surgeries were performed by a single surgeon having 10 years of post-fellowship experience. Surgical technique used was anterior thoraco-lumbar for dorsal spine and retro peritoneal in lumbar spine cases. Clinical and Radiological outcomes were assessed after 3 months. Clinical outcomes were evaluated using Modified Macnab's criteria, categorized as Excellent (no pain, no mobility restriction, normal activity), Good (occasional non-radicular pain, symptom relief, modified work), Fair (improved function but still handicapped/unemployed), and Poor (persistent symptoms, need for further surgery at the same level) [13]. Radiological outcomes were assessed via MRI, measuring intervertebral space height (IH) in millimeters and Segmental Angle (SA) in degrees. The MRI scans were conducted with a 1.5 Tesla Siemens Magnetom Avanto machine and using standard spine protocols to obtain intervertebral space height (IH, in mm) and segmental angle (SA, in degrees). Plain films were performed on a Shimadzu RAD speed Pro digital system and when required, CT scans were performed on a 64-slice GE Optima CT660 system. All radiological measurements were completed on a pre-defined proforma by the relevant surgical and radiology teams to maintain consistency and reproducibility of reports. The demographic information, including name, age, gender, and site of pathology, was obtained directly from patients who were enrolled in the study. All relevant details were recorded using a pre-designed proforma at the time of enrollment to ensure accurate documentation. The data were entered and analysed in SPSS version 25.0. Quantitative variables like age, inter-vertebral space height (IH) and Segmental Angle (SA) were calculated as mean and SD. Qualitative variables like gender and clinical outcome were calculated as frequency and percentage. The data were stratified by age and gender to account for potential effect modifiers. The normality of data was assessed by Shapiro wilk test, the comparison of pre and post Change in Inter-vertebral

space height (mm) and Segmental angle in degree was analyzed by paired sample t-test. After stratification, an independent sample t-test was, with a p-value ≤ 0.050 considered statistically significant.

RESULTS

In table 1, the majority (63.4%) were between 31-50 years of age, while 36.6% were aged 12-30 years. Regarding gender distribution, 60.0% of the patients were male, and 40.0% were female. Most patients (66.7%) had a BMI within the range of 17-25 kg/m², whereas 33.3% had a BMI greater than 25 kg/m². The primary causes of dorsolumbar spine pathologies were caries of the spine (56.6%) and trauma (43.4%).

Table 1: Demographic of Patients

Age Group	Frequency (%)
12-30 Years	22 (36.6)
31-50 Years	38 (63.4)
Gender	
Male	36 (60.0)
Female	24 (40.0)
BMI (Kg/m²)	
17-25	40 (66.7)
>25	20 (33.3)
Causes	
Caries Of the Spine	34 (56.6)
Trauma Of Supine	26 (43.4)

In table 2, the outcomes of anterior column reconstruction showed a mean increase in intervertebral space height of 9.46 ± 1.52 mm and a mean change in segmental angle of $0.72^\circ \pm 0.49^\circ$. According to Modified Macnab's criteria, clinical outcomes were rated as Excellent in 28.3% of patients, Good in 45%, Fair in 23.3%, and Poor in 3.3%, indicating a predominantly positive response to the procedure. There was significant mean change in intervertebral space height and segmental angle. $p \leq 0.05$ indicates statistical significance.

Table 2: Post Procedure Clinical and Radiological Outcomes of Anterior Column Reconstruction

Variables	Mean $\pm$ SD / Frequency (%)		
	Pre	Post	p-Value
Change in Inter-vertebral space height (mm)	9.46 ± 1.52	1.52 ± 0.19	<0.0001
Change in Segmental angle in degree	$0.72^\circ \pm 0.49^\circ$	$0.49^\circ \pm 0.06^\circ$	<0.0001
Clinical Outcome by Modified Macnab's criteria			
Excellent	17 (28.3)		
Good	27 (45)		
Fair	14 (23.3)		
Poor	2 (3.3)		

Results from independent sample t test (*) indicates $p \leq 0.05$

In table 3, Stratification of intervertebral space height based on age and gender revealed no significant difference

between the age groups, with a mean height of 9.414 ± 1.369 mm for patients aged 12-30 years and 9.497 ± 1.614 mm for those aged 31-50 years ($p = 0.842$). However, gender stratification showed a trend toward higher intervertebral space height in females (10.188 ± 0.930 mm) compared to males (8.918 ± 1.662 mm), though the difference was not statistically significant (P -value > 0.050).

Table 3: Stratification for inter-vertebral space height with respect to age and Gender

Variable	Age group	Mean $\pm$ SD	p-Value
Inter Vertebral Space Height (mm)	12-30 Years	9.414 ± 1.369	0.842
	31-50 Years	9.497 ± 1.613	
	Male	8.918 ± 1.662	0.071
	Female	10.188 ± 0.930	

Results from independent sample t test (*) indicates $p \leq 0.050$

In table 4, Stratification of segmental angle based on age and gender showed no statistically significant differences. Patients aged 12-30 years had a mean segmental angle of $0.876 \pm 0.522^\circ$, compared to $0.646 \pm 0.475^\circ$ in those aged 31-50 years ($p = 0.089$). Similarly, gender stratification revealed a mean segmental angle of $0.791 \pm 0.496^\circ$ in males and $0.642 \pm 0.501^\circ$ in females (P -value > 0.050).

Table 4: Stratification for Segmental Angle with Respect to Age and Gender

Variable	Age group	Mean $\pm$ SD	p-Value
Segmental Angle	12-30 Years	0.876 ± 0.5224	0.089
	31-50 Years	0.646 ± 0.4746	
	Male	0.791 ± 0.4963	0.256
	Female	0.642 ± 0.5014	

Results from independent sample t test (*) indicates $p \leq 0.050$

DISCUSSION

Spinal diseases impair the backbone and include conditions like kyphosis, dorsalgia, and cervical spine disorders. Common cervical issues, such as degenerative disc disease, stenosis, and disc herniation, often result from aging and cause pain or numbness. These conditions vary in severity and prevalence. The findings of current study reported that the majority 36.6% were in age group of 12-30 years and 63.4% were in age group of 31-50 years. There were 60% were male whereas 40% were females. Thoracolumbar fractures are more frequent in men, and the peak incidence is observed between 20 and 40 years [14, 15]. In current study it was reported that the primary causes of dorsolumbar spine pathologies were caries of the spine (56.6%) and tumor or trauma (43.4%). Blunt trauma with high energy is the main cause of thoracic spine injuries. 65 of these injuries are due to motor vehicle accidents and falls from height, with sports injuries and violence accounting for the remaining percentage. Other damage such as rib fractures, pneumothorax, hemothorax and, less commonly, large vessel injuries,

hemopericardium and diaphragmatic rupture are usually associated with these high velocity injuries [16, 17]. The long bone fractures and head trauma can cause spinal injuries to go unnoticed, seat belt fractures (Chance) and flexion-distraction injuries are often associated with intra-abdominal visceral injuries [18]. Unnoticed thoracic and lumbar spine injuries can occur in up to 36% of cases, especially when there is high-energy physical trauma and a change in mental status [19]. In this study we found that clinical outcome was excellent in 28.3%, good in 45%, fair in 23.3% and poor in 3.3%. It was found that significant mean change in intervertebral space height was 1.52 ± 0.19 and mean change in segmental angle was 0.49 ± 0.06 . In a study, according to clinical outcome, as per Macnab's criteria, 95.3% patients reported excellent outcome [12]. According to radiological outcome, mean inter-vertebral space height was 9.4 ± 2.1 mm pre-operatively and 11.5 ± 1.4 mm after 3 months with a mean change 2.1 ± 0.7 mm and mean segmental angle was 17.9 ± 8.4 ° pre-operatively and 17.6 ± 5.6 ° after 3 months with a mean change 0.3 ± 2.8 ° [20].

This study is limited by its single-center design, relatively small sample size, and short follow-up duration of three months, which restricts assessment of long-term fusion rates, implant-related complications, and functional recovery. The absence of a comparative control group also limits definitive conclusions regarding superiority over other reconstruction techniques. Future multicenter randomized studies with longer follow-up periods are recommended to evaluate long-term spinal stability, implant subsidence, quality-of-life outcomes, and comparison with alternative grafting or expandable cage systems.

CONCLUSIONS

In the present study, we evaluated the clinical and radiological outcomes of anterior column reconstruction using cylindrical titanium mesh cages for dorsolumbar spine pathologies. The findings demonstrate that this technique is safe and reliable, leading to significant improvements in patient recovery and spinal alignment. Overall, cylindrical titanium mesh cages appear effective in restoring spinal stability and promoting favorable early clinical and radiographic outcomes.

Authors' Contribution

Conceptualization: MDS

Methodology: MDS, SS, MMH, R

Formal analysis: TA

Writing and Drafting: MDS, TA, SF, AH

Review and Editing: MDS, TA, SF, AH, SS, MMH, R

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Original Article



Predicting Adverse Pregnancy Outcomes in First Time Mothers: The Role of Maternal Body Mass Index

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ABSTRACT

Maternal underweight during pregnancy can profoundly "programme" the fetal physiology and metabolism, which may end up in chronic illnesses later in life, including diabetes mellitus, cerebrovascular disease and hypertension. **Objective:** To figure out the likelihood of untoward events among underweight nulliparous women. **Methods:** A descriptive cross-sectional study was performed in the Obstetrics and Gynaecology Department, Nishtar Hospital, Multan, for the period of four months from December 2024 to March 2025 using non-probability consecutive sampling. Around 401 women were included after fulfilling the selection criteria. Data were collected through a specialized form and reviewed using SPSS Version 20.0. **Results:** Mean age was 28.98 ± 4.21 years among the participants. Mean height was 165 ± 7.43 centimeter, and mean weight was 52.21 ± 3.25 kilograms. Mean body mass index (BMI) was 18.11 ± 0.23 kg/m². Cesarean delivery was reported among 73 (18.2%), pre-eclampsia in 57 (14.2%), preterm delivery in 165 (41.1%) and low-birth-weight babies were 126 (31.5%). **Conclusions:** The results reported an upsurge in the incidence of undesirable pregnancy outcomes such as preterm births and low birth weight babies among underweight first-time mothers. Proper counselling of these cases regarding weight gain before conception can help to lessen these adverse events and can be helpful in subsequent pregnancies.

INTRODUCTION

Maternal obesity consistently receives considerable attention in the research. Conversely, maternal underweight appears to be relatively under investigated, particularly among nulliparous women [1]. Many pregnant women develop harmful practices to lose weight. Underweight status and nulliparity present a unique confluence of risk factors that can significantly impact pregnancy outcomes [2]. Pregnancy-related low maternal weight (BMI <18.5 kg/m²) is known to increase the prevalence of low birth weight babies and the likelihood that the kids would grow up to be obese and have high blood pressure [3]. Preterm delivery, fetal growth restriction, and

hypertension are among the adverse pregnancy outcomes that these women are more likely to experience [4]. According to the World Health Organization (WHO), a person is considered underweight if their body mass index (BMI) is less than 18.5 kg/m², normal if it is between 18.5 and 24.99 kg/m², overweight if it is between 25.00 and 29.9 kg/m², and obese if it is greater than 30 kg/m² [5]. Low BMI and inadequate weight gain during pregnancy exacerbate the problems [6]. Based on pre-pregnancy BMI, the Institute of Medicine (IOM) recommends a certain gestational weight gain (GWG). It states GWG: 12.5–18 kg is recommended for underweight mothers [7]. Around 9.7%



of mothers are underweight around the globe, while the incidence is three times higher (24%) in South Asia [8]. About 14.4% of women in reproductive years have low BMI according to the National Nutritional Survey in Pakistan [8]. Maternal underweight was reported among 7.5% of women in France [9]. The effects of low BMI on outcomes of pregnancy, particularly among first-time mothers, have received relatively less attention. The precarious balance between maternal nutrient stores and fetal development highlights the need for targeted research. This knowledge gap is particularly concerning as low maternal weight has lasting implications for the future health of the newborn. By investigating birth outcomes in underweight first-time mothers, this study intends to bridge this gap. There is no such study conducted in Pakistan on this topic previously. The results would help clinicians to anticipate these untoward events among first-time mothers, and we hope to inform the development of targeted interventions for future pregnancies. It ultimately improves the excellence of care.

Maternal underweight in first-time mothers is an important but relatively under-researched contributor to adverse pregnancy outcomes such as preterm birth, low birth weight, and pre-eclampsia. Despite increasing global evidence, limited locally generated data exist in Pakistan to clearly define the magnitude and impact of low BMI in nulliparous women. Therefore, this study aimed to determine the frequency of adverse pregnancy outcomes among underweight first-time mothers and to evaluate the association between maternal BMI and perinatal complications. It also sought to identify high-risk groups to support early preventive and nutritional interventions.

METHODS

This was a descriptive cross-sectional research conducted in the labour ward (Obstetrics and Gynaecology), Nishtar Hospital, Multan, from December 2024 to March 2025 after approval from the ethical committee with ERB No. 18957/NMU. Non-probability consecutive sampling technique was used. A sample size of 401 was determined by following the formula. $n = z^2pq/d^2$, where $p = 11.5\%$ (hypothesized frequency of preterm births in underweight women) [1], $q = 100 - p$, $d = 0.031$ (3.11% margin of error), $z = 1.96$ (95% confidence interval). Underweight primigravida women who had pre-pregnancy BMI less than 18.5 Kg/m^2 , 20–40 years old, with gestational age between 24–38 weeks (on ultrasound) were enrolled. This study chose only first-time mothers who presented in labour ward for planned delivery because the study focuses on the targeted high-risk population. First-time mothers might be more vulnerable to pregnancy-related complications due to their inexperience with pregnancy. This study controls the impact of parity on pregnancy outcomes and can

potentially improve the outcome for future pregnancies. Women with a history of scarred uterus (myomectomy scar), presence of fetal anomalies like congenital heart disease, inherited metabolic disorders, neural tube defects and women with a previous history of diabetes, hypertension and cardiac conditions (confirmed by clinical record) were excluded. A written informed consent was taken. Data about pre-pregnancy BMI were collected via antenatal record; however, the accuracy of self-reported weights may be subject to recall bias. Using the self-reported pre-pregnancy weight cutoff criteria suggested by the WHO, the conventional calculation is weight (kg) divided by the square of body height (m) (underweight, $<18.5 \text{ kg/m}^2$). Outcome variables were preterm delivery, pre-eclampsia and cesarean delivery and low birth weight. Preterm delivery was described as the start of labour between 24–37+6 weeks of pregnancy. All those cases who had systolic pressure above 140 mm Hg and diastolic pressure $>90 \text{ mmHg}$ measured at least two times with 4 hours' interval after 20 weeks of gestation and proteinuria $\geq 300 \text{ mg/day}$, were labelled as pre-eclampsia, till delivery. Cesarean section delivery was labelled when the baby is born through an incision in the abdomen. Low birth weight referred as the birth weight of less than 2.5 kg as measured on a digital weighing scale. Demographic data were collected via a specialized questionnaire. Each participant gave informed consent beforehand. Additionally, they received a briefing on the study's goals, guaranteeing the privacy of the data they submitted. Every method used in the study complies with the Helsinki Declaration and its later modifications as well as the institution's ethical standards. SPSS version 20.0 was used to analyze the data. For numerical data such as patient age, height, weight, and gestational age, the mean and standard deviation were computed. For outcome variables such as birth weight, pre-eclampsia, premature labor, and cesarean section, frequencies and percentages were calculated. The demographic variables were socioeconomic status, educational level, age groups and residential status. Effect modifiers like age, educational status, residential status, and socioeconomic status were controlled by making stratified tables. A chi-square test was used after stratification to determine their effect on the outcome. p -values equal to or less than 0.050 were considered significant.

RESULTS

The study included a total of 401 women who met the inclusion criteria. The mean age of our study cases was 28.98 ± 4.21 years (with a range of 20–40 years). The majority, 239 (59.6%), were between 20–30 years of age, and 162 (40.4%) were between 31–40 years. Out of 401 women, 241 (60.1%) were from rural areas and 160 (39.9%)

were from urban areas. Around 39 (9.7%) women had no formal education, and 362 (90.27%) were educated till matriculation. About 271(67.6%) were from low socioeconomic status (<Rs. 15,000 / month) and 130 (32.4%) from moderate socioeconomic status (Rs. 16000/- to 40000/month)(Table 1).

Table 1: Socio-Demographic Variables among Participants (n=401)

Variables	Categories	Frequency (%)
Age (Years)	20 – 30 Years	239 (59.6%)
	31 – 40 Years	162(40.4%)
Residence	Rural	241(60.1%)
	Urban	160(39.9%)
Education	Illiterate	39(9.7%)
	Literate	362 (90.3%)
Socioeconomic Status	Low (<Rs. 15000/Month)	271(67.6%)
	Moderate (Rs 16000/- To 40000 /Month)	130(32.4%)

The study results indicated that the mean height was 165 ± 7.43 centimeter and the mean weight was 52.21 ± 3.25 kilograms. Mean body mass index (BMI) was 18.11 ± 0.23 kg/m². Mean gestational age was 38.74 ± 2.85 weeks. Cesarean delivery was in 73 (18.2%) participants, pre-eclampsia was in 57(14.2%) women, preterm delivery was in 165 (41.1%), and low birth weight babies were 126(31.5%) (Table 2).

Table 2: Pregnancy Outcomes in First-Time Mothers with Low BMI (n=401)

Outcome Variables	Yes	No	Total
Pre-Eclampsia	57(14.2%)	344 (85.8%)	401(100%)
Cesarean Section	73(18.2%)	328 (81.8%)	401(100%)
Preterm Delivery	165 (41.1%)	236 (58.9%)	401(100%)
Low Birth Weight	126 (31.5%)	275 (68.6%)	401(100%)

Pre-eclampsia, preterm delivery, Low birth weight and cesarean section deliveries were stratified concerning age, residential status, socioeconomic status, and level of education. "A significant association was observed between maternal age and preterm birth ($p=0.003$). Younger mothers (20–30 years) had a higher incidence of preterm delivery (56.06%) compared to older mothers (31–40 years, 18.92%), suggesting age-related vulnerability in underweight nulliparous women." However, no significant link was found between cesarean section, low birth weight and pre-eclampsia across different age groups in thin, lean first-time mothers (Table 3).

Table 3: Stratification of Pregnancy Outcomes According to Age in First-Time Mothers with Low BMI

Outcome Variables			Age Groups		p-value
			20–30 Years (239)	31–40 Years (162)	
Cesarean Delivery	Yes	73	31(12.9%)	42 (25.9%)	0.147
	No	328	208 (87.1%)	120 (74.1%)	

Pre-Eclampsia	Yes	57	17(7.1%)	40 (24.7%)	0.199
	No	344	222 (92.9%)	122 (75.3%)	
Pre-Term Birth	Yes	165	134 (56.06%)	31 (18.92%)	0.003
	No	236	105 (43.93%)	131 (80.08%)	
Low Birth Weight	Yes	126	78 (32.63%)	48 (29.63%)	0.762
	No	275	161 (67.36%)	114 (70.27%)	

When we compared our outcome variables with socioeconomic status, cesarean section and pre-eclampsia were not significantly related to socioeconomic status in first-time mothers with low BMI ($p=0.140$, $p=0.072$, respectively). Thin, lean first-time mothers who belonged to low socioeconomic status had a significantly increased risk of preterm birth ($p<0.001$) and low birth weight (0.023) (Table 4).

Table 4: Stratification of Outcomes During Pregnancy According to Socioeconomic Status in First-Time Mothers with Low BMI

Outcome Variables			Socio-Economic Status		p-value
			Low (<Rs. 15000/ Month) (n=271)	Moderate (Rs 16000/- To 40000 /Month) (n=130)	
Cesarean Delivery	Yes	73	18	55	0.140
	No	328	253	75	
Pre-Eclampsia	Yes	57	13	44	0.072
	No	344	258	86	
Pre-Term Birth	Yes	165	139	26	<0.001
	No	236	132	104	
Low Birth Weight	Yes	126	29	97	0.023
	No	275	242	33	

DISCUSSION

A low birth weight, preterm baby is more likely to be born to thin, lean first-time moms. It is often recommended that these women put on weight before getting pregnant [8]. However, it is unknown what body mass index is best for women who wish to become pregnant. This study found very few studies in which outcomes of pregnancy are assessed in nulliparous women with low BMI. Research done in the USA compared the birth outcomes between mothers with normal or decreased BMI. They found that women with decreased BMI were mostly nulliparous [10]. Among 401 women, the mean age was 28.98 ± 4.21 years (with a range of 20–40 years). A study from Japan reported a 34 ± 4.5 years mean age in lean pregnant females. These results are on the higher side compared to our study results [4]. A study from Qatar showed the mean age was 25.2 ± 4.6 among pregnant women with low BMI [5]. In another study done in France, shown mean age of 29 ± 10 years was shown among women with low BMI during pregnancy, which is close to our results [6]. Of these 401 study cases, 241 (60.1%) were from rural areas, and 160 (39.9%) were from poor socioeconomic status. A study done in India reported similar results [11]. This study found that more than one-third of participants, 165 (41.1%), had preterm deliveries.

Pre-eclampsia was found among 57 (14.2%) of participants. Cesarean section deliveries were reported in 73 (18.2%), and low birth weight was found in 126 (31.5%). In India, research done in nulliparous women with low BMI reported pre-eclampsia in 3.3 %, Cesarean section in 11.3% and preterm births in 12.1 % underweight women, which are quite lower than our results [11]. This was likely because more than 20,000 samples were extracted from the Aberdeen Maternity and Neonatal Databank (AMND) in their study. However, our findings align with research suggesting that younger underweight mothers may face nutritional deficiencies or inadequate gestational weight gain, exacerbating preterm labour risks [12]. Further studies should explore whether biological immaturity or socioeconomic factors (e.g., delayed prenatal care in younger women) drive this association in low-BMI populations. According to research in China, the association between preterm birth and socioeconomic position was mediated by prenatal weight growth and BMI. In women with Low gestational weight gain and suboptimal BMI, there was a significant relationship between preterm birth and low socioeconomic status. However, only half of the participants were first-time mothers in the study [12]. The study found no significant relationship between pre-eclampsia and socioeconomic status; similar to another study done in Peshawar, where no significant relationship was found between pre-eclampsia and socioeconomic status ($p=0.98$) [13]. Our results showed that there was no impact of socioeconomic status on the rate of cesarean section among first-time mothers with low BMI ($p=0.14$). Only 6.6% women with low socioeconomic status had cesarean delivery, close to the results of research done in Bangladesh, where it was 8.7% [14]. In another study, women with low BMI had a markedly elevated risk for preterm delivery (OR:1.9) [7]. Another study in France reported that 43% primigravidas with low BMI had preterm births, which was almost similar to our results, i.e 165 (41.1%), likely because the sample size was close to our study ($n=407$) [9]. Low BMI in mothers had an increased risk of preterm birth (OR of 1.06, 95% CI (1.04–1.09) according to another study in China [15]. About 19.9% of underweight women had preterm deliveries in a study of Pakistan, lower than our results, possibly because of a different study design [16]. An Indian study found that underweight women had a higher chance of having a small-for-gestational-age child and a premature birth [17]. In an Iranian study, the same complications were reported among women with low BMI [18]. Current results showed that there was a significant association of low birth weight (LBW) with socioeconomic status in first-time mothers with low BMI ($p=0.023$). A study done by Sathi *et al.* using secondary data from Demographic and Health Surveys from six South

Asian countries showed the increased prevalence of low birth weight babies among women belonging to low socioeconomic status. After applying the logistic regression model, children from the poorest background had low birth weight (AOR:1.53, 95% CI:1.41-1.67) [19]. In an Indian study, 36.9% of nulliparous women with low BMI had newborns with low birth weight [20], close to our results. It could be because of quite similar demographics among the studies. Another Indian study showed a significant link between birth weight and low BMI among mothers with the odds ratio of 1.44 and 95% CI: 1.05, 1.65) [21]. Another Pakistani study showed that among patients who had a BMI $<25\text{kg/m}^2$, about 16.7% newborns had birth weight $<2500\text{ gm}$, which is almost half compared to our results [22]. Another study showed that being underweight at any time during pregnancy increased the risk of LBW babies' odds ratio of 1.2; 95% CI (1.2–1.3) [23]. A study in France showed that significant relationship between low birth weight and BMI $<18.5\text{ kg/m}^2$ in early pregnancy [24]. The inverse relationship between younger maternal age (20–30 years) and preterm birth in underweight first-time mother's contrasts with some studies where advanced maternal age (>35 years) is typically linked to higher preterm risk [25, 26]. In another Chinese research, cesarean section was 13.8% among primipara with low BMI; less than our study, where abdominal delivery was among 73 (18.2%) women [15]. An Indian study showed a 10% abdominal delivery rate among first-time mothers with BMI $<18.5\text{kg/m}^2$ [20]. A study done in Pakistan this year showed the cesarean section rate among thin, lean first-time mothers was 13.8%; less than our results. This is probably due to the increased sample size in our study [1]. Li *et al.* China reported that low BMI in nulliparous women was significantly associated with lower risk of cesarean delivery (AOR (adjusted odds ratio) = 0.74, 95% CI (0.62–0.90)) [2]. A study from Qatar reported a 16.8% cesarean section rate among women with low BMI, close to our results [5]. When we stratified pregnancy outcomes like cesarean section, pre-eclampsia, low birth weight, and preterm delivery among nulliparous women with low BMI according to age, we found that only preterm birth was significantly correlated ($p=0.003$). Maternal age showed no significant association with cesarean delivery ($p=0.147$) or pre-eclampsia ($p=0.199$). Younger mothers (20–30 years) had lower cesarean rates (12.9%) than older mothers (31–40 years: 25.9%), though this difference was not statistically significant. Likewise, the incidence of pre-eclampsia was similar across all age groups (7.1% vs. 24.7%, $p=0.199$). Similarly, in China, women over 35 with low BMI and significant gestational weight gain had a higher risk of premature delivery [25]. In a different Chinese research, 23.2% of women who were first-time moms with low BMI had a higher chance of giving birth to an LBW baby (AOR =

1.44, 95% CI (1.1–1.89)). Additionally, they discovered that among first-time moms with low BMI, there was a significant statistical correlation between age and premature delivery ($p=0.001$) [2]. Maternal age had no effect on cesarean sections among nulliparous mothers with low BMI ($p=0.147$). Nonetheless, a Korean study revealed a strong correlation between first-time moms' age and abdominal delivery [26]. According to a Chinese study, women under 35 who had a BMI of less than 18.5 kg/m² had a decreased risk of preeclampsia after correcting for other factors (OR=0.588, 95% CI=0.487–0.708) [27]. According to our findings, 57 individuals (14.2%) had pre-eclampsia. This may be because pre-eclampsia is also a risk factor for the first pregnancy. There was no statistically significant difference in the probability of pre-eclampsia across the various age groups with low BMI ($p=0.199$). In study done by Bibi et al. in Pakistan showed PIH was 7.7% among women with low BMI, which is almost half of our results. This may be because of a smaller number of participants included in their study [1]. In a research done in Qatar, 1% thin lean mothers had gestational hypertension [5]. The risk of pre-eclampsia in women with a BMI <18.5 kg/m² was 5.9% in an American research [10]. Li et al. from China reported that among first-time moms, being underweight was substantially linked to a decreased risk of gestational hypertension (AOR=0.45, 95% CI (0.2–0.82)) [2]. This is one of the few studies that emphasizes the pregnancy outcomes of thin and lean first-time mothers. Nishtar Hospital, Multan, is the hub of South Punjab, where women from various neighboring regions congregate. Hence, the findings of this research will be significantly more useful in guiding the establishment of national guidelines in Pakistan.

The study is limited by its single-center, cross-sectional design, which restricts generalizability and causal interpretation of findings. Possible recall bias in pre-pregnancy weight estimation and lack of control for all confounding variables (such as dietary intake and gestational weight gain) may also influence results. Future research should include large-scale, multicenter prospective cohort studies with accurate BMI tracking and broader adjustment for confounders. Additionally, targeted nutritional counseling and interventional studies are recommended to assess whether improving maternal BMI before and during pregnancy can reduce adverse outcomes.

CONCLUSIONS

The results showed that underweight women had increased rates of unfavorable perinatal outcomes, including preterm births among 41% women and low birth weight babies among around one third of women. The targeted group may have long-term maternal and newborn

complications as a result of these unfavorable outcomes. It can be avoided if these cases receive effective counselling in terms of weight gain before conception.

Authors' Contribution

Conceptualization: AA

Methodology: ST, KR, ANR, S

Formal analysis: AA, SK

Writing review and editing: AA, ST, KR, ANR, S

Review and Editing: AA, ST, KR, ANR, S

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Enhancing Diagnostic Precision and Clinical Outcomes with FNAC in Parotid Gland Masses

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ABSTRACT

Parotid gland tumors present with diverse histopathological profiles, making accurate preoperative diagnosis essential for appropriate management. Fine Needle Aspiration Cytology (FNAC) provides a minimally invasive technique to differentiate between benign and malignant lesions. **Objectives:** To evaluate the diagnostic accuracy of ultrasound-guided FNAC, categorized using the Milan System, in parotid gland masses by correlating cytological findings with final histopathological diagnoses. **Methods:** A prospective observational study was conducted over 12 months, involving 100 patients with clinically suspected parotid gland tumors at a tertiary care center. Patients were enrolled based on predefined inclusion and exclusion criteria. Ultrasound-guided FNAC was performed using 22-gauge needles, and aspirates were categorized per the Milan System. All participants subsequently underwent parotidectomy, and histopathology was used as the reference standard. Data analysis was conducted using SPSS version 26.0 to determine sensitivity, specificity, predictive values, and overall diagnostic accuracy. **Results:** Among the 100 cases, FNAC classified 48 as benign, 12 as malignant, and 5 as non-diagnostic. The most frequent benign and malignant tumors were pleomorphic adenoma (41%) and mucoepidermoid carcinoma (14%), respectively. FNAC demonstrated a sensitivity of 90.4%, specificity of 96.1%, positive predictive value (PPV) of 92.3%, negative predictive value (NPV) of 94.8%, and an overall accuracy of 93.5%. The highest diagnostic concordance was observed in Milan categories IVa and VI. **Conclusions:** It was concluded that FNAC, when guided by ultrasound and interpreted through the Milan System, demonstrates high diagnostic accuracy for parotid masses. It is a cost-effective first-line diagnostic tool, especially beneficial in resource-limited settings.

INTRODUCTION

Salivary gland tumors, especially those originating in the parotid gland, constitute a diverse and complex group of neoplasms that present notable diagnostic and therapeutic difficulties [1]. These lesions display a wide histopathological range, with nearly 70% of all salivary gland tumors occurring in the parotid gland. They encompass benign entities like pleomorphic adenomas and aggressive malignancies such as muco-epidermoid and adenoid cystic carcinomas [2]. An accurate diagnosis before surgery is critical for determining the surgical approach, ensuring facial nerve preservation, guiding

prognosis, and planning for any necessary adjuvant treatment. Nonetheless, clinical evaluation and imaging modalities alone often fall short in terms of sensitivity and specificity for differentiating between benign and malignant parotid lesions [3]. Fine Needle Aspiration Cytology (FNAC) has emerged as one of the main minimally invasive methods of preoperative examination of parotid gland tumors [4]. It has the benefits of being simple, economical and able to give a quick cellular diagnosis with minimal morbidity to the patient. The last twenty years have witnessed the development of FNAC from a simple



cytological method to a complex one that has been aided by the use of ancillary studies like immunocytochemistry and molecular profiling. FNAC performed with ultrasound guidance has even higher sample adequacy and diagnostic yield, and far fewer non-diagnostic or indeterminate results [5]. Despite its broad clinical application, the utility of FNAC in salivary gland pathology remains somewhat debated due to overlapping cytomorphologic characteristics among different tumor types and the inherent challenges of cytological interpretation [6]. To mitigate these limitations, the Milan System for Reporting Salivary Gland Cytopathology was introduced as a structured, tiered classification system designed to enhance communication between pathologists and clinicians and support more informed therapeutic planning [7]. However, real-world data evaluating the diagnostic accuracy, predictive values, and clinical impact of this system, especially in resource-constrained healthcare settings, remain limited [8]. With the world healthcare moving to precision medicine, the importance of precise, early, and less invasive diagnostic tools in head and neck oncology has gained even greater importance, as the morbidity of surgery in these parts can be quite high. The early stratification of patients by FNAC could assist in minimizing the unnecessary surgery of benign lesions and facilitating earlier treatment of malignant lesions [9]. FNAC diagnostic properties have also been supplemented with the use of advanced adjunctive technologies like cell block methods, flow cytometry, and next-generation sequencing, which enable the detection of molecular markers that can guide treatment and long-term monitoring [10]. FNAC is especially beneficial in low- and middle-income nations with undeveloped diagnostic infrastructure; it is a cost-efficient method of addressing diagnostic gaps and reducing healthcare disparities [11]. Consequently, a comprehensive reassessment of FNAC's diagnostic performance in parotid gland lesions, especially within high-volume clinical environments, is both timely and essential to support evidence-based clinical practices and improve patient-centred outcomes [12]. Although previous studies have highlighted the role of FNAC in salivary gland tumors, limited evidence exists regarding its diagnostic reliability in real-world tertiary settings, especially when using standardized cytological systems like the Milan System. Furthermore, there is a paucity of data from resource-constrained healthcare environments where diagnostic tools must be both cost-effective and precise.

Although Fine Needle Aspiration Cytology (FNAC) is widely used for the preoperative evaluation of parotid gland masses, variability in diagnostic performance and reporting standards continues to limit its uniform clinical application. The introduction of the Milan System has

improved standardization; however, real-world evidence assessing its diagnostic accuracy in tertiary care settings, particularly within resource-constrained healthcare systems, remains limited. Furthermore, few prospective studies have correlated ultrasound-guided FNAC findings with definitive histopathology using structured reporting frameworks. This gap necessitates a focused evaluation of FNAC's diagnostic reliability and clinical utility in routine practice. This study aimed to assess the diagnostic accuracy of ultrasound-guided FNAC in evaluating parotid gland masses, compare its cytological results with final histopathological findings, and examine its relevance in guiding clinical decisions and surgical management.

METHODS

This prospective observational study was carried out at a single Tertiary Care Academic Hospital in the Department of Otolaryngology and Head and Neck Surgery, in collaboration with the Department of Histopathology. This study was conducted over 12 months from 24 January 2024 to 24 January 2025 and aimed to evaluate the diagnostic performance of FNAC in patients presenting with parotid gland masses. Ethical approval was granted by the Institutional Review Board (IRB) under protocol number IMDC/DS/IRB/248, and written informed consent was obtained from all participants by the principles of the Declaration of Helsinki. The sample size was calculated using the standard formula for estimating proportions in diagnostic studies, which is based on a 95% confidence level ($Z = 1.96$), an assumed prevalence of 50% to allow for maximum variability ($p = 0.5$), and a 5% margin of error ($d = 0.05$). This yielded a theoretical sample size of 384. However, due to practical limitations and the single-center design, a pragmatic sample of 100 patients was selected, consistent with similar diagnostic accuracy studies in the literature. Participants were recruited according to predefined inclusion and exclusion criteria. Inclusion criteria included patients aged 18 years or older with a primary, untreated parotid gland mass and a clinical indication for both FNAC and surgical excision. Exclusion criteria encompassed a history of prior treatment for parotid tumors, recurrent lesions, evidence of distant metastasis at presentation, or contraindications to FNAC, such as bleeding disorders or localized infection. All patients underwent a thorough clinical evaluation, followed by high-resolution ultrasonography (USG) of the parotid region, which served as guidance for the FNAC procedure. The use of ultrasound improved needle targeting and reduced the rate of inadequate samples. FNAC was carried out by an experienced histopathologist using a 22-gauge needle, without the administration of local anesthesia. From each lesion, 2–3 needle passes were obtained. Smears were prepared as both air-dried for Giemsa staining and alcohol-fixed for Papanicolaou staining. Cytological evaluation was performed following the Milan

System for Reporting Salivary Gland Cytopathology (MSRSGC), which classifies findings into six diagnostic categories: Category I (Non-diagnostic), Category II (Non-neoplastic), Category III (Atypia of undetermined significance), Category IVa (Benign neoplasm), Category IVb (Salivary gland neoplasm of uncertain malignant potential, or SUMP), Category V (Suspicious for malignancy), and Category VI (Malignant). These standardized categories were used alongside clinical assessment to inform surgical planning. Following FNAC, all patients proceeded to definitive parotidectomy. The excised specimens were evaluated by an independent pathologist, using the 2022 World Health Organization (WHO) classification criteria for salivary gland tumors. Final histopathological diagnosis served as the reference standard to assess the diagnostic accuracy of FNAC. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 26.0. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were computed by comparing cytological findings with the corresponding histopathological diagnoses. In addition, concordance between Milan System categories and final histopathology was analyzed. Continuous variables were reported as mean $\pm$ standard deviation, while categorical variables were summarized as frequencies and percentages. A p-value less than 0.050 was considered indicative of statistical significance.

RESULTS

The study comprised 100 patients presenting with parotid gland masses. The mean age was 47.6 ± 13.4 years, with an age range of 18 to 76 years. A slight male predominance was noted, with 58 male (58%) and 42 female (42%). The most frequent clinical symptom was a painless swelling, reported in 82% of patients, followed by painful masses in 12%, and facial nerve involvement in 6%. Right-sided parotid gland involvement was seen in 56% of cases, whereas 44% had lesions on the left side. Fine Needle Aspiration Cytology (FNAC) yielded diagnostic results in 95% of patients, while 5% were categorized as non-diagnostic. According to the Milan System for Reporting Salivary Gland Cytopathology, the most commonly assigned category was IVa (Benign neoplasm), representing 48% of all cases (Table 1).

Table 1: Cytological Classification of FNAC Based on the Milan System (n=100)

Milan Category	Cytological Diagnosis	Number of Cases
Category I	Non-diagnostic	5
Category II	Non-neoplastic	12
Category III	Atypia of undetermined significance (AUS)	6
Category IVa	Benign neoplasm	48

Category IVb	Salivary gland neoplasm of uncertain malignant potential (SUMP)	8
Category V	Suspicious for malignancy	9
Category VI	Malignant	12

Final histopathological evaluation revealed that 55% of the lesions were benign tumors, including pleomorphic adenoma, Warthin tumor, and basal cell adenoma. Malignant neoplasms constituted 23% of the cases and included mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, and carcinoma ex pleomorphic adenoma. Additionally, 9% of the lesions were categorized as inflammatory or non-neoplastic, such as chronic sialadenitis. Rare tumor types accounted for the remaining 14% of the histopathological findings (Table 2).

Table 2: Final Histopathological Diagnosis of Parotid Gland Lesions (n=100)

Histopathological Diagnosis	Number of Cases
Pleomorphic Adenoma	41
Warthin Tumor	7
Basal Cell Adenoma	3
Mucoepidermoid Carcinoma	14
Adenoid Cystic Carcinoma	5
Acinic Cell Carcinoma	4
Carcinoma Ex Pleomorphic Adenoma	3
Chronic Sialadenitis (Non-Neoplastic Lesion)	9
Other Rare Tumors (E.G., Oncocytoma, Myoepithelial Carcinoma)	14

FNAC demonstrated strong diagnostic performance in distinguishing malignant from benign parotid gland lesions. The sensitivity for detecting malignancy was 90.4%, specificity was 96.1%, with a positive predictive value (PPV) of 92.3% and a negative predictive value (NPV) of 94.8%. The overall diagnostic accuracy of FNAC was calculated to be 93.5%, underscoring its reliability as a preoperative diagnostic modality (Table 3).

Table 3: Diagnostic Accuracy Metrics of FNAC in Parotid Gland Masses

Diagnostic Metric	Value (%)
Sensitivity for Malignancy	90.4
Specificity for Malignancy	96.1
Positive Predictive Value	92.3
Negative Predictive Value	94.8
Overall Diagnostic Accuracy	93.5

The results of this prospective study support the great diagnostic value of ultrasound-guided fine needle aspiration cytology (FNAC) in the evaluation of parotid gland masses. FNAC provided diagnostic information in 95% of patients, and the most common cytological group was that of benign neoplasms, mainly pleomorphic adenomas (48%). These findings were confirmed by final histopathological examination, which showed that benign

tumors prevailed (55%), with malignant lesions (23%), and non-neoplastic diseases, namely chronic sialadenitis (9%). The histological spectrum was made up of rare tumor types, which were 14%. FNAC had a strong diagnostic performance, exhibiting sensitivity of 90.4%, specificity of 96.1%, positive predictive value (PPV) of 92.3%, negative predictive value (NPV) of 94.8, and an overall accuracy of 93.5. These findings support the fact that FNAC, especially when directed by ultrasound and interpreted according to the Milan System, is a safe and least invasive way of preoperative analysis and categorization of parotid gland lesions.

DISCUSSION

Fine needle aspiration cytology (FNAC) continues to be a pillar in the preoperative evaluation of salivary gland lesions, especially those that occur in the parotid gland [13, 14]. With a sensitivity of 90.4, a specificity of 96.1 and an accuracy of 93.5, FNAC in this study has shown itself to be a superb diagnostic procedure. The findings are consistent with those of former research by Reerds *et al.*, and Tripathi *et al.*, who also indicated the quality of FNAC in salivary gland diagnostics, particularly in the interpretation of organized reporting paradigms like the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC). The present results reaffirm the existing clinical applicability of FNAC, especially under conditions wherein proper, non-invasive diagnostic procedures are determined as essential in the decision-related surgical planning, irrespective of resource availability [10, 11]. Refinement of the salivary gland cytopathology due to the implementation of the Milan System has been remarkable in that it allows risk-stratification and tiering of the diagnosis method, thus enhancing its consistency and easing communication between these two structures. The FNAC category IVa (benign neoplasm) was the most commonly assigned during our cohort, and its correlation with the final histopathology was always with the pleomorphic adenoma. This observation corresponds with those of big studies that agreed strongly between Milan categories and histopathological outcomes as reported by Tochtermann *et al.*, and Han *et al.*, [8, 15]. Furthermore, Milan categories V (suspicious malignancy) and VI (malignant) in our study proved that they were well aligned with known malignant tumors, including mucoepidermoid carcinoma and adenoid cystic cancer, indicating a predictive advantage of these Milan categories in daily diagnostic practice [16, 17]. Recent advances in cytopathology emphasize the role of ancillary techniques in improving the diagnostic yield of FNAC. Cell block preparation, immunocytochemistry, and molecular profiling are increasingly used to complement cytomorphologic assessment, particularly in cases with

overlapping features. For example, molecular markers such as CRTC1-MAML2 fusion in mucoepidermoid carcinoma and MYB-NFIB translocation in adenoid cystic carcinoma offer specific diagnostic and prognostic value and can now be detected in FNAC-derived material. The practical implications of FNAC are particularly profound in resource-limited healthcare systems, where it offers a low-cost, rapid, and accurate tool for patient stratification. By enabling differentiation between benign and malignant parotid lesions, FNAC prevents unnecessary surgical interventions, facilitates appropriate treatment pathways, and ultimately reduces healthcare costs. Nguyen *et al.*, in a systematic review and meta-analysis, emphasized that FNAC maintains high sensitivity and specificity across both academic and community settings when performed with ultrasound guidance and interpreted using standardized systems such as the Milan classification. In our study, the use of real-time ultrasound guidance yielded a low non-diagnostic rate (5%), supporting its essential role in improving aspirate adequacy and diagnostic reliability [18]. Studies by Nguyen and Giang and Nassif *et al.*, confirm that the integration of these molecular adjuncts into FNAC workflows significantly improves diagnostic confidence in indeterminate categories [18, 19]. This was a single-center study with a sample size of 100 patients, which may limit generalizability to larger populations with broader histological diversity. Moreover, although interpretations were made according to the Milan System and confirmed by experienced pathologists, interobserver variability remains an inherent challenge in cytopathological diagnosis. Finally, the absence of long-term clinical follow-up data precludes assessment of FNAC's prognostic utility and its impact on recurrence rates or disease-free survival [19]. Finally, this study supports the robust diagnostic role of ultrasound-guided FNAC enhanced through structured interpretation using the Milan System in evaluating parotid gland lesions. It offers a high degree of sensitivity and specificity, particularly in distinguishing between benign and malignant tumors, and holds immense clinical value in both well-resourced and resource-limited settings. The multicenter studies, where a larger population of cases is involved, molecular cytopathology, and long-term clinical follow-up are obligatory, and these studies should be used to further define diagnostic accuracy, particularly in the Milan stages III, IVb. The combination of cytomorphology and molecular profiling, diagnostic imaging refers to the future of personalized diagnosis in salivary gland pathology [20].

This study was limited by its single-center design and relatively modest sample size, which may restrict generalizability to broader populations with greater histopathological diversity. Interobserver variability in

cytological interpretation and the absence of long-term follow-up data further limit assessment of prognostic implications and recurrence outcomes. Additionally, ancillary molecular and immunocytochemical techniques were not incorporated, which may have enhanced diagnostic precision in indeterminate categories. Future multicenter studies with larger cohorts, integration of molecular diagnostics, and longitudinal follow-up are recommended to further validate and refine the clinical role of FNAC in parotid gland pathology.

CONCLUSIONS

It was concluded that FNAC, used with ultrasound guidance and with the analysis of the structure of the Milan system, is a highly sensitive, specific, and precise alternative to the distinction of benign and malignant salivary parotid tumors. These observations confirm its further application in a clinical practice as an informative preoperative diagnostic tool. It was more reliable in categories IVa, V, and VI in Milan, and a problem of diagnostic uncertainty also occurred in categories III and IVb. These results justify the application of FNAC not only as a minimally invasive and low-cost preoperative diagnostic technique but also as a definitive process to improve clinical decision-making, in particular, and the healthcare system in general, where resources are scarce. Overall, the study supports the use of FNAC to plan surgery, avoid unnecessary procedures, and instill the element of patient-centered care, thereby complying with our goals and considerations. It should be attempted in the future to introduce the use of FNAC coupled with molecular and immunocytochemical add-ons that can further improve the diagnostic accuracy of this procedure, especially in cytological indeterminate diseases.

Authors' Contribution

Conceptualization: RR

Methodology: RR, ZN, FS

Formal analysis: BA

Writing and Drafting: MI, HTK

Review and Editing: MI, HTK, RR, ZN, FS, BA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Frequency of Septal Perforation in Submucous Resection of Nasal Septum

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ABSTRACT

Deviated nasal septum (DNS) is a frequent cause of nasal obstruction and is commonly treated through submucous resection (SMR). Although effective, SMR carries a risk of septal perforation, which can lead to long-term morbidity. **Objectives:** To determine the frequency of septal perforation following submucous resection (SMR) of the nasal septum using the tunnel-in technique. **Methods:** This descriptive observational study was conducted at the Department of ENT, Lady Reading Hospital, Peshawar, from September 2024 to February 2025. A total of 203 patients aged 18–60 years undergoing SMR for symptomatic DNS were enrolled through consecutive non-probability sampling. Patients with prior nasal surgery, trauma, or coexisting nasal pathology were excluded. All surgeries were performed by ENT consultants using a standardized technique. Septal perforation was assessed via endoscopy on the 10th postoperative day. **Results:** Out of 203 patients, 43 (21.2%) developed septal perforation. The mean age was 38.96 ± 12.74 years; the mean disease duration was 19.52 ± 10.46 months. Perforation showed a significant association with gender ($p=0.005$) and age group ($p=0.025$), while no significant link was found with the side of deviation or disease duration. **Conclusions:** Septal perforation was a relatively common postoperative complication of SMR, with higher occurrence in females and older individuals. Careful patient selection and surgical precision are key to reducing risk.

INTRODUCTION

The surgical correction of a deviated nasal septum has evolved significantly over the decades [1]. In 1929, Metzenbaum developed one of the earliest approaches focused on manipulating the caudal septum, then Peer in 1937 suggested straightening and repositioning the septum to the midline. Such endeavours have contributed to what is now referred to as Submucous Resection (SMR), one of the classical techniques employed for dealing with surgically correctable deviated septa [2]. Deviated nasal septum (DNS) presents one of the most common conditions encountered in otorhinolaryngology clinics and continues to be a principal reason for undergoing nasal surgery. It is associated with symptoms such as breathing difficulty through the nose, chronic headaches, and postnasal drainage. In practice, management of DNS is

algorithm-based towards surgical options, whether it be conventional or endoscopic. Despite the existence of more modern techniques, submucous resection persists as the go-to approach because of ease and effectiveness when treating substantial deviations [3]. Killlan *et al.* advanced the idea of SMR by highlighting submucosal access along with tissue conservation. Nevertheless, complications such as septal perforation led to a move towards more conservative approaches like septoplasty. Despite this change, SMR continues to be relevant in many settings because of its effectiveness, especially when performed using the tunnelling technique by experienced surgeons [4]. Numerous researchers have focused on the disadvantages of SMR surgery, especially concerning the potential postoperative complications. A. Gravina *et al.*



showed that inadequate visibility in the traditional approaches, as compared to endoscopy, may lead to increased trauma of the mucosa layer due to limited or inadequate scrutiny, increasing the chances for septal perforations [5]. This also explains why Garg and colleagues has endorsed endoscopic methods because they have a far greater degree of visualization and therefore accuracy as well as precision [6]. Reported rates of septal perforation differ widely among studies, ranging from 2.2% to 5%. This variability can be attributed to multiple factors, including the type of surgical technique (traditional SMR vs. endoscopic septoplasty), experience of the surgeon, and duration of postoperative follow-up. For instance, endoscopic techniques tend to yield lower complication rates due to enhanced visualization, while short follow-up intervals may underreport delayed perforations. Alrobian *et al.* documented rates of 2.2% and 3.2% [7], while Al Sulaiti *et al.* noted a 2.5% incidence following submucous resection. Sarin *et al.* observed a 5% rate with postoperative splint use [8]. Septal perforations, although sometimes asymptomatic, can cause whistling sounds during breathing, nasal crusting, epistaxis, and a sensation of nasal blockage. The purpose of this study was to assess the frequency of septal perforation in patients undergoing. To quantify such symptoms and their impact on quality of life, validated scoring systems such as the NOSE (Nasal Obstruction Symptom Evaluation) scale and the Visual Analogue Scale (VAS) have been widely used in literature. Several studies have demonstrated that septal perforation can lead to significantly higher NOSE scores, indicating worse nasal function and patient-reported outcomes [6]. Submucous resection (SMR) remains a commonly performed surgical procedure for symptomatic deviated nasal septum, particularly in resource-limited settings. However, reported rates of septal perforation vary widely in the literature, and most available data originate from studies on septoplasty or endoscopic techniques rather than classical SMR using the tunnelling approach. Furthermore, local evidence assessing the true frequency of septal perforation and its associated demographic risk factors in tertiary care hospitals is limited. This gap underscores the need for updated, region-specific data to better evaluate complication rates and optimize surgical practice. This study aims to assess the frequency of septal perforation in patients undergoing SMR using the tunnelling technique by experienced ENT surgeons. By focusing on identifying associated demographic and surgical risk factors, this study aims to provide insight into optimizing surgical techniques and reducing postoperative complications. Understanding the prevalence and predictors of this complication may help refine surgical protocols and improve patient outcomes.

METHODS

This research was structured as a descriptive, observational study conducted at the Department of ENT, Lady Reading Hospital, Peshawar. This study aims to determine the frequency of septal perforation following submucous resection of the nasal septum (SMR). The study extended from September 2024 to February 2025. Before initiating data collection, ethical clearance was obtained from the Institutional Review Board (IRB) of Lady Reading Hospital, Medical Teaching Institution (MTI), Peshawar. The approval was issued under Ref. No. 972/LRH/MTI, certifying that the study met all ethical requirements. Furthermore, the synopsis was formally approved by the Research Evaluation Unit (REU) of CPSP, under Ref No: CPSP/REU/ENT-2022-022-1394. A consecutive non-probability sampling method was utilized. Every patient who was eligible and fulfilled the inclusion criteria during the study period was enrolled in a sequential manner until the required sample size was reached. The required sample size was calculated using the World Health Organization (WHO) sample size calculator. Considering a 5% expected frequency of septal perforation [9], with a 95% confidence level and a 3% margin of error, the final calculated sample size was 203 participants. The 3% margin of error was selected to allow for a narrower confidence interval around the estimated prevalence [9], improving precision. A formal power analysis was not conducted, as the primary aim of this study was to estimate prevalence rather than test a specific hypothesis. The study protocol received ethical clearance from the institutional review committee. All patients gave appropriate informed written consent before participating. Each patient was informed of the study aims, steps involved, and their option to withdraw at any stage without any impact on their healthcare. Inclusion Criteria were defined as follows: participants were enrolled if they were within the age range of 18–60 years, of either gender, and diagnosed with symptomatic deviated nasal septum scheduled for SMR via the Outpatient Department (OPD). The study excluded patients presenting with additional nasal pathologies such as nasal polyps or chronic rhinosinusitis, as well as individuals with a history of previous nasal surgeries or traumatic nasal injuries. These criteria were essential to minimize confounding variables that could skew the assessment of septal perforation outcomes. After obtaining informed consent, participants' demographic details and clinical history were recorded on a standardized proforma. All patients were evaluated for signs of previous nasal trauma or surgery. Preoperative imaging was performed using computed tomography (CT) of the paranasal sinuses (CT PNS). The scans were reviewed for features such as mucosal thickening, sinonasal polyps, sinus opacification, air-fluid

levels, bony erosions, mucocoeles, and anatomical variants like concha bullosa. Only patients with normal sinus anatomy and no coexisting pathology were included. All SMR procedures were conducted by experienced ENT consultants. The surgical approach involved raising a mucoperichondrial flap using a freer elevator under direct visualization. The deviated portion of the nasal septal cartilage was excised using Luc's forceps. Surgical adequacy was confirmed by midline repositioning of mucosal flaps and by bilateral nasal cavity inspection for residual deviation. Although no formal intraoperative checklist was used, a standardized operative protocol was followed for every case. This included bilateral tunnelling technique, careful elevation of mucoperichondrial flaps, minimal cartilage excision, and consistent use of nasal splints to protect flap positioning. All surgeries were performed by the same surgical team to ensure consistency. Once correction was ensured, the mucosal flaps were repositioned without sutures and secured using bilateral nasal splints, fixed with 1/0 silk through-and-through sutures. The nasal cavities were packed with polyfax ointment-soaked gauze. Post-operative instructions included saline nasal douching, avoidance of nose blowing, and pain control with paracetamol. Endoscopic evaluation for septal perforation was performed on the 10th postoperative day, coinciding with the removal of nasal splints. This timing was selected as most early perforations, if present, would become clinically apparent by this point due to mucosal necrosis or incomplete healing. While delayed perforations can occur, the 10th day was standardized across all cases to ensure uniformity of follow-up. To ensure reliability, data collection was performed using a structured and pre-validated proforma, and all assessments (pre- and post-operatively) were conducted by the same surgical team to reduce inter-observer variability. Surgical protocols were standardized. Validity was reinforced by excluding patients with potential confounding factors, using imaging (CT PNS) and direct endoscopic visualization to confirm diagnosis and outcomes. Data entry was double-checked by an independent reviewer. Data were analyzed using SPSS version 20.0. Categorical variables such as gender, presence of septal perforation, side of deviation, and grouped age and disease duration were expressed as frequencies and percentages. Continuous variables like age and duration of disease were summarized using mean $\pm$ standard deviation, along with minimum and maximum values. Chi-square tests were applied to assess associations between septal perforation and demographic or clinical factors. A p -value ≤ 0.05 was considered statistically significant. Post-stratification was conducted for effect modifiers, and the strength of associations was measured using Cramer's V. Additionally, binary logistic

regression was performed to identify independent predictors of septal perforation, with adjusted odds ratios (AORs) and 95% confidence intervals reported. Results were presented in tabular and graphical formats for clarity and comparison with a 95% confidence level and a 3% margin of error, the final calculated sample size was 203 participants. The study protocol received ethical clearance from the institutional review committee. All patients gave appropriate informed written consent before participating. Each patient was informed of the study aims, steps involved, and their option to withdraw at any stage without any impact on their healthcare. Inclusion Criteria were defined as follows, where subjects were enrolled if: Participants were within the age range 18 -60 years old, both male and female. And patients diagnosed with symptomatic deviated nasal septum who were admitted via the Outpatient Department (OPD) and scheduled for SMR. The study excluded patients presenting with additional nasal pathologies such as nasal polyps or chronic rhinosinusitis. And individuals with a history of previous nasal surgeries or traumatic nasal injuries. These criteria were essential to minimize confounding variables that could skew the assessment of septal perforation outcomes. After obtaining informed consent, participants' demographic details and clinical history were recorded on a standardized proforma. All patients were evaluated for signs of previous nasal trauma or surgeries. Imaging, including CT scan of the paranasal sinuses (PNS), was performed to rule out coexisting sinus disease and assess nasal anatomy. All SMR procedures were conducted by experienced ENT consultants. The surgical approach involved raising a mucoperichondrial flap using a freer elevator, under direct visualization. The deviated portion of the nasal septal cartilage was excised using Luc's forceps. Surgical adequacy was confirmed by midline repositioning of mucosal flaps and by bilateral nasal cavity inspection for residual deviation. Once correction was ensured, the mucosal flaps were repositioned without sutures and secured using bilateral nasal splints, fixed with 1/0 silk through-and-through sutures. The nasal cavities were packed with polyfax ointment-soaked gauze. Post-operative instructions included saline nasal douching, avoidance of nose blowing, and pain control with paracetamol. Splints were removed on the 10th post-operative day, and nasal endoscopy was performed to detect any signs of septal perforation. To ensure reliability, data collection was performed using a structured and pre-validated proforma, and all assessments (pre- and post-operatively) were conducted by the same surgical team to reduce inter-observer variability. Surgical protocols were standardized. Validity was reinforced by excluding patients with potential confounding factors. Using imaging (CT PNS) and direct endoscopic visualization to confirm diagnosis

and outcomes. Data entry was double-checked by an independent reviewer. Data were analyzed using SPSS version 20. Categorical variables such as gender, presence of septal perforation, side of deviation, and grouped age and disease duration were expressed as frequencies and percentages. Continuous variables like age and duration of disease were summarized using mean $\pm$ standard deviation, along with minimum and maximum values. Chi-square tests were applied to assess associations between septal perforation and demographic or clinical factors. A p -value ≤ 0.050 was considered statistically significant. Post-stratification was conducted for effect modifiers, and the strength of associations was measured using Cramer's V. Results were presented in tabular and graphical formats for clarity and comparison.

RESULTS

Out of the 203 patients included in this study, the gender distribution was slightly skewed toward female, with 108 (53.2%) female and 95 (46.8%) male. The mean age of the participants was 38.96 ± 12.74 years, ranging from 18 to 60 years. On average, patients had experienced nasal obstruction symptoms for 19.52 ± 10.46 months, with durations ranging from 1 month to 36 months. Postoperatively, septal perforation was detected in 43 patients, yielding a prevalence of 21.2%. The 95% confidence interval for this prevalence was 15.4% to 26.9%, providing a statistically sound estimate of the true rate of this complication in the study population (Table 1).

Table 1: Demographics and Septal Perforation Frequency (n=203)

Parameters	Category / Value	Frequency (%)	Range
Gender	Male	95 (46.8%)	—
	Female	108 (53.2%)	—
Age (Years)	Mean $\pm$ SD	38.96 ± 12.74	18 – 60
Duration of Disease	Mean $\pm$ SD	19.52 ± 10.46	1 – 36 Months
Septal Perforation	Yes	43 (21.2%)	—
	No	160 (78.8%)	—
95% CI for Perforation	—	15.4% – 26.9%	—

A statistically significant association was found between gender and the occurrence of septal perforation. Among the 95 male patients, 12 (12.6%) developed perforation, while 31 out of 108 female patients (28.7%) were affected. The difference was significant ($\chi^2 = 7.820$, $p = 0.005$), with a Cramer's V value of 0.196 indicating a moderate strength of association. These findings suggest that females had a higher risk of developing septal perforation following submucous resection. When patients were grouped by age, a statistically significant trend emerged ($\chi^2 = 7.414$, $p = 0.025$). Only 6 (9.8%) patients aged 18–30 years developed septal perforation. This rose to 17 (23.3%) in the 31–45 age group and peaked at 20 (29.0%) among those aged 46–60 years. These results highlight a clear increase in risk with

advancing age, suggesting that older patients may be more susceptible to mucosal injury or impaired healing (Table 2).

Table 2: Association Between Gender and Septal Perforation, Age Group and Septal Perforation

Variables	Perforation: Yes	Perforation: No	Chi-square (χ^2)	p-Value	Cramer's V
Gender					
Male	12 (12.6%)	83 (87.4%)	7.820	0.005	0.196
Female	31 (28.7%)	77 (71.3%)			
Age Group (Years)					
18–30	6 (9.8%)	55 (90.2%)	7.414	0.025	0.191
31–45	17 (23.3%)	56 (76.7%)			
46–60	20 (29.0%)	49 (71.0%)			

Analysis of the relationship between the side of nasal septal deviation and septal perforation revealed no statistically significant association ($\chi^2 = 1.469$, $p = 0.226$). Among patients with left-sided deviation, 20 (18.0%) developed perforation compared to 23 (25.0%) of those with right-sided deviation. Despite this numerical difference, the lack of statistical significance indicates that the laterality of deviation may not influence the risk of postoperative perforation. An analysis of the duration of nasal symptoms revealed no significant association with the development of septal perforation ($\chi^2 = 1.062$, $p = 0.588$). Twelve patients with symptoms lasting less than 12 months (19.0%) developed perforation, as did 12 patients (18.8%) with 12–24 months of disease and 19 patients (25.0%) with symptoms persisting beyond 24 months. Although there was a mild upward trend with longer symptom duration, it was not statistically meaningful (Table 3).

Table 3: Association Between Side of Deviation and Septal Perforation, Duration of Disease and Septal Perforation

Variables	Perforation: Yes	Perforation: No	Chi-square (χ^2)	p-Value
Side of Deviation				
Left	20 (18.0%)	91 (82.0%)	1.469	0.226
Right	23 (25.0%)	69 (75.0%)		
Duration (Months)				
<12	12 (19.0%)	51 (81.0%)	1.062	0.588
12-24	12 (18.8%)	52 (81.2%)		
>24	19 (25.0%)	57 (75.0%)		

To assess whether age, gender, side of septal deviation, and duration of disease were independent predictors of septal perforation, a binary logistic regression analysis was performed. The model was statistically significant ($\chi^2 = 20.227$, $df = 6$, $p = 0.003$), indicating that the included variables meaningfully predicted the likelihood of perforation. The Hosmer–Lemeshow goodness-of-fit test was non-significant ($p = 0.101$), suggesting that the model fit the data well. The Nagelkerke R^2 value was 0.147, showing that approximately 14.7% of the variation in septal perforation was explained by the model. The classification

accuracy improved to 81.3% with the inclusion of predictors. After adjusting for all covariates, female gender emerged as a significant independent predictor of septal perforation, with females having higher odds of developing perforation compared to males (AOR = 0.338; 95% CI: 0.157-0.730; $p=0.006$). Similarly, age group 31-45 years was significantly associated with increased risk (AOR = 4.498; 95% CI: 1.579-12.816; $p=0.005$) when compared to the reference age group of 18-30 years. However, the 46-60-year group did not show a statistically significant association (AOR = 1.471; $p=0.340$). The side of septal deviation (right vs. left) was not significantly associated with perforation in the adjusted model (AOR = 1.678; $p=0.168$), nor was duration of disease. Both duration categories (12-24 months and >24 months) did not show statistically meaningful differences in risk when compared to those with disease duration less than 12 months. These results suggest that female gender and middle-aged patients (31-45 years) are at greater risk for septal perforation following submucous resection, independent of anatomical laterality or symptom duration (Table 4).

Table 4: Multivariable Logistic Regression Predicting Septal Perforation (n=203)

Predictor Variable	Adjusted Odds Ratio (AOR)	95% Confidence Interval	P-Value
Gender			
Female	0.338	0.157 – 0.730	0.006 **
Septal Deviation Side			
Right	1.678	0.804 – 3.505	0.168
Age Group			
31-45 Years	4.498	1.579 – 12.816	0.005 **
46-60 Years	1.471	0.666 – 3.251	0.340
Duration of Disease			
12-24 Months	0.943	0.363 – 2.446	0.904
>24 Months	0.552	0.227 – 1.342	0.190

Reference categories: Gender = Male; Septal Deviation Side = Left; Age = 18-30 years; Duration = <12 months. AOR: Adjusted Odds Ratio; CI: Confidence Interval. Bolded p-values <0.050 indicate statistical significance.

The occurrence of septal perforation increases progressively with age. The lowest rate of perforation was observed in the 18-30 age group (6 cases), while the highest was seen in patients aged 46-60 years (20 cases). In contrast, the number of patients without perforation decreases slightly with age. A chi-square analysis confirmed that the difference in perforation rates between age groups was statistically significant ($p=0.025$), suggesting a potential link between older age and higher risk of septal perforation following submucous resection. The chart illustrates the frequency of septal perforation among three age groups (18-30, 31-45, and 46-60 years). Each group displays the number of patients who developed septal perforation (blue bars) versus those who did not (orange bars). (Figure 1).

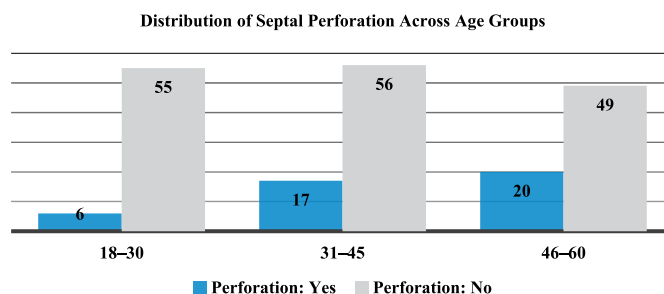


Figure 1: Distribution of Septal Perforation Across Age Groups

DISCUSSION

This study aimed to determine the frequency and associated factors of septal perforation following submucous resection (SMR) in patients with symptomatic deviated nasal septum. Out of 203 patients, a perforation rate of 21.2% was noted, which was substantially higher than most previously reported rates, typically ranging from 1% to 10%. This discrepancy may reflect variations in surgical technique, patient selection, and follow-up protocols, and indicates that despite SMR being considered a standard procedure, it continues to pose significant complication risks in some patient groups. Earlier studies on septal perforation reported rates between 1% and 5%. Eren et al. reported a 2.7% prevalence of perforations post-septoplasty [10], while Davis et al. noted a 3.5% rate in their retrospective study [11]. Similarly, Behery et al. described a 5% occurrence and advocated for splint wear to reduce mucosal injury and adhesion formation during postoperative healing [12]. Research conducted by Bansberg and Miglani highlighted that mucoperichondrial preservation alone does not guarantee protection from perforation and that improper dissection can increase risk [13]. Likewise, Pai et al. emphasized that older patients undergoing bilateral flap elevation are particularly prone to iatrogenic mucosal injury if not meticulously managed [14]. These findings support our study's observation that perforation was significantly associated with age over 45 years ($p=0.025$). Our analysis also showed that female gender was significantly associated with higher perforation rates (28.7% in females vs. 12.6% in male). Although limited studies have focused on gender-based healing differences, Khan, suggested that hormonal influences and mucosal sensitivity may contribute to differential healing patterns between male and female [15]. Further research is needed to determine whether these are biologically driven or related to behavioral differences in postoperative care compliance. No statistically significant association was observed between the side of septal deviation and the occurrence of perforation ($p=0.226$), in agreement with Blioska, who noted that the laterality or angle of deviation did not influence complication rates when a consistent surgical

technique was applied [16]. Perforation risk also showed a clear age-related trend. Perforation rates increased progressively with advancing age. This supports findings by Noor *et al.* who noted that reduced mucosal thickness and vascularity in older adults may impair wound healing [17]. Gan *et al.* similarly found that complication rates increase in patients over 40 due to decreased tissue elasticity and delayed mucosal regeneration [18]. In contrast, duration of nasal symptoms was not associated with perforation risk, as also noted by Khaled *et al.* who found no relationship between symptom duration and mucosal healing in SMR [19]. This suggests that intraoperative tissue condition, rather than chronicity of symptoms, may be a more relevant factor for predicting outcomes. All procedures in this study were performed using a standardized method involving bilateral mucoperichondrial flap elevation, cartilage resection using Luc's forceps, and application of polyfax-soaked packing with splints. According to Park *et al.* meticulous flap elevation and the use of splints significantly reduce the risk of perforations [20]. Huang *et al.* emphasized the role of routine postoperative endoscopic surveillance in early detection of mucosal complications [21]. The use of bilateral nasal splints for 10 days in this study aligns with best practice protocols and appears to have minimized trauma during early healing. Although intraoperative mucosal tears were not formally recorded as a variable in our data collection tool, the surgical team monitored for such events during dissection. Anecdotally, most cases with visible flap damage were closely observed, but no direct correlation was statistically analyzed between intraoperative tears and postoperative perforation. This has been acknowledged as a limitation of the study. This study's higher-than-expected rate of septal perforation underscores the importance of surgical precision, intraoperative vigilance, and tailored postoperative care, especially in higher-risk groups such as older adults and female patients. While many findings align with the existing literature, some, particularly the gender disparity, require further prospective investigation.

This study was limited by its single-center observational design and short postoperative follow-up of 10 days, which may have underestimated delayed perforations. Intraoperative mucosal tears were not formally documented, limiting detailed assessment of surgical predictors. Additionally, patient-reported outcome measures such as NOSE or quality-of-life scores were not evaluated. Future multicenter prospective studies with longer follow-up, standardized intraoperative documentation, and incorporation of validated symptom scoring systems are recommended to better define long-term outcomes and refine preventive surgical strategies.

CONCLUSIONS

This study found a septal perforation rate of 21.2% following submucous resection (SMR) of the nasal septum. A statistically significant association was observed between septal perforation and both age and gender, with female patients and those in older age groups being more prone to this complication. In contrast, the side of septal deviation and duration of disease were not significantly associated with perforation outcomes. These findings suggest that demographic variables, particularly gender and age, may influence the risk of postoperative septal perforation in patients undergoing SMR, even when a standardized surgical technique is applied.

Authors' Contribution

Conceptualization: NZ

Methodology: KH, NU, JK

Formal analysis: NZ, HURA, KH, NU, JK

Writing and Drafting: NZ, HURA, NU, JK

Review and Editing: NZ, HURA, NU, JK, KH

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Assessing the Effect of Hormonal Contraceptives on Oxidative Stress and Lipid Metabolism in Reproductive Age Women

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ABSTRACT

Women of reproductive age frequently use hormonal contraceptives for family planning and regulating menstrual cycles. There is growing apprehension, however, regarding the potential long-term metabolic and cardiovascular effects of these contraceptives due to their impact on oxidative stress and lipid metabolism. **Objective:** To assess the impact of hormonal contraceptive use on oxidative stress markers and lipid profile parameters in reproductive-age women. **Methods:** This comparative cross-sectional study encompassed 150 women aged 18 to 40 years, evenly split into users and non-users of hormonal contraceptives. From each participant, blood samples were drawn to assess oxidative stress Markers Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), Superoxide Dismutase (SOD), catalase, Glutathione Peroxidase (GPx), as well as lipid profile parameters such as total cholesterol, triglycerides, LDL-C, HDL-C, and the LDL/HDL ratio. For the analysis, appropriate parametric and non-parametric tests were applied for the statistical comparisons. **Results:** Hormonal contraceptive users had significantly higher MDA levels and reduced TAC, SOD, GPx, and catalase activity, indicating elevated oxidative stress and impaired antioxidant defenses ($p < 0.001$). Lipid profile analysis revealed significantly increased total cholesterol, triglycerides, and LDL-C, along with reduced HDL-C and elevated LDL/HDL ratios among users compared to non-users ($p < 0.001$). **Conclusions:** Hormonal contraceptive use in reproductive-age women is associated with increased oxidative stress and an unfavorable lipid profile. These biochemical alterations may raise the risk of cardiovascular complications with long-term use. Regular monitoring and preventive strategies, including lifestyle counseling and antioxidant support, may help mitigate these risks.

INTRODUCTION

Hormonal contraceptives are an effective family planning method and regulatory tool in reproductive health used globally [1]. These agents, which mainly contain synthetic estrogens and progestins, influence the female reproductive system by suppressing ovulation, changing the secretion from the cervix, and altering the endometrium [2]. While the mitigative role they play in reducing unintentional pregnancies and managing menstruation cycles is well documented, emerging studies indicate that these synthetic hormones may have wider

physiological impacts [3]. The possible effects of hormonal contraceptives on the balance of oxidative stress within the body as an emerging concern is noteworthy [4]. Within the context of medicine, oxidative stress is defined as an imbalance between the Reactive Oxygen Species (ROS) production and an organism's ability to neutralize these harmful byproducts using various antioxidant defenses. Estrogens, which have a unique mix of both pro- and antioxidant effects, may metabolically produce Reactive Oxygen Species (ROS) in hepatic and peripheral tissues [5,



6]. This increased oxidant stress can lead to damage of lipids and proteins as well as DNA injury which contributes to and/or exacerbates many pathological states. For this reason, the use of hormonal contraceptives may increase women's risk of developing condition associated with chronic oxidative stress, especially with long-term use [7]. At the same time, contraceptive hormones are known to affect lipid metabolism [8]. Lipid changes associated with the use estrogen-containing contraceptives include increased hepatic lipoprotein synthesis resulting in total cholesterol, LDL-C, and triglyceride increases and reduction of HDL-C [9, 10]. Such changes, particularly when combined with other metabolic or lifestyle factors, might increase the risk of cardiovascular events in women over the long term. Nevertheless, the degree and reliability of these changes are different for specific formulations, populations, and individual health conditions which underscores the importance of investigating biochemical consequences in different demographic settings [11]. Although oxidative stress and lipid changes have been studied separately, limited research explores their combined effects in women using hormonal contraception [12]. Given the rising use of these contraceptives in developing countries like Pakistan where dietary habits and antioxidant status vary there was a pressing need to examine their interconnected impact in this population. Thus, this study aimed to evaluate the influence of hormonal contraceptives on oxidative stress markers and lipid profile parameters among women of reproductive age. By comparing hormonal contraceptive users with non-users, we aimed to provide a more comprehensive understanding of the biochemical changes associated with contraceptive use and to identify potential early indicators of cardiovascular or metabolic risk.

Hormonal contraceptives are widely used by women of reproductive age for family planning and menstrual regulation; however, their potential metabolic and biochemical effects remain a growing concern. Evidence suggests that these contraceptives may influence oxidative stress pathways and alter lipid metabolism, potentially increasing the risk of cardiovascular complications with long-term use. Although several studies have examined oxidative stress or lipid changes independently, limited research has evaluated their combined impact among hormonal contraceptive users. Moreover, there is a scarcity of population-specific data from developing countries such as Pakistan, where lifestyle and nutritional factors may influence oxidative balance and lipid metabolism. The findings could help inform safer prescribing practices and guide the development of targeted preventive strategies, such as antioxidant supplementation or periodic lipid monitoring.

METHODS

This comparative cross-sectional study was conducted to evaluate the effects of hormonal contraceptive use on oxidative stress markers and lipid profile in women of reproductive age. The study was carried out at Health Net Hospital, Peshawar, from May 2023 to October 2024. Pakistani women were selected due to the unique interplay of dietary patterns, environmental exposures (urban pollution, low antioxidant intake), and limited health awareness regarding long-term contraceptive use, all of which may influence oxidative stress and lipid metabolism. Thus, localized data were necessary to tailor clinical recommendations. Ethical approval was granted by the Ethics Review Committee of Health Net Hospital (Ref: 3059/HNH/HR). Written informed consent was obtained, and confidentiality was maintained via coded identifiers. The sample size was calculated using OpenEpi software, based on a previously reported standardized effect size of 0.5 for Malondialdehyde (MDA) levels, with 95% confidence and 80% power, yielding 75 participants per group (total = 150) [13]. A non-probability purposive sampling technique was used to recruit participants from gynecology outpatient clinics. Inclusion criteria were women aged 18–40 years, using hormonal contraceptives for at least 6 months or not using any in the past year, and willing to provide a blood sample. Exclusion criteria were females with diagnosed metabolic, autoimmune, or chronic inflammatory diseases; current infections; and use of antioxidants, corticosteroids, or lipid-lowering drugs. Data were collected over a period of six months. After obtaining consent, participants were interviewed using a structured questionnaire to document demographic data (age, BMI, parity, marital status, education, physical activity, and smoking history) and clinical details, including type of hormonal contraceptive used Combined Oral Contraceptive Pills (COCPs), injectables (depot medroxyprogesterone acetate), or subdermal implants along with duration of use and menstrual regularity. Contraceptive use duration was verified via both self-report and cross-checked with medical prescription records whenever available. Participants were grouped as follows Group 1: Hormonal contraceptive users (n = 75) and Group 2: Non-users (n = 75). After 8–12 hours of overnight fasting, 5 mL of venous blood was collected. Serum was separated for lipid profile testing (total cholesterol, triglycerides, LDL-C, HDL-C, LDL/HDL ratio). Plasma was used for oxidative stress markers MDA via TBARS assay, TAC via FRAP method, SOD via colorimetric assay, Catalase via hydrogen peroxide decomposition and GPx using ELISA-based coupled enzyme reaction kits. Assays followed manufacturer protocols in the hospital biochemistry lab. Laboratory staff were blinded to

participant group status. All tests were done in duplicate using the same instruments and reagents, with random re-testing of 10% samples (CV <10%) to ensure reliability. Data were analyzed using IBM SPSS version 25.0. Continuous variables were expressed as mean $\pm$ SD or median (IQR), and categorical variables as frequencies (%). Normality was assessed with the Shapiro-Wilk test and histograms. Group differences were tested using independent t-tests or Mann-Whitney U tests (for non-parametric data), and Chi-square or Fisher's exact test for categorical variables. Effect sizes were reported with Cramér's V where applicable. Significance was set at $p < 0.050$, with 95% confidence intervals provided where relevant. Complete-case analysis was used for missing data; no imputation was applied as data completeness exceeded 95%.

RESULTS

The comparison of demographic and clinical characteristics between groups revealed that the mean age of users was significantly higher than non-users (29.8 ± 5.49 vs. 27.8 ± 5.48 years, $p = 0.025$), suggesting a possible age-related trend in hormonal contraceptive use. However, there was no statistically significant difference in Body Mass Index (BMI) between the two groups ($p = 0.420$). Marital status, parity, and education level showed no meaningful differences either, indicating similar socio-demographic backgrounds. Notably, smoking status showed a borderline significant difference ($p = 0.050$), with a higher proportion of smokers among non-users. Although this association was weak, Cramér's V (0.160) suggests a small effect size. Physical activity levels were also comparable between the groups, with no statistical significance observed ($p = 0.596$) (Table 1).

Table 1: Comparison of Demographic and Clinical Characteristics between Hormonal Contraceptive Users and Non-Users (n = 150)

Variables	Hormonal Users Mean $\pm$ SD / Frequency (%)	Non-Users Mean $\pm$ SD / Frequency (%)	p-Value
Age (Years)	29.8 ± 5.49	27.8 ± 5.48	0.025 ^a
BMI (Kg/m ²)	24.68 ± 3.40	25.12 ± 3.33	0.420 ^b
Marital Status (Married)	69 (92.0)	65 (86.7)	0.290
Parity ≥ 2	46 (61.3)	40 (53.3)	0.322
Education Level $\geq$ Secondary	42 (56.0)	48 (64.0)	0.381
Smoking (Yes)	2 (2.7)	8 (10.7)	0.050 ^c
Physical Activity (Moderate /Active)	40 (53.3)	46 (61.3)	0.596

^aMann-Whitney U test

^bIndependent samples t-test

^cChi-square test; Cramér's V = 0.160 (small effect size)

Among the hormonal users, combined oral contraceptive pills (COCPs) were the most commonly used method (40%), followed by injectables (33.3%) and implants (26.7%). The overall rate of menstrual irregularity was 18.7%. No

meaningful statistical relationship was found between contraceptive type and menstrual irregularity ($p = 0.523$) and Cramér's V indicated a negligible effect size (0.131). The mean duration of contraceptive use among these women was 20.6 ± 9.18 months, with a range from 6 to 35 months, indicating diverse long-term exposure among the participants (Table 2).

Table 2: Distribution of Contraceptive Methods, Duration of Use, and Menstrual Irregularity among Hormonal Contraceptive Users Only (n = 75)

Variable	Sub-categories	Frequency (%) / Mean $\pm$ SD	p-Value	Cramer's V
Menstrual Irregularity	Yes	14 (18.7)	-	-
	No	61 (81.3)	-	-
Type of Hormonal Contraceptive	COCP	30 (40.0)	0.523	0.131
	Implant	20 (26.7)	-	-
	Injectable	25 (33.3)	-	-
Duration of Use (Months)	Mean $\pm$ SD	20.6 ± 9.18	-	-
	Range	6 – 35	-	-

Analysis of oxidative stress biomarkers showed significant differences between hormonal contraceptive users and non-users. Malondialdehyde (MDA), a key marker of lipid peroxidation, was substantially higher in users (4.83 ± 0.34 vs. 3.93 ± 0.32 nmol/mL; $p < 0.001$), indicating elevated oxidative stress. In contrast, total antioxidant capacity (TAC) was significantly lower in users (1.40 ± 0.19 vs. 1.60 ± 0.20 mmol/L; $p < 0.001$), suggesting reduced systemic antioxidant defenses. Furthermore, enzymatic antioxidants Antioxidant enzymes namely SOD, catalase, and GPx were notably reduced among hormonal contraceptive users, with all differences statistically significant ($p < 0.001$). This suggests a trend toward greater oxidative burden and diminished enzymatic defense in this population (Table 3).

Table 3: Comparison of Oxidative Stress Markers between Groups (n = 150)

Variable	Hormonal User Mean $\pm$ SD	Non-User Mean $\pm$ SD	p-Value	95% CI of Mean Difference
MDA (nmol/mL)	4.83 ± 0.34	3.93 ± 0.32	<0.001	0.797 – 1.008
TAC (mmol/L)	1.40 ± 0.19	1.60 ± 0.20	<0.001	-0.269 – -0.140
SOD (U/mL)	123.10 ± 8.99	133.81 ± 10.49	<0.001	-13.86 – -7.56
Catalase (U/mL)	30.21 ± 2.62	32.24 ± 3.29	<0.001	-2.99 – -1.06
GPx (U/mL)	52.52 ± 4.94	58.52 ± 3.99	<0.001	-7.44 – -4.55

Lipid profile analysis revealed marked alterations among hormonal contraceptive users compared to non-users. Median total cholesterol levels were significantly higher in users, as evidenced by the Mann-Whitney U test ($p < 0.001$), although confidence intervals for the difference could not be calculated due to non-parametric analysis. Triglyceride and LDL-C levels were both significantly elevated in users (163.04 ± 21.73 vs. 142.99 ± 20.78 mg/dL and 129.20 ± 8.24 vs. 114.77 ± 11.14 mg/dL, respectively; $p < 0.001$ for both), while

HDL-C was significantly lower in users (43.66 ± 3.45 vs. 48.35 ± 4.21 mg/dL; $p < 0.001$). These differences reflect a more atherogenic lipid profile in hormonal users. Additionally, the LDL/HDL ratio was significantly higher in users (2.93 ± 0.30 vs. 2.30 ± 0.29 ; $p < 0.001$, Mann-Whitney U), further supporting the potential adverse cardiovascular implications of hormonal contraceptive use (Table 4).

Table 4: Comparison of Lipid Profile Parameters between Hormonal Contraceptive Users and Non-Users (n=150)

Lipid Parameter	Hormonal User (Mean $\pm$ SD)	Non-User (Mean $\pm$ SD)	Test Used	P-Value	95% CI of Mean Difference
Total Cholesterol (mg/dL)	209.07 $\pm$ 13.99	189.42 $\pm$ 16.65	Mann-Whitney U	<0.001	-
Triglycerides (mg/dL)	163.04 $\pm$ 21.73	142.99 $\pm$ 20.78	Independent t-test	<0.001	13.19 – 26.91
LDL-C (mg/dL)	129.20 $\pm$ 8.24	114.77 $\pm$ 11.14	Independent t-test	<0.001	11.27 – 17.59
HDL-C (mg/dL)	43.66 $\pm$ 3.45	48.35 $\pm$ 4.21	Independent t-test	<0.001	-5.93 – -3.45
LDL/HDL Ratio	2.93 $\pm$ 0.30	2.30 $\pm$ 0.29	Mann-Whitney U	<0.001	-

As depicted in figure 1, the oxidative stress marker MDA was considerably elevated among hormonal contraceptive users (4.83 ± 0.34 nmol/mL) compared to non-users (3.93 ± 0.32 nmol/mL), suggesting heightened lipid peroxidation. Conversely, all antioxidant markers TAC, SOD, Catalase, and GPx were consistently lower in users than in non-users. Specifically, mean TAC was reduced from 1.60 to 1.40 mmol/L, SOD from 133.81 to 123.10 U/mL, Catalase from 32.24 to 30.21 U/mL, and GPx from 58.52 to 52.52 U/mL. These statistically significant differences highlight a shift towards oxidative imbalance in hormonal users, potentially reflecting increased metabolic oxidative burden or decreased enzymatic defense activity. This clustered bar chart illustrates the mean concentrations of oxidative stress (MDA) and antioxidant defense markers (TAC, SOD, Catalase, GPx) in both groups. Hormonal users demonstrated significantly higher levels of MDA, indicating increased oxidative stress, alongside significantly reduced antioxidant levels across all markers measured. These trends support the hypothesis that hormonal contraceptive use may be associated with altered redox balance and compromised antioxidant capacity.

Comparative Levels of Oxidative Stress and Antioxidant Biomarkers in Hormonal Contraceptive Users and Non-Users

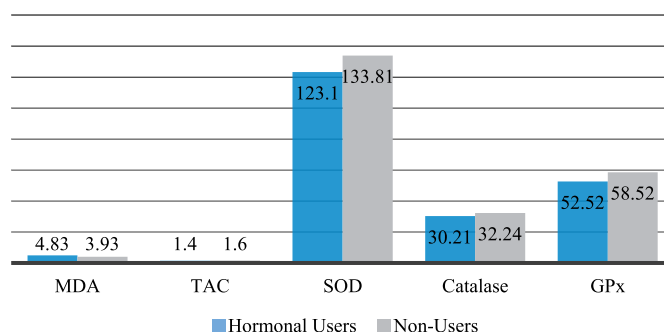


Figure 1: Comparative Levels of Oxidative Stress and Antioxidant Biomarkers in Hormonal Contraceptive Users and Non-Users

DISCUSSION

In this study, hormonal contraceptive users exhibited significantly elevated oxidative stress, reflected through higher MDA values and suppressed activities of antioxidant enzymes (SOD, GPx, Catalase, TAC), suggesting a compromised redox balance likely driven by estrogen-induced Reactive Oxygen Species (ROS). Moreover, we found a pronounced dysregulation of lipid metabolism, with increased total cholesterol, triglycerides, LDL-C, and reduced HDL-C levels among users indicating a shift toward an atherogenic lipid profile. These biochemical changes reinforce the hypothesis that hormonal contraceptive use can trigger oxidative imbalance and metabolic alterations that may raise long-term cardiovascular risks. These findings correlate with more established evidence. Sultan et al., in 2025 documented elevated MDA levels and diminished antioxidant enzyme activity in laboratory rodents treated with oral contraceptives [13]. Turki et al., in 2023 reported systematic changes in the markers of oxidative stress with differing classes of hormonal contraceptives, supporting the association of contraceptive hormone use with disruption of the oxidative balance [14]. These results highlight the need to explore antioxidant supplementation strategies for long-term users and conduct mechanistic in vivo studies on protective interventions. On the metabolic side, Cagnacci et al., in 2023 confirmed significant dyslipidemia in OCP users through a meta-analysis, while Quinn et al., 2021 noted elevated total cholesterol levels in users, with variable changes in LDL-C after adjusting for confounders [15]. Counsel users on lifestyle interventions like diet and exercise; tailor contraceptive methods based on individual lipid profiles [16]. Drejza et al., in 2022 further explained how estrogen exposure promotes oxidation of LDL, potentiating atherosclerosis. Co-treatment with antioxidants may reduce vascular damage [17]. Include MDA screening as a routine check in contraceptive health evaluations. Reductions in antioxidant enzymes were

observed similarly supported by Hashemi *et al.*, in 2023, who demonstrated significant drops in SOD, catalase, and GPx among contraceptive users. Explore nutraceutical or pharmacologic antioxidant support to maintain redox balance [18]. To advance diagnostic precision, Zhang *et al.*, in 2024 proposed novel biomarkers for oxidative stress applicable in inflammation and hormone-related conditions [19]. Evaluate these emerging markers in future contraceptive safety trials. Santander *et al.*, (2024) stressed the need for advanced and standardized oxidative stress quantification techniques in human research [20]. Employ high-fidelity biochemical assays in future studies to enhance accuracy and comparability.

This study has several limitations, including its cross-sectional design, which limits the ability to establish causal relationships between hormonal contraceptive use and biochemical alterations. Additionally, the sample size was relatively small and drawn from a single healthcare facility, which may affect the generalizability of the findings. Variations in the type and duration of contraceptive use were not analyzed in detail, which could influence oxidative and metabolic outcomes. Future longitudinal studies with larger and more diverse populations are recommended to explore long-term biochemical effects and to evaluate potential preventive strategies such as antioxidant supplementation and regular metabolic monitoring.

CONCLUSIONS

This study demonstrated that hormonal contraceptive use in women within the fertility window was significantly linked with increased oxidative stress and adverse lipid profile changes. Users exhibited elevated levels of MDA and reduced antioxidant defenses, including SOD, GPx, Catalase, and TAC. Additionally, unfavourable shifts in lipid parameters such as higher total cholesterol, triglycerides, LDL-C, and lower HDL-C were evident among users compared to non-users. These biochemical alterations suggest a potential increase in long-term cardiovascular and metabolic risks in women using hormonal contraception. Therefore, routine biochemical monitoring, lifestyle counselling, and consideration of antioxidant strategies may be crucial components of safe contraceptive use.

Authors' Contribution

Conceptualization: RIK

Methodology: AH, FS, SA¹

Formal analysis: AH, FS, SA¹, SA²

Writing and Drafting: AM, RIK, SA¹, SA²

Review and Editing: AM, FS, RIK, SA¹, SA²

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Frequency of Hypertension in Patients with Intracranial Hemorrhage Presenting to Emergency Department

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ABSTRACT

Intracranial haemorrhage is a serious neurological emergency with high morbidity and mortality. Hypertension is a known major risk factor; however, local data regarding its frequency in intracranial haemorrhage patients remain limited. **Objectives:** To determine the frequency of hypertension among patients with intracranial haemorrhage presenting to the Emergency Department (ED) of Lady Reading Hospital, Peshawar. **Methods:** This cross-sectional study was conducted at the ED of Lady Reading Hospital from April to September 2023. A total of 182 patients aged 30–70 years, diagnosed with intracranial haemorrhage via CT scan, were enrolled using consecutive sampling. Blood pressure, BMI, demographic data, and socioeconomic status were recorded. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or self-reported antihypertensive medication use. Data were analyzed using SPSS version 26.0, with the chi-square test ($p < 0.050$ considered significant). **Results:** Patients had a mean age of 50.24 ± 12.24 years and a mean BMI of 25.74 ± 4.41 kg/m². Hypertension was found in 155 patients (85.2%). There were no significant associations between hypertension and gender ($p = 0.364$), age groups ($p = 0.817$), or socioeconomic status ($p = 0.613$). **Conclusions:** Hypertension prevalence was high among intracranial haemorrhage patients. This emphasizes the need for improved hypertension management and preventive strategies in the community.

INTRODUCTION

Intracranial haemorrhage constitutes a severe clinical condition that threatens one's life due to bleeding from the inside of the skull. It encompasses epidural hematoma, subdural haemorrhage, and both subarachnoid and intraparenchymal haemorrhage [1]. While each type differs in its pathophysiology, presentation, and prognosis, each form poses a serious threat to health and can lead to severe outcomes if not identified and managed promptly. These types of bleeding are diagnosed with neuroimaging, and most commonly, non-contrast CT scans [2, 3]. Epidural hematoma usually arises following trauma and is frequently arterial in origin, often due to injury to the middle meningeal artery [4]. Subdural haemorrhage involves venous bleeding into the space between the dura mater

and arachnoid mater, often after blunt head trauma. Subarachnoid haemorrhage occurs when blood accumulates in the subarachnoid space, either from trauma or rupture of an aneurysm. Among these, intraparenchymal haemorrhage bleeding directly into the brain tissue is commonly associated with longstanding hypertension and forms the focus of this study [5, 6]. Hypertension has been recognized as one of the most important modifiable risk factors for both ischemic and haemorrhagic strokes [7]. Elevated systolic and diastolic blood pressures have been consistently associated with an increased risk of cerebral haemorrhage. Studies have shown that poorly controlled blood pressure not only increases the risk of primary intracerebral haemorrhage



but also raises the likelihood of recurrent events. Furthermore, undiagnosed or untreated hypertension often contributes silently to vessel fragility, predisposing individuals to spontaneous haemorrhage even in the absence of trauma [8]. Several studies across different populations have reported a high prevalence of hypertension among patients presenting with intracranial haemorrhage. Dong and colleagues reported a hypertension rate of 88% in such patients, while Lioutas et al. found the frequency to be 86.3%. These figures highlight a strong correlation between elevated blood pressure and spontaneous cerebral bleeding events [9, 10]. However, there is a distinct lack of local epidemiological data in Pakistan, particularly from tertiary care emergency departments, quantifying the frequency of hypertension among patients with intracranial haemorrhage. Most available studies are international, and their findings may not fully reflect the regional burden or healthcare context. This absence of region-specific evidence limits the development of targeted prevention and screening strategies in our population. Given the burden of stroke-related emergencies in tertiary hospitals and the limited local data on risk factor prevalence, this study was designed to determine the frequency of hypertension among patients with intracranial haemorrhage presenting to the Emergency Department at Lady Reading Hospital, Peshawar.

Intracranial haemorrhage remains a major neurological emergency with high morbidity and mortality, and hypertension is widely recognized as its most important modifiable risk factor. However, despite global evidence demonstrating a strong association between elevated blood pressure and haemorrhagic stroke, region-specific data quantifying the frequency of hypertension among intracranial haemorrhage patients in Pakistan are limited. Most available studies are international and may not reflect the local demographic and healthcare context. This gap highlights the need for localized epidemiological evidence from tertiary care emergency settings to guide preventive strategies and risk factor control. This study aims to inform clinicians about the magnitude of this preventable risk factor in our setting and to support more effective strategies for early detection, prevention, and patient education regarding blood pressure control.

METHODS

This was a cross-sectional descriptive study conducted to determine the frequency of hypertension among patients presenting with intracranial haemorrhage to the Emergency Department. The research was carried out in the Department of Emergency Medicine at Lady Reading Hospital (LRH), Peshawar, a major tertiary care hospital providing emergency services to a large population across Khyber Pakhtunkhwa. The duration of the study was six

months, from April 2023 to September 2023, following formal approval of the research synopsis by the College of Physicians and Surgeons Pakistan (CPSP) and ethical clearance by the Institutional Review Board (IRB) of LRH. Formal ethical approval was granted by the IRB of Lady Reading Hospital under Reference No. 682/LRH/MTI, and the research protocol was also approved by CPSP under Reference No. CPSP/REU/EMD-2020-022-224. These approvals ensured compliance with ethical research standards, data confidentiality, and patient safety. All participants or their legally authorized representatives were provided with detailed information about the study, including objectives, procedures, and potential risks and benefits. Written informed consent was obtained before participation. Participants were assured that their data would be kept confidential and their care would not be affected by refusal or withdrawal from the study. The sample size was calculated using the WHO sample size calculator, assuming a 95% confidence level, 5% margin of error, and an expected hypertension prevalence of 86.3% based on prior studies [10]. The final sample included 182 patients. A consecutive non-probability sampling technique was employed, enrolling all eligible patients who presented during the study period and fulfilled the inclusion criteria. Inclusion criteria were male and female aged 30 to 70 years with a diagnosis of intracranial haemorrhage confirmed by neuroimaging. Exclusion criteria included known cases of hyperaldosteronism, subarachnoid haemorrhage, or structural brain lesions such as tumours. Intracranial haemorrhage was diagnosed using non-contrast computed tomography (CT) scans of the brain, interpreted by qualified radiologists following standard emergency protocols. Hyper-dense regions indicative of acute haemorrhage was used to confirm the diagnosis. Hypertension was defined as any of the following: systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or self-reported use of antihypertensive medication within the last two weeks. Blood pressure was measured using a digital, calibrated sphygmomanometer after the patient was seated calmly for at least five minutes. Three readings were taken at two-minute intervals, and the average of the three was recorded as the final blood pressure value. Height and weight were measured using standardized instruments to calculate BMI. Data collection was done using a pre-tested structured proforma. Variables collected included age, gender, BMI, socioeconomic status, and clinical data. No additional laboratory or imaging tests were conducted beyond standard emergency care. To minimize observer bias, all CT scans were interpreted by radiologists who were blinded to the patient's blood pressure status. Data collectors were trained on standardized measurement protocols to further ensure objectivity and consistency. Data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables (e.g., age, BMI, SBP, DBP) were

expressed as means $\pm$ standard deviations, while categorical variables (gender, hypertension status, socioeconomic group) were summarized using frequencies and percentages. Associations between hypertension and independent variables (gender, age group, socioeconomic status) were assessed using the Chi-square test. A p-value <0.050 was considered statistically significant.

RESULTS

Out of 182 patients presenting with intracranial haemorrhage, the mean age was 50.24 ± 12.24 years, reflecting a predominance of middle-aged individuals. The mean BMI was 25.74 ± 4.41 kg/m², placing most patients in the overweight category. Systolic and diastolic blood pressures averaged 143.59 ± 21.36 mmHg and 90.49 ± 11.76 mmHg, respectively, indicating elevated blood pressure in this cohort and suggesting a significant burden of hypertension in these patients (Table 1).

Table 1: Demographic and Clinical Characteristics (n=182)

Variables	Mean $\pm$ SD
Age (Years)	50.24 $\pm$ 12.24
BMI (kg/m ²)	25.74 $\pm$ 4.41
SBP (mmHg)	143.59 $\pm$ 21.36
DBP (mmHg)	90.49 $\pm$ 11.76

Among the 182 patients, 155 (85.2%) had hypertension, while 27 (14.8%) were normotensive. Females comprised 100 (54.9%) of the study population, and males 82 (45.1%). This shows a high overall prevalence of hypertension in both genders (Table 2).

Table 2: Frequency of Hypertension and Gender Distribution (n=182)

Variables	Frequency (%)
Hypertension	
Yes	155 (85.2%)
No	27 (14.8%)
Gender	
Female	100 (54.9%)
Male	82 (45.1%)
Total	182 (100%)

When comparing gender and hypertension status, 83/100 female (83%) and 72/82 male (87.8%) were hypertensive. The Chi-square test revealed no significant association between gender and hypertension: $\chi^2(1, N=182) = 0.823$, $p=0.364$. Although the proportion of hypertensive males was slightly higher, the difference was not statistically meaningful (Table 3).

Table 3: Gender and Hypertension Association (n=182)

Gender	Hypertension Yes (%)	Hypertension No (%)	Total	$\chi^2(df)$	p-value
Female	83 (83%)	17 (17%)	100	0.823 (1)	0.364
Male	72 (87.8%)	10 (12.2%)	82		
Total	155	27	182		

Age-wise, participants were divided into four categories. The highest number of hypertensive cases occurred in the 50–59 age group (44 cases). However, no significant association was found between age group and hypertension: $\chi^2(3, N=182) = 0.935$, $p=0.817$ (Table 4).

Table 4: Association between Age Group and Hypertension (n=182)

Age Group (Years)	Hypertension Yes (%)	Hypertension No (%)	Total	$\chi^2(df)$	p-value
30–39	40 (87%)	6 (13%)	46	0.935 (3)	0.817
40–49	31 (88.6%)	4 (11.4%)	35		
50–59	44 (84.6%)	8 (15.4%)	52		
60–70	40 (81.6%)	9 (18.4%)	49		
Total	155	27	182		

The study presents the association between socioeconomic status and hypertension among patients with intracranial haemorrhage. The highest proportion of hypertensive individuals was observed in the low socioeconomic group, with 58 out of 66 patients (87.9%) affected, followed closely by the high-income group at 85.7%, and the middle-income group at 81.7%. Despite these numerical differences, the Chi-square test did not demonstrate a statistically significant association between socioeconomic status and hypertension, with $\chi^2(2, N=182) = 0.979$, $p=0.613$. This indicates that hypertension was prevalent across all economic strata without a significant trend favouring one group over another. The overall prevalence of hypertension was 85.2%, with a 95% confidence interval of 80.1% to 90.3%, reflecting a consistently high burden in this population regardless of socioeconomic background (Table 5).

Table 5: Socioeconomic Status and Hypertension Association (n=182)

Socio-economic Groups	Hypertension Yes (%)	Hypertension No (%)	Total	$\chi^2(df)$	p-value	95% CI for Hypertension Prevalence
High	48 (85.7%)	8 (14.3%)	56	0.979 (2)	0.613	80.1% – 90.3%
Middle	49 (81.7%)	11 (18.3%)	60			
Low	58 (87.9%)	8 (12.1%)	66			
Total	155 (85.2%)	27 (14.8%)	182			

DISCUSSION

In the current study, hypertension was notably prevalent (85.2%) among patients presenting with intracranial haemorrhage at Lady Reading Hospital's Emergency Department. These findings align closely with previously published studies, reinforcing the critical role that hypertension plays in the pathogenesis of haemorrhagic stroke [11–13]. Our study's findings correspond well with the frequency reported by Dong *et al.* who found an 88% prevalence of hypertension in patients suffering from intracranial haemorrhage [9]. Similarly, Tran *et al.* documented a hypertension prevalence rate of 86.3%

among patients experiencing intracerebral haemorrhage [14]. Such consistency across diverse populations and healthcare settings underscores hypertension as a universal, primary, and preventable risk factor for cerebral haemorrhage [15]. Interestingly, despite hypertension's high overall prevalence in our study, statistical analyses revealed no notable relation between hypertension and variables like gender or age groups. A slightly higher proportion of male patients (87.8%) compared to female (83%) were hypertensive, but the difference was not statistically significant ($p=0.364$). Goswami and Nanda, reported this absence of significant gender difference aligns with global stroke data, suggesting hypertension's widespread prevalence across genders without notable disparities [16]. Similarly, the distribution of hypertension across different age categories did not demonstrate significant variation ($p=0.817$), though numerically higher cases were found within the 50–59 years' age bracket. This was consistent with global stroke epidemiological data like Nazeer *et al.* and Patel *et al.* suggesting that hypertension prevalence increases with advancing age but does not significantly differ between middle-aged and older age groups in intracerebral haemorrhage patients [17, 18]. The socioeconomic analysis revealed a slightly higher hypertension rate within low socioeconomic groups (87.9%), though statistical significance was not reached ($p=0.613$). This finding echoes other studies like Ullah *et al.* and Prabhu *et al.* indicating that individuals from lower socioeconomic strata typically face barriers to accessing routine healthcare, contributing to poorer chronic disease management and subsequently higher rates of uncontrolled hypertension [19, 20]. The substantial prevalence of hypertension identified underscores the importance of rigorous public health initiatives [21]. Effective preventive strategies must prioritize early diagnosis, routine blood pressure screening, community education, and accessible hypertension management programs. Current international guidelines highlight effective antihypertensive management as pivotal in reducing stroke risk. Therefore, integrating such protocols in routine emergency department practices, along with public health measures, might substantially mitigate stroke incidence and related complications.

This study was limited by its single-center cross-sectional design, which restricts causal inference and generalizability to broader populations. Blood pressure measurements obtained during the acute emergency phase may also reflect stress-induced elevations rather than chronic hypertension in some patients. Additionally, long-term outcomes and blood pressure control status prior to presentation were not assessed. Future multicenter prospective studies with longitudinal follow-

up and evaluation of hypertension control patterns are recommended to better understand risk stratification and improve preventive interventions.

CONCLUSIONS

Hypertension was found to be highly prevalent among patients presenting with intracranial haemorrhage at the emergency department of Lady Reading Hospital, Peshawar. This observed frequency aligns closely with international data, reinforcing hypertension as a significant and modifiable risk factor for haemorrhagic stroke. No statistically significant associations were found between hypertension and demographic variables such as age, gender, or socioeconomic status, indicating that elevated blood pressure affects a broad cross-section of the population. These findings underscore the need for comprehensive public health initiatives focused on community awareness, routine blood pressure screening, and lifestyle modification programs. In addition, integrating standardized hypertension screening protocols into emergency department triage workflows, along with establishing referral pathways for long-term follow-up in primary care, may enhance early detection and long-term control.

Authors' Contribution

Conceptualization: HM

Methodology: HM, SA

Formal analysis: HM, SA

Writing and Drafting: HM, SA

Review and Editing: HM, SA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Effects of Home Blood Sugar Monitoring on HbA1c Among Diabetes Mellitus Patients Attending a Tertiary Care Hospital in Peshawar

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ABSTRACT

Diabetes mellitus (DM), encompassing both type 1 and type 2, has escalated worldwide over the last twenty years, resulting in elevated death and morbidity rates. Prior research indicates that home blood glucose monitoring enhances metabolic control and aids in alleviating the atherosclerotic effects of type 2 diabetes mellitus. **Objectives:** To evaluate the effect of home blood glucose monitoring on HbA1c levels among diabetic patients at Lady Reading Hospital (LRH), Peshawar. **Methods:** This quasi-experimental study was performed over six months in the Department of General Medicine at LRH, Peshawar, including 62 diabetic patients. Participants were directed to assess fasting blood glucose thrice weekly for three months, maintaining their existing medical care. HbA1c was measured before and during the intervention. Means and standard deviations were used to evaluate continuous variables in SPSS version 22.0. A paired t-test was used to compare pre- and post-intervention mean HbA1c levels, with $p < 0.050$ indicating statistical significance. **Results:** The mean age of participants was 45 ± 12.29 years, with 61% male and 39% female. The average diabetes duration was 10 ± 5.8 years. Pre-monitoring HbA1c was $9.62 \pm 1.87\%$, which significantly reduced to $8.02 \pm 1.19\%$ after three months (mean difference = 1.6% , $p = 0.001$). Significant reductions were observed across all age groups, genders, weight categories, and diabetes durations ($p < 0.050$). **Conclusions:** Home blood glucose monitoring significantly improves glycemic control in diabetic patients, as evidenced by the reduction in HbA1c levels, consistent across various demographics.

INTRODUCTION

The worldwide prevalence and incidence of diabetes mellitus (DM), encompassing both type 1 and type 2, have markedly escalated over the last twenty years, with forecasts suggesting continued expansion. Diabetes is linked to several chronic consequences that elevate morbidity and death globally [1]. Ensuring adequate blood glucose regulation is essential for reducing these problems, and HbA1c serves as a vital metric for evaluating long-term glycemic control and comprehensive diabetes care. HbA1c testing may yield erroneous results in persons

with hemoglobin problems, chronic renal illness, or anemia [2]. Research, including results from the Diabetes Control and Complications Trial (DCCT) and later investigations, has shown substantial data concerning the health advantages of sustaining normal or near-normal blood glucose levels, especially for individuals receiving insulin treatment [3]. Self-monitoring of blood glucose (SMBG) has demonstrated efficacy in evaluating an individual's medication response. Subjects who continued self-monitoring of blood glucose (SMBG) maintained stable



HbA1c levels, while those who discontinued SMBG exhibited an increase [4, 5]. Meta-analyses have shown that regular SMBG can reduce HbA1c by 0.25–0.3%. However, while SMBG helps patients monitor their blood glucose levels, it is not enough on its own to reduce blood glucose; it must be integrated into comprehensive diabetes management strategies that include medication, diet, and exercise [6, 7]. The worldwide prevalence of diabetes is significant, with around 463 million individuals aged 20–79 impacted, constituting 9.3% of the global adult demographic [8]. Disturbingly, 232 million individuals remain undiagnosed, with 79% located in middle- and low-income nations. Twenty percent of those aged 65 and older are diagnosed with diabetes. An extra 374 million individuals are at risk of getting type 2 diabetes. In 2019, diabetes led to 4.2 million fatalities worldwide and incurred healthcare expenses of no less than USD 760 billion, or 10% of total adult healthcare spending [8, 9]. Pakistan exhibits the third-highest prevalence of diabetes, with 19.4 million documented cases. By 2030, this figure is anticipated to increase to 26.2 million, and by 2045, to 37.1 million [10]. Research conducted at the Diabetic Clinic in Multan indicated a mean HbA1c of 8.47%, with just 31.2% of individuals attaining improved glycemic control. Variables including education, BMI, hypertension, comorbidities, diabetes knowledge, and self-care practices (e.g., exercise, glucose monitoring, medication adherence, and food management) were substantially correlated with glycemic control ($P < 0.05$) [11]. SMBG has been shown to help insulin-dependent diabetics better regulate their blood glucose levels by adjusting insulin dosages based on their readings [12]. The efficacy of self-monitoring of blood glucose (SMBG) in persons with type 2 diabetes who are not undergoing insulin therapy has been variable among research trials. Certain studies indicate enhanced glycemic control when self-monitoring of blood glucose (SMBG) is integrated with dietary modifications, whilst others demonstrate diminished advantages [13, 14]. Previous studies have shown that home-monitoring of blood glucose [15]. Despite the increasing data endorsing the advantages of SMBG, there is a deficiency of localized studies regarding its effects within the setting of Pakistan. This study is to evaluate the effect of home blood glucose monitoring on HbA1c levels in diabetes mellitus patients at Lady Reading Hospital, Peshawar.

Diabetes mellitus continues to pose a major public health burden in Pakistan, with suboptimal glycemic control observed in a large proportion of patients. Although self-monitoring of blood glucose (SMBG) has shown beneficial effects on HbA1c reduction in international studies, evidence from local tertiary care settings remains limited. Variations in healthcare access, patient education, and adherence patterns may influence the effectiveness of

SMBG in our population. This lack of region-specific data highlights the need to evaluate the impact of home blood glucose monitoring on glycemic control among Pakistani patients. The present study aimed to assess HbA1c levels before and following individual blood glucose monitoring. The hypothesis posits that regular home blood glucose monitoring will lead to a decrease in HbA1c levels.

METHODS

This quasi-experimental study was performed in the Department of General Medicine at Lady Reading Hospital (LRH), Peshawar, during a duration of six months, from July 14, 2023, to January 14, 2024. Study approval was taken from the Ethical Review Committee of the hospital (Ref. No. 416/LRH/MTI). The sample size was determined with the WHO sample size calculator program for hypothesis testing of two population means (two-sided) [14]. The principal assumptions were a significance level of 5%, a statistical power of 80%, an expected mean HbA1c level of 8.66 ± 1.76 prior to intervention, and 7.89 ± 1.28 after intervention. The ultimate sample size was established at 62 patients based on these characteristics. A non-probability sequential sampling method was utilized. The inclusion criteria were individuals aged 30 to 60 years, of both genders, diagnosed with type II diabetes mellitus for over one year, and possessing an initial HbA1c level over 6.5%. Patients were excluded if they had a history of hypertension, renal or hepatic illness, or could not afford a glucometer. Patients were recruited from the outpatient department following ethical approval, and all participants provided informed consent. Baseline demographic data, including age, gender, weight (measured using a standardized digital scale), and diabetes duration, were recorded. Participants were instructed to monitor fasting blood glucose three times a week for three months using their own glucometers. The selected frequency of monitoring is informed by previous research, which demonstrates that assessing blood glucose three times weekly yields adequate data to see daily variations while being feasible for patients in practical environments. No modifications were implemented to their prescription antidiabetic medication during the trial duration. HbA1c levels were evaluated at baseline and again at the end of the three-month duration [16]. Data were gathered via a predetermined proforma. All of the data were examined with IBM SPSS Statistics version 22.0. Continuous data, including age, weight, duration of diabetes, and HbA1c values, were presented as means and standard deviations. Categorical characteristics, including gender, were presented as frequencies and percentages. A paired t-test was employed to evaluate the difference in mean HbA1c levels pre- and post-intervention. The threshold for statistical significance was established at a p-value of less

than 0.050. Stratified analyses were done to control for potential confounding variables (age, gender, weight, and diabetes duration), and paired t-tests were utilized for each subgroup to evaluate the significance of changes within these groups.

RESULTS

The current study examined the age distribution of 62 patients: 23% (n=14) were 30-40 years old, 37% (n=23) were 41-50 years old, and 40% (n=25) were 51-60 years old. The average age was 45 ± 12.29 years. The gender distribution of the 62 patients was 61% male (n=38) and 39% female (n=24). Diabetes duration was also analyzed: 40% (n=25) of patients had diabetes for less than 10 years, whereas 60% (n=37) had diabetes for more than 10 years. The average duration of diabetes was 10 ± 5.88 years. In terms of weight, 42% (n=26) of patients weighed less than 80 kg, while 58% (n=36) weighed more than 80 kg. The average weight was 80 ± 12.09 kg (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Participants

Variables	Frequency
Age Distribution	30-40 years
	23% (n=14)
	41-50 years
Gender	37% (n=23)
	51-60 years
	40% (n=25)
Male	61% (n=38)
	Female
Duration of DM	40% (n=25)
	≤ 10 years
	60% (n=35)
Weight	>10 years
	42% (n=26)
≤ 80 Kg	58% (n=36)
	>80 Kg

A study of HbA1c readings before and after three months of home-based blood glucose monitoring in 62 individuals with type 2 diabetes mellitus revealed that the mean HbA1c level before to monitoring was $9.62 \pm 1.87\%$. Subsequent to the intervention, it markedly decreased to $8.02 \pm 1.19\%$. The paired t-test revealed a statistically significant mean difference of 1.6 ± 0.68 , with a p-value of 0.001 (Table 2).

Table 2: Comparison of HbA1c Levels before and After Home Monitoring

HbA1c Level	Before Home monitoring	After Home monitoring	Mean Difference	p-Value
Mean $\pm$ SD	9.62 ± 1.87	8.02 ± 1.19	1.6 ± 0.68	0.001

Subsequent to home glucose monitoring, stratified examination of HbA1c levels revealed statistically significant decreases in all groups. The 30-40 years cohort had the most significant decrease in HbA1c, decreasing from $8.93 \pm 1.11\%$ to $7.73 \pm 1.02\%$ ($p=0.006$) in age-based stratification. Notable enhancements were also noted in the 41-50 and 51-60 age cohorts ($p=0.010$ and $p=0.003$, respectively). In gender-based stratification, males exhibited a decline from $9.58 \pm 1.80\%$ to $8.13 \pm 1.23\%$

($p=0.001$), while females demonstrated a fall from $9.65 \pm 1.85\%$ to $8.10 \pm 1.27\%$ ($p=0.001$). Concerning the length of diabetes, patients with a duration of ≤ 10 years exhibited an improvement from $9.56 \pm 1.81\%$ to $8.07 \pm 1.25\%$ ($p=0.001$), whereas those with a period of >10 years improved from $9.69 \pm 1.93\%$ to $8.23 \pm 1.31\%$ ($p=0.001$). Weight-based analysis demonstrated significant reductions in HbA1c levels in both the ≤ 80 kg (from $9.52 \pm 1.83\%$ to $8.15 \pm 1.30\%$, $p=0.003$) and >80 kg cohorts (from $9.59 \pm 1.89\%$ to $8.21 \pm 1.30\%$, $p=0.001$) (Table 3).

Table 3: Stratified Analysis of HbA1c Reduction by Age, Gender, Duration of Diabetes, and Weight

Study variables		Before Home monitoring	After Home monitoring	Mean Difference	p-Value
Age	30-40 years	8.93 ± 1.11	7.73 ± 1.02	1.2 ± 0.09	0.006
	41-50 years	9.23 ± 1.35	8.19 ± 1.29	1.04 ± 0.06	0.011
	51-60 years	9.58 ± 1.62	8.66 ± 1.41	0.92 ± 0.21	0.037
Gender	Male	9.58 ± 1.80	8.13 ± 1.23	1.45 ± 0.57	0.001
	Female	9.65 ± 1.85	8.10 ± 1.27	1.55 ± 0.58	0.001
Duration of DM	≤ 10 years	9.56 ± 1.81	7.73 ± 1.02	1.49 ± 0.56	0.001
	>10 years	9.69 ± 1.93	8.23 ± 1.31	1.46 ± 0.62	0.001
Weight	≤ 80 Kg	9.52 ± 1.83	8.15 ± 1.30	1.37 ± 0.53	0.003
	>80 Kg	9.59 ± 1.88	8.21 ± 1.37	1.38 ± 0.51	0.001

DISCUSSION

This quasi-experimental study illustrates the potential advantages of enabling diabetes patients to self-monitor their blood glucose levels, especially in a context of escalating diabetes prevalence. The research had 62 individuals, with a mean age of 45 ± 12.29 years, including 61% men and 39% females. The average duration of diabetes among the subjects was 10 ± 5.88 years. Concerning weight, 42% of patients weighed ≤ 80 kg, whereas 58% weighed >80 kg, with a mean weight of 80 ± 12.09 kg. The research indicated a substantial reduction in the mean HbA1c level during home monitoring. Before the intervention, the average HbA1c level was $9.62 \pm 1.87\%$, which decreased to $8.02 \pm 1.19\%$ after three months of home blood glucose monitoring. This is in close alignment with prior findings. HbA1c levels were consistently lower in the Best_group compared to the other groups at all time points (all $P < 0.001$). However, the proportion of patients achieving target HbA1c levels of $<6.5\%$ or $<7.0\%$ declined over time [17]. The mean HbA1c among 1,198 patients with diabetes was $8.01 \pm 1.76\%$, with over 66% exhibiting HbA1c levels above 7%, indicating poor glycemic control. The highest average HbA1c was observed in patients with a diabetes duration of more than 10 years ($8.47 \pm 1.77\%$) [18]. The impact of self-monitoring on HbA1c levels was also reported in study 56% of patients had good or fair HbA1c levels compared to controls. A study shows that effective self-management is generally associated with better glycaemic control, with dietary control being the most

significant factor linked to HbA1c levels [19]. Another study found that regular blood glucose monitoring and diet adherence enhanced glycemic control and patient empowerment, comparable with worldwide literature. These findings imply that frequent blood glucose monitoring and diet adherence might greatly enhance diabetes treatment. Our research highlights the importance of lifestyle factors, such as smoking, in diabetes control. Smokers had diminished Diabetes Empowerment Scores (DES), perhaps due to the development of peripheral neuropathy, a common symptom among diabetics. This finding supports previous research linking smoking and poor foot care to diabetic neuropathy [20, 21]. Similar study, adhering to a specific diet for the past seven days significantly enhanced the empowerment of a type II diabetes patient. Our findings, along with those of Hernandez-Tejada [22], indicate that adhering to a proper specialized diet over the past seven days fosters empowerment among [23]. The mean estimated overall Diabetes Empowerment scores of smokers are 0.088 times higher than those of non-smokers when foot care days increase by one. Smokers may develop peripheral diabetes neuropathy, lowering empowerment scores. Our study supports other findings that smoking and poor foot care can cause peripheral diabetes neuropathy [24]. The provision of home monitoring kits, such as HbA1c residential kits, can improve routine glucose monitoring, enabling patients to assume responsibility of their diabetes care. [7, 25]. The use of advanced technology, such as the FreeStyle Libre system, has demonstrated a reduction in hypoglycemic episodes and an enhancement in overall glucose variability in persons with Type 1 and Type 2 diabetes [26]. The enhancement in HbA1c levels associated with home blood glucose monitoring corroborates the findings of FreeStyle Libre technology, indicating that consistent self-monitoring is essential for managing glucose fluctuation [14, 27]. Drawn from a single tertiary care hospital, the sample size was rather small (n=62), so restricting the generalizability of the results to the larger diabetic population. Adherence to home glucose monitoring was self-reported, which would introduce reporting bias. The lifestyle elements including diet and physical activity which can also affect glycemic control were not under control or documented during the course of the study.

This study was limited by its single-center quasi-experimental design and relatively small sample size, which may restrict the generalizability of the findings. The absence of a control group and reliance on self-reported adherence to home monitoring may also introduce bias. Additionally, lifestyle factors such as diet, physical activity, and medication adherence were not objectively monitored during the study period. Future large-scale randomized

controlled trials with longer follow-up durations and structured monitoring of lifestyle variables are recommended to better establish the long-term effectiveness of home blood glucose monitoring in improving glycemic outcomes.

CONCLUSIONS

This study shows, via a notable decrease in HbA1c levels, regular personal tracking of blood glucose levels considerably improves glycemic management in individuals with type II DM. The impact was constant across several weight ranges, genders, diabetes durations, and age groups. Highlighted during patient counselling, home glucose monitoring should be included into regular diabetes control strategies. To get better metabolic results, healthcare professionals have to make sure patients are informed, equipped, and driven to regularly undertake self-monitoring.

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Authors' Contribution

Conceptualization: SAS, MTHK

Methodology: SAS, SA, SU, MTHK

Formal analysis: SAS, SA, MB, YNK, SU

Writing and Drafting: SAS, SA, MB, YNK, SU, MTHK

Review and Editing: SAS, SA, MB, YNK, SU, MTHK

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Serum Adiponectin Levels and Their Association with Age, Gender and Waist Circumference: Insights from a Cross-Sectional Study

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ABSTRACT

Adipose tissue secretes the adipokine adiponectin, which is essential for insulin sensitivity, cardiovascular health, and metabolic control. Although prior studies suggest that age and waist circumference (WC) influence adiponectin levels, contradictory results indicate the need for further research. **Objectives:** To evaluate and compare serum adiponectin levels among individuals of different age groups and waist circumference categories. **Methods:** A cross-sectional study was conducted with 50 individuals. Age, WC, body mass index (BMI), and gender were among the anthropometric information gathered. Spearman's correlation was used to test serum adiponectin levels and their relationships with these factors. The threshold for statistical significance was $p < 0.050$. **Results:** The average amount of adiponectin in the blood was 5.59 ± 1.94 ng/mL. Adiponectin did not significantly correlate with either WC ($r = +0.17$, $p = 0.160$) or age ($r = -0.06$, $p = 0.600$). Furthermore, although somewhat higher in females, adiponectin levels did not significantly correlate with either gender ($p = 0.470$) or BMI ($r = +0.10$, $p = 0.370$). **Conclusion:** It was concluded that results show no significant relationships of adiponectin with WC, in contrast to previous research that found an inverse link with WC or an age-related increase in adiponectin. This could be the result of unmeasured confounding variables, including food and lifestyle, sample size restrictions, or demographic characteristics. More extensive research is needed to elucidate these connections and investigate adiponectin's potential as a biomarker for metabolic diseases.

INTRODUCTION

Obesity is a serious health issue in both industrialized and developing nations, and one-third to half of adults suffer from it. Obesity is more common in women than in male in developing nations, and it is predicted to affect 70% of the population in the coming years. Although the exact processes behind the association between obesity and an

elevated risk of metabolic disease remain unclear, strong evidence suggests that adipose tissue secretions play a role in this relationship [1]. Some of the most significant biological substances, known as adipokines, are produced by adipose tissue, an endocrine organ that has a unique function in controlling immunological responses and



metabolism. Adiponectin, one of the adipokines of adipose tissue, has positive effects on the lipid profile, enhances tissue sensitivity to insulin, and functions as an anti-diabetic hormone. It is essential for controlling inflammation, lipid homeostasis, and glucose metabolism. It is an important biomarker in metabolic and cardiovascular disorders and has been extensively researched for its insulin-sensitizing, anti-inflammatory, and cardioprotective qualities [2]. Adiponectin is the only adipokine that doesn't encourage metabolic dysfunction since, although being released by adipose tissue, its levels strangely drop in people with obesity and metabolic syndrome (MS), demonstrating its inverse association with adiposity. Two main receptors, AdipoR1 and AdipoR2, which are expressed in skeletal muscle, the liver, and endothelial cells, regulate its biological activities [3]. Adiponectin is a topic of interest in both clinical and research contexts because of its inverse association with obesity, which makes it a possible biomarker for metabolic diseases. Serum adiponectin levels are influenced by several factors, including lifestyle, hormones, and genetic factors [4]. Age and waist circumference are two of these that have been extensively researched because of their substantial effects on adiponectin levels. Metabolic indicators are measurable biological markers that reflect the state of metabolic processes in the body, often used to assess an individual's risk for metabolic disorders such as obesity, type 2 diabetes, and cardiovascular diseases. Key metabolic indicators include anthropometric measurements like body mass index (BMI) and waist circumference (WC), which provide insights into overall and central adiposity. Biochemical markers, such as serum adiponectin levels, play crucial roles in metabolic regulation by influencing insulin sensitivity, inflammation, and lipid metabolism [5]. Elevated or reduced levels of these indicators can signal disruptions in metabolic homeostasis, thereby serving as valuable tools in the early detection, monitoring, and management of metabolic health and disease risk. Adiponectin levels are affected by metabolic function, inflammatory processes, and body composition changes that occur with ageing. Despite the typical decrease in insulin sensitivity seen in older persons, research has revealed that serum adiponectin levels tend to rise with age [6]. Changes in the distribution of adipose tissue, hormonal fluctuations, and persistent low-grade inflammation in the aged population are some of the causes of this contradictory tendency. Furthermore, there are sex-specific variations in the dynamics of adiponectin with age. Due in part to variations in fat distribution and the impact of sex hormones, women often have higher levels of adiponectin than men [7]. These results demonstrate the intricate relationship between adiponectin regulation, age, and gender [8]. Waist circumference (WC) is a key indicator

of metabolic health and a recognized indicator of central obesity. WC precisely measures visceral adiposity, which is more strongly linked to metabolic dysfunction than body mass index (BMI), which does not distinguish between lean and fat mass. Although previous research has highlighted an inverse relationship between adiponectin levels and obesity, particularly central adiposity, findings regarding its association with age and gender remain inconsistent. Some studies suggest adiponectin levels increase with age, potentially reflecting compensatory mechanisms or altered adipose tissue function, while others report contradictory trends. Given the growing prevalence of obesity and metabolic syndrome, particularly in diverse populations, it is essential to clarify how physiological factors like age and anthropometric measures such as waist circumference independently and jointly influence serum adiponectin levels. This study aims to fill this knowledge gap by systematically analyzing the relationships between adiponectin, age, waist circumference and BMI in a sample of healthy adults of both genders, thereby contributing to improved metabolic risk assessment and potential therapeutic targeting. A thorough investigation is necessary to elucidate the combined influence of these parameters on adiponectin regulation, given the contradictory results on their interplay. To clarify the separate and combined impacts of age and weight, gender and BMI, this study was designed to compare serum adiponectin levels by these variables. Adiponectin's function in metabolic health and disease risk can be better understood by taking into account how its levels change with physiological and anthropometric variables like age and waist circumference.

Adiponectin is widely recognized as a protective adipokine with significant roles in insulin sensitivity and metabolic regulation; however, evidence regarding its relationship with age, gender, and waist circumference remains inconsistent. While several studies report inverse associations with central obesity and age-related variations, findings differ across populations and ethnic groups. Moreover, limited local data exist evaluating these associations in healthy Pakistani adults. This gap necessitates further investigation to clarify the independent and combined effects of anthropometric and demographic variables on serum adiponectin levels. This study aimed to bridge the knowledge gap regarding adiponectin regulation by systematically analyzing its relationship with age, waist circumference and BMI. The findings could help improve metabolic risk assessment and possibly guide future endocrinology and metabolic health research.

METHODS

It was a cross-sectional analytical study. For sampling, a non-probability convenience sampling method was used. It

was conducted at Multan Medical and Dental College and its attached clinical hospital from June 2024 to December 2024. Ethical approval was obtained from the relevant institutional review board (IRB No. C-92-1046), and written informed consent was obtained from all participants before data collection. Participant confidentiality was maintained by assigning unique identification codes and securely storing data in password-protected files accessible only to the research team. The outcome variable used for sample size calculation was serum adiponectin level. As the study aimed to estimate the mean serum adiponectin level in the population, the sample size was calculated using the formula for estimating a single mean: $n = (Z_{1-\alpha/2} \cdot \sigma/d)^2$. Where: $Z_{1-\alpha/2}=1.96$ (corresponding to 95% confidence level), $\sigma=9\text{ng/mL}$ (assumed standard deviation based on international literature) and $d=2.5\text{ng/mL}$ (acceptable margin of error). The standard deviation reported serum adiponectin variability between 7 to 10 ng/mL in healthy adults. Based on this, a conservative SD of 9 ng/mL was selected for the present calculation. This yielded a sample size of approximately 50 individuals, which was deemed adequate for estimating the mean serum adiponectin levels with acceptable precision. A total of 50 healthy individuals, 27 males (54 %) and 23 females (46%), were enrolled in the study. There were males and females above the age of 18. Pregnant females, individuals with a BMI less than 18 and patients currently or recently diagnosed with COVID-19 and any other chronic disease were excluded from the study. For anthropometric measurements, waist circumference (WC) was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest using a non-stretchable measuring tape. Participants were asked to stand upright with feet close together, arms at the sides, and abdomen relaxed. The tape was applied snugly without compressing the skin, and two measurements were taken and averaged to ensure accuracy. In the same way, height was measured in centimeters in standing posture, and weight was measured by standardized weighing scale in Kilograms. To calculate body mass index (BMI), height and weight measurements were used by taking weight in kilograms and height in meters squared with the following formula. $\text{BMI} = \text{kg/m}^2$. Where Kg=person's weight in kilograms and m^2 = height in meters square. A person is said to be overweight if their BMI is 25 or above; a healthy range is between 18.5 and 24.9. About 5 cc of blood was taken using aseptic technique, and serum was separated and centrifuged to determine the outcome variable, serum adiponectin level by ELISA. Serum adiponectin levels were determined using a commercially available ELISA kit (Crystal Chem). All assays were performed according to the manufacturer's instructions, with appropriate standards and controls included to ensure data quality and reproducibility. Data for this study were analysed using

P.A.S.W 18.0 (formerly SPSS). Quantitative data, including age, BMI, waist circumference, and serum adiponectin levels, were expressed as mean $\pm$ standard deviation (SD) to summarize central tendency along with variability. Spearman's rank correlation coefficients were calculated to evaluate the associations between serum adiponectin levels and key anthropometric variables, including age, gender, body mass index (BMI), and waist circumference. This method was selected to isolate the independent influence of variables such as age and waist circumference on adiponectin. The assumptions for correlation analysis, including linearity and normal distribution, were evaluated before implementation. For statistically significant results, the p-value was set at $p\text{-value} \leq 0.050$.

RESULTS

Study presents the descriptive statistics for the demographic and clinical parameters of the study participants. For continuous variables, mean, standard deviation, median, and interquartile range (IQR) were reported. The p-values presented in Table 1 correspond to the results of normality testing (Shapiro-Wilk test) for continuous variables, which inform the choice between parametric and non-parametric tests in subsequent analyses. The mean serum adiponectin level for the overall cohort was 5.53 ± 1.94 ng/mL, with males showing a mean level of 5.42 ± 1.35 ng/mL and females 5.74 ± 2.58 ng/mL; however, the difference was not statistically significant ($p=0.470$), as determined using independent samples t-test. Mean values were also compared across groups of waist circumference and age, and although variations were observed, no statistically significant differences were found ($p>0.050$), as determined using one-way ANOVA. Correlation analysis indicated weak and statistically non-significant relationships between adiponectin and age, BMI, waist circumference and gender.

Table 1: Participants' Demographics and Fundamental Characteristics (n=50)

Sr.No	Characteristics	Frequency (%)		'p*' for normality
1	Gender	Male	27(54%)	—
		Female	23(46%)	
—	—	Mean $\pm$ SD	Median $\pm$ IQR	—
2	Age (Years)*	34.65 ± 11.39	33.00 ± 21.00	<0.001
3	BMI (kg/m^2)*	27.74 ± 7.63	26.90 ± 15.00	<0.001
4	Waist Circumference Inches*	38.73 ± 12.55	36.00 ± 19.00	<0.001
5	Serum Adiponectin in ng/mL	5.53 ± 1.94	5.34 ± 2.64	0.050

p-value indicates the results of the Shapiro-Wilk normality test for continuous variables.

Findings demonstrate no statistically significant variation amongst levels of mean serum adiponectin across waist circumference groups ($p>0.050$) (Figure 1).

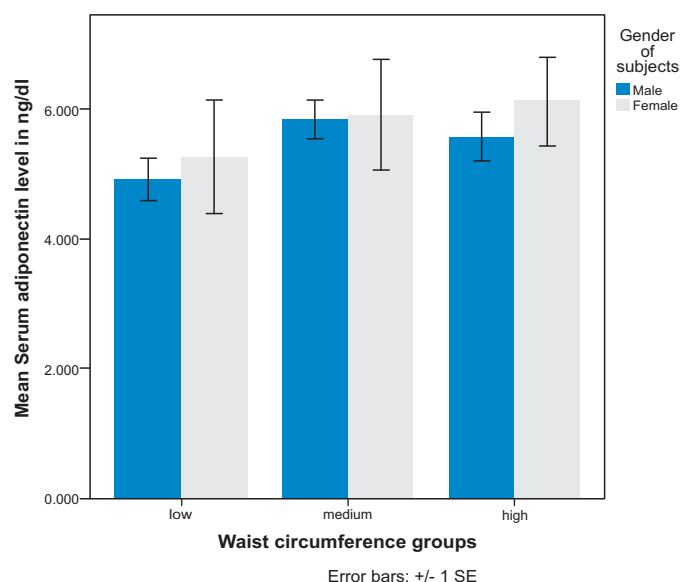


Figure 1: Mean Serum Adiponectin Levels Distribution According to Waist Circumference Groups ($p > 0.050$)

Findings demonstrate no statistically significant variation amongst levels of mean serum adiponectin across waist circumference age groups (Figure 2).

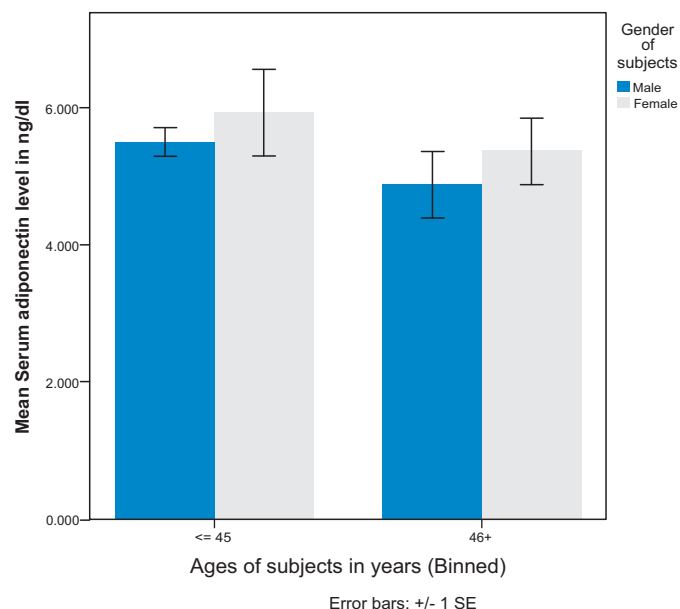


Figure 2: Mean Serum Adiponectin Levels Distribution According to Age Groups ($p > 0.050$)

The results indicate no statistically significant correlations between adiponectin and any of these variables. Specifically, the correlation coefficients were as follows: age ($r = -0.06$, $p = 0.600$), gender ($r = +0.001$, $p = 0.960$), BMI ($r = +0.10$, $p = 0.370$), and waist circumference ($r = +0.17$, $p = 0.160$). These findings suggest that within this sample, serum adiponectin levels are not significantly associated with variations in age, sex, general obesity (BMI), or central obesity (waist circumference). Our findings do not demonstrate a significant correlation between

adiponectin and age; this discrepancy may be attributed to several factors, including differences in sample size, population characteristics, or underlying metabolic conditions. These findings are presented and align with the study's aim to evaluate the independent and combined influence of age and waist circumference on serum adiponectin levels (Table 2).

Table 2: Spearman Correlation Showing Relationship Between Serum Adiponectin and Anthropometric Variables

Sr. No	Variables	Correlation Coefficient (r)	p-value
1	Age	- 0.06	0.600
2	Gender	+ 0.001	0.960
3	Body Mass Index	+ 0.10	0.370
4	Waist Circumference	+ 0.17	0.160

DISCUSSION

The present study aimed to examine the relationship between serum adiponectin levels, age, waist circumference (WC) and BMI in a cohort of adults. Given adiponectin's well-documented role in metabolic regulation and its inverse association with obesity and metabolic syndrome (MS), it's crucial to understand how its levels vary with age and WC. It is critical for assessing metabolic health risks. However, our findings indicate no statistically significant associations between serum adiponectin and the examined anthropometric parameters, including age, gender, BMI, and WC. Our results show no significant relationship between adiponectin and age, which is in contrast to several previous studies that claim a rise in serum adiponectin levels with ageing [9, 10]. According to another study, ageing is typically connected to higher adiponectin levels because of changes in the composition of adipose tissue and hormonal fluctuations [11]. The observed changes in adiponectin regulation with age may also be influenced by genetic, dietary, and lifestyle variations. According to research, adiponectin levels in healthy people tend to rise with age, perhaps as a result of hormonal changes or a decrease in body fat [12]. A large cohort study by Li et al. observed significantly higher adiponectin levels in older adults and postulated that this rise may reflect adipose tissue remodeling or altered hormonal signals associated with ageing [13]. One important factor influencing adiponectin levels is waist circumference, which is a gauge of central obesity. Adiponectin and waist circumference are inversely correlated, with lesser adiponectin secretion resulting from an increase in visceral fat. WC and adiponectin levels are inversely correlated in numerous studies; those with higher levels of abdominal obesity also have lower levels of circulating adiponectin [14]. Current findings, however, did not show a statistically significant correlation between WC and serum adiponectin. This may be attributed to the use of WC as a general proxy for central

obesity, which does not distinguish between subcutaneous and visceral adipose compartments. Imaging techniques such as CT or MRI could provide a more precise estimation of visceral fat, which may better explain variations in adiponectin levels. Our results do not indicate a significant correlation between WC and serum adiponectin levels, even though WC is a commonly used indicator of central obesity and metabolic risk. Because adipose tissue development, especially visceral fat, is associated with reduced adiponectin secretion, prior studies have consistently shown an adverse connection between adiponectin and abdominal obesity [15]. The sample size may limit the statistical ability to detect tiny alterations, which could be one reason for our study's lack of significance. Individual differences in fat distribution should also be taken into account. Although WC is a general predictor of abdominal obesity, it is unable to distinguish between visceral and subcutaneous adipose tissue, both of which may have distinct effects on adiponectin secretion [16]. Furthermore, dyslipidemia and elevated insulin resistance are linked to excessive visceral fat storage, and these conditions also lead to the downregulation of adiponectin [17]. In comparison to males, females had somewhat higher mean adiponectin levels; however, this difference was not statistically significant ($p=0.47$). This pattern is in line with earlier studies that show that adiponectin levels vary by gender, with women typically having greater levels than men [18]. In a recent study, adiponectin levels were significantly higher in women across all age groups [19]. Interestingly, although adiponectin is often inversely associated with BMI [20], our study did not find this relationship to be significant. Recent evidence confirmed adiponectin's negative correlation with BMI and fat mass, independent of insulin resistance and other metabolic parameters. The absence of this pattern in our study might be due to BMI's limited ability to distinguish between fat and lean mass or due to unaccounted factors such as physical activity, dietary intake, and inflammatory markers. In our study, no significant relationships between serum adiponectin and other anthropometric measurements, such as BMI, were found by the correlation analysis ($r=+0.10$, $p=0.370$). Because obesity suppresses adiponectin secretion, prior research has found an inverse link between adiponectin and BMI [21]. Our lack of significance could be related to the relatively small sample size or the absence of stratification by menopausal status, which is known to influence adiponectin expression. The current study's lack of statistical significance, however, raises the possibility that these disparities are influenced by other variables such as genetic predisposition, dietary practices, and lifestyle choices.

The current study's lack of statistical significance,

however, raises the possibility that these disparities are influenced by other variables such as genetic predisposition, dietary practices, and lifestyle choices. This study was limited by its relatively small sample size and single-center design, which may reduce statistical power and limit generalizability. The use of convenience sampling and absence of advanced measures of visceral adiposity, such as imaging techniques, may have restricted the precision of obesity assessment. Additionally, potential confounders including dietary habits, physical activity, hormonal status, and inflammatory markers were not evaluated. Future large-scale, multicenter studies incorporating longitudinal follow-up and comprehensive metabolic profiling are recommended to better elucidate adiponectin's role as a biomarker of metabolic health.

CONCLUSIONS

It was concluded that there were no discernible correlations between serum adiponectin levels and age, gender, waist circumference, or BMI. Although prior studies indicate that adiponectin is essential for metabolic health, its levels are probably influenced by the intricate interactions of numerous physiological and environmental variables. To elucidate these connections and investigate the possible application of adiponectin as a biomarker for metabolic and cardiovascular disorders, more extensive research is required. It is still crucial to comprehend the factors that influence adiponectin variance to create focused therapies that enhance metabolic health outcomes. Preventive medicine, clinical practice, and public health are all significantly impacted by the study's conclusions.

Authors' Contribution

Conceptualization: ZH

Methodology: ZH, HF, AA, ZC, TM²

Formal analysis: HF, SR, TM¹,

Writing and Drafting: MZ, SS, ZC, FH

Review and Editing: MZ, SS, ZC, FH, ZH, HF, AA, SR, TM¹, TM²

All authors approved the final manuscript and take responsibility for the integrity of the work

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Original Article



Beyond the Gag Reflex: Understanding Soft Palate Variations for Better Dental Care

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ABSTRACT

The gag reflex is a defense process to protect the airway from irritants. In a few patients, exaggerated reflexes jeopardize the dental treatment and compromise the dental procedures.

Objectives: To evaluate the potential association of the severity of gag reflex with types of soft palate in patients attending to prosthodontic clinic and to find out the association within gender, age groups. **Methods:** A cross-sectional observational study included 250 patients of both genders who needed dentures, were selected. Gag reflex was checked by touching the anterior to posterior part of the maxilla and mandible with a dental mirror while taking impressions. Gag Reflex Index (GRI) was used for the assessment of gag response. The reaction of the patients was recorded on V grades. The types of soft palates were classified via house classification as I, II, and III. **Results:** The soft palate forms frequently observed were soft palate drop type I, 60.0% followed by type II, 31.6% and 8.0% patients had type III soft palate drop. The gag reflex grade V was 5.6%, grade IV was 4.8%, grade III was 8.4%, grade II was 22.0% and grade I was 59.2%. The association of gag reflex grades with gender and types of soft palate drop was found to be significant, 0.020 and <0.001. However, with different age groups, insignificant results were obtained, p 0.070. **Conclusions:** The study concluded that the severity of gagging is found more in female patients and patients with type II and III soft palatal anatomy. Dentists need to evaluate different soft palatal types, especially when dealing with female patients needing prosthodontic treatment.

INTRODUCTION

The pharyngeal reflex, also known as the gag reflex, is a complex involuntary phenomenon in human physiology. Though the gag reflex is a protective defense response to keep the airway clear of irritants, in a few patients the extreme response elicits and jeopardizes the dental treatment [1]. During dental procedures, especially fabricating complete and partial dentures in prosthodontics, the frequency of gagging is common. The prosthodontic procedures, such as steps of making dentures like try selection, impression taking, determining vertical and horizontal jaw relation, denture insertion, and removal, elicit gag reflex. There can be external and internal stimuli that trigger the gagging response. External

stimuli such as the sight of a mouth mirror, impression trays, taste, and smell of impression materials can trigger the gag reflex [2,3]. Intraoral stimuli, such as the soft palate anatomy, show hyposensitive and hypersensitive responses. The trigger points of the gag reflex are associated with the types of soft palate. The soft palate is a muscular, mobile fold that is suspended from the hard palate posteriorly between the oropharynx and nasopharynx [4]. In the two domes of the hard palate, the muscles of the soft palate are inserted, and they hang down posteriorly and help in speech and swallowing [5]. There are three types of soft palate based on the angle that it forms with the hard palate. Type I is the soft palate angle



with the hard palate that is horizontal, shallow <10 degrees angle, and flat. Type II soft palate makes an angle between 10–45 degrees, whereas type III palate runs down, making a sharp angle of 70 degrees [6]. In denture patients, the posterior denture seal is made, and the posterior extension of the maxillary denture is always kept anterior to the mobile tissues of the soft palate. Any extension ahead of the movable soft palate tissues elicits gagging [7]. Patients with type II and III soft and hard palate anatomy greatly affect the posterior denture seal, as there is more mobile tissue and contact, and a lack of contact with the denture during speech and swallowing triggers gagging [8]. Prosthodontic treatment modalities to minimize the gagging reflex should be practiced. To cope with the gagging reflex and for practicing smooth dentistry, various prosthodontic modalities to control the gag reflex can be used [9]. The methods to manage gag reflex include psychological intervention, relaxation, distraction, desensitization, and cognitive behavior therapy. Practicing these modalities not only prevents disturbance, delay, and repetition of treatment but also saves time and cost of the procedure [10]. It is empirical to identify the severity of gagging in prosthodontic patients so that the dentist has the idea of dealing with the patient via standard treatment procedures or practicing alternative methods to control the gag reflex and get a successful and comfortable treatment outcome [11]. Care is needed, especially when dealing with geriatric patients during impression taking with alginate and impression compound [12]. Depending on the patient's condition and accurate diagnosis, the gagging can be controlled, and any disturbance that can jeopardize the steps of dental procedures can be rectified [11]. The soft palate plays a critical role in the gag reflex, and its morphology can influence the severity of gagging [13]. By understanding individual variations in gag reflex and soft palate anatomy, prosthodontists can tailor their approaches to minimize discomfort and anxiety and can improve patient compliance and treatment success rates. To the best of our knowledge, no study in our region has been conducted to evaluate the types of soft palate and gag reflex frequency in prosthodontic patients.

The gag reflex is a common challenge in prosthodontic practice, particularly during impression-making and denture fabrication. Although previous studies have explored gag reflex prevalence and management strategies, limited research has evaluated its association with specific soft palate morphologies using standardized classifications. Furthermore, regional data examining the relationship between gag reflex severity, soft palate types, gender, and age groups remain scarce. This highlights the need for locally generated evidence to better guide clinical assessment and treatment planning in prosthodontic patients. The study aimed to evaluate the potential

association of the severity of gag reflex with types of soft palate in patients attending to prosthodontic clinic and also find out the association within gender, age groups.

METHODS

A cross-sectional observational study of 3 months duration from 20th Feb 2025 till 20th May 2025 was carried out in the department of Prosthodontics of Lahore Medical and Dental College Lahore. Ethical clearance was obtained from the Ethical Review Board of the Dental College. Every patient was comfortably seated in the dental chair in upright position with straight legs on the chair and facing the dentist. A total of 250 patients of both gender; needing complete and partial dentures presented to the OPD of clinic with in the age range from 20 till 80 years were included in the study. The sample size was calculated from the RAO Soft Epi calculator against a 20.0% prevalence of type III gag reflex in patients, with 95% confidence interval, keeping margin of error 5%. Non-probability purposive sampling technique was used for sample selection. Healthy patients requiring complete and partial dentures within the selected age range were included. Patients with Congenital and developmental soft and hard tissue defects, palatopharyngeal incompetencies, a history of oral/maxillofacial trauma, and patients wearing obturators were excluded from study. Verbal consent was taken. The gag severity index (GSI) was used to find out the severity of gagging and the patients were divided into 5 grades based on the severity of gagging reflex. Grade V: Patients start to gag just by sitting into the dental chair on their first dental visit. [14] Grade IV: Patients start to gag during visual examination. Grade III: Patients who gag when the maxilla is touched by the mouth mirror from anterior palate to the post dam area and in the mandible when the mirror was moved from the labial sulcus to the lingual sulcus and to the retromolar pad. Grade II: Patients who gag while taking primary impression with alginate and impression compound in stock trays. Grade I: Patients who felt little controllable gag during primary impression taking. Two experienced prosthodontists evaluated the gag reflex and evaluated the soft palate types and decided them by agreement. The types of soft palates noted were classified based on House Classification as I, II, III [15]. Class I: drop of soft palate concerning hard palate is horizontal, flat extension posteriorly, minimum muscle activity, making an angle with hard palate <10 degrees. Type II: The drop of soft palate is more than 45 degrees with a gradual slope and moderate muscle activity, making an angle with the hard palate from 10–45 degrees. Type III: The drop is more than a 45-degree angle concerning the hard palate, steep descent of the soft palate. The patients were divided into 3 groups concerning age, i.e., Group I: 20–40, Group II: 41–60 years, Group III: 61–80 years. The Data was analyzed using SPSS

Version 26. Qualitative variables were presented as frequencies and percentages, whereas the quantitative variables were presented as means and SD. Chi-square square used to find out the association of gag reflex with gender, age groups, and soft palate types. p -value <0.050 will be the significance level.

RESULTS

Out of 250 patients 111 (44.4 %) were males and 139 (55.6 %) were female patients. The patients age ranged from 20 to 80 years with mean age of 53.79 ± 13.50 SD. 41 (16.4 %) of patients were of younger age group from 20–40 years, 120 (48.0 %) were from 41–60 years, and 88 (35.2%) patients presented were from older age group. The type of soft palate forms frequently observed was soft palate drop type I 151 (60.0%) followed by type II 79 (31.6%) and only 20 (8.0 %) patients had type III soft palate drop. The gag reflex grade V was 14 (5.6 %), grade IV was 12 (4.8 %), grade III was 21 (8.4 %), grade II was 55 (22.0 %), and grade I was 148 (59.2%) (Table 1).

Table 1: Frequency Distribution of Gag Reflex Grades and Types of Soft Palate Drops. N=250.

Gag Reflex Grades					Soft Palate Types		
Grade I n %	Grade II n %	Grade III n %	Grade IV n %	Grade V n %	Drop I n %	Drop II n %	Drop III n %
148 (59.2)	55 (22.0)	21 (8.4)	12 (4.8)	14 (5.6)	151 (60.0%)	79 (31.6)	20 (8.0)

The association of gag reflex grades with gender was found to be significant 0.020. The association of different age groups with gag reflex was found to be insignificant p 0.730 however, gag reflex severity (grade I–V) increases with the increasing grade of types of soft palate drop (I, II, III), and a significant association was found p value <0.001 (Table 2).

Table 2: Association of Gag Reflex Grades with Age Groups, Gender, and Soft Palate Types; N=250

Variables	Gag Reflex Grades					p-Value
	Grade I n (%)	Grade II n (%)	Grade III n (%)	Grade IV n (%)	Grade V n (%)	
Age Groups						
20-40 yrs	27 (65.9)	10 (24.4)	1 (2.4)	2 (4.9)	1 (2.4)	0.070
41-60 yrs	80 (66.7)	23 (19.2)	10 (8.3)	5 (4.2)	2 (1.7)	
61-80 yrs	55 (62.5)	21 (23.9)	10 (11.4)	0 (0.0)	2 (2.3)	
Gender						
Male	78 (52.7)	20 (36.4)	7 (33.3)	3 (25.0)	3 (21.4)	0.020
Female	70 (47.3)	35 (63.6)	14 (66.7)	9 (75.0)	11 (78.6)	
Soft Palate Types						
Drop I	129 (87.2)	18 (32.7)	2 (9.5)	1 (8.3)	1 (7.1)	<0.001
Drop II	18 (12.2)	35 (63.6)	17 (81.0)	8 (66.7)	1 (7.1)	
Drop III	1 (0.7)	2 (3.6)	2 (9.5)	3 (25.0)	12 (85.7)	

Significance level $p < 0.050$

DISCUSSION

Dental practitioners frequently encounter the challenge of gagging during procedures, which can hinder or even prevent effective treatment despite advancements in modern dentistry. Understanding the causes and impact of gagging is essential for improving patient comfort and acceptance of dental treatment [16, 17]. In the present study, grade I gag reflex was the most frequent (59.2%), followed by grade II (22.0%), while severe grades IV (4.8%) and V (5.6%) were the least common. These findings align with those of Alamgir et al., who reported grade I (40.0%) and grade II (32.7%) as the most frequent, with lower rates for grades IV (6.7%) and V (0.7%) [14]. Similarly, Meshni et al. found a 49.1% prevalence of gagging in their patients [18]. Current results showed a higher proportion of female patients (55.6%) compared to males (44.4%). Although grade I was the most common in both genders, severe gag reflexes were more frequent in females. Specifically, grade IV occurred in 75.0% of females and 25.0% of males, while grade V was observed in 78.6% of females and 21.4% of males. The association between gag reflex grades and gender was statistically significant ($p=0.02$). These findings agree with Alamgir et al., who also reported a higher prevalence of exaggerated gag reflex in females (59.3%) compared to males (40.7%) [14], as well as studies from Saudi Arabia and other regions reporting similar trends [19–21]. Gender differences in jaw size and psychological sensitivity, as suggested by Stefos et al., may partially explain these findings [22]. Regarding soft palate morphology, type I was the most common (60.0%), followed by type II (31.6%) and type III (8.0%). The association between gag reflex severity and soft palate type was highly significant ($p < 0.001$). Patients with type I soft palate predominantly exhibited grade I gag reflex (87.2%), whereas severe grades IV and V were rare (8.3% and 7.1%, respectively). In contrast, type II was more frequently associated with higher gag reflex grades, including grade IV (66.7%). Type III showed the most severe response, with 85.7% of patients having grade V gag reflex. These observations correspond with Halboub et al., who reported a significant correlation between soft palate type and gagging, with more severe gagging in type II and III morphologies [19]. Anatomically, a steep drop from the hard palate and reduced posterior surface area in types II and III may predispose to increased gag sensitivity due to reduced tolerance for impression trays [4]. Age did not show a statistically significant association with gag reflex severity ($p=0.730$, not significant). However, most patients were middle-aged (41–60 years; 48.0%), followed by older adults (61–80 years; 35.2%), with younger adults (20–40 years) representing the smallest group (16.4%). Grade I gag reflex was the most frequent across all age groups, while

severe grades IV and V were uncommon. Similar findings were reported by Alamgir et al., where a mild gag reflex was more prevalent in younger patients, while a moderate gag reflex appeared more in middle-aged individuals [14]. The study was conducted in a single clinic, limiting generalizability. Its cross-sectional design prevents causal conclusions. Psychological factors affecting the gag reflex were not evaluated, and subjective grading may introduce bias.

This study was limited by its single-center, cross-sectional design, which restricts causal inference and generalizability. The use of purposive sampling and subjective clinical grading may introduce observer bias, and psychological factors influencing gag reflex were not assessed. Future multicenter studies with larger, more diverse populations and incorporation of objective assessment tools and psychological profiling are recommended. Longitudinal research may further clarify the predictive value of soft palate morphology in managing gag reflex during prosthodontic treatment.

CONCLUSIONS

The severity of gagging is found more in female patients and patients with type II and III soft palatal anatomy. Dentists need to evaluate different soft palatal types, especially when dealing with female patients needing prosthodontic treatment.

Authors' Contribution

Conceptualization: TH

Methodology: KQ, AN, TH

Formal analysis: MHR

Writing and Drafting: MM, KY, SN

Review and Editing: MM, KY, SN, MHR, KQ, AN, TH

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Original Article



Impact of Formative Feedback on Skill Acquisition in Simulation-Based Training

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ABSTRACT

Simulation-based learning is widely used in healthcare education to teach clinical skills in a safe, structured environment. However, the integration of systematic formative feedback within simulation remains inconsistent, particularly in undergraduate programs. **Objectives:** To evaluate the impact of structured formative feedback on clinical skill acquisition, self-reported confidence, and learner satisfaction among undergraduate students in medicine, dentistry, and nursing. **Methods:** A quasi-experimental study was conducted at Rawal Institute of Health Sciences with 72 undergraduate students. Participants were recruited via convenience sampling and randomly assigned to either a feedback group or a control group (n=36 each). Both groups performed the same simulation tasks, but only the feedback group received structured, real-time formative feedback after the initial assessment. Data collection included pre- and post-test knowledge scores, Objective Structured Clinical Examination (OSCE) performance, confidence rating scales, and satisfaction questionnaires. Data were analyzed using SPSS version 26.0. **Results:** The feedback group showed significantly higher post-test and OSCE scores compared to the control group ($p<0.001$), with large effect sizes (Cohen's $d>1.5$). Improvement scores and post-training confidence ratings were also significantly greater in the feedback group. Learner satisfaction scores in the feedback group were consistently high across all domains. **Conclusions:** Structured formative feedback in simulation-based training leads to substantial improvements in clinical performance, learner confidence, and satisfaction. These findings support the routine incorporation of feedback into undergraduate simulation curricula, particularly in resource-limited educational settings.

INTRODUCTION

Simulation-based learning has transformed healthcare education by offering students the opportunity to develop clinical reasoning and procedural skills in a realistic yet controlled environment [1]. It reduces the risk to actual patients, supports repetitive practice, and bridges the gap between theoretical knowledge and clinical application, which is essential in outcome-based curricula [2, 3]. However, the effectiveness of simulation hinges on the quality of feedback provided during or after the session.

Formative feedback, defined as timely, specific input aimed at guiding learners toward improvement, is widely recognized as a cornerstone of experiential learning [4]. It promotes reflection, reinforces strengths, and addresses gaps in performance [5]. Yet, in many undergraduate programs, feedback during simulation remains unstructured, inconsistent, or absent. Although numerous international studies have explored simulation-based training, most have been conducted in high-resource



settings or postgraduate contexts, often focusing on performance metrics alone [6-8]. Far fewer studies have examined formative feedback at the undergraduate level, particularly in diverse healthcare disciplines like medicine, dentistry, and nursing. Even less attention has been paid to how feedback affects learner confidence and satisfaction, which are crucial for motivation and long-term competence development [9]. In the Pakistani and broader South Asian context, the lack of organized feedback integration in simulation-based training is even more pronounced [10, 11]. Medical, dental, and nursing institutions in low-resource settings often adopt simulation without the structured debriefing that maximizes its pedagogical value. There was currently a paucity of local evidence on how feedback influences clinical skill development, learner confidence, or satisfaction with simulation-based instruction. As such, educators are left without data-driven strategies to enhance the value of simulation for undergraduates in these contexts. There is currently no structured model for delivering formative feedback in simulation-based training at the undergraduate level in Pakistan. This gap leads to suboptimal skill acquisition and undermines the potential benefits of simulation pedagogy. By comparing outcomes between those who received structured feedback and those who did not, this study aims to contribute context-specific evidence to inform future curriculum design in resource-limited undergraduate health education.

Simulation-based learning is widely adopted in undergraduate health education; however, the integration of structured formative feedback within simulation sessions remains inconsistent, particularly in low-resource settings. While international literature supports the value of feedback in enhancing clinical competence, limited evidence exists from South Asian undergraduate programs across medicine, dentistry, and nursing. Moreover, few local studies have simultaneously evaluated objective performance outcomes alongside learner confidence and satisfaction. This gap underscores the need for context-specific research to guide structured feedback implementation in undergraduate simulation curricula. This study aimed to evaluate the effect of structured formative feedback on clinical skill acquisition, self-reported confidence, and satisfaction among undergraduate students in a simulation setting.

METHODS

A quasi-experimental study was conducted at the clinical skills lab of Rawal Institute of Health Sciences from January 2025 to May 2025. The simulation setting was equipped with standardized manikins, skill stations, trained facilitators, and audio-visual recording capabilities. Ethical approval for this study was granted by

the Institutional Review Board (IRB) of Rawal Institute of Health Sciences, Islamabad, under reference number RIHS/IRB/31/2025. This research used a quasi-experimental design with two groups: one receiving formative feedback and the other receiving no feedback with standard simulation instruction. A total of 72 participants were recruited for this study through convenience (non-probability) sampling, including undergraduate students from MBBS, BDS, and Nursing programs. Participants were then randomly assigned to two equal groups using a computer-generated simple randomization list. This randomization list was generated and maintained by an independent staff member not involved in training or data collection to ensure allocation concealment. The sample size was determined using G*Power software version 3.1.9.7, applying an independent-samples t-test model. The parameters set for calculation included an effect size (Cohen's *d*) of 0.8, a power of 0.80, and a significance level (α) of 0.05, which yielded a required sample size of 64 participants (32 per group). To account for potential dropouts or incomplete responses, the final sample was expanded to 72. The chosen effect size was based on findings from an interventional study by Lebdaï et al. [12]. Informed written consent was obtained from all participants after explaining the purpose, process, and voluntary nature of participation. Confidentiality was maintained, and no personally identifiable information was used. Participants were randomly allocated into two equal groups ($n=36$ each): Group A (Feedback Group): Received structured formative feedback after simulation, and Group B (Control Group): Completed the same simulation tasks but without any formal feedback. All participants, regardless of discipline (MBBS, BDS, Nursing), undertook the same simulation tasks: CPR, IV cannulation, and basic airway management (bag-valve-mask ventilation). These procedures were selected for their cross-disciplinary relevance, as they are foundational emergency skills required in medical, dental, and nursing education. Group allocation was blinded to data analysts, although blinding of participants was not possible due to the intervention. Inclusion criteria were undergraduate health sciences students (3rd year or above). Voluntary consent to participate and no prior participation in the same simulation modules. Exclusion criteria were prior training in the simulation stations. incomplete pre-/post-assessment data and withdrawal of consent. A structured skill assessment checklist was done. Developed and validated by subject experts. It included stepwise criteria for each simulation task, scored out of 100. OSCE Score Sheet: A standardized Objective Structured Clinical Examination (OSCE), scored out of 20 by two blinded assessors. This OSCE format followed established protocols as described by Harden and Gleeson (1979) and

further validated in simulation-based medical education [13]. Confidence Questionnaire: A 5-point Likert scale (1 = not confident, 5 = very confident) was used pre- and post-simulation to assess self-reported confidence. The scale was adapted from validated tools in similar simulation studies [14]. Satisfaction Survey: Completed only by the feedback group, assessing satisfaction across five domains (clarity, timeliness, usefulness, relevance, and overall satisfaction). This questionnaire was developed for this study and reviewed by experts for content validity. It was pilot-tested with 10 students, and internal consistency was confirmed (Cronbach's alpha = 0.86). Both groups attended a pre-simulation orientation. Participants then completed a pre-test knowledge assessment and a baseline skill performance using manikins on standardized stations (IV cannulation, CPR, Basic Life Support). Feedback Group: Received real-time formative feedback after the pre-test, including verbal comments, video playback, and structured improvement guidance aligned with defined performance criteria. Control Group: Performed the same tasks but received no feedback until the final debriefing. All participants then completed a post-test assessment and OSCE. Confidence and satisfaction data were collected using structured, self-administered tools. To ensure instrument reliability, all checklists and rating tools were pilot-tested. Inter-rater reliability for OSCE scores was high (Cohen's Kappa > 0.85). Simulation stations and checklists were developed through expert consensus and aligned with curriculum standards, ensuring both content and face validity. Feedback scripts were standardized, and facilitators received calibration training to reduce bias. All statistical analyses were performed using IBM SPSS Statistics version 26.0. All statistical analyses were performed using IBM SPSS version 26. Data were cleaned and checked for missing values; only complete cases were included in the final analysis. Descriptive statistics (means $\pm$ SD, frequencies, percentages) were used to summarize demographic and performance variables. Tests for normality (Kolmogorov-Smirnov and Shapiro-Wilk) were applied within each group to all continuous outcome variables, supported by histograms and Q-Q plots. All main variables demonstrated approximate normality, allowing the use of parametric tests. For between-group comparisons, Independent Samples t-tests were used for continuous variables (pre-test scores, post-test scores, OSCE scores, confidence ratings), and Chi-square tests were applied for categorical data (e.g., gender, year of study, discipline). Levene's Test for Equality of Variances was applied before each t-test. Cohen's d effect sizes and 95% confidence intervals were reported to quantify the magnitude of group differences. Cohen's d values were interpreted as small (0.2), medium (0.5), and large (≥ 0.8). Although pre- and

post-assessments were administered, the analysis emphasized between-group differences using change scores (improvement) as the primary outcome. A sub-analysis was conducted for the feedback group (n=36), where descriptive statistics were used to summarize satisfaction across five feedback domains.

RESULTS

Both groups were statistically comparable in terms of age, gender, year of study, clinical experience, and prior feedback or simulation exposure. However, the field of study significantly differed between groups ($p=0.006$), with the feedback group having a higher proportion of nursing students. Cramer's V of 0.379 indicates a moderate association. This variation should be considered when interpreting learning outcomes, as baseline discipline may influence simulation performance (Table 1).

Table 1: Baseline Demographic Characteristics of Participants (n=72)

Variables	Category	Feedback Group (n=36)	Control Group (n=36)	p-Value / Statistic
Age	Mean $\pm$ SD	23.01 $\pm$ 1.68	23.22 $\pm$ 1.62	0.593
Gender	Male	17 (47.2%)	18 (50.0%)	0.814
	Female	19 (52.8%)	18 (50.0%)	
Year of Study	3 rd Year	16 (44.4%)	17 (47.2%)	0.813
	Final Year	20 (55.6%)	19 (52.8%)	
Field of Study	MBBS	15 (41.7%)	24 (66.7%)	$\chi^2=10.366$, df=2, $p=0.006$, Cramer's V=0.379
	BDS	8 (22.2%)	10 (27.8%)	
	Nursing	13 (36.1%)	2 (5.6%)	
Prior Simulation Exposure	Yes	13 (36.1%)	14 (38.9%)	0.808
	No	23 (63.9%)	22 (61.1%)	
Clinical Experience	<6 Months	17 (47.2%)	19 (52.8%)	0.637
	≥ 6 Months	19 (52.8%)	17 (47.2%)	
Previous Feedback Sessions	None	12 (33.3%)	19 (52.8%)	0.247
	1-2 Sessions	15 (41.7%)	11 (30.6%)	
	≥ 3 Sessions	9 (25.0%)	6 (16.7%)	

The two groups had similar pre-test scores, confirming equal baseline knowledge ($p=0.694$). The pre- and post-tests referred to structured written knowledge assessments scored out of 100. After training, the feedback group demonstrated significantly greater improvement in test performance and skill execution, with large effect sizes (Cohen's $d > 2$). Notably, OSCE scores were also significantly higher in the feedback group, reinforcing the value of formative feedback in enhancing clinical competence (Table 2).

Table 2: Knowledge and Skill Scores Before and After Simulation-Based Training (n=72)

Measures	Feedback Group (Mean ± SD)	Control Group (Mean ± SD)	Mean Difference	95% CI	p-Value	Effect Size (Cohen's d)
Pre-Test Score	57.60 ± 5.63	57.13 ± 4.53	0.48	-1.93 to 2.88	0.694	0.09
Post-Test Score	83.66 ± 7.60	72.76 ± 5.57	10.90	7.77 to 14.03	<0.001	1.61
Improvement Score	26.06 ± 5.11	15.63 ± 4.33	10.42	8.19 to 12.65	<0.001	2.18
OSCE Score (out of 20)	17.56 ± 0.96	14.65 ± 1.71	2.91	2.26 to 3.56	<0.001	2.00

Pre- and post-test scores reflect structured written assessments; OSCE scores reflect practical skill performance out of 20

Pre-training confidence was statistically similar between groups ($p=0.771$). However, post-training, the feedback group reported significantly higher confidence (mean=4.36 vs. 3.48, $p<0.001$), suggesting that formative feedback enhances both skill and self-perception (Table 3).

Table 3: Self-Reported Confidence Levels Before and After Training (n=72)

Confidence Measure	Feedback Group (Mean ± SD)	Control Group (Mean ± SD)	Mean Difference	95% CI	p-Value
Confidence (Pre-Test)	2.79 ± 0.52	2.75 ± 0.61	0.04	-0.23 to 0.31	0.771
Confidence (Post-Test)	4.36 ± 0.44	3.48 ± 0.41	0.87	0.67 to 1.07	<0.001

The feedback group also reported high satisfaction across all five domains, with mean scores above 4.5. "Overall Satisfaction" (4.82) and "Usefulness for Improvement" (4.81) received the highest ratings (Table 4).

Table 4: Satisfaction with Feedback in Feedback Group Only (n=36)

Satisfaction Domain	Mean ± SD
Clarity of Feedback	4.66 ± 0.30
Timeliness of Feedback	4.68 ± 0.30
Usefulness for Improvement	4.81 ± 0.19
Relevance to Clinical Skills	4.60 ± 0.40
Overall Satisfaction	4.82 ± 0.27

DISCUSSION

This study aimed to explore the role of formative feedback in enhancing clinical skill acquisition during simulation-based training. The findings strongly support the hypothesis that structured, timely feedback significantly improves performance, confidence, and learner satisfaction. Participants who received formative feedback demonstrated higher post-test and OSCE scores than those in the control group. The feedback group's mean improvement score exceeded the control group by over 10 points, with large effect sizes (Cohen's $d>2$), indicating

substantial educational benefit. These results align with previous findings by Cole and Pannekoeke, who emphasized that high-quality feedback enhances learning when it is timely, specific, and actionable [15, 16]. Self-reported confidence also increased more markedly in the feedback group, echoing the findings of Kaur et al. Yang et al. and Agostino et al. who reported enhanced student confidence and reduced performance anxiety following feedback-supported simulation [17-19]. Satisfaction levels in the feedback group were uniformly high, with the highest scores for "Overall Satisfaction" (mean=4.82) and "Usefulness for Improvement" (mean=4.81). These ratings indicate that learners viewed the feedback not merely as corrective but as a supportive and motivating element of their learning. These findings are consistent with prior research, who highlighted the emotional and educational impact of feedback during simulation-based education [20-22]. Although demographic characteristics were balanced between groups, the distribution of disciplines (MBBS, BDS, Nursing) was not. The feedback group had a higher proportion of nursing students, while the control group had more MBBS participants. While no formal subgroup analysis was conducted, the consistently superior performance and satisfaction outcomes across the feedback group suggest that the intervention was beneficial regardless of academic background. Future studies should perform discipline-specific subgroup analyses to evaluate whether feedback effectiveness differs significantly across fields. Simulation-based education is now widely recognized as a safe and effective modality for developing clinical competence [23-25]. However, this study reaffirms that the educational impact of simulation is highly dependent on the quality of feedback and debriefing provided. Structured formative feedback helps transform simulation from a passive activity into a reflective, improvement-focused learning experience.

This study was limited by its single-institution setting and relatively small sample size, which may affect generalizability. The imbalance in participant disciplines between groups and the quasi-experimental design may also introduce potential confounding factors. Additionally, long-term retention of skills was not assessed. Future multicenter randomized trials with larger, discipline-stratified samples and longitudinal follow-up are recommended to evaluate sustained competency gains and to develop standardized feedback models for simulation-based undergraduate training.

CONCLUSIONS

This study demonstrated that incorporating structured formative feedback into simulation-based training leads to measurable improvements in clinical skill performance (OSCE and post-test scores), increased self-reported

confidence, and high learner satisfaction. These results reinforce the critical role of feedback in enhancing the educational value of simulation. By embedding feedback as a routine part of simulation training, educational programs can foster more effective and learner-centered skill development. Future research should explore the retention of skills over time and investigate discipline-specific impacts of feedback to guide tailored simulation curricula.

Authors' Contribution

Conceptualization: AHA

Methodology: MZB, FP, NG

Formal analysis: ZA, MZB, FP

Writing and Drafting: AHA, ZA, NJ, NG

Review and Editing: AHA, ZA, NJ, NG, MZB, FP

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article



Efficacy of Percutaneous Nephrolithotomy in Pediatric Renal Stone Clearance in Khyber Pakhtunkhwa: A Cross-Sectional Analytical Study

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ABSTRACT

Renal stone disease is increasingly recognized in the Pediatric population and poses significant clinical challenges. Timely and effective intervention is essential to prevent long-term complications such as recurrent infections, renal damage, or impaired growth. Percutaneous nephrolithotomy (PCNL) has emerged as a key surgical technique in managing moderate to large renal stones in children, but data on its efficacy and safety in the local context remain limited.

Objectives: To assess the effectiveness of PCNL in achieving renal stone clearance in Pediatric patients aged 5 to 15 years presenting to a tertiary care centre in Khyber Pakhtunkhwa.

Methods: This descriptive study was conducted at the Department of Urology, Institute of Kidney Diseases, Peshawar. A total of 216 children with uncomplicated, single renal stones measuring ≤ 8 mm, confirmed on a KUB X-ray, were enrolled through consecutive non-probability sampling. Standard PCNL was performed under general Anesthesia, and clearance was assessed postoperatively. Data were analyzed using SPSS version 23.0. Chi-square test was used for associations between stone clearance and variables age, gender, stone size, site, and operative time. **Results:** Stone clearance was achieved in 78.2% of cases. Clearance was higher in children with smaller stones (≤ 5 mm) and shorter operative times, though the differences were not significant ($p > 0.050$). No major procedural complications were reported.

Conclusions: PCNL is an effective and safe procedure for treating Pediatric renal stones. While factors like stone size and operative duration may influence outcomes, further large-scale studies are warranted to confirm these associations in the Pediatric population of low-resource settings.

INTRODUCTION

Pediatric urolithiasis is a growing concern worldwide, with a rising incidence attributed to changes in dietary patterns, metabolic disorders, and environmental factors [1]. In children, renal stones present a unique challenge due to anatomical and physiological differences, making both diagnosis and management more complex compared to adults [2]. Early detection and timely intervention are

crucial to prevent complications such as infection, obstruction, and long-term renal impairment [3, 4]. Among the various treatment options, Percutaneous Nephrolithotomy (PCNL) has emerged as a preferred modality for managing moderate to large renal calculi, especially in cases where extracorporeal shock wave lithotripsy (ESWL) or conservative approaches fail [5].



Compared to ESWL, PCNL offers higher stone clearance rates in a single session and is less dependent on stone composition or anatomical variations, making it especially advantageous for pediatric patients with moderate-to-large stones [6]. With technological advancements and the development of miniaturized instruments, PCNL has become safer and more feasible even in pediatric populations [6, 7]. However, despite its increasing use, concerns remain regarding its efficacy, safety profile, and potential complications in younger patients [8]. In the context of Pakistan, particularly in regions like Khyber Pakhtunkhwa, existing data on pediatric PCNL is limited in both scope and scale. Most studies are either small, single-center reports or lack detailed analysis of clinical outcomes and predictive factors [9]. Additionally, there is a scarcity of published data in the national literature addressing pediatric PCNL using miniaturized techniques. Socioeconomic constraints, variation in clinical expertise, and differing access to health care facilities often influence treatment outcomes. Understanding the success rate and associated factors of PCNL in local pediatric populations is therefore essential to inform practice and guide improvements in surgical care. By generating indigenous evidence, this study aims to contribute to the optimization of pediatric stone management strategies in similar low-resource settings.

Although Percutaneous Nephrolithotomy (PCNL) has become an established minimally invasive technique for the management of pediatric renal stones, its clinical outcomes can vary depending on patient characteristics, surgical expertise, and healthcare resources. Most of the available evidence on pediatric PCNL originates from developed countries or specialized centers with advanced facilities. In Pakistan, particularly in Khyber Pakhtunkhwa, there is limited published data evaluating the efficacy and predictors of stone clearance following PCNL in children. This lack of region-specific evidence creates a gap in understanding the real-world effectiveness of PCNL in local pediatric populations. This study aimed to evaluate the efficacy of PCNL in achieving renal stone clearance among children aged 5 to 15 years treated at a tertiary care center in Peshawar. In doing so, it also explores the influence of demographic and clinical factors such as age, gender, stone size, location, and operative time on stone clearance.

METHODS

This was a cross-sectional analytical study conducted to evaluate the efficacy of percutaneous nephrolithotomy (PCNL) in achieving renal stone clearance among pediatric patients. The study was carried out at the Department of Urology, Institute of Kidney Diseases (IKD), Peshawar, a tertiary care referral center in Khyber Pakhtunkhwa,

Pakistan. The study was conducted over six months, from Jun 16, 2023, to November 16, 2023. Before the commencement of the study, approval was obtained from the Institutional Ethical Committee of the Institute of Kidney Diseases, under reference number 463. Written informed consent was obtained from the parents or guardians of all participants. A total of 216 pediatric patients were included. The sample size was calculated using the WHO sample size estimation formula, assuming a 90% stone clearance rate, a 95% confidence level, and a 4% margin of error. A non-probability consecutive sampling technique was employed. All eligible patients presenting within the study duration and meeting the inclusion criteria were enrolled consecutively. Although convenient for recruitment, this method may introduce selection bias and may limit generalizability of the findings to broader pediatric populations. Inclusion criteria were children aged between 5 and 15 years diagnosed with a single, uncomplicated renal stone measuring ≤ 8 mm on KUB X-ray were included. While PCNL is typically reserved for stones larger than 10 mm, this threshold was chosen based on local practice guidelines and to assess the efficacy of PCNL in smaller stones where ESWL was either contraindicated, previously failed, or not available. Exclusion criteria were Patients with anatomical renal abnormalities (e.g., horseshoe or malrotated kidney), staghorn calculi or complex stones, positive urine cultures, bleeding disorders, deranged renal function, or other systemic comorbidities were excluded. Once consent was secured, all eligible children underwent standardized PCNL procedures under general anesthesia. A 15 Fr mini-nephroscope was used, and tract dilation was performed using serial coaxial dilators up to 16 Fr, suitable for pediatric access. The stones were accessed via the posterior calyx, and pneumatic lithotripsy was employed to fragment the stones. Fragments were extracted using a three-prong grasper. A nephrostomy tube was placed in all patients and removed on the second postoperative day. Stone clearance was assessed using a KUB X-ray on the first postoperative day. Follow-up imaging was not routinely performed unless clinically indicated, due to resource constraints and the need to minimize radiation exposure in children. Data were collected using a structured proforma that included demographics (age and gender), stone characteristics (size, site, and location), operative details (operative time in minutes), and clinical presentation (e.g., vomiting, flank pain, or left abdominal pain >4 on VAS). Outcomes assessed included stone clearance on the first postoperative day and length of hospital stay. All patients underwent baseline investigations, including urine culture, renal function tests, and coagulation profiles. Radiological confirmation of stone size and location was performed

using a KUB X-ray. To ensure data reliability, stone size and operative time measurements were taken by trained staff using standardized tools. Validity was maintained through consistent surgical protocols, identical equipment, and lithotripsy methods across cases. The pre-tested proforma helped minimize interobserver variation. The data were analyzed using IBM SPSS version 23.0. Descriptive procedures (Frequencies, Descriptive) were used to summarize numerical variables as mean $\pm$ standard deviation, and categorical variables as frequencies and percentages. Normality of continuous data was tested using the Shapiro-Wilk test to justify the use of mean and SD. For inferential analysis, the Chi-square test (Crosstabs procedure) was used to evaluate associations between stone clearance and variables such as age group, gender, stone size (dichotomized using the sample median of 5 mm), operative time (cutoff at 35 minutes), and stone site. A p -value ≤ 0.050 was considered statistically significant.

RESULTS

The descriptive analysis of continuous variables revealed that the age of participants ranged from 5 to 14 years, with a mean $\pm$ SD of 9.50 ± 2.89 years. The average stone size was 4.06 ± 1.69 mm, ranging from 1.1 to 7.0 mm. Operative time varied between 32.1 and 52.0 minutes, and the mean surgical duration was 42.04 ± 5.62 minutes. These values provide a foundational understanding of the clinical characteristics of pediatric patients undergoing PCNL, Table 1.

Table 1: Descriptive Statistics of Continuous Variables (n=216)

Variables	Minimum	Maximum	Mean $\pm$ SD
Age (Years)	5	14	9.50 ± 2.89
Stone Size (mm)	1.1	7.0	4.06 ± 1.69
Operative Time (Minutes)	32.1	52.0	42.04 ± 5.62

The age-wise distribution of participants showed that the majority (57.4%) were in the 5–10 years' group, while 42.6% were aged 11–15 years. Male patients were predominant (66.2%) compared to females (33.8%), reflecting a gender trend consistent with pediatric urolithiasis literature, Table 2.

Table 2: Demographic Characteristics of the Study Population (n=216)

Variables	Category	Frequency (%)
Age Group	5–10 Years	124 (57.4%)
	11–15 Years	92 (42.6%)
Gender	Male	143 (66.2%)
	Female	73 (33.8%)

The relationship between age group and stone clearance. Children aged 5–10 years had a clearance rate of 80.6%, while those aged 11–15 years had a slightly lower rate at 75.0%. However, this difference was not statistically significant ($\chi^2 = 0.989$, $df=1$, $p=0.320$). Similarly, male had a

clearance rate of 79.0%, and female 76.7%, which was also statistically non-significant ($\chi^2 = 0.151$, $df=1$, $p=0.697$), Table 3.

Table 3: Association of Stone Clearance with Age Group and Gender (n=216)

Variables	Category	Clearance Achieved, n (%)	Not Achieved, n (%)	Total	χ^2 (df), p-value
Age Group	5–10 Years	100 (80.6%)	24 (19.4%)	124	0.989 (1), 0.320
	11–15 Years	69 (75.0%)	23 (25.0%)	92	
Gender	Male	113 (79.0%)	30 (21.0%)	143	0.151 (1), 0.697
	Female	56 (76.7%)	17 (23.3%)	73	

To justify categorical comparisons, the study used data driven cutoffs based on the median values observed in our cohort for stone size (5 mm) and operative time (35 minutes). These were used to dichotomize the variables for chi-square analysis. Stone clearance was higher in children with stones ≤ 5 mm (81.7%) compared to those with stones > 5 mm (71.6%). This difference approached borderline significance ($\chi^2 = 2.897$, $df=1$, $p=0.089$). Operative time also did not significantly affect outcomes. Among those with procedures ≤ 35 minutes, 77.1% achieved clearance, while the > 35 -minute group had a clearance rate of 78.5% ($\chi^2 = 0.030$, $df=1$, $p=0.863$). The stone site (distal vs proximal) showed nearly identical results, with no statistical difference ($\chi^2 = 0.000$, $df=1$, $p=0.983$), Table 4.

Table 4: Association of Stone Clearance with Stone Size, Operative Time, and Stone Site (n=216)

Variables	Category	Clearance Achieved, n (%)	Not Achieved, n (%)	Total	χ^2 (df), p-value
Stone Size	≤ 5 mm	116 (81.7%)	26 (18.3%)	142	2.897 (1), 0.089
	> 5 mm	53 (71.6%)	21 (28.4%)	74	
Operative Time	≤ 35 min	27 (77.1%)	8 (22.9%)	35	0.030 (1), 0.863
	> 35 min	142 (78.5%)	39 (21.5%)	181	
Stone Site	Distal	83 (78.3%)	23 (21.7%)	106	0.000 (1), 0.983
	Proximal	86 (78.2%)	24 (21.8%)	110	

To further quantify the strength of association between potential predictors and stone clearance, I performed a binary logistic regression analysis. Although none of the variables were statistically significant, stone size showed a trend toward significance ($p=0.088$), suggesting a potential influence on clearance outcomes. The results, expressed as odds ratios with 95% confidence intervals. To complement the chi-square analysis, a binary logistic regression was performed to estimate the effect sizes of key predictors on stone clearance. The regression model included age group, gender, stone size, operative time, and stone site. While none of the predictors reached statistical significance at the 0.05 level, stone size demonstrated a borderline association with the outcome (OR=1.79, 95% CI: 0.92–3.49, $p=0.088$), suggesting that larger stones may be associated with lower clearance rates. Age group (OR=1.43,

95% CI: 0.74–2.76, $p=0.292$) and gender (OR=1.15, 95% CI: 0.58–2.30, $p=0.686$) showed weak associations with the outcome, and their wide confidence intervals included the null value, indicating a lack of strong predictive power. Similarly, operative time and stone site did not show meaningful associations, with ORs close to 1 and p -values of 0.648 and 0.910, respectively. The overall model did not significantly improve prediction over chance ($\chi^2 = 4.156$, $df=5$, $p=0.527$), and the Hosmer-Lemeshow test ($p=0.219$) indicated a good model fit. These findings reinforce that none of the clinical factors evaluated, including age, gender, stone size, operative duration, or location, were statistically significant predictors of stone clearance in this cohort, although stone size may warrant further investigation in larger, powered studies, Table 5.

Table 5: Binary Logistic Regression for Predictors of Stone Clearance ($n=216$)

Predictors	Odds Ratio (OR)	95% CI	p-value
Age Group (11–15 vs. 5–10)	1.43	0.74 – 2.76	0.292
Gender (Female vs. Male)	1.15	0.58 – 2.30	0.686
Stone Size (per mm ↑)	1.79	0.92 – 3.49	0.088
Operative Time (per min ↑)	0.81	0.34 – 1.98	0.648
Stone Site (Distal vs. Proximal)	0.96	0.50 – 1.86	0.910

The stone clearance rates were slightly higher in children with smaller stones (≤ 5 mm), shorter procedures (≤ 35 minutes), and distal stone locations. However, these differences did not reach statistical significance. The consistency in clearance rates across subgroups indicates that none of these clinical predictors had a major impact on outcome in this cohort (Figure 1).

Stone Clearance Rates by Stone Size, Operative Time, and Stone Site

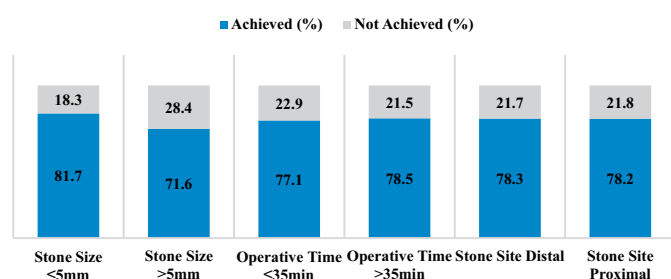


Figure 1: Stone Clearance Rates by Stone Size, Operative Time, and Stone Site

DISCUSSION

In this study involving 216 pediatric patients who underwent PCNL, a stone clearance rate of 78.2% was achieved. While this figure is moderately successful, it falls short of the $>90\%$ clearance rates reported in several regional and international studies. For example, Rehman *et al.* reported a 93.3% clearance rate in Iraqi children undergoing mini-PCNL, and Ahmad *et al.* observed similar outcomes in infants treated with miniaturized approaches [10, 11]. The relatively lower clearance rate in the present

study may be attributed to several contextual factors. Firstly, only the first postoperative day imaging was used for outcome assessment, without follow-up imaging to confirm residual fragments, potentially underestimating true clearance. Secondly, the inclusion of small stones (≤ 8 mm) rather than larger stones, which are typically more suitable for PCNL, may have influenced procedural effectiveness. Moreover, resource limitations, varied surgical experience, and institutional protocols may also have played a role in the observed discrepancy. Despite the modest clearance rate, PCNL remains effective for selected pediatric populations. Mahmood *et al.* demonstrated a significantly higher clearance rate with PCNL (92.9%) compared to ESWL (53.6%) in infants, supporting the reliability of PCNL even for younger age groups [12]. Other multicenter studies have consistently reported clearance rates ranging from 86% to 91.1%, reinforcing the value of PCNL as a minimally invasive standard of care [13]. This study also found no significant associations between stone clearance and variables such as age, gender, stone size, operative time, or anatomical location. These findings are consistent with a randomized controlled trial conducted, which reported that sheath size and procedural duration did not significantly impact stone-free outcomes in children [14]. However, the lack of statistical significance in our analysis may partly reflect limited statistical power for detecting small effect sizes. The logistic regression analysis indicated a borderline association between stone size and clearance ($p=0.088$), suggesting that with a larger sample, this factor might reach significance. This limitation has been acknowledged and highlights the need for more extensive, adequately powered studies to explore these relationships further. The role of predictive tools in pediatric stone management is becoming increasingly recognized. Akdogan *et al.* and Fernandez *et al.* demonstrated that scoring systems like CROES and Guy's Stone Score can be helpful in pediatric populations, even though they were originally developed for adults [15, 16]. Recent consensus frameworks, such as the Pediatric PCNL Reporting Checklist, advocate for consistent definitions and outcome measures, which could improve comparability across future studies [17]. Furthermore, broader research supports the superiority of PCNL over ESWL in terms of stone clearance and patient-reported outcomes such as pain, anxiety, and hospital stay duration [18, 19]. This adds weight to the argument for using PCNL as a preferred treatment, especially in settings where follow-up compliance and access to alternative technologies may be limited [20]. In summary, although the clearance rate observed in this study was slightly lower than in previous reports, the procedure remains safe and effective. The consistency of outcomes across age groups,

genders, and stone characteristics suggests that PCNL continues to hold value in pediatric urolithiasis management, particularly in low-resource settings. This study has several limitations that should be acknowledged. It was conducted at a single tertiary care center using a consecutive non-probability sampling method, which may limit the generalizability of the findings. Additionally, stone clearance was assessed only on the first postoperative day using KUB X-ray, and long-term follow-up imaging was not performed to evaluate residual fragments or recurrence. Future multicenter studies with larger sample sizes and longer follow-up periods are recommended to better evaluate long-term outcomes and identify significant predictors of successful stone clearance in pediatric patients undergoing PCNL.

CONCLUSIONS

Percutaneous nephrolithotomy is a safe and effective treatment option for pediatric renal stones, achieving a stone clearance rate of 78.2% in this cohort. While the clearance rate was modest compared to some international benchmarks, the procedure showed consistent outcomes regardless of age, gender, stone size, operative duration, or anatomical site. These findings align with the study's objective to assess the efficacy of PCNL in a local pediatric population. The results also underscore the importance of context-specific evaluations, especially in regions with limited access to alternative modalities like ESWL. The study reinforces the utility of PCNL, particularly miniaturized approaches, as a first-line option for renal stones up to 8 mm in pediatric patients.

Authors' Contribution

Conceptualization: WK

Methodology: TSK, RAK, MK, AA

Formal analysis: WK, RAK, MK, AA

Writing and Drafting: WK, TSK, AIK

Review and Editing: WK, TSK, AIK, RAK, MK, AA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Prevalence and Associated Factors of Obesity in Children Aged 2-11 Years at a Tertiary Care Hospital in Islamabad

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ABSTRACT

Childhood obesity is a rising health concern globally, with an increasing trend in many low middle-income countries like Pakistan, due to rapid urbanization and lifestyle changes like unhealthy dietary practices and lack of physical activity. **Objectives:** To find out the prevalence of obesity and some associated variables, such as demographic, socioeconomic, and lifestyle factors, among the children aged 2 to 11 years visiting a tertiary care hospital in Islamabad, Pakistan. **Methods:** The descriptive cross-sectional study was conducted from May 10, 2024, to November 10, 2024, at the Pediatric Department of the Avicenna Medical Complex in Islamabad. 220 children aged 2-11 years were recruited using consecutive sampling. Obesity was defined as a BMI $\geq +2$ SD on WHO percentile charts, and data related to its associated factors were collected. SPSS version 26.0 was used to analyze data and report descriptive statistics; chi-square tests were performed to determine statistical significance. **Results:** The prevalence of obesity was 7% (n=15). Among participants, 57% were aged 2-6 years, 59% were male, and 63% resided in rural areas. An insignificant association was found between obesity and age, gender, socioeconomic status, or family history ($p>0.050$). A higher obesity trend was observed in urban areas (11%) than rural areas (4%), though it was statistically insignificant ($p=0.053$). Most of the children were physically active (88%), with high obesity (54%) reported in inactive children. **Conclusions:** Childhood obesity was low, with no significant associations found with key demographic or socioeconomic factors. However, urban residence and physical inactivity showed trends toward higher obesity risk.

INTRODUCTION

The growing problem of childhood obesity is becoming a substantial public health concern worldwide. According to the World Health Organization (WHO), there is a fourfold increase in obesity among children and adolescents from 2% in 1990 to 8% in 2022 globally [1]. It is defined by WHO as body mass index (BMI) equal to or higher than the 95th percentile compared to the members of the same sex and age group [1]. Childhood obesity has skyrocketed across the globe in the past few decades, becoming a dangerous threat to both short and long-term healthcare. The spread of this increasing epidemic is caused by a synergy of genetics, poor diet and eating patterns, lack of exercise, and environmental factors [2-4]. Notably, the spread of

obesity among children is no longer restricted to developed nations but is on the rise in low- and middle-income countries (LMICs), including Pakistan, where urbanization and lifestyle changes are proliferating this issue [5]. There is a sustained growth of child obesity in Pakistan, as it has been noted all over the world. This alarming increase is due to urbanization and transition to poor nutrition habits, which in turn have been attributed to less physical activity [6]. Research demonstrates that urban children, especially those in capital cities such as Islamabad, are more vulnerable since the processed food that is high in energy, as well as soft drinks, are readily available, and the chances of engaging in physical exercise outside are low. Moreover,



a socio-economic context, such as income level and the level of parental education, significantly affects dietary and life habits, contributing to the aggravation of the situation even further [7, 8]. Obesity has led to the elevated risk of developing non-communicable diseases that encompass hypertension, type 2 diabetes mellitus, and cardiac problems that are costing the medical system significant sums [9]. The risk window is mostly among youngsters during childhood (2-11 years old) can develop habits, and their influence on the lifelong state of health. The risks of having problems of mental health, including childhood obesity, leading to the lack of confidence, depression, and anxiety among obese children, are other threats to childhood obesity and the increased likelihood of obesity developing in adulthood [7, 9]. Primary prevention of obesity at this early age is therefore important to curtail the long-term burden of diseases caused by obesity. In Pakistan, although several studies have focused on exploring the trend of obesity among school-going children, there is insufficient evidence available about obesity prevalence among children in the age range of 2-11 years [10, 11]. Since tertiary hospitals are referral hospitals covering a wide array of populations, it is a distinct asset to examine the prevalence rate of obesity among all ages. The children served in these hospitals represent different socio-economic groups and are thus optimal environments because of their low financial capabilities to seek alternative healthcare providers. Regional trends and risk factors associated with obesity are thus easily identified in such clinical settings. It is still unclear to what extent childhood obesity exists or what predisposing factors play a role in childhood obesity in Islamabad. This disparity brings to light a necessity to conduct more wide-scaled studies that capture not only the prevalence of obesity but also extend to underlying factors like dietary habits, physical exercise, parental enlightenment, and economic background [12]. Addressing these factors is essential for designing more focused public health initiatives to combat the rising prevalence of childhood obesity. By analyzing hospital-based data, this study seeks to provide an expanding body of literature on childhood obesity in Pakistan.

Childhood obesity is an emerging public health concern in Pakistan, yet reliable data for younger children, particularly those aged 2-11 years, remain limited. Most local studies focus on school-aged adolescents, with insufficient attention to early childhood and hospital-based populations. Furthermore, the interplay between demographic, socioeconomic, and lifestyle factors in this age group has not been adequately explored in the Islamabad region. This lack of context-specific evidence highlights the need to determine the prevalence and associated factors of obesity in young children attending

tertiary care facilities. This study aimed to find out the frequency of obesity in children between the age group of 2-11 years presenting at a tertiary care hospital in Islamabad.

METHODS

A descriptive cross-sectional study was done in the Pediatric Department, Avicenna Medical Complex (AMC), Islamabad, to find out the prevalence rate of obesity in children aged between 2-11 years. The validity period of the study lasted six months, starting May 10, 2024, to November 10, 2024. The sample size was computed using the WHO sample size calculator, where the confidence level was set as 95%, the estimated prevalence of obesity was assumed to be approximately 7.5% and a margin of error of 5% was considered [13]. 220 children were involved at different ages, both male and female. Non-probability consecutive sampling was implemented. The inclusion criteria included both male and female children aged 2 to 11 years who either presented to the tertiary care hospital in Islamabad or were admitted to the same. The study only involved children whose parents or legal guardians gave informed consent. As well, the participants had to be clinically stable during the assessment period, and detailed and valid anthropometric data, like height, weight, and age, could be collected. But children with congenital syndromes and chronic systemic illnesses or endocrine disorders that may affect their growth and weight, such as hypothyroidism or Cushing syndrome, were excluded. Moreover, the children using long-term drugs that have a known impact on body weight, including corticosteroids or antiepileptic drugs, and those with incomplete or inadequate anthropometric or clinical measures were excluded from the research. These criteria were adopted to retain the integrity and interest of the study population to provide a more accurate measure concerning the occurrence of obesity and its causal issues. The study was approved by the hospital's ethical committee under letter no Ref ERC: KRL-HI-PUB-ERC/Mar24/6 to rule out any ethical concerns, before the commencement of data collection. Written informed consent was obtained from the parents or guardians of all participating children. Participants who were eligible for the study were enrolled from the Pediatric Outpatient Department (OPD) and the Pediatric Ward of Avicenna Medical Complex (AMC). A trained researcher measured each child's height using a stadiometer, whereas weight was measured on a digitally calibrated scale. Both measurements were performed using WHO standardized protocols [14]. Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2), which was then plotted on the WHO age- and sex-specific BMI percentile charts to measure the obesity in the children. Children

whose BMI was greater than the 2nd standard deviation (+2SD) percentile were classified as obese. Information related to the variables such as age, gender, weight, height, BMI, place of residence, socioeconomic background, levels of physical activity, screen time, and any family history of obesity was collected using a structured questionnaire. Physical activity was characterized as participating in a moderate exercise activity of around 30 minutes daily or an activity that exceeds two hours during a course of one week. Children who have screen time exposure of more than two hours per day were classified as having high screen time, which is associated with an elevated risk of obesity [15]. To make the data collection process accurate and consistent, the supervisor was an expert consultant, having a minimum of five years of experience in treating pediatric patients. Strict exclusion criteria were taken into consideration so that the study outcome would be less prone to biases. The possible confounders in our study were age, gender, socioeconomic background, family history of obesity, and place of residence, and they were stratified either during data collection or the data analysis stage in an attempt to limit bias. The data were analyzed using the Statistical Package of Social Sciences (SPSS) version 26.0. In the case of continuous variables, age, weight, height, and BMI, mean and standard deviation have been calculated as descriptive statistics. Frequency distribution and percentage were used to reveal categorical variables, such as gender, residence, socioeconomic status, level of physical activity, family history of obesity, and status of obesity. Before arriving at any potential relationships, the Chi-square test was used to determine the relationships, whereby a $p\text{-value} \leq 0.05$ was used as a significant relationship.

RESULTS

The study comprised 220 children, of which 125 (57%) were aged between 2-6 years and 95 (43%) were aged 7-11 years. The mean age was 7 ± 3.81 years. Out of all the participants, males were 130 (59%), whereas female were 90 (41%). In terms of residence, 139 (63%) children were from rural areas, while 81 (37%) were from urban areas. With regards to the socioeconomic status, 108 (49%) children were from poor families, 90 (41%) were middle class, and 22 (10%) were classified as rich. A majority of 194 (88%) children were physically active, while 26 (12%) were not. A family history of obesity was reported in 46 (21%) children. Obesity was observed in 15 (7%) children, while 205 (93%) were not obese. The association between obesity and related factors, including gender, age, residence, socioeconomic background, physical activity, and family history, are summarized in table 1.

Table 1: Demographic Characteristics of Participants (n=220)

Characteristics	n (%)
Age	
2-6 Years	125 (57%)
7-11 Years	95 (43%)
Gender	
Male	130 (59%)
Female	90 (41%)
Residence	
Rural	139 (63%)
Urban	81 (37%)
Socioeconomic Background	
Poor	108 (49%)
Middle Class	90 (41%)
Rich	22 (10%)
Family History of Obesity	
Yes	46 (21%)
No	174 (79%)
Obesity	
Yes	15 (7%)
No	205 (93%)
Physical Activity	
Positive	194 (88%)
Negative	26 (12%)

Our study results indicate that obesity among children between the age group of 2-11 years in the study sample was low, with 7% of children classified as obese. There were no significant associations between obesity and numerous factors such as gender, age, socioeconomic background, or genetic tendency for obesity. However, the results suggest a higher prevalence of obesity in the urban areas as compared to the rural areas, although the difference turned out to be statistically insignificant ($p > 0.053$). Additionally, children who were not physically active were more likely to be obese, though this finding also did not reach the significance level ($p > 0.050$), as mentioned in table 2.

Table 2: Stratification of Obesity by Key Factors Using Chi-Square Test (n=220)

Factor	Obesity (Yes)	Obesity (No)	Total	2p-value (95% CI)
Age				
2-6 years	8 (6%)	117 (94%)	125	—
7-11 years	7 (7%)	88 (93%)	95	
Gender				
Male	10 (8%)	120 (92%)	130	—
Female	5 (6%)	85 (94%)	90	
Residence				
Rural	6 (4%)	133 (96%)	139	>0.053 (0.94-7.70)
Urban	9 (11%)	72 (89%)	81	
Physical Activity				
Positive	1 (1%)	193 (99%)	194	>0.050 (0.49-1.52)
Negative	14 (54%)	12 (46%)	26	

Genetic Tendency			
Yes	5 (11%)	41 (89%)	46
No	10 (6%)	164 (94%)	174

>0.050 (1.87-19.86)

DISCUSSION

The current study aimed to determine the frequency of obesity among children in the age group of 2-11 years. The findings indicate that obesity prevalence in this population was relatively low, with only 7% of the children being classified as obese. The lower obesity rates were consistent with the other parts of the world, but still concerning, given the growing global burden of childhood obesity [1]. While the overall prevalence of obesity in the study sample was low, we found no significant associations between obesity and key demographic factors such as age, gender, socioeconomic background, or family history of obesity. Previous studies have demonstrated that socioeconomic background can impact the prevalence of childhood obesity, with children from lower socioeconomic backgrounds often exhibiting higher obesity rates due to factors such as unhealthy eating habits, inadequate access to healthy food, and reduced physical activity [16, 17]. In contrast, our findings suggest that socioeconomic status did not significantly correlate with obesity in this study, which may reflect the homogeneous distribution of socioeconomic status among the participants. The study population consisted of children from low- to middle-income families, with 49% classified as poor and 41% as middle class, which may limit the generalizability of the results to higher-income populations. In terms of physical activity, 88% of the children in our study were reported to be physically active. However, despite the considerable proportion of physically active children, obesity was still observed in 7% of the sample. This is consistent with other studies that indicate that while physical activity is necessary for sustaining a healthy weight, it alone may not be sufficient to prevent obesity [16, 18]. Factors such as dietary habits, screen time, and genetic predispositions also play a significant role in the development of obesity, but these factors were not thoroughly explored in the current study. For instance, studies found that sedentary behaviors like excessive screen time are strongly associated with obesity in children, suggesting the importance of addressing lifestyle factors in comprehensive obesity prevention strategies [19, 20]. The association between obesity and residence (rural vs. urban) showed a different pattern, with an elevated prevalence of obesity in the urban areas (11%) compared to the rural areas (4%). Although this difference did not reach statistical significance ($p=0.0538$), it is compatible with the expanding body of evidence that indicates urbanization contributes to an increased risk of childhood obesity. Urban children may have access to a greater variety of high-calorie foods,

increased sedentary behaviors (such as excessive screen time), and limited access to physical activity spaces [21]. This is especially concerning in developing countries like Pakistan, where urbanization is rapidly increasing, leading to a shift in dietary patterns and lifestyle behaviors that promote obesity. Interestingly, the study did not find any statistically significant relationship between genetic predisposition and obesity. While family history is known to be an important determinant of obesity risk [22], it is worth pointing out that it is not the only determining factor of obesity that is controlled by genes. The environmental conditions, like food habits, physical exercises, and economic status, are key factors that predispose a child to obesity [17, 23]. Lack of a notable association in the current study could also be attributed to the low percentage of children that had a genetic predisposition (21%) or it could be because the sample in question is small.

This study was limited by its single-center, hospital-based design and use of non-probability consecutive sampling, which may restrict generalizability to the wider community. The relatively small number of obese cases reduced the statistical power to detect significant associations. Additionally, dietary patterns and detailed sedentary behaviors were not comprehensively assessed. Future multicenter, community-based studies with larger sample sizes and inclusion of detailed nutritional, behavioral, and longitudinal data are recommended to better understand risk determinants and guide targeted prevention strategies.

CONCLUSIONS

The study concluded that the prevalence of obesity among children in this study was comparatively low. The results emphasize the need to address key risk factors for childhood obesity, such as physical activity, dietary habits, and sedentary behaviors. Interventions targeting lifestyle changes, predominantly in urban settings, may be beneficial for preventing the rise of obesity in future generations. Moreover, continued surveillance of childhood obesity trends is necessary for mounting some efficient public health strategies.

Authors' Contribution

Conceptualization: A

Methodology: A, AV, RV, MK

Formal analysis: A, AV, RV, MK, BZ

Writing and Drafting: AV, RV, MAB, MK, BZ

Review and Editing: AV, RV, MAB, MK, BZ, A

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Association of Gastro-Esophageal Reflux Disease with Persistent Cough in Infants

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ABSTRACT

Gastroesophageal reflux disease (GERD) is widely recognized, alongside upper airway cough syndrome (also known as postnasal drip syndrome) and eosinophilic airway inflammation, as one of the predominant causes of chronic cough. Numerous global respiratory societies have published cough management guidelines that advocate for the assessment and treatment of GERD as a fundamental aspect of the diagnostic and therapeutic framework for addressing chronic cough. **Objectives:** To determine the association of gastroesophageal reflux disease with persistent cough in infants. **Methods:** This case-control study was conducted in the Department of Paediatric Medicine at The Children's Hospital and The Institute of Child Health, Lahore, from August 25, 2022, to February 25, 2023. This study was conducted on infants with complaints of persistent cough and healthy controls. These two groups underwent baseline assessment carried out by physicians and a diagnosis of GERD was made through a barium swallow test. The data were analyzed through SPSS version 25.0. Odds ratio (OR) was calculated to measure the association between persistent cough and GERD. **Results:** Among case patients, the mean age was 2.92 ± 2.17 months, and 3.67 ± 2.41 months among control patients. By comparing GERD between case and control groups, it was found that the percentage of GERD was 17.6% in case children and 5.9% control children. The difference was significant ($p=0.033$) and the risk ratio ($OR=3.429$). **Conclusions:** The presence of gastroesophageal reflux disease exhibited a notable correlation with the occurrence of chronic cough in the infant population.

INTRODUCTION

Gastroesophageal reflux involves the backward flow of stomach contents towards the esophagus, often leading to vomiting or regurgitation. This common occurrence, more noticeable after meals, can progress to GERD, causing discomfort and complications. For infants, regurgitation is a key symptom requiring effective management by caregivers and healthcare professionals. Understanding the transition from reflux to GERD is essential for developing effective treatment plans and relieving the condition's impact on individuals and families [1]. Infantile regurgitation, a common and typically harmless physiological process affecting about 70% to 85% of newborns in their first two months of life, tends to improve as infants grow [2]. Although persistent regurgitation beyond 90 days may lead to ongoing issues until around

nine years old, it's important to note that in 95% of cases, gastroesophageal reflux resolves on its own by age one without major intervention. Concerning parents, most cases of infant regurgitation do not require aggressive treatment; instead, they often resolve as the child develops naturally [3, 4]. Gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) can result in various symptoms and complications like weight loss, respiratory issues, and feeding difficulties. An anti-reflux barrier, formed by the crural diaphragm and lower esophageal sphincter (LES), is crucial in preventing gastric content from flowing back into the esophagus. The LES acts as a strong muscular barrier at the gastroesophageal junction, stopping reflux. This barrier, along with other elements, maintains the upper gastrointestinal tract's



balance, preventing reflux-related disorders. Dysfunction in this system can lead to health complications [5]. The right crus of the diaphragm supports the lower esophageal sphincter (LES) to prevent gastroesophageal reflux. Failure in these mechanisms, compounded by delayed gastric emptying, can lead to reflux issues like GERD. Gastric emptying is affected by meal characteristics. Refluxate in the esophagus triggers clearance actions to prevent harmful effects. Primary and secondary peristalsis, along with the upper esophageal sphincter, aid in clearing refluxate. Understanding these processes is crucial for managing GERD and similar conditions effectively [6]. Following gastroesophageal reflux, primary peristalsis initiates movement through the esophagus in infants, while secondary peristalsis becomes dominant post-reflux to clear gastric acid, especially critical during sleep to prevent potential harm like apnea, mucosal damage, and bradycardia. Effective peristaltic activity is crucial to avoid adverse outcomes. Diagnosing infantile GERD involves a detailed medical history and physical examination since no single symptom or test definitively confirms the condition or predicts treatment response accurately [7, 8]. Studies in medical research and clinical observations of patients with a chronic cough show varying rates of gastroesophageal reflux disease prevalence, ranging from 5% to 41%. This indicates a significant difference in the frequency of this condition among individuals with persistent cough symptoms [9, 10]. GERD plays a significant role in chronic cough development, as supported by respiratory organizations emphasizing the importance of managing GERD for effective cough treatment. Studies using advanced monitoring methods confirm the link between cough episodes and reflux, strengthening the understanding of how GERD and cough interact. Integrated therapeutic approaches are crucial in clinical settings to address this relationship [11]. Diagnostic studies include endoscopy, barium studies, multi-channel intraluminal impedance and pH monitoring; the latter now being considered the most accurate method for evaluation of the association between cough and reflux [12, 13]. Regrettably, there exists an exceedingly restricted amount of locally produced literature that pertains specifically to this particular topic of interest, which significantly hampers our understanding and analysis of the subject matter at hand.

Persistent cough in infancy presents a diagnostic challenge, with gastroesophageal reflux disease (GERD) increasingly recognized as a potential contributing factor. However, reported prevalence rates vary widely, and most evidence originates from international populations using advanced diagnostic modalities not readily available in resource-limited settings. In Pakistan, locally generated

data examining the association between GERD and persistent cough in infants remain scarce. This gap underscores the need for context-specific research to better guide clinical evaluation and management strategies. This study aimed to provide valuable insights and contribute significantly to the field by examining and elucidating the intricate relationship that exists between gastroesophageal reflux disease (GERD) and persistent cough, thereby enhancing our overall comprehension of these interconnected medical issues.

METHODS

After taking approval from the hospital's Ethical Committee and written informed consent from parents, this case-control study was conducted in the Department of Paediatric Medicine, Children's Hospital, and The Institute of Child Health, Lahore, from August 25, 2022, to February 25, 2023, with CPSP Ref No. CPSP/REU/PED/2017-075-4516. A total of 136 infants were enrolled in this study after fulfilling the selection criteria (non-probability consecutive sampling). A sample size of 136 (68 cases / 68 controls) was calculated by a 95% confidence level with 80% power of test and expected percentage of GERD as 22% in cases and 7% in controls. The sample size was calculated with the following formula.

$$n = \frac{[Z_{1-\alpha}\sqrt{2\bar{P}(1-\bar{P})} + Z_{1-\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)}]^2}{(P_1 - P_2)^2}$$

The inclusion criteria were cases as infants of both genders exhibiting a persistent cough, per the operational definition and controls as infants of both genders who did not exhibit a persistent cough (after consent of guardian), while individuals presenting with any pre-existing diagnoses related to cough or abdominal discomfort, including but not limited to infections, asthma, or acute gastroenteritis and individuals with a documented history of abdominal surgical procedures and the guardian of the patient failing to provide consent were excluded from this study. The study included male and female infant cases with complaints of persistent cough and healthy controls. These two groups underwent baseline assessments carried out by physicians and a diagnosis of GERD was made through a barium swallow test that was interpreted by a radiologist. All data was recorded on a questionnaire. GERD was considered present if it was positive on the barium swallow test (when the contrast moves back in the esophagus). Persistent cough was defined as a cough that lasted more than 2 weeks. The data were subjected to analysis utilizing SPSS version 25.0. Qualitative variables, such as gender and results from the barium swallow examination, were represented in terms of frequencies and percentages, while the quantitative variable, namely age, was examined with its mean and standard deviations.

The odds ratio (OR) was computed to evaluate the correlation between chronic cough and gastroesophageal reflux disease (GERD). An OR greater than 1 was deemed statistically significant. The data were stratified according to age and sex. Following stratification, the adjusted odds ratio (OR) was calculated, with an OR exceeding 1 considered significant, alongside a p-value of less than or equal to 0.050 being regarded as significant.

RESULTS

A total of 136 patients (68 cases/68 controls) were included in this investigation and a comparison of gender distribution was observed. Among the case group, there were 37 (54.4%) male subjects and 31 (45.6%) female subjects, whereas within the control group, there were 35 (51.5%) male subjects and 33 (48.5%) female subjects (Table 1).

Table 1: Demographic Characteristics of Participants (n=106)

Gender	Cases	Controls	Total
Male	37 (54.4%)	35 (51.5%)	72 (52.9%)
Female	31 (45.6%)	33 (48.5%)	64 (47.1%)
Total	68 (100.0%)	68 (100.0%)	136 (100.0%)

In the case group, 45 (66.2%) of the subjects were categorized within the <6 months' age bracket, while 23 (33.8%) fell into the >6 months' category. In the control group, 43 (63.2%) were in the <6 months' age bracket, and 25 (36.8%) were in the >6 months' category. The mean age for the case group was 2.92 ± 2.17 months, while for the control group, it was 3.67 ± 2.41 months (Table 2).

Table 2: Comparison of Age Distribution Between Groups

Age Group	Cases	Controls	Total
<6 months	45 (66.2%)	43 (63.2%)	88 (64.7%)
>6 months	23 (33.8%)	25 (36.8%)	48 (35.3%)
Total	68 (100.0%)	68 (100.0%)	136 (100.0%)

It was determined that the incidence of GERD was 12 (17.6%) among the case group and 4 (5.9%) within the control group. This disparity was statistically significant ($p=0.033$), with an odds ratio of (OR=3.429) (Table 3).

Table 3: Association of GERD With Persistent Cough

GERD Status	Cases (n = 68)	Controls (n = 68)	Total (n = 136)	p-Value	Odds Ratio (OR)
Yes	12	4	16	0.033	3.429
No	56	64	120		
Total	68	68	136		

It was determined that the incidence of GERD was 4 (10.8%) in males and 8 (25.8%) in females among the case group. GERD incidence was 2 (5.7%) in males and 2 (15.6%) in females within the control group. This disparity was statistically insignificant ($p=0.434$), with an odds ratio of (OR=2.000) in males and was statistically significant ($p=0.030$), with an odds ratio of (OR=5.391) in females (Table 4).

Table 4: Association of GERD With Persistent Cough

Gender	GERD Status	Cases	Controls	Total	p-Value	Odds Ratio (OR)
Male	Yes	4	2	6	0.434	2.000
	No	33	33	66		
	Total	37	35	72		
Female	Yes	8	2	10	0.030	5.391
	No	23	31	54		
	Total	31	33	64		

It was determined that the incidence of GERD in the case group was 6 (13.3%) in the age group <6 months and 6 (26.08%) in the age group >6 months. Within the control group, GERD incidence was 3 (6.9%) in the age group <6 months and 1 (4%) in the age group >6 months. This disparity was statistically insignificant ($p=0.325$), with an odds ratio of (OR=2.051) in the age group <6 months and statistically significant ($p=0.030$), with an odds ratio of (OR=8.471) in the age group >6 months (Table 5).

Table 5: Association of GERD With Persistent Cough

Age Group	GERD	Cases	Controls	Total	p-Value	Odds Ratio (OR)
<6 months	Yes	6	3	9	0.325	2.051
	No	39	40	79		
	Total	45	43	88		
>6 months	Yes	6	1	7	0.030	8.471
	No	17	24	41		
	Total	23	25	48		

DISCUSSION

Gastroesophageal reflux (GER) has been considered to be one of the factors of recurrent or persistent respiratory symptoms in every age group. Therefore, the common anti-reflux drugs are used in the treatment of many children with persistent cough, wheezing, or recurrent respiratory problems. Nevertheless, the connection is yet to be thoroughly studied because there is less opportunity to receive trustworthy research like endoscopy, barium investigations, and the more precise multi-channel intraluminal impedance in combination with pH monitoring [14]. Out of 136 patients included in this study, the case group had 54.4% males and 45.6% were females. The control group had 51.5% males and 48.5% females. Regarding the age distribution, 66.2% were <6 months of age in the case group, while 33.8% were >6 months of age. In the control group, 63.5% were <6 months of age, while 36.8% were >6 months of age. In our study, it was established that the prevalence of GER in the case group was 17.6% whereas the comparative analysis of the control group revealed a significantly lower prevalence rate of 5.9%. An Indian study by Jain et al. showed that 22% of kids with persistent coughing displayed GERD symptoms compared to only 7% in the control group. This highlights the need to consider GERD as a potential cause of pediatric

respiratory problems [13]. Chang et al. studied factors causing persistent cough in infants and children with a history of cough lasting at least a month and normal chest X-rays. This study showed cough variant asthma as the main cause (32%), followed by sinusitis (23%) and GERD (15%). Therefore, identification of causes is crucial for guiding treatment and outcome [12]. Similarly, a Swiss study by Mallet MC et al., revealed that asthma and asthma-like conditions were diagnosed in 132(36%) of 363 children, while upper respiratory cough syndrome in 48(13%) and GERD in 23(6%). It highlighted again that chronic cough is closely related to GERD [15]. Chen X had concluded that out of 85 children investigated for chronic cough 3(3.5%) had GERD [16]. A large pediatric study by Gan Y et al., showed that 30% of children with chronic cough had acid reflux, and many others showed weakly acidic events [17]. A 2023 review in the Brazilian Journal of Otorhinolaryngology underscored non-acid reflux (detected by impedance pH monitoring) as a frequent contributor to cough in children [18]. In scenarios where gastric contents are neutralized after eating, reflux events with non-acidic pH may go undetected. By combining impedance with pH monitoring, reflux events can be categorized based on pH levels for a better understanding [19]. Its recent upsurge has therefore led to the finding of non-acid reflux, and thus the exhaustion experienced by the doctors when they find that acid suppression will go nowhere in yanking airway reflux [20]. In Pakistan, no large-scale cohorts linking infant GER with cough exist, and they often don't isolate cough outcomes, while international data show that cough is a common symptom of GER. Also, there is limited specific data using advanced diagnostic methods like 24-hour impedance pH monitoring in infants. Most local studies rely on basic imaging like barium swallow (in our case, due to limitations of resources) or symptom questionnaires, so Pakistan would benefit if large-scale cohort or case-control studies were carried out.

This study was limited by its single-center design and modest sample size, which may restrict generalizability. The use of barium swallow testing, while practical, has lower sensitivity compared to 24-hour pH impedance monitoring, potentially leading to underdiagnosis of non-acid reflux. Additionally, the case-control design limits causal inference. Future multicenter studies incorporating advanced diagnostic techniques and longitudinal follow-up are recommended to better elucidate the temporal relationship between GERD and persistent cough in infants.

CONCLUSIONS

Gastroesophageal reflux disease exhibited a noteworthy and statistically significant correlation with the occurrence of persistent cough in the population of infants studied, suggesting a potential underlying

pathophysiological relationship that warrants further investigation into the mechanisms by which this gastrointestinal disorder may contribute to respiratory symptoms in this vulnerable age group.

Authors' Contribution

Conceptualization: SA

Methodology: SJA, BZ

Formal analysis: AML, SJA, SJ

Writing and Drafting: SA, AML

Review and Editing: SA, AML SJA, SJ, SA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Original Article



Association of Xerostomia with Diabetes a Cross Sectional Study in Subset of Karachi

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ABSTRACT

Xerostomia, is a common oral symptom of Diabetic Mellitus (DM). It has a detrimental impact on clinical procedures and outcomes due to decreased saliva. Considering its impact on oral cavity and dental procedures it is important to identify the Association of xerostomia with diabetes.

Objective: To identify the prevalence and association of xerostomia in diabetic patients subset of Karachi. **Methods:** It was a cross sectional study conducted from January 2024 to October 2024. The calculated sample size was 63 which was increased to 75. Patients reporting to OPD with history of diabetes were recruited and they were advised to get their HbA1c and random blood sugar level (RBS) checked. After getting their HbA1c and RBS reports their stimulated salivary flow rate was calculated. Stimulated salivary flow less than 0.7ml/min was considered as low. Chi square and independent t-test was applied for comparison at 95% confidence interval and p value less than 0.05 was considered as significant. **Results:** The xerostomia was found to be present in 47 (62.66%) participants. The salivary flow was identified as 0.46 ± 0.31 in diabetic patients with xerostomia, compared to female, male diabetic patients had less salivary flow at 7.01 ± 0.62 HbA1c and 220.53 ± 5.12 RBS. **Conclusions:** There was 62.66% prevalence in diabetic patients in the recruited subset of Karachi. Males had more prevalence than females. Higher HbA1c and RBS levels were associated with the presence of xerostomia.

INTRODUCTION

Dry mouth, or xerostomia, is a common oral symptom of Diabetic Mellitus (DM) [1]. Compared to the non-diabetic population, xerostomia has been documented as one of the common symptoms in people with type 1 and type 2 diabetes, which has a substantial negative influence on oral health and quality of life [2]. The prevalence of xerostomia in diabetics has been documented as 12.5% to 53.5% depending on the hyperglycemic profile of the individual with the diabetes. According to one study, xerostomia was reported by 43% in diabetes patients, with a greater

prevalence in women [3]. Age, type of diabetes, and length of illness do not seem to have a major impact on prevalence, while some data have pointed to a link between worse glycemic control and longer disease duration [4]. The Oral manifestations of xerostomia are diverse and clinically significant, and they have a considerable impact on how well dental and medical therapies work. Common symptoms of xerostomia include thick, stringy saliva, frequent thirst, a dry or sticky feeling in the mouth, and trouble speaking, chewing, swallowing, and tasting food.



These symptoms have been reported to cause dietary modifications and nutritional deficiencies [5]. Xerostomia diminishes the Saliva's cleansing and buffering properties which leads to a rise in cariogenic bacteria, a decrease in oral pH, and an increase in plaque accumulation. These factors significantly increase the risk of dental caries, particularly along the cervical margins, root surfaces, and under crown margins, as well as periodontal disease and dentinal hypersensitivity [6]. Additionally, Xerostomia can exacerbate oral pain and discomfort by predisposing individuals to recurrent oral infections, particularly oral candidiasis, which can manifest as burning mouth syndrome, angular cheilitis, geographic tongue, or white plaques. While a lack of salivary mucins hinders wound healing and defense against toxins and pathogens, the friability of the mucous membranes increases the risk of aphthous ulcers, mucositis, and traumatic lesions [7]. Xerostomia has a detrimental impact on clinical procedures and outcomes due to decreased saliva, which degrades natural oral defenses and complicates restorative and prosthetic dental treatments [8]. In dental implantology, dry mouth increases the risk of infection and implant failure due to weakened oral health and healing ability. For denture wearers, xerostomia reduces denture retention, stability, and comfort, needing unique denture design adjustments as well as the use of adhesives or lubricants to enhance fit and prevent mucosal damage. Additionally, patients with xerostomia may have discomfort, difficulty eating, swallowing, and speaking, which can impair cooperation during treatments and have a detrimental impact on long-term results [9, 10]. Assessing xerostomia in diabetic patients prior to dental procedure is critical because xerostomia, caused by hyperglycemia-induced dehydration, microvascular damage, and neuropathy, greatly impacts oral health and quality of life. Saliva is essential for lubricating oral tissues, neutralizing acids, and avoiding tooth decay, mucosal infections, and biofilm buildup. Xerostomia increases the risk of oral ulcers, periodontal disease, difficulties chewing and swallowing, and delayed wound healing, all of which can complicate dental treatments and recovery. Early detection and management of xerostomia in diabetics can help prevent these issues, resulting in safer and more effective dental care outcomes [11, 12].

Xerostomia is frequently reported among patients with diabetes mellitus; however, the reported prevalence varies widely across different populations and clinical settings. Although international studies have demonstrated an association between poor glycemic control and reduced salivary flow, region-specific data from Karachi remain limited. Furthermore, few local studies have objectively measured stimulated salivary flow alongside HbA1c and RBS levels to establish a clear clinical correlation. This gap

highlights the need to evaluate the prevalence and metabolic association of xerostomia among diabetic patients in the local population. Considering the importance of saliva for dental procedures and prostheses it is important to document the prevalence and association of xerostomia according to the disease pathogenesis of community hence the study aims to identify the prevalence and association of xerostomia in diabetic patients of Karachi so that they can be offered treatments with good outcome with least failure due to xerostomia.

METHODS

It was a cross sectional study conducted at Department of Oral and Maxillofacial Surgery of Abbasi Shaheed Hospital and Karachi Medical and Dental Colleges from January 2024 to October 2024. The study was approved by the ERB of the Karachi Medical and Dental Colleges, Abbasi Shaheed hospital (Ref no: 16/22). The sample size was estimated by using sealed envelope software keeping the prevalence of diabetes at 21% at 95% confidence interval and 5% margin of error [3]. The calculated sample size was 63 which was adjusted to 75. Patients reporting to OPD with history of dry mouth who given written consent to participate in the study were selected by convenient sampling technique and they were advised to get their HbA1c and Random Blood Sugar level (RBS) checked. Their demographic data were taken from the hospital standard OPD form. Patients with HbA1c greater than 6.5, RBS greater than 180 mg/dl without and mental disability and drug history (except diabetes) were included in the study. Patients on hormonal therapy, taking steroids, and with history of cancer or chemotherapy and those who did not consent to participate in the study were excluded. After getting their HbA1c and RBS reports their stimulated salivary flow rate was calculated. Briefly, the salivary flow measurement to be performed by having patients sitting comfortably and asking patient to chew sterile wax for 5 minutes and with the head slightly tilted forward asking the patient to spit in the measuring cup. All patients who used dental prostheses were required to remove them during measurement before testing the stimulated saliva, and to rinse their mouth for 1 minute before sampling, and then their oral cavity was evaluated to ensure no possibility of substances were in their oral cavity. The saliva produced during a period of 1 minute was collected and measured in a container. The volume of salivary flow was calculated in ml/min (millimeter per minute). The patient was instructed not to swallow any amount of saliva that is being produced. Stimulated salivary flow less than 0.7ml/min was considered as low [13]. All the observations were performed by the primary investigator of the study. Statistical analysis was done by using SPSS version 24.0. Frequency and percentages were calculated to identify the

prevalence of xerostomia. Chi square analysis was performed for finding the association between presence of xerostomia and population gender. Independent t-test was applied for comparison of mean between the groups at 95% confidence interval and p value less than 0.050 was considered as significant.

RESULTS

The 75 selected patients had a mean age of 52.43 ± 6.25 years. There were 43 (57.33%) male and 32 (42.67%) were female participants. The males had the mean age of 48.21 ± 5.61 and females had 52.27 ± 6.36 . The xerostomia was found to be present in 47 (62.66%) participants. Figure 1 presents the presence of xerostomia in male and female participants.

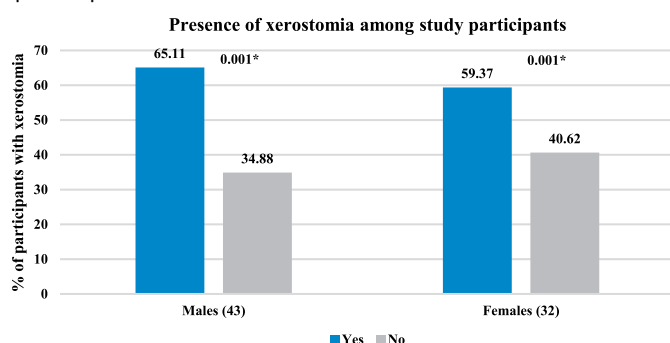


Figure 1: Percentage of Xerostomia Among the Study Population

*Significant p-Value

The salivary flow was identified as 0.46 ± 0.31 in diabetic patients with xerostomia, compared to female, male diabetic patients had less salivary flow at 7.01 ± 0.62 HbA1c and 220.53 ± 5.12 RBS. When the salivary flow, HbA1c and RBS were compared between presence and absence of xerostomia a significant difference was identified. Table 1 shows the Comparison of salivary flow, HbA1c and RBS between patients with and without xerostomia.

Table 1: Comparison of Salivary Flow, HbA1c and RBS Between Patients with and without Xerostomia (n=75)

Total Participants			
Variables	With Xerostomia Mean $\pm$ SD	Without Xerostomia Mean $\pm$ SD	p-Value
Salivary Flow	0.46 ± 0.31	1.21 ± 0.28	0.042
HbA1c	7.62 ± 1.21	6.8 ± 0.96	0.033*
RBS	231.18 ± 8.93	192.11 ± 10.31	0.001*
Male			
Salivary Flow	0.41 ± 0.33	0.99 ± 0.38	0.049*
HbA1c	7.01 ± 0.62	6.7 ± 0.9	0.032*
RBS	220.53 ± 5.12	190.6 ± 6.66	0.051
Female			
Salivary Flow	0.48 ± 0.19	0.67 ± 0.22	0.071
HbA1c	7.12 ± 0.80	6.9 ± 0.5	0.912
RBS	224.51 ± 6.17	199.33 ± 8.23	0.015*

*Significant p-value

The salivary flow was identified as 0.46 ± 0.31 in diabetic

patients with xerostomia, compared to female male diabetic patients had less salivary flow at 7.01 ± 0.62 HbA1c and 220.53 ± 5.12 RBS. When the salivary flow, HbA1c and RBS were compared between presence and absence of xerostomia a significant difference was identified. Table 1 shows the Comparison of salivary flow, HbA1c and RBS between patients with and without xerostomia.

DISCUSSION

Xerostomia is a common and serious consequence often seen in people with diabetes mellitus. In current study the prevalence of xerostomia was found to be 62.66%, which is found to be in range of previously published research, that states prevalence of xerostomia in DM patients varies greatly, ranging from 12.5% to 76.4% [14-16]. This variation in the results has been attributed to variations in the populations under study, patient ages, the types of diabetes mellitus, and the various approaches used to evaluate xerostomia [3]. Furthermore, it has been documented that diabetes-related xerostomia has a complex pathophysiology that includes dehydration from osmotic diuresis, autonomic neuropathy, microvascular abnormalities, and changes in salivary gland function brought on by chronic hyperglycemia. Research has repeatedly shown that, in comparison to healthy controls, diabetes patients have decreased resting and stimulated salivary flow rates. Additionally, it has been documented that the type of diabetes (type 1 or type 2) has no discernible effect on xerostomia; nonetheless, it has been shown that the duration of the disease matters for both types. Xerostomia is more likely to occur in patients with a prolonged history of diabetes. The symptoms like mucosal dryness, such as ocular and vaginal dryness, frequently accompany xerostomia in diabetes patients, indicating a more extensive systemic involvement of exocrine glands that may be connected to autonomic neuropathy. The dysregulation of salivary gland nitric oxide synthase enzymes and their cofactors, which are essential for preserving normal glandular function, may be one of the underlying molecular precursors of xerostomia in diabetic patients [6, 17]. In the current study we males (65.11%) were found to have greater prevalence than females (59.37%), which is contrary to documented literature. Over the past five years, several studies have consistently shown that xerostomia is more common in women. This is frequently explained by hormonal factors like menopause, which alter salivary gland function and enhance women's complaints of dry mouth. A research published in 2022 found that 61.2% of xerostomia cases were in females as opposed to men, with a similar incidence throughout age groups but a definite overall female preponderance [18]. Similarly, in 2023 research of older persons revealed that xerostomia was much more common in women than in men, with a prevalence ratio of 1.44. The study linked this to

characteristics including depression, arthritis, and polypharmacy, which are more common in women and lead to symptoms of dry mouth [19]. Numerous reasons may have contributed to the current study's reversal of this trend, which indicates a greater incidence among men. First, this discrepancy may be caused by population-specific characteristics including lifestyle, genetic background, and environmental conditions. Second, prevalence estimates and gender comparisons may be impacted by methodological variations such as sample makeup, age distribution, and data collecting methods (e.g., self-reported questionnaires vs clinical examinations). Diabetes mellitus greatly decreases salivary gland function, resulting in hyposalivation and the subjective impression of dry mouth [17]. This is supported by the reported salivary flow rate of 0.46 ± 0.31 ml/min in diabetic individuals with xerostomia. Because saliva is essential for digesting, mouth lubrication, antibacterial defense, and mucosal integrity, this decrease in salivary flow is a major cause of xerostomia [20]. Interestingly, the findings showing that male diabetes patients had reduced salivary flow and a higher HbA1c level (7.01 ± 0.62) and Random Blood Sugar (RBS) of 220.53 ± 5.12 mg/dL points to a clear correlation between poor glycemic management and decreased salivary secretion. Diabetes-related hyperglycemia causes autonomic neuropathy and microvascular damage to the salivary glands, which lowers saliva production [21, 22]. This is in line with other research that found a correlation between higher HbA1c and higher prevalence of xerostomia and lower salivary flow. Despite having higher glycemic indices, men exhibit less salivary flow. This gender difference might be due to differences in the severity of the illness, medication use, or lifestyle choices like smoking and drinking alcohol, which are known to worsen salivary gland dysfunction [23]. With the finding of the prevalence of xerostomia in the diabetic individuals the current study highlights the need of conducting more multicentric studies with larger sample size to generalize the findings as in the current research findings are limited to a single center data and smaller sample size. Furthermore, the study recommends that the salivary flow method used to assess the xerostomia should be taught to all dental graduates to prevent the complications of the procedures associated with xerostomia.

This study was limited by its single-center design and relatively small sample size, which may restrict the generalizability of the findings. The use of convenient sampling and absence of a non-diabetic control group may also limit broader comparison. Additionally, long-term follow-up and assessment of duration of diabetes were not included, which could influence salivary gland dysfunction. Future multicenter studies with larger cohorts, inclusion of control groups, and longitudinal evaluation of glycemic control and salivary parameters are recommended to

strengthen evidence and improve clinical applicability.

CONCLUSIONS

There was 62.66% prevalence in diabetic patients in the recruited subset of Karachi. Males had more prevalence than females. Higher HbA1c and RBS levels were associated with the presence of xerostomia among study population.

Authors' Contribution

Conceptualization: NUA, AKH

Methodology: NUA, AKH

Formal analysis: GMP, PR, SZA

Writing And Drafting: NUA, AKH, GMP, PR, SZA

Review and Editing: NUA, AKH, GMP, PR, SZA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Head and Neck Cancer Reconstruction with or without Internal Lining Using Various Flaps in a Tertiary Care Hospital

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ABSTRACT

Reconstructive surgeries of the head and neck with or without the use of internal lining must be thoroughly evaluated for post-operative complications and functional outcomes unclear phrasing. **Objectives:** To compare the surgical outcomes, complication rates, and functional outcomes of head and neck cancer reconstruction surgeries performed with or without internal lining using various flap techniques in a Tertiary Care Hospital setting. **Methods:** This one-year prospective comparative study at Al-Tibri Medical College included 139 head and neck cancer patients undergoing resection and reconstructive surgery with or without internal lining. Data on demographics, tumor, surgical, and postoperative outcomes were analyzed using SPSS version 23.0, applying appropriate statistical tests with significance set at $p < 0.050$. **Results:** From 139 patients, operative time was significantly longer in Group A (with flap and internal lining) than in Group B ($p < 0.001$). Postoperative complications were more common in Group A, with higher rates of wound infection (15.7% vs. 5.8%, $p = 0.040$) and overall complications (28.6% vs. 11.6%, $p = 0.010$). Functional outcomes favored Group B, with significantly better swallowing (82.6% vs. 55.7%, $p = 0.007$) and speech intelligibility (79.7% vs. 60%, $p = 0.040$). Hospital stays over 7 days were more common in Group A (35.7% vs. 14.5%, $p = 0.009$). The need for secondary intervention was higher in Group A, but not statistically significant. Overall, Group B demonstrated fewer complications and better postoperative functional recovery. **Conclusions:** Head and neck reconstruction without internal lining resulted in fewer complications, shorter hospital stay, and better functional recovery than reconstruction with internal lining. Careful patient selection can optimize outcomes and surgical efficiency.

INTRODUCTION

According to the global ranking, head and neck cancers rank as the seventh most common cancers. They are reported with various groups of tumors, and mainly include the aero-digestive tract. Head and neck cancers are still a challenge to manage, and require an extensive multidisciplinary approach to treat advanced levels of disease, like surgical techniques, systemic approach and radiotherapy. Generally, the treatment is based on two key

components, such as site-specific or histology-specific. Further studies are required to explore the strategies for the management of such advanced diseases and reduce the rate of complications [1]. Head and neck cancers create a specific health burden globally, and even with advanced management and techniques, the mortality and morbidity rates are significant [2]. Head and neck reconstructive procedures followed by new advanced methods have an

impact on patient outcomes, specifically single-stage restoration of a massive area, including mucosal lining of the oral cavity to pharyngeal and esophageal region. The reconstruction approach depends on either maintaining the structural integrity or simply restoring function. According to recent studies, a specific algorithm provides better outlines for reconstruction procedures with improved patient outcomes [3]. Reconstructive surgeries using free tissue relocation of a specially pectoralis major flap with or without internal lining must be guideline specific to achieve a positive outcome. The functional outcomes include breathing, swallowing, vocalization and mastication [4]. Moreover, among the young population and especially females, cosmetic appearance after reconstructive surgeries is one of the considering factors. With the advancements in surgical procedures, reconstructive surgeries of the head and neck region using flaps either with or without internal lining have now become the first line of treatment [5]. It can aid in improving both the cosmetic and functional aspects using tissues from various sites (having similar features to the defective site) [6]. The use of flaps in reconstructive head and neck surgeries is being reported increasingly, with a success rate of 95 to 98 % cases [7]. Literature reports that as high as 97 % of head and neck reconstructive cases require flaps for recovering from deficits and restoration of the underlying structures [8]. In around 20 to 30 % of head and neck cancers, recurrence takes place at the primary tumor site, causing failure of reconstructive surgeries in the majority of cases [9]. It remains a challenging task where recurrence takes place after surgery. In such cases, the options for treatment are chemotherapy, salvage surgery, palliative care, radiation and/or a combination of any two from them [10]. The basic purpose is to repair the malignant regions and make it less invasive, with maximum restoration of other healthy tissues and underlying structures. Presently, for reconstructive surgeries, micro-vascular transfer of free tissue in the region of the head and neck is the most common [11]. Head and neck reconstruction is a very complex process. The range of reconstruction varies from simple lining defects to complex defects that involve bone and soft tissue [12]. However, one of the most important aspects of reconstructive surgery, the success rate depends on how early the disease is diagnosed and a proper management plan accordingly [13]. An early presentation along with TNM stage is low reconstruction will be easier in comparison to patients that present late or with advanced TNM stage of cancer, causing difficult and challenging reconstruction with an extensive invasive procedure [14]. Patients' cosmetic requirements and fitness for major surgery are key aspects for successful reconstruction of head and neck surgeries using flaps [15]. In this way, optimal

functional as well as aesthetic outcomes are achieved [16]. The use of free flaps helps in providing a more reliable wound coverage with a better functional outcome, with superior cosmetic and minimal morbidity of the donor site [17]. Depending upon the site of size and composition of the recipient's defects, various free flaps are used. In addition, the preference of both patient and surgeon and the expertise of the surgeon are of paramount importance [18]. Flaps from perforators have gained rapid popularity because of their main benefits, which spare the underlying muscle, resulting in reduced morbidity of the donor site and possibly improving outcomes aesthetically [19]. Regarding the choice of flaps, most surgeons tend to prefer small soft tissue and lining defects, while larger defects of soft tissue have a complex, composite variety requiring reconstruction of bone as well [20].

Head and neck cancer reconstruction following tumor resection is a complex surgical process aimed at restoring both functional and aesthetic outcomes. Various flap techniques, with or without internal lining, are used to repair defects; however, the choice of technique can significantly influence postoperative complications and patient recovery. Despite advances in reconstructive surgery, there remains limited comparative evidence regarding the effectiveness of reconstruction with versus without internal lining in terms of functional outcomes and complication rates. Furthermore, data from tertiary care settings in developing countries are scarce, highlighting the need for studies that evaluate these approaches in local clinical practice. This study aimed to compare the surgical outcomes, complication rates, and functional results of head and neck cancer reconstruction performed with or without internal lining using various flap techniques in a tertiary care hospital setting.

METHODS

This prospective comparative study was carried out at the Department of Ear, Nose and Throat (ENT) of multiple tertiary care hospitals for a period of one year (from June 2024 to May 2025). Ethical approval was obtained from the IRB of Al-Tibri Medical College and Hospital, IERC/ATMC/14(01-2024)/50. Using a purposive sampling technique, patients that undergoing cancer resection in the region of the head and neck, which followed reconstructive surgery either with or without internal lining using various flap techniques, were included in the study. Patients above the age of 18 years of either gender, with confirmed head and neck cancer (histopathologically) that require surgical excision along with reconstruction. For the reconstruction technique, free, regional or local flaps were used. In addition, patients having a complete medical record and follow-up data were included in the research. Patients having incomplete operative or clinical data, with

recurrent cancer needing salvage surgery, and patients who were lost to follow-up after surgery were excluded from the research. The sample size was calculated using the Open EPI freely available online software for sample size calculation. Using a 95% confidence level and 5% margin of error, and frequency of complications rates from head and neck reconstructive surgeries at 10 % as reported in a study, the sample size came out to be 139 [21]. Patients were divided into two groups (A and B), group A including patients undergoing reconstruction with internal lining, while group B included patients who underwent reconstruction without internal lining. For data collection, patient consent was taken, and a self-designed questionnaire was used. Collected data included demographics such as age, gender, smoking status and co-morbidities. In terms of tumor characteristics, the site, size and TNM staging were recorded. Type of resection and flap used (free, local or regional), operative time and whether internal lining was used were also recorded. Post-operative complications included necrosis of the flap, dehiscence of the wound or infection. Functional outcomes included swallowing or speech, duration of hospital stay and any need for revision of surgery. The measure of outcomes included primary outcomes such as the rate of complication and survival of flap in both groups, while secondary outcomes included recovery of function, duration of hospital stay and any need for secondary intervention. Data analysis was carried out using SPSS version 23.0. Mean and standard deviation were reported for continuous variables after testing of data normality. Data were compared by applying the Student's t-test or Mann-Whitney U test as appropriate. Frequency and percentages were reported for categorical variables and were tested using chi-square or Fisher's exact test for comparison. A p-value of <0.050 was taken as statistically significant.

RESULTS

The study presents the baseline demographic and clinical characteristics of the study population. The mean age of patients was comparable between the two groups (54.2 ± 11.3 years in Group A vs. 53.7 ± 10.8 years in Group B, $p=0.780$). There was no significant difference in gender distribution, smoking status, or presence of co-morbidities between the groups. Tumor characteristics, including site, size, and TNM stage, were also similar across both groups. The most common tumor site was the oral cavity in both groups, followed by the oropharynx. Segmental mandibulectomy was the most frequently performed resection type in both groups, with no statistically significant difference ($p=0.770$). In Group A, flap types included free (54.3%), local (28.6%), and regional (17.1%) flaps. Operative time was significantly longer in Group A than Group B (6.5 ± 1.2 vs. 5.1 ± 1.0 hours, $p<0.001$) (Table 1).

Table 1: Demographic Information and History of Patients

Variables		Group A (n=70)	Group B (n=69)	p-value
Age (Years)	—	54.2 ± 11.3	53.7 ± 10.8	0.780
Gender	Male	50 (71.4%)	47 (68.1%)	0.670
	Female	20 (28.6%)	22 (31.9%)	
Smoking Status	—	28 (40%)	27 (39.1%)	0.910
Co-Morbidities	—	30 (42.9%)	31 (44.9%)	0.820
Tumor Site	Oral Cavity	40 (57.1%)	38 (55.1%)	0.960
	Oropharynx	18 (25.7%)	19 (27.5%)	
	Others	12 (17.1%)	12 (17.4%)	
Tumor Size (cm)	—	3.8 ± 1.1	3.7 ± 1.0	0.640
TNM Stage	T3	39 (55.7%)	41 (59.4%)	0.680
	T4	31 (44.3%)	28 (40.6%)	
	N0	53 (75.7%)	50 (72.5%)	
	N1	17 (24.3%)	19 (27.5%)	
Type Of Resection	Segmental Mandibulectomy	44 (62.9%)	45 (65.2%)	0.770
	Composite Resection	26 (37.1%)	24 (34.8%)	
Flap Type	Free	38 (54.3%)	—	—
	Local	20 (28.6%)	—	
	Regional	12 (17.1%)	—	
Operative Time (Hours)	—	6.5 ± 1.2	5.1 ± 1.0	<0.001*

Results outline the postoperative complications following head and neck reconstructive surgery. Flap necrosis occurred in 8.6% of patients in Group A. Wound dehiscence was observed in 11.4% of Group A and 5.8% of Group B patients ($p=0.240$). Wound infection was significantly more common in Group A (15.7%) than in Group B (5.8%) ($p=0.040$). The overall complication rate was significantly higher in Group A (28.6%) than in Group B (11.6%) ($p=0.010$) (Table 2).

Table 2: Post-Operative Complications After Head and Neck Reconstructive Surgery (n=139)

Complications	Group A (n=70)	Group B (n=69)	p-value
Flap Necrosis	06 (8.6%)	—	—
Wound Dehiscence	08 (11.4%)	04 (5.8%)	0.240
Wound Infection	11 (15.7%)	04 (5.8%)	0.040*
Any Complication	20 (28.6%)	08 (11.6%)	0.010*

Findings summarize the functional outcomes at follow-up. Unimpaired swallowing was reported in 55.7% of Group A than 82.6% of Group B ($p=0.007$). Good speech intelligibility was achieved in 60% of Group A versus 79.7% of Group B patients ($p=0.040$). Hospital stays longer than 7 days were significantly more common in Group A (35.7%) than in Group B (14.5%) ($p=0.009$). The need for secondary intervention was higher in Group A (11.4%) than in Group B (4.3%), although this difference did not reach statistical significance ($p=0.130$) (Table 3).

Table 3: Functional Outcome of Patients After Head and Neck Reconstructive Surgery (n=139)

Functional Outcomes	Group A (n=70)	Group B (n=69)	p-value
Swallowing Unimpaired	39 (55.7%)	57 (82.6%)	0.007 *
Speech Intelligibility (Good)	42 (60%)	55 (79.7%)	0.04 *
Hospital Stay >7 Days	25 (35.7%)	10 (14.5%)	0.009 *
Secondary Intervention Required	08 (11.4%)	03 (4.3%)	0.130

DISCUSSION

In this study of 139 patients, baseline demographics, smoking status, co-morbidities, and tumor characteristics were somewhat similar between groups. Operative time was significantly longer in Group A (with flap and internal lining) than in Group B ($p < 0.001$). Postoperative complications were more common in Group A, with higher rates of wound infection (15.7% vs. 5.8%, $p = 0.040$) and overall complications (28.6% vs. 11.6%, $p = 0.010$). Functional outcomes favoured Group B, with significantly better swallowing (82.6% vs. 55.7%, $p = 0.007$) and speech intelligibility (79.7% vs. 60%, $p = 0.040$). Hospital stays over 7 days were more common in Group A (35.7% vs. 14.5%, $p = 0.009$). The need for secondary intervention was higher in Group A, but not statistically significant. Overall, Group B demonstrated fewer complications and better postoperative functional recovery. In line with our research, the published literature that has compared head and neck reconstructive surgeries with or without internal lining has reported similar results [22]. In our research, an operative time was reported in our study in group A (with internal lining). Similarly, in other studies, a prolonged operative time was observed with internal lining due to the use of additional tissue preparation and setting [23]. In addition, higher rates of complication (especially wound dehiscence and infection) were reported in more extensive reconstructions (with flap) as than those without a flap. Literature also states similar findings, the possible reason behind higher rates of complications due to surgery-induced trauma and a higher risk of ischemia [24]. By the conclusion of some studies, similar findings were found in the present study. With regards to the functional outcomes such as swallowing and speech, reconstruction was easier when surgery was simple, provided the defect was adequately closed without internal lining [25]. In line with our study, longer duration of hospital stay was reported in other research as well, since internal lining flap procedures needed a more complex approach [26]. Moreover, the functional outcomes are only assessed for short-term follow-ups (one month), not reflecting long-term recovery. Furthermore, the varying expertise of surgeons and perioperative care might have influenced the outcomes. For patient safety, we need to work for early and proper diagnostic criteria.

This study has several limitations, including its relatively short follow-up period, which restricts the assessment of long-term functional and oncological outcomes. Additionally, variations in surgical expertise, flap selection, and perioperative care across centers may have influenced the results. The sample size and purposive sampling technique may also limit the generalizability of the findings. Future multicenter studies with larger cohorts and longer follow-up durations are recommended to better evaluate long-term functional recovery, quality of life, and optimal reconstructive strategies for head and neck cancer patients.

CONCLUSIONS

This study demonstrated that head and neck reconstructive surgery without the use of internal lining is associated with reduced operative time, postoperative complications, and better functional outcomes than reconstruction with internal lining. While flap survival rates in Group A were acceptable, the higher rates of wound infection, longer hospital stay, and reduced swallowing and speech function highlight the need for careful patient selection and technique optimization when using internal lining. Reconstruction without internal lining may be a preferable option in suitable cases, balancing surgical efficiency with improved postoperative recovery. Further prospective studies are warranted to confirm these findings and guide reconstructive decision-making.

Authors' Contribution

Conceptualization: MRD
 Methodology: MRD, ZA, VKK, GSM, AW
 Formal analysis: MRD, GSM, AW
 Writing and Drafting: ZA, VKK, ABM
 Review and Editing: ZA, VKK, ABM, MRD, GSM, AW

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Acceptance of Post-Partum Intrauterine Contraceptive Device During Cesarean Section

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ABSTRACT

The world population is increasing, and approximately 115 million women have unmet needs for family planning. Institutional deliveries are increasing. Institutional deliveries and cesarean sections provide an excellent opportunity to provide women with a long-term, safe, effective and reversible method of contraception in the form of Post-Partum Intrauterine Contraceptive Device (PPIUCD). **Objective:** To assess the acceptability of PPIUCD as a method of family planning. **Methods:** A descriptive cross-sectional study was conducted on patients undergoing elective or emergency cesarean sections (C-section) in the Department of Obstetrics and Gynaecology, Social Security Teaching Hospital, Multan Road, Lahore. 116 women were counselled, and in those who opted for it, an IUCD was placed inside the uterus after delivery of the placenta during C-section. This study set 95% confidence (Z=1.96) expected prevalence p from prior literature/pilot, and a conventional margin of error d=0.05 (typical range 0.03–0.05). Where applicable, the study applied finite population correction, then inflated for design effect (if clustered) and 10% nonresponse. **Results:** Total acceptance rate was 38.79%. The majority of the patients belonged to the age group 19 to 30 years, and the mean age was 30.42 ± 5.28 years. Parity was >2 in 56.9% patients, while in 43.1% parity was ≤2. 24.14% clients were uneducated, and 76.72% belonged to a poor socio-economic group. **Conclusions:** PPIUCD as inserted during cesarean section is an effective, acceptable and safe method of contraception, with the rate of acceptance of 38.79%. Previous cesarean history and proper counselling enhance acceptance.

INTRODUCTION

The world population is 8.2 billion. China and India are at the top with approximately 1.43 billion each, Pakistan is on No. 5 with a population of 250 million, according to world population meter. Pakistan's population is equivalent to 3% of the total world's population, out of which 35% are residents of urban areas [1]. The average life expectancy in Pakistan is around 67 years; a very high rate of infant mortality is noted, which is estimated to be around 55.8 deaths per 1,000 live births [2]. The population size in the urban areas is high, with 35% of the urban residents residing in urban centers, and this poses unique difficulties to family planning and reproductive health care services. This renders the immediate deployment of effective

contraceptive measures all the more imminent, especially taking into consideration the steep numbers of unwanted pregnancies associated with socio-economic issues like illiteracy and poverty [3]. Traditionally, contraception after birth is advised to start in six weeks after birth; though there has been a growing case to start the use of long contraceptives like the Postpartum Intrauterine Contraceptive Device (PPIUCD) immediately after childbirth, especially during cesarean section. The PPIUCD has been identified to be safe, highly effective, cost-efficient and breastfeeding compatible, thus strongly recommended to women during the postpartum phase [4, 5]. It is reported that short-term insertion immediately after



cesarean birth is not only a form of prevention of unintended pregnancy but is also more effective in terms of the provision of long-term contraceptives to postcesarean women [6]. Moreover, studies indicate that tolerance of PPIUCDs in cesarean sections is known to correlate with high retention rates and satisfaction of users [7, 8]. Although the use of PPIUCD insertion is beneficial, there has been a downright lack in acceptance; hence the need to explore the areas that play an important role in the outcome of whether women will accept or not [9]. The counselling and education of healthcare providers are very important factors that determine whether a woman will use PPIUCDs during postpartum visits. Evidence suggests that engaged attention and interactive counselling play a huge role in increasing the acceptance of PPIUCDs among women [10, 11]. Additionally, socio-economic factors like level of education and prior usage of contraceptives also play a critical role in DFP by women since it has been observed that the more learning a woman acquires, the greater is the acceptance rate of the PPIUCD [12]. Along with personal and socio-economic factors, there are certain issues specifically connected with cesarean sections that do not favor the introduction of PPIUCDs. The significant aspect of the surgery of a cesarean section may be observed with mothers showing more willingness and interest in the employment of contraceptive techniques since this is the time when they can be introduced to effective family planning techniques right after delivery [13]. It is noteworthy that a significant number of women do not know about the safety and effectiveness of PPIUCDs during breastfeeding, and the problem of a misguiding culture, which does not allow women to make informed decisions regarding the choice of contraceptive, is also widespread [14]. Therefore, a fundamental training of healthcare providers on counselling strategies and the elaboration of the education outreach are the key measures to increase PPIUCD acceptance rates [15, 16].

Despite the proven safety and effectiveness of Post-Partum Intrauterine Contraceptive Devices (PPIUCD), their utilization during cesarean section remains suboptimal in many low- and middle-income countries, including Pakistan. Although institutional deliveries are increasing, opportunities for immediate postpartum contraception are often underutilized. Local data exploring acceptance rates and associated demographic and obstetric factors remain limited, particularly in public sector hospitals. This gap highlights the need to assess acceptance patterns to inform targeted counselling and policy interventions. This study aims to elucidate the acceptance rate of PPIUCDs during cesarean sections, contributing to enhanced family planning outcomes and improved maternal health in Pakistan.

METHODS

This was a descriptive cross-sectional study conducted during November 2019 to March 2020 in the Department of Obstetrics and Gynaecology, Social Security Teaching Hospital, Multan Road, Lahore. Ethical clearance was obtained from the ethical committee of the Social Security Teaching Hospital, Multan Road, Lahore (No.10/19). The study population was 116 full-term antenatal women attending labor room and undergoing elective or emergency cesarean section. $n = Z^2 P(1-P)/d^2$ [17]. $n=116$, n = required sample size, $Z=95\%$ confidence interval (1.96), P = prevalence (27.2%) [18] and d = margin of error (8.1%). Informed Consent was taken before counselling. Patients were counselled about PPIUCD on three occasions: 1. During the antenatal period, 2. At their admission to labor ward and 3. Before going to the operating theatre for elective or emergency cesarean section. All antenatal women admitted for delivery in our hospital were instructed for PPIUCD. Women in the reproductive age group, i.e. 18-44 years of age, Gestational age 36 to 40 weeks, undergoing elective or emergency cesarean section, after counselling, who opted for PPIUCD with no history of infections, Hb >8gm/dl and AMTSL universally provided after delivery of the baby were included in the study. While women having fever during labor, having active STD or high risk for STD, lower genital tract infection, ruptured membranes for >18 hours before cesarean section, uterine abnormalities e.g., Bicornuate uterus, septate uterus, fibroid uterus distorting uterine cavity, unresolved postpartum hemorrhage, uterine atony and patients who refused for PPIUCD were excluded from the study. Following delivery of the placenta uterine cavity was inspected for the presence of malformations. The IUCD was removed from the insertion sleeves. The uterus is stabilized by grasping it at the fundus. IUCD is held between the middle and index fingers. It was inserted inside the uterus through a uterine incision and released at the fundus of the uterus. The hand was removed slowly and carefully from the uterus, not to dislodge the IUCD. Enough care was taken not to include IUCD strings during uterine closure. The IUCD client card was filled out afterwards, showing the type of IUCD and the date of insertion. She was informed again of the side effects of the IUCD and about the normal postpartum period. Follow-up visit for IUCD planned, written on the card and informed to the patient. At the time of discharge, she was asked about any queries about IUCD and to report to the hospital at any time if she had: foul-smelling vaginal discharge, Severe lower abdominal pain, fever, chills or feeling of being unwell, Suspicion of pregnancy or Suspicion of IUCD expelled. The data were entered and analyzed using IBM SPSS version 26.0. The continuous variables are expressed as Mean $\pm$ SD,

whereas the categorical variables are in the form of frequencies and percentages.

RESULTS

A total of 116 women were included in the study. The mean age of women was 30.42 ± 5.28 years. 80 (68.97%) women were 19 to 30 years of age, and 36 (31.03%) women were 31 to 40 years of age. 28 (24.14%) women were uneducated, 66 (56.90%) had primary to intermediate level of education, and 22 (18.97%) had bachelor's or higher level of education. Parity was ≤ 2 in 50 (43.10%) women and > 2 in 66 (56.90%) women. Among all the women, 89 (76.72%) had low socioeconomic status, and 27 (23.28%) had middle socioeconomic status, Table 1.

Table 1: Baseline Details of All Patients

Characteristics	Frequency (%), Mean $\pm$ SD
Mean Age (Years)	30.42 $\pm$ 5.28
Age (Years)	
19 to 30	80 (68.97%)
31 to 40	36 (31.09%)
Education	
Uneducated	28 (24.14%)
Primary to Intermediate	66 (56.9%)
Bachelor's or Higher Level	22 (18.97%)
Parity	
≤ 2	50 (43.1%)
> 2	66 (56.9%)
Socio-Economic Status	
Low	89 (76.72%)
Middle	27 (23.28%)

Among the study population, 33 (28.45%) patients had a history of one previous Cesarean section, 45 (38.79%) had previous two Cesarean sections, 17 (14.66%) had previous 3 Cesarean sections, and 21 (18.10%) had previous normal vaginal deliveries, Table 2.

Table 2: Previous History of C-Sections

Previous History of C-section	Frequency (%)
1	33 (27.45%)
2	45 (38.79%)
3	17 (14.66%)
SVDs	21 (18.1%)

Among all the included patients, the acceptance rate of PPIUCD was 45 (38.79%), while 71 (61.21%) women refused to adopt the IUCD method for contraception due to different reasons, Figure 1.

Acceptance Rate of PPIUCD

■ Acceptance Rate of PPIUCD

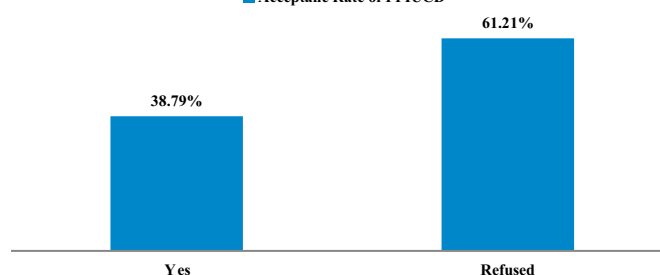


Figure 1: Acceptance Rate of PPIUCD

Among patients who accepted PPIUCD 10 (22.2%), patients had a history of previous one Cesarean section, 15 (33.3%) had previous two Cesarean sections, and 20 (44.4%) cases had previous three Cesarean sections, Table 3.

Table 3: Acceptance of PPIUCD in Women Who Have a Previous History of C-Sections

Characteristics	Frequency (%)
Previous History of C-Section	
1	10 (22.2%)
2	15 (33.3%)
3	20 (44.4%)

PPIUCD acceptance rate increased with the increasing number of previous Cesarean sections

DISCUSSION

The acceptance of PPIUCD among women undergoing C-sections is critical in maternal healthcare, chiefly given the observed acceptance rate of 38.79% in the current study. This percentage reveals a range of influencing factors, including parity, educational background, and previous delivery experiences. The demographic data of the participants show a mean age of 30.42 years, with the majority between the age group of 19 to 30 years, which is in line with previous research indicating that younger women tend to have a higher acceptance of long-acting reversible contraceptives [8]. It seems that educational level is also tied to acceptance; 24.14% of the group had no education, and 56.90% finished only primary to intermediate school. Therefore, giving more educational information and counselling may increase the rate of acceptances, based on studies demonstrating that education and counselling aid in using contraception postpartum [19, 20]. What is interesting is that those who had prior cesarean sections were more likely to accept PPIUCD. According to the data, the more cesareans someone had had, the higher the acceptance rate: a large fraction, 44.4%, of women who accepted had three or more prior cesareans, 33.3% had two and 22.2% had one. More experience with C-section deliveries seems to lead women to be happier with the procedure and what it means for their family planning after childbirth. This discovery is backed by results demonstrating that how postpartum contraception is

presented can strongly affect women's acceptance and opinion [21]. Also, most individuals involved (76.72%) were ranked as low socio-economic status. Such a status might make gaining access to contraceptive services more difficult for them. Since financial problems and lack of access to healthcare can affect whether PPIUCD is accepted, this context is very important [22]. Making healthcare policies and support programs better may offer a way to raise the satisfaction of postpartum women and earn higher acceptance rates for them. Though a high acceptance rate of PPIUCD is positive for health services, the fact that many women did not use PPIUCD calls for increased efforts. Learning what leads women to refuse IUCD can improve how counselling and education are carried out, as studies have revealed that false beliefs about the safety and effectiveness of IUD are common [23]. This study was limited by its single-center, cross-sectional design and relatively small sample size, which may restrict the generalizability of findings. Long-term follow-up to assess continuation rates, expulsion, complications, and patient satisfaction was not conducted. Additionally, reasons for refusal were not explored in depth. Future multicenter studies with longitudinal follow-up and qualitative assessment of barriers to acceptance are recommended to strengthen evidence and guide effective postpartum family planning strategies.

CONCLUSIONS

It was concluded that PPIUCD is an acceptable and practical postpartum contraceptive method in the course of cesarean section. The socioeconomic status, education, and parity affect the acceptance. Increased awareness and targeted counselling can go a long way to increasing its acceptability, aiding improved family planning results.

Authors' Contribution

Conceptualization: GI

Methodology: GI

Formal analysis: GI

Writing and Drafting: ZH, SJ, AA, KUK, AH

Review and Editing: ZH, SJ, AA, KUK, AH, GI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Time to Complete Retinal Vascularization After Anti-VEGF Among Preterm Neonates in Pakistan

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ABSTRACT

Retinopathy of prematurity (ROP) is a leading cause of preventable blindness in children. Anti-VEGF agents are widely used for treatment, but they pose concerns regarding delayed or incomplete retinal vascularization. There is limited local data on the vascularization timeline in Pakistani preterm neonates following anti-VEGF therapy. **Objectives:** To determine the time required to achieve complete retinal vascularization after intravitreal anti-VEGF injection in preterm neonates with ROP and to identify clinical predictors influencing this timeline. **Methods:** This prospective cohort study was conducted over 1.5 years from December 2023 to May 2025 at the neonatal nursery of the Pediatric Ward, Liaquat University of Medical and Health Sciences, Jamshoro. A total of 63 preterm neonates with treatment-requiring ROP received either Bevacizumab or Ranibizumab. Demographic, clinical, and treatment-related data were collected. Time to complete vascularization and postmenstrual age (PMA) at vascularization were recorded. ANOVA was used to assess statistical differences between subgroups. **Results:** The mean time to complete vascularization was 10.5 ± 2.0 weeks' post-treatment, with a PMA of 44.5 ± 2.1 weeks. Delayed vascularization (>50 weeks) occurred in 8.5% and reactivation in 6.4% of neonates. Stage 3 ROP, Zone I disease, and Bevacizumab were associated with slightly longer vascularization times, but none of these comparisons were statistically significant ($p > 0.050$). **Conclusions:** Retinal vascularization typically completes within 10–12 weeks after anti-VEGF therapy. Although not statistically significant, trends suggest extended follow-up is advisable in neonates with more severe disease or ZONE I ROP.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vaso-proliferative retinal disorder that occurs almost exclusively in premature infants due to incomplete vascular development of the retina. With improvements in neonatal care and survival of very low birth weight infants, ROP has emerged as a major cause of avoidable childhood blindness globally, particularly in low- and middle-income countries (LMICs) like Pakistan [1]. According to the World Health Organization, over 15 million babies are born prematurely every year, and approximately 32% of surviving infants

weighing less than 1500 grams may develop ROP [2]. In Pakistan, neonatal mortality remains high, and the burden of prematurity-related complications, including ROP, is increasing steadily [3, 4]. Traditionally, laser photocoagulation has been the gold standard for treating threshold or type 1 ROP. However, intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents such as Bevacizumab and Ranibizumab have gained popularity due to their efficacy in posterior ROP, ability to preserve peripheral retina, and favorable anatomical outcomes [5].



Anti-VEGF therapy is especially effective in Zone I or aggressive posterior ROP (APROP), where laser treatment is often technically challenging and less effective [6]. Despite its therapeutic benefits, anti-VEGF use poses a unique challenge, the delayed or incomplete retinal vascularization that may extend for months' post-treatment, thereby necessitating prolonged and careful follow-up to monitor for disease recurrence or persistent avascular retina [7]. The timing of complete retinal vascularization following anti-VEGF therapy is a critical clinical endpoint, as it has implications for scheduling follow-ups, evaluating reactivation risk, and planning additional interventions. Several international studies have reported wide variability in the time to full vascularization, with some cases completing by 48–52 weeks postmenstrual age (PMA), while others may take significantly longer or fail to vascularize completely [8]. Factors influencing vascular maturation post-treatment include gestational age at birth, birth weight, zone and stage of ROP, and type of anti-VEGF agent used [9]. Ranibizumab, owing to its shorter systemic half-life, has been associated with relatively earlier revascularization compared to Bevacizumab [10]. In Pakistan, there is a significant gap in locally generated data regarding the time course of retinal vascularization following anti-VEGF therapy. Most neonatal units do not have standardized ROP treatment protocols or long-term follow-up systems, increasing the risk of undetected persistent avascular retina or late recurrence. The scarcity of evidence makes it difficult for ophthalmologists and neonatologists to counsel families regarding the expected duration of follow-up or predict the timeline of retinal maturation.

Despite the increasing use of intravitreal anti-VEGF therapy for the management of retinopathy of prematurity (ROP), the timeline for complete retinal vascularization after treatment remains variable and not well established, particularly in low- and middle-income countries. Most available evidence originates from developed settings, while locally generated data from Pakistan are scarce. This lack of regional evidence makes it difficult for clinicians to predict vascularization outcomes and determine appropriate follow-up schedules for preterm neonates. Therefore, further research is needed to evaluate the vascularization timeline and associated clinical predictors in the local neonatal population. This study aimed to evaluate the time to complete retinal vascularization following anti-VEGF therapy in Pakistani preterm neonates and to identify potential clinical variables that may influence this timeline.

METHODS

This prospective cohort study was conducted over a duration of 1.5 years at the Neonatal Nursery of Pediatric

Ward, Liaquat University of Medical and Health Sciences, Jamshoro. Ethical approval was obtained from the institutional review board before the commencement of the study by the ethical review committee of the Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, vide letter No. LUMHS/Dir/Ophth/-24. All neonates diagnosed with treatment-requiring ROP from December 2023 to May 2025 were assessed for eligibility and recruited consecutively following parental consent. The sample size was calculated via the Open Epi sample size calculator by taking the prevalence of ROP in Preterm neonates as 15.8% [11] with a 10% margin of error and a 97% confidence interval. Inclusion criteria comprised preterm neonates born at ≤ 34 weeks of gestation and/or with a birth weight ≤ 2000 grams, who received either Bevacizumab (0.625 mg) or Ranibizumab (0.25 mg) intravitreal injections as the primary treatment for ROP. Infants with congenital ocular anomalies, previous laser photocoagulation, or incomplete follow-up data were excluded. Baseline data were collected from hospital records and verified by the study team at enrollment. ROP zone, stage, and laterality were determined through dilated retinal examination by a pediatric ophthalmologist using indirect ophthalmoscopy (Keeler Vantage Plus), following the International Classification of ROP (ICROP, 3rd edition). Zone I includes the central posterior retina, Zone II extends to the nasal ora serrata, and Zone III comprises the peripheral temporal retina. Staging was based on disease severity: Stage 1 (demarcation line), Stage 2 (ridge), and Stage 3 (extraretinal proliferation). Systemic risk factors such as sepsis, oxygen therapy, mechanical ventilation, intraventricular hemorrhage, and necrotizing enterocolitis were identified from documented neonatal diagnoses. Each patient was followed at 1, 3, and 6 months' post-treatment, based on international guidelines and adapted for local feasibility, considering compliance challenges and follow-up limitations in the Pakistani healthcare setting. At every follow-up, indirect ophthalmoscopy was performed by a qualified ophthalmologist to assess retinal vascular progression, disease regression, or recurrence. Indirect ophthalmoscopy was performed using a Keeler Vantage Plus headset with a 20D condensing lens under topical anesthesia. The primary outcome variable was the time (in weeks) from anti-VEGF administration to the point of complete retinal vascularization, defined as full extension of retinal vessels to zone III without any active neovascularization or plus disease. Secondary outcomes included postmenstrual age (PMA) at completion of vascularization, presence of persistent avascular retina, reactivation of ROP, and any injection-related complications. Data were entered and analyzed using SPSS version 25.0. Descriptive statistics were used to summarize patient characteristics. Data were normally

distributed, and the Normality of data distribution was measured via the Shapiro-Wilk test. Comparative analyses of time to complete vascularization across clinical subgroups (ROP stage, ROP zone, anti-VEGF type) were conducted using one-way ANOVA. A p-value of <0.050 was considered statistically significant.

RESULTS

The majority were male (61.9%), delivered via cesarean section (57.1%), and born as singletons (74.6%). The mean gestational age was 29.5 ± 1.5 weeks, and the mean birth weight was 1250 ± 200 grams, aligning with known risk parameters for ROP in premature infants, Table 1.

Table 1: Demographic Characteristics (n=63)

Variables	Frequency (%)
Gender	
Male	39 (61.9%)
Female	24 (38.1%)
Mode of Delivery	
Cesarean Section	36 (57.1%)
Normal Vaginal	27 (42.9%)
Birth Type	
Singleton	47 (74.6%)
Multiple	16 (25.4%)
Mean Gestational Age	29.5 ± 1.5 Weeks
Mean Birth Weight	1250 ± 200 Grams

Results outline the clinical characteristics. Most neonates had Stage 2 ROP (68.3%) followed by Stage 3 (28.6%). Zone II was the most common site of disease (61.9%), with bilateral involvement seen in 90.5% of cases. Common systemic risk factors included sepsis (20.6%), oxygen therapy (19.0%), and ventilation (17.5%), indicating a high burden of neonatal complications contributing to ROP progression, Table 2.

Table 2: Clinical Characteristics

Variables	Frequency (%)
GenderROP Stage	
Stage 1	02 (3.2%)
Stage 2	43 (68.3%)
Stage 3	18 (28.6%)
ROP Zone	
Zone I	19 (30.2%)
Zone II	39 (61.9%)
Zone III	05 (7.9%)
Laterality	
Bilateral	57 (90.5%)
Unilateral	6 (9.5%)
Systemic Risk Factorsr	
Sepsis	13 (20.6%)
O2 Therapy	12 (19.0%)
Ventilation	11 (17.5%)
IVH	9 (14.3%)
NEC	8 (12.7%)

None	10 (15.9%)

Findings describe the distribution of time to complete retinal vascularization. The mean time to complete vascularization post anti-VEGF treatment was 10.5 ± 2.0 weeks, with a median of 10 weeks and a range of 6–16 weeks. Delayed vascularization beyond 24 weeks was observed in 8.5% of cases, and ROP reactivation occurred in 6.4% of neonates, Table 3.

Table 3: Distribution of Time to Complete Retinal Vascularization

Variables	Value
Mean Time (Weeks Post Anti-VEGF)	10.5 ± 2.0 Weeks
Median Time	10 Weeks
Range	6 – 16 Weeks
Delayed Vascularization (>24 Weeks PMA)	4 (8.5%)
ROP Reactivation After Regression	3 (6.4%)

This study compares vascularization timing by clinical predictors. Stage 3 ROP, Zone I involvement, and Bevacizumab treatment were associated with numerically longer times to complete vascularization. However, ANOVA p-values showed no statistically significant differences among ROP stage (p=0.369), zone (p=0.197), or anti-VEGF type (p=0.980), Table 4.

Table 4: Comparative Analysis of Time to Complete Retinal Vascularization by Key Predictors (n=63)

Predictor Variables	Subgroup	Mean Time to Vascularization (Weeks)	95% CI (Time)	Delayed Vascularization (>50 Weeks)	p-value
ROP Stage	Stage 1	9.5 ± 1.5	8.43 – 10.57	1 (10%)	0.369
	Stage 2	10.3 ± 1.6	9.73 – 10.87	1 (6.1%)	
	Stage 3	11.3 ± 2.2	10.21 – 12.39	2 (11.1%)	
ROP Zone	Zone I	11.2 ± 2.1	10.19 – 12.21	2 (10.5%)	0.197
	Zone II	10.0 ± 1.8	9.42 – 10.58	2 (6.3%)	
	Zone III	10.7 ± 2.0	8.73 – 12.67*	0 (0.0%)	
Anti-VEGF Type	Bevacizumab	10.7 ± 2.0	10.08 – 11.32	3 (6.8%)	0.980
	Ranibizumab	10.1 ± 2.1	9.16 – 11.04	1 (5.3%)	

The results illustrate the cumulative outcomes of retinal vascularization, ROP reactivation, and delayed vascularization at 1, 3, and 6 months post-anti-VEGF treatment. It highlights a progressive increase in complete vascularization and a gradual emergence of complications requiring continued follow-up, Figure 1.

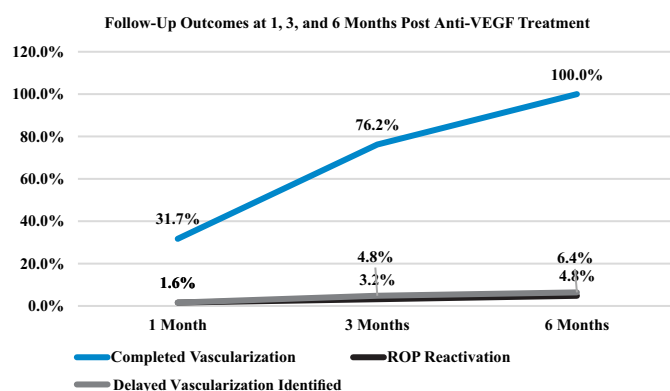


Figure 1: Follow-Up Outcomes at 1, 3, and 6 Months Post Anti-VEGF Treatment (n=63)

DISCUSSION

This study aims to evaluate the time to complete retinal vascularization after intravitreal anti-VEGF therapy in preterm neonates with ROP and to explore clinical factors influencing this timeline. The mean time to complete vascularization was found to be 10.5 ± 2.0 weeks, with a mean PMA at completion of 44.5 ± 2.1 weeks. These findings are consistent with previously published literature reporting vascularization completion within 10–12 weeks' post-treatment, typically around 44–46 weeks PMA [12]. In the present study, delayed vascularization beyond 50 weeks PMA was observed in 8.5% of cases. This rate is relatively low compared to international data, where delayed or incomplete vascularization has been reported in 10–20% of infants, depending on the anti-VEGF agent used and the severity of disease [13]. Kumawat *et al.* noted that delayed retinal maturation is more commonly associated with Zone I and Stage 3 ROP, similar to trends observed in current cohort [14]. Although not statistically significant, present findings indicated longer vascularization time in Stage 3 disease (11.3 ± 2.2 weeks) compared to Stage 1–2 (9.5 – 10.3 weeks), and in Zone I (11.2 ± 2.1 weeks) compared to Zone II–III (10.0 – 10.7 weeks). These observations are in line with a study by Dikopf *et al.* who found that posterior Retina of Prematurity and more advanced stages are associated with delayed vascularization and higher risk of persistent avascular retina [15]. The anti-VEGF agent used also influenced the outcome. Although the difference was not statistically significant ($p=0.980$), Bevacizumab-treated infants exhibited slightly longer times to vascularization compared to Ranibizumab (10.7 vs. 10.1 weeks). Similar findings were reported in the CARE-ROP study and other recent meta-analyses, which suggested that Ranibizumab, due to its shorter systemic half-life, may allow earlier revascularization than Bevacizumab [16, 17]. However, the clinical significance of this difference remains debated. Reactivation after initial regression was observed in 6.4% of cases, comparable to previously reported rates by Mintz-Hittner *et al.* in the BEAT-ROP trial (8%) [18]. The slightly

lower reactivation rate in present cohort may be attributed to differences in follow-up duration, disease severity at baseline, or treatment protocols. This reinforces the need for structured and extended follow-up after anti-VEGF therapy, especially in Zone I and Stage 3 disease. Persistent avascular retina was observed in a minority (14.3%), a known risk factor for late-onset complications such as retinal tears or detachment [19]. Current study contributes local evidence that supports global trends and highlights the need for national ROP screening and monitoring guidelines. Globally, the debate continues regarding the superiority of anti-VEGF agents versus laser therapy. Although anti-VEGF allows continued peripheral retinal development and is more effective in posterior ROP, concerns remain regarding systemic VEGF suppression and unpredictable vascular outcomes [20].

This study has several limitations that should be acknowledged. The sample size was relatively small and data were collected from a single tertiary care center, which may limit the generalizability of the findings. Additionally, the follow-up duration was limited and longer monitoring may be required to fully assess late reactivation or persistent avascular retina. Future multicenter studies with larger sample sizes and extended follow-up periods are recommended to validate these findings and to develop standardized ROP follow-up protocols in Pakistan.

CONCLUSIONS

Current findings support a follow-up strategy stratified by disease severity and anti-VEGF type. While anti-VEGF therapy was generally effective in achieving retinal vascularization within 10–12 weeks, neonates with Zone I or Stage 3 ROP and those treated with Bevacizumab may require extended monitoring. Although subgroup differences were not statistically significant, clinical trends reinforce the need for individualized, risk-adapted protocols. This study adds valuable local data to the limited evidence base on post-anti-VEGF outcomes in Pakistani preterm neonates, supporting context-specific follow-up planning.

Authors' Contribution

Conceptualization: MNM

Methodology: MNM, AJ, MLM, IG, AKN

Formal analysis: SC

Writing and Drafting: AJ, MLM, MM

Review and Editing: AJ, MLM, MM, IG, AKN, SC

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Frequency and Pattern of Congenital Heart Disease in Term Neonates Presenting in Respiratory Distress at Tertiary Care Hospital, Larkana

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ABSTRACT

Congenital heart disease (CHD) is a leading cause of infant morbidity and mortality. This is particularly the case in resource-limited settings where diagnosis is commonly delayed. **Objectives:** To assess the frequency and pattern of CHD among term neonates who presented with respiratory distress at a tertiary care hospital in Larkana, Pakistan. **Methods:** This cross-sectional study was conducted at the Department of Pediatrics, Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, Pakistan, from December 1, 2024, to June 7, 2025. A total of 105 term neonates presenting with respiratory distress were enrolled. Each neonate underwent detailed clinical examination and echocardiographic evaluation to identify structural heart defects. Demographic and perinatal data were also collected to explore associations with different CHD types. Statistical analysis was performed using SPSS version 22.0. **Results:** CHD was diagnosed in 41.9% of the neonates. The most common defect was a ventricular septal defect (24.8%), followed by an atrial septal defect (15.2%) and patent ductus arteriosus (12.4%). Cyanotic defects were less frequent, with tetralogy of Fallot identified in 6.7% and transposition of the great arteries in 2.9%. No statistically significant associations were found between CHD and neonatal age, gender, or mode of delivery. **Conclusions:** A significant proportion of term neonates with respiratory distress had underlying CHD, with acyanotic lesions being more common. These findings support the incorporation of routine echocardiographic screening and timely specialist referral for symptomatic neonates, particularly in resource-constrained healthcare settings.

INTRODUCTION

Congenital heart disease (CHD) is a group of anomalies that cause morphological and functional issues in the heart or main blood arteries from birth. Globally, 240,000 newborns die within 28 days after birth from congenital disease, and 170,000 die aged between one month and five years [1, 2]. CHD can present in various ways, with some patients remaining asymptomatic until discovered in late infancy or early childhood. Other extremes include cyanosis, heart

failure, or both at neonatal age [3]. Neurodevelopmental delay is a common condition in children with CHD, which affects 46% of them [4]. Hence, the full physical examination on a newborn infant, along with heart auscultation and immediate echocardiography, is the key feature in the early diagnosis and management, thereby decreasing the morbidity and mortality from delayed diagnosis [5]. The crucial hemodynamic alteration in the



process after birth is the transformation from fetal circulation, in which the oxygenation takes place within the placenta, to the postnatal circulation, where the oxygenation takes place in the lungs [6]. In fetal circulation, the oxygen-rich blood from the placenta returns to the right atrium (RA) via the umbilical vein and the ductus venosus; the oxygen-rich blood then passes through the foramen ovale and is transferred into the left ventricle (LV), which sends the oxygenated blood towards the brain and the heart, both with great metabolic demands [7, 8]. Blood with lower oxygen levels from the superior vena cava (SVC), the portal veins, and the coronary sinus, along with that from the lower body through the inferior vena cava (IVC), is primarily channeled to the right ventricle (RV). The RV then pumps this blood into the descending aorta via the main pulmonary artery and the ductus arteriosus, ultimately reaching the placenta for oxygenation [9, 10]. Under the system, the central shunts (ductus arteriosus, ductus venosus, and foramen ovale) are important in the normal circulation in the fetus. At birth, oxygen is transferred in the lung bed, receiving independent blood from the right ventricle (RV), while the left ventricle (LV) will deliver the oxygenated blood into the systemic circulation. In the cycle process, these shunts are redundant and will close within the first hours or days of life [11, 12]. Subhani et al. identified the prevalence of congenital heart disease as follows: VSD at 37%, ASD at 12.3%, patent ductus arteriosus at 11.1%, tetralogy of Fallot at 6.2%, and transposition of the great arteries at 2.5% [13]. A more recent study showed 13% of live-born infants had severe CHDs and were released undiagnosed from the hospital at birth [14]. Respiratory distress is one of the most common clinical presentations in neonates with congenital heart disease, especially in those with left-to-right shunts or obstructive lesions. Failure to recognize cardiac causes early can delay life-saving interventions [15]. Consequently, general pediatricians need to understand that the early identification and prompt interventions to stabilize these patients, along with their transfer to a suitable cardiac center, are vital for enhancing outcomes in critically ill individuals. In Pakistan, especially in underserved regions like Larkana, limited access to pediatric cardiology services and diagnostic tools often results in delayed or missed diagnoses of CHD. Studying term neonates, who are typically expected to be low-risk, can uncover the hidden burden of CHD in this group, aiding in early detection and timely referral. Unfortunately, there is a dearth of national data on the incidence or prevalence of congenital heart disease (CHD) that might indicate the disease burden of congenital heart defects in our nation, even though sparse hospital-based research at the regional level has been conducted in attempting to show the prevalence of CHD. Additionally, there isn't a national registration system

in place at the moment to determine the overall number of instances. The age at which these patients are first diagnosed remains unknown. Most studies have taken the age at which cases of CHD present at the study center as the age of initial diagnosis. The data gathered from this study will give us insight into the extent of the issue in our country. Ultimately, this will assist us in formulating preventive strategies through regular screening. Congenital heart disease (CHD) is a significant cause of neonatal morbidity and mortality, particularly in developing countries where early diagnosis is often delayed. Respiratory distress is a common presenting symptom in neonates; however, its association with underlying structural heart defects is frequently overlooked in routine clinical evaluation. In Pakistan, especially in peripheral regions such as Larkana, there is limited local data describing the frequency and pattern of CHD among term neonates presenting with respiratory distress. This lack of region-specific evidence highlights the need for studies that can support early detection and guide timely referral and management strategies. This study aimed to assess the frequency and pattern of CHD among term neonates who presented with respiratory distress at a tertiary care hospital in Larkana, Pakistan.

METHODS

This cross-sectional study was conducted in the Department of Pediatrics, Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, Pakistan, from 1 December 2024 to 7 May 2025. Ethical approval was obtained from the Institutional Ethical Review Committee of the College of Physicians and Surgeons, Pakistan (Ref. No. CPSP/REU/PED/-2022-221-6986), and written informed consent was obtained from parents or guardians after explaining the study purpose, risks, and benefits. The sample size of 105 neonates was calculated using WHO software, based on a previously reported frequency of patent ductus arteriosus of 11.1% from a study at Pak Emirates Military Hospital, Rawalpindi, with a 95% confidence level and a 6% margin of error. Patients were recruited through non-probability consecutive sampling. Term neonates aged 0–14 days presenting with respiratory distress were eligible if they exhibited at least one of the following: respiratory rate ≥ 60 breaths/min, oxygen saturation $\leq 88\%$, or arterial blood gas showing $p\text{CO}_2 \geq 60$ mmHg. Additional indicators included murmur, cyanosis with or without feeding difficulty, clinical features of congestive heart failure, or a pre- and post-ductal SpO_2 difference greater than 3%. Neonates were excluded if parental consent was not provided, or if they had congenital anomalies such as meningomyelocele or spina bifida, or clinical diagnoses of sepsis or necrotizing enterocolitis. A detailed history and clinical examination

were performed by the principal investigator, and echocardiography was carried out by a pediatric cardiologist with more than 10 years of experience. Congenital heart diseases were diagnosed according to established echocardiographic criteria, including ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricular septal defect, tetralogy of Fallot, and transposition of the great arteries. All findings were recorded on a pre-designed data collection form. Data were analyzed using SPSS version 22.0, with descriptive statistics (frequencies, percentages) applied to categorical variables and associations between clinical variables and congenital heart disease assessed using the Chi-square test, considering a p -value < 0.050 as statistically significant.

RESULTS

105 term neonates were enrolled who presented with respiratory distress at our tertiary care facility. Most infants were between 8 and 14 days old (55.2%), and the gender distribution was nearly equal, with 51.4% males and 48.6% females. The majority were delivered via normal vaginal delivery (79%), and 71.4% had a gestational age of more than 37 weeks. Maternal characteristics showed that 59% of mothers had a parity greater than three, and 65.7% had been pregnant more than three times. Roughly half of the families reported a monthly income of $\leq 75,000$ PKR, and most mothers had either primary (50.5%) or secondary (25.7%) education, while a small proportion (3.8%) were illiterate, Table 1.

Table 1: Distribution of Baseline Characteristics among the Study Participants

Variables		N (%)
Neonatal Age	01 to 07 days	47 (44.8)
	08 to 14 days	58 (55.2)
Gender	Male	54 (51.4)
	Female	51 (48.6)
Mode of Delivery	Cesarian	22 (21)
	Normal vaginal delivery	83 (79)
Gestational Age	≤ 37 weeks	30 (28.6)
	> 37 weeks	75 (71.4)
Parity	≤ 3	43 (41)
	> 3	62 (59)
Gravida	≤ 3	36 (34.3)
	> 3	69 (65.7)
Family Monthly Income	≤ 75000 per month	54 (51.4)
	> 75000 per month	51 (48.6)
Educational Status	Illiterate	04 (3.8)
	Primary	53 (50.5)
	Secondary	27 (25.7)
	Higher	21 (20)

The study found that 24.8% of neonates were diagnosed with a ventricular septal defect, making it the most

common congenital heart defect. Other common congenital heart defects include atrial septal defect (15.2%), patent ductus arteriosus (12.4%), tetralogy of Fallot (6.7%), and transposition of great arteries (2.9%). CHD was diagnosed in 44 neonates (41.9%). Among these, acyanotic defects were more common (Table 2)

Table 2: Frequencies of CHD Types

CHD Type	Acyanotic/Cyanotic	N (%)
Ventricular Septal Defect (VSD)	Acyanotic	26 (24.8)
Atrial Septal Defect (ASD)	Acyanotic	16 (15.2)
Patent Ductus Arteriosus (PDA)	Acyanotic	13 (12.4)
Tetralogy of Fallot (TOF)	Cyanotic	7 (6.7)
Transposition of the Great Arteries (TGA)	Cyanotic	3 (2.9)

None of the congenital heart defects (Ventricular Septal Defect (VSD) ($p=0.230$), Atrial Septal Defect (ASD) ($p=0.310$), Patent Ductus Arteriosus (PDA) ($p=0.480$), Tetralogy of Fallot (TOF) ($p=0.140$), Transposition of the Great Arteries (TGA) ($p=0.250$) showed a statistically significant difference in prevalence between the two neonatal age groups. The findings suggest that the distribution of these CHDs does not significantly vary between neonates aged 01–07 days and those aged 08–14 days (Table 3).

Table 3: Distribution of Congenital Heart Defects by Age Group in Neonates

Variables		Age		p-Value
		01 to 07 Days	08 to 14 Days	
Ventral Septal Defect	Yes	09 (19.1)	17 (29.3)	0.230
	No	38 (80.9)	41 (70.7)	
Atrial Septal Defect	Yes	09 (19.1)	07 (12.1)	0.310
	No	38 (80.9)	51 (87.9)	
Patent Ductus Arteriosus	Yes	07 (14.9)	06 (10.3)	0.480
	No	40 (85.1)	52 (89.7)	
Tetralogy of Fallot	Yes	05 (10.6)	02 (3.4)	0.140
	No	42 (89.4)	56 (96.6)	
Transposition of the Great Arteries	Yes	00 (00)	03 (5.2)	0.250
	No	47 (100)	55 (94.8)	

Across all types of congenital heart defects (Ventricular Septal Defect (p -value: 0.86), Atrial Septal Defect (p -value: 0.900), Patent Ductus Arteriosus (p -value: 0.680), Tetralogy of Fallot (p -value: 0.630), Transposition of the Great Arteries (p -value: 0.610), showing, no statistically significant differences were found between male and female neonates (all p -values > 0.050). While the distribution patterns varied slightly across subgroups, the findings did not suggest any strong demographic predictors of specific heart defects within this cohort (Table 4).

Table 4: Distribution of Congenital Heart Defects by Gender in Neonates

Variables		Gender		p-Value
		Male	Female	
Ventral Septal Defect	Yes	13 (24.1)	13 (25.5)	0.860
	No	41 (75.9)	38 (74.5)	
Atrial Septal Defect	Yes	08 (14.8)	08 (15.7)	0.900
	No	46 (85.2)	43 (84.3)	
Patent Ductus Arteriosus	Yes	06 (11.1)	07 (13.7)	0.680
	No	48 (88.9)	44 (86.3)	
Tetralogy of Fallot	Yes	03 (5.6)	04 (7.8)	0.630
	No	51 (94.4)	47 (92.2)	
Transposition of the Great Arteries	Yes	01 (1.9)	02 (3.9)	0.610
	No	53 (98.1)	49 (96.1)	

DISCUSSION

In the present study, neonates were admitted with respiratory distress at a referral center in Larkana. Ventricular septal defect (VSD) was the most common lesion, followed in decreasing frequency by atrial septal defect (ASD), patent ductus arteriosus (PDA), tetralogy of Fallot (TOF), and transposition of the great arteries (TGA). These findings are consistent with regional and international data. Sehar *et al.* reported VSD as the most frequently occurring acyanotic CHD, accounting for 27.5% of congenital defects at their center in Rawalpindi [16]. In our study, demographic characteristics such as age, gender, and mode of delivery did not show statistically significant associations with the type of CHD. Comparable findings were reported by previous studies, which observed that respiratory distress was the leading presenting feature, and demographic factors were not predictive of CHD type [17, 18]. In our cohort, respiratory distress was indeed the most frequent symptom, reinforcing that common neonatal presentations may mask underlying structural heart disease. This highlights the importance of routine echocardiographic evaluation in neonates with unexplained respiratory distress [16, 19]. Late diagnosis remains a persistent problem, particularly in cyanotic CHDs such as TOF and TGA. Previous studies highlighted the risks of delayed recognition, which contribute significantly to preventable morbidity and mortality due to missed opportunities for timely intervention [18, 20]. Although maternal and perinatal factors were not evaluated in detail in our study, other research has established their significance. Islam *et al.* reported maternal diabetes, hypertension, and antipyretic drug exposure as risk factors for CHD [17], while Dey *et al.* identified perinatal complications as predictors of poor outcomes in neonates with CHD [19]. Aryal *et al.* further emphasized the association of congenital birth defects with broader maternal health indicators in South Asia [21]. Collectively, these findings underscore gaps in early

identification and referral pathways for CHD in neonatal populations. The spectrum of CHD observed in our study aligns with findings from Bangladesh and other South Asian cohorts, where acyanotic lesions such as VSD and ASD predominate [17, 19]. The higher burden of left-to-right shunt lesions suggests an urgent need for early detection to prevent long-term complications such as pulmonary hypertension and Eisenmenger syndrome [16, 20]. In Pakistan, pediatric cardiology services remain concentrated in major cities, limiting access for neonates in peripheral regions. Both Qazi *et al.* and Javed *et al.* emphasized the necessity of expanding pediatric cardiac services to secondary and district-level hospitals to facilitate earlier diagnosis and reduce the burden of delayed treatment [18, 20]. Taken together, our results highlight that while demographic factors may not predict CHD type, respiratory distress remains a key presenting feature that warrants prompt echocardiographic evaluation. Universal screening strategies, rather than selective risk-based approaches, may be more effective in ensuring early detection and timely management of CHD in resource-limited settings.

This study has certain limitations, including its single-center design and relatively small sample size, which may limit the generalizability of the findings. Additionally, the cross-sectional nature of the study does not allow assessment of long-term clinical outcomes or progression of congenital heart disease. Detailed evaluation of maternal risk factors and perinatal complications was also beyond the scope of this research. Future multicenter studies with larger sample sizes, comprehensive maternal and neonatal risk assessment, and longitudinal follow-up are recommended to better understand the burden and outcomes of CHD in neonates.

CONCLUSIONS

The study reveals a high prevalence of congenital heart disease in full-term neonates with respiratory distress, with ventricular septal defect being the most common diagnosis. It emphasizes the need for routine echocardiographic screening and improved referral systems to reduce morbidity and mortality in resource-limited healthcare settings.

Authors' Contribution

Conceptualization: ZA, ZAM

Methodology: ZAM, SAJ

Formal analysis: SAS, SAJ

Writing and Drafting: ZA, VKG, DB

Review and Editing: ZA, VKG, DB, SAS, SAJ, ZAM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Clinical Profile and Predictors of Posterior Reversible Encephalopathy Syndrome at Tertiary Care Hospital, Peshawar

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ABSTRACT

Posterior Reversible Encephalopathy Syndrome is an acute neurological condition characterized by reversible subcortical vasogenic edema, often presenting with seizures, headache, visual disturbances, and altered mental status. **Objectives:** To evaluate the clinical profile, risk factors, radiological findings, and outcomes of Posterior Reversible Encephalopathy Syndrome patients at a tertiary care hospital in Peshawar. **Methods:** This prospective cohort study was conducted at Northwest General Hospital and Research Center, Peshawar, from January 2023 to March 2025. Ninety patients diagnosed with Posterior Reversible Encephalopathy Syndrome through clinical presentation and Magnetic Resonance Imaging confirmation were enrolled using non-probability consecutive sampling. Data on demographics, risk factors, symptoms, imaging, outcomes, and length of hospital stay were collected and analyzed. Descriptive analysis of the study was performed through SPSS version 25.0. **Results:** Among 90 patients, 61 (67.8%) were females, 29 (32.2%) were males. The mean age was 35.92 ± 3.16 years. Seizures (70%), headache (56.7%), and altered mental status (54.4%) were the most common symptoms. Hypertension (53.3%) and postpartum eclampsia (50.8% of females) were the leading risk factors. Magnetic Resonance Imaging showed parieto-occipital/cerebellar involvement in 74.4% and bilateral lesions in 96.7%. Most patients (92.2%) recovered and were discharged, while 7.8% passed away. **Conclusions:** Posterior Reversible Encephalopathy Syndrome is more prevalent in young females with underlying hypertension or postpartum complications. Early recognition and management can result in favorable outcomes. This study highlights the importance of timely diagnosis to prevent irreversible damage.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiological condition characterized by bilateral reversible vasogenic edema of the subcortical white matter, mostly in the parieto-occipital region. This causes a range of acute or subacute neurological symptoms, including headache, mental status changes, seizures, and visual impairment. PRES is typically suspected in patients with severe hypertension, renal failure, autoimmune diseases, eclampsia, or immunosuppressive medicines. Frequent neurological evaluations and neuroimaging using computed

tomography or magnetic resonance imaging are required to diagnose and assess the illness [1, 2]. This syndrome mostly affects young and middle-aged people, predominantly females, and may present a variety of clinical symptoms, like visual disturbances, headaches, seizures, and impaired consciousness. Magnetic Resonance Imaging reveals oedema, typically affecting the posterior subcortical areas. Triggering factors include hypertension, pre-eclampsia/eclampsia, renal failure, cytotoxic agents, and autoimmune conditions [3]. PRES is a reversible but often underdiagnosed neurological



condition associated with a range of triggers such as hypertension, renal failure, autoimmune disorders, and eclampsia. This study aims to evaluate the clinical characteristics, risk factors, and radiological patterns of PRES, and to identify factors associated with in-hospital mortality and clinical outcomes among patients admitted to our center. While PRES has been well-documented globally, most of the available literature from Pakistan, particularly from Peshawar, consists of case reports, with very limited research-based studies. There is a lack of comprehensive local data regarding its clinical presentation, risk factors, and outcomes in our population. Posterior Reversible Encephalopathy Syndrome (PRES) is an increasingly recognized neurological condition associated with hypertension, renal dysfunction, and pregnancy-related complications. Despite its clinical importance, the condition remains underdiagnosed due to its variable presentation and limited awareness among clinicians. Most available evidence is derived from international studies, while local data from Pakistan, particularly from Peshawar remain scarce and are mainly limited to case reports. This lack of comprehensive regional evidence highlights the need for systematic research to better understand the clinical profile, risk factors, and outcomes of PRES in the local population. This study aims to evaluate the clinical profile, risk factors, radiological findings, and outcomes of Posterior Reversible Encephalopathy Syndrome patients at a tertiary care hospital in Peshawar.

METHODS

This prospective cohort study was carried out in the Neurology Department of Northwest General Hospital and Research Center, Peshawar, from February 2025 to April 2025. Ethical approval (Ref# IRB&EC/2024-GH/0245) was obtained from the Institutional Review Board and Ethical Committee of Alliance Health Care Private Limited, and written informed consent was taken from all participants. Patients presenting to the emergency or neurology departments with acute neurological symptoms suggestive of posterior reversible encephalopathy syndrome (PRES), such as seizures, headache, visual disturbances, or altered mental status, were clinically assessed and underwent magnetic resonance imaging (MRI). Using a non-probability consecutive sampling technique, only those with bilateral, symmetrical vasogenic edema predominantly involving the posterior brain regions on MRI were included. The sample size ($n=90$) was calculated at a 95% confidence level, 5% margin of error, and an expected frequency of systemic hypertension of 6.2% [4]. Inclusion criteria were age >18 years, either gender, and both clinical and radiological confirmation of PRES. Patients with inconclusive or normal MRI findings,

alternative neurological diagnoses, pre-existing major neurological disease, or those who declined participation were excluded. PRES was defined as bilateral, symmetrical hyperintense signals on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences predominantly in the parieto-occipital lobes, without significant diffusion restriction on diffusion-weighted imaging (DWI) and infarction, confirmed by a consultant radiologist. Electroencephalography (EEG) was performed in patients with seizures or unexplained altered mental status, fundoscopy was conducted in patients with visual complaints, and obstetric history was obtained in pregnant or postpartum women to assess for pre-eclampsia/eclampsia. Data were collected prospectively using a structured proforma, including demographic details, clinical presentation, blood pressure readings, medical and obstetric history, medication use, laboratory investigations (CBC, renal and liver function tests, electrolytes, autoimmune profile, and urine protein where relevant), fundoscopy and EEG findings, radiological results, treatment strategies, and short-term clinical outcomes. Management included blood pressure control, antiepileptic therapy, and intensive care admission in cases of severe neurological compromise, hemodynamic instability, or refractory seizures. Patients were followed during their hospital stay to assess disease progression and treatment response. Data were analyzed using SPSS version 25.0; numerical variables were expressed as mean $\pm$ SD or median (IQR) after normality testing, and categorical variables as frequencies and percentages. The independent t-test or Mann-Whitney U test was used for continuous variables, and Fisher's exact test for categorical variables to compare outcomes based on discharge status.

RESULTS

The study included 90 patients diagnosed with PRES, predominantly females 61 (67.8%). The mean age of patients was 35.92 ± 3.16 years. Clinically, seizures were the most common presentation, 63 (70%), and hypertension was the most prevalent risk factor, present in 48 (53.3%) patients. Renal involvement was observed in 27 (30%) patients and 9 (10%) diagnosed with chronic kidney disease. Imaging findings predominantly showed parieto-occipital and cerebellar involvement in 67 (74.4%) patients, Table 1.

Table 1: Demographics, Clinical Profile, Risk Factors, Imaging, and Outcomes PRES patients

Variables	Frequency (%) /Mean $\pm$ S.D
Demographics	
Males (n, %)	29 (32.2%)
Females (n, %)	61 (67.8%)

Age (mean $\pm$ SD) years	35.92 $\pm$ 3.16 years
Clinical Profile	
Seizures (n, %)	63 (70%)
Headache (n, %)	51 (56.7%)
Visual Impairments (n, %)	28 (31.1%)
Altered Mental Status (n, %)	49 (54.4%)
Vomiting (n, %)	17 (18.9%)
Fever (n, %)	15 (16.7%)
Quadriperesis and Hemiparesis (n, %)	11 (12.2%)
Risk Factors	
Hypertension (n, %)	48 (53.3%)
Postpartum/Eclampsia (n, %)	31/61 (50.8%) (Females)
Renal Diseases (n, %)	27 (30%)
Chronic Kidney Disease (n, %)	9 (10%)
Imaging Profile	
Parieto-occipital and Cerebellar Involvement (n, %)	67 (74.4%)
Subcortical Lesions (n, %)	64 (71.1%)
Bilateral Involvement (n, %)	87 (96.7%)

There was no statistically significant difference in age or gender distribution between discharged and died patients ($p > 0.050$). However, hospital stay was significantly shorter in patients who died compared to those discharged (median 6 vs. 9 days, $p = 0.045$). The p-value was calculated by using the t-test, the Mann-Whitney U test, and Fisher's Exact test, Table 2.

Table 2: Comparison of demographic and clinical variables between patients discharged and those who died during hospitalization for PRES

Variable	Discharged (n=83)	Died (n=7)	P-Value
Age (years) Mean $\pm$ SD	33.6 $\pm$ 2.9	36.0 $\pm$ 11.2	0.590
Hospital Stay Median (IQR)	9 days (IQR = 5)	6 days (IQR = 3)	0.045
Female (n, %)	56/61 (91.8%)	5/61 (8.2%)	0.999
Male (n, %)	27/29 (93.1%)	2/29 (6.9%)	

Axial FLAIR MRI scan of the brain, demonstrating a large, hyperintense lesion in the left temporal lobe. The lesion shows surrounding vasogenic edema and is causing mass effect with effacement of the temporal sulci, Figure 1.



Figure 1: Axial FLAIR MRI scan of the brain, demonstrating a large, hyperintense lesion in the left temporal lobe

T2-weighted axial MRI scan of the brain at the level of the lateral ventricles. The image shows a well-defined, hyperintense lesion within the right posterior frontal lobe, Figure 2.

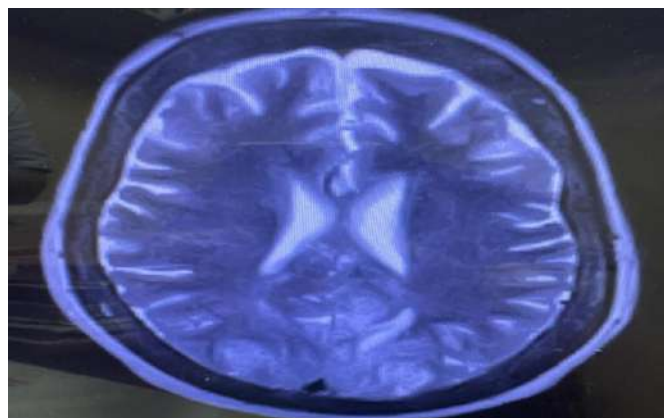


Figure 2: T2-weighted axial MRI scan of the brain at the level of the lateral ventricles

Axial FLAIR MRI scan of the brain, at the level of the parietal lobes. A small, discrete focus of hyperintensity is seen in the subcortical white matter of the left parietal lobe, Figure 3.

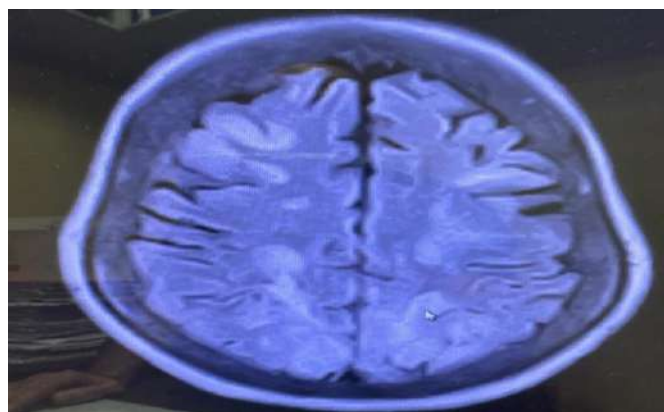


Figure 3: Axial FLAIR MRI scan of the brain, at the level of the parietal lobes

DISCUSSION

This study evaluated the clinical profile, risk factors, radiological patterns, and outcomes of patients diagnosed with PRES in a tertiary care hospital in Peshawar. The most frequent presenting symptoms—seizures, headaches, visual disturbances, and altered mental status—were consistent with previous reports by William et al. [5] and Ghanem et al. [6], where seizures were observed in up to 79.01% of cases. These features reflect the underlying pathophysiological hallmark of PRES: vasogenic edema, predominantly affecting the parieto-occipital lobes [5, 7]. The similarity of our findings to reports from other populations underscores the consistent presentation of PRES across regions. Hypertension was the most common associated condition, frequently occurring in combination

with preeclampsia and eclampsia in pregnant or postpartum women [8]. A systematic review also highlighted its significant association with PRES in systemic lupus erythematosus (SLE) patients, stressing the importance of strict blood pressure control [9]. Renal failure, with or without immunosuppressive therapy, is another important contributor [10]. Autoimmune diseases such as SLE, particularly when treated with cyclophosphamide, pose an elevated risk due to both disease-related vascular inflammation and treatment-related endothelial injury [11, 9]. In addition, cytotoxic and immunosuppressive drugs especially cyclosporine and tacrolimus—are well-recognized precipitants, particularly in transplant and oncology patients [12]. As in previous studies, we observed a higher prevalence of PRES in females, largely due to pregnancy-related cases, consistent with Seitz *et al.* [13] and Ranasingha and Bandara [14]. William *et al.* [5] similarly reported eclampsia as the most frequent risk factor in a Pakistani cohort. These findings highlight the need for heightened clinical vigilance in pregnant and postpartum women, where the condition may progress rapidly if not promptly addressed. The link between PRES and pregnancy is further supported by Hossain *et al.* [15], who demonstrated a significant association with gestational age. Barai and Aher [4] reported that, in 97 PRES cases, the male-to-female ratio was 1:18, with headache, seizures, altered sensorium, and visual disturbances being the most common symptoms. Antepartum eclampsia, postpartum eclampsia, and preeclampsia were the main risk factors, followed by systemic hypertension and renal disease. Radiologically, the occipital lobe was most frequently involved, with subcortical hypodensities seen in all patients. Although most patients recovered well, the authors emphasized that PRES is not always reversible and can lead to morbidity or mortality [1]. In current cohort, the proportion of male patients (32.2%) was higher than reported in most literature, which generally shows female predominance. This pattern is consistent with a study in hemodialysis patients, where 72% of PRES cases were male, suggesting that renal failure may increase risk in this group [16]. Hypertension, renal impairment, and immunosuppressive drug use were notable risk factors in our series, corroborating findings from Hinduja, [17] and William *et al.* [5]. Our overall prognosis was favorable, with 92.2% of patients discharged, comparable to the reversibility rates reported by Hinduja, [17]. Nevertheless, severe cases, particularly those with comorbidities such as myelodysplastic syndromes or cerebral hemorrhage, have worse outcomes, as shown by Takigawa *et al.* [18] and Lim *et al.* [19]. Persistent neurological deficits, including visual and motor impairments, may also occur, potentially affecting long-term quality of life [20]. The in-hospital

mortality rate in our study (7.8%) was between the ranges reported in literature, 11.2% [21] and 2.17% [22]. All deceased patients presented with severe neurological compromise and significant comorbidities, such as chronic kidney disease, postpartum eclampsia with multiorgan dysfunction, or poorly controlled hypertension. Shorter hospital stays in these patients compared to survivors likely reflected rapid deterioration despite standard care. Late presentation and advanced disease stage at admission appear to have been major contributors to mortality in our setting. Our median hospital stay was shorter than reported by Goyal and Jeswani, [23] and de Farias Bressan *et al.* [24], which may reflect differences in disease severity, timeliness of intervention, and healthcare resource availability. The reversibility of PRES with timely management, especially blood pressure control and treatment of underlying causes, remains a key finding, consistent with the literature [17]. Early recognition is critical to preventing permanent neurological damage, as also stressed by Khanum *et al.* [25].

This study has limitations, including its single-center design, small sample size, short follow-up, and lack of treatment monitoring, which may limit generalizability. Additionally, the study focused primarily on short-term in-hospital outcomes and lacked long-term follow-up to assess neurological recovery or recurrence of PRES. Future multicenter studies with larger cohorts and long-term follow-up are needed to confirm these findings and refine prognostic assessments in PRES.

CONCLUSIONS

Our study findings highlight that PRES predominantly affects young to middle-aged females and commonly presents with seizures, headaches, altered mental status, and visual disturbances. The most frequent risk factors identified were hypertension, postpartum eclampsia, and renal dysfunction. MRI typically revealed bilateral parieto-occipital lobe and cerebellum involvement. Most patients had favorable outcomes with early diagnosis and treatment. Recognizing these clinical and radiological predictors can facilitate timely diagnosis and management, thereby reducing morbidity and mortality associated with PRES.

Authors' Contribution

Conceptualization: ANN

Methodology: ANN

Formal analysis: HK, ANN

Writing and Drafting: AH, H, ANN, NAK

Review and Editing: AH, H, ANN, NAK, HK

All authors approved the final manuscript and take responsibility for the integrity of the work

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Original Article



Level of Integration in Modular System Curriculum in Medical Colleges of KPK, Pakistan

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ABSTRACT

Integrated medical education links basic sciences with clinical exposure, enhancing critical thinking. The World Federation of Medical Education (WFME) standards now require integrated teaching for graduates seeking US residency. KPK implemented Harden's Ladder integration in 2018, but the extent of its integration is unknown. **Objective:** To assess the integration level using Harden's Ladder of Integration of medical colleges in KPK and examine variations across institutions, faculty profiles, and demographic data. **Methods:** A cross-sectional study was conducted from October 2024 to February 2025 across 13 public and private medical colleges within KPK. Faculty members received a validated questionnaire based on Harden's Ladder, which was distributed through convenience sampling. The study employed Chi-square and Fisher's exact tests to investigate the relationship between faculty demographics and levels of integration. **Results:** 99 faculty members participated. All faculty members reported full implementation of Step 5, which represents temporal coordination, whereas Steps 7-11 showed implementation in ≤50% of colleges (7 colleges). Senior faculty members with >3 years of experience observed better integration levels. The statistical analysis revealed significant institutional differences ($p < 0.050$) that were evenly distributed across colleges. **Conclusions:** Temporal coordination (Step 5) is fully implemented, but advanced integration is inconsistent. Faculty/institutional factors significantly influence outcomes, potentially compromising WFME accreditation requirements for US residency eligibility. Targeted interventions are recommended to bridge this gap.

INTRODUCTION

Curriculum integration organizes education across disciplines into unified themes [1]. The World Federation of Medical Education (WFME) standards now require integrated teaching, as part of accreditation, necessary for graduates seeking US residency [2]. This policy was initially scheduled to be implemented by 2023 but was delayed until 2024 due to the COVID-19 pandemic [3].

Before 2018, KPK employed a traditional subject-based curriculum (separate preclinical sciences, followed by clinical years) that hindered linking basic science to clinical relevance. In 2018, KPK adopted Harden's Ladder to shift to an integrated curriculum, combining basic sciences with early clinical exposure through methods such as problem-based and team-based learning. This approach enhances



clinical relevance, fosters critical thinking and problem-solving, and promotes active, engaging learning [4]. In a study of two cohorts of medical graduates from Utrecht Medical School, one cohort was taught a traditional curriculum and the other a vertically integrated curriculum. Graduates from an integrated curriculum made career decisions earlier and matched to residencies faster [5]. Similar results were obtained from a study in the Netherlands [6]. In a study conducted in South India to evaluate the effectiveness of an integrated curriculum based on student feedback, 56.7% of students regarded the integrated session as "very good," and 25.4% rated it as "excellent" [7]. In a study conducted in Karachi, which evaluated the Integrated Learning Program (ILP) for undergraduate medical students, 78% of the students and 72% of faculty members expressed overall satisfaction with the program. Significant improvement in test performance was recorded [8]. In a study to evaluate challenges in a shift from a conventional to an integrated system in Pakistan, challenges in five dimensions were recognized by the authors: "Integrated Modular Curriculum (IMC) development, implementation, faculty transformation/change, institutional and regulatory body context" [9]. Since KPK's integrated curriculum was rolled out from 2018-19 and extended to final-year students by 2023-24, its level of implementation has not been evaluated.

Curriculum integration has become a key requirement in modern medical education to improve the connection between basic and clinical sciences. Although the modular integrated curriculum based on Harden's Ladder was introduced in medical colleges of Khyber Pakhtunkhwa (KPK) in 2018, the extent to which different levels of integration have been implemented across institutions remains unclear. Most previous studies in Pakistan have focused on student perceptions or institutional challenges rather than systematically evaluating integration levels using a standardized framework. Therefore, there is a need to assess the current status of curriculum integration across medical colleges in KPK. This study, therefore, aimed to assess curriculum integration (via Harden's Ladder) in KPK medical colleges and examine differences by institution, faculty background, and demographics.

METHODS

This cross-sectional study, employing a convenience sampling technique, was conducted in 13 public and private medical schools in Khyber Pakhtunkhwa, Pakistan, from 1 October 2024 to 25 February 2025. This study did not perform a formal sample size calculation because, study tried to include the entire population of eligible faculty members from medical colleges in KPK province. Since study attempted to include the whole population, and the

final number was based on actual responses, a separate sample size formula was not applicable. This approach was supported by research methodology literature, which stated that when the full population was surveyed (census), sample size estimation was not required. As stated in the following study on PubMed about sample size requirements [10]. Inclusion was limited to faculty with Certificate in Health Professions Education (CHPE) or Master of Health Professions Education (MHPE) qualifications to ensure that participants had a formal understanding of educational principles and could provide informed responses on curriculum integration. IRB approval was obtained before data collection (IRB #129/GJMS/JC), and informed consent was implied through voluntary participation. A study was conducted with a structured questionnaire based on Harden's 11-step Integration Ladder, which has been validated in previous work [11, 12]. The questionnaire had 11 questions with binary (YES/NO) responses (one question corresponded to each step). Recognizing that asking a busy curriculum leads to distinguishing among five subtly different levels of agreement could lead to confusion, especially around unlabeled mid-scale options like "neutral," we obtained the original author's written permission to simplify each item into a binary Yes/No question. Specifically, responses of "agree" or "strongly agree" (4-5 on the original scale) were re-coded as YES (Present), while all lower ratings (1-3) became NO (Absent). No composite integration score was calculated; rather, each of the 11 steps was analyzed separately to reflect the presence of that integration step. Two medical education specialists reviewed the adapted instrument to ensure that each Yes/No item accurately reflected its intended integration domain, and their expert appraisal confirmed its content alignment. This dichotomous format had three clear advantages: it reduced respondent fatigue by eliminating finer grading, it removed ambiguity about what degree of agreement constitutes meaningful integration, and this binary approach focused analysis on whether each step of the Ladder was adopted, rather than on finer gradations of implementation. Questionnaires were distributed by medical students to 230 faculty members during routine academic activities, with students acting solely as neutral facilitators. As they held no evaluative authority, the risk of response bias was minimal. To ensure data quality, 61 responses were excluded due to incompleteness or lack of CHPE/MHPE qualification. Data obtained from participants were screened based on the inclusion criteria. 61 out of the total 160 responses (38.1%) were purposefully excluded due to incompleteness or lack of CHPE/MHPE qualifications to ensure participant competency and data validity in evaluating Harden's model. The final sample (n=99) retained broad institutional

coverage (13 colleges) and adequate power for statistical detection of key associations. Data were entered in Microsoft Excel version 2024 and analyzed using SPSS version 23.0. The association of categorical variables and response to the levels of 11 steps of Harden's ladder of integration was determined using the chi-square test and Fisher's exact test (where applicable). Harden described eleven levels of integration, from isolated teaching to full, student-driven integration. These levels are briefly described as: **Isolation:** Departments teach entirely independently, with no coordination or reference to other subjects, students must create links themselves.

Awareness: Teachers are informed about what colleagues cover in other departments (via shared objectives or handouts), but no explicit effort is made to integrate content for learners. Harmonization: Teachers consult one another when planning, so related topics combine rather than duplicate, yet each subject still stands alone. **Nesting:** A subject-based course "infuses" a few objectives or topics drawn from other disciplines to enrich its teaching. Temporal Coordination: Related topics across disciplines are scheduled at the same time, although taught separately but in parallel to highlight connections. **Sharing:** Two (or more) disciplines jointly design and deliver sessions around overlapping concepts, treating them as ends in themselves. **Correlation:** Within a primarily subject-based

curriculum, standalone integrated sessions bring together common themes from multiple subjects. **Complementary:** Integrated sessions become more frequent and structured, weaving themes through subject teaching rather than remaining occasional add-ons.

Multidisciplinary: Multiple disciplines contribute to a single, theme-based course, each retains its identity but works toward a common focus. **Interdisciplinary:** Subject boundaries blur: content from various fields combines into a new, unified course without obvious discipline labels.

Transdisciplinary: All discipline distinctions dissolve. Learning revolves around real-world problems or themes, and students themselves drive integration.

RESULTS

Ninety-nine faculty (53.5% male, 46.5% female) participated, primarily lecturers (49.5%) and mostly with >3 years' experience (80.8%). All faculty reported full implementation of Step 5 (temporal coordination), indicating synchronized scheduling across disciplines. Agreement declined markedly at higher steps: only ~35-50% of faculty reported Steps 6-9, and ~23-25% reported Steps 10-11. This trend indicates robust horizontal integration but weak multidisciplinary/interdisciplinary integration (Table 1).

Table 1: Demographics and Frequency of Faculty Agreement for Each Step of Integration

Steps of Integration	Overall Responses (n=99)	Gender		Experience		Designation			
		Male (n=46)	Female (n=53)	<3 Years (n=19)	>3 Years (n=80)	Lecturer (n=49)	Assistant Professor (n=20)	Associate Professor (n=14)	Professor (n=16)
Step 1	0	0	0	0	0	0	0	0	0
Step 2	48	24	24	10	38	25	7	11	5
Step 3	81	39	42	13	68	43	15	10	13
Step 4	78	38	40	13	65	38	15	12	13
Step 5	98	45	53	19	79	48	20	14	16
Step 6	35	12	23	8	27	13	10	3	9
Step 7	47	27	20	5	42	25	12	3	7
Step 8	50	29	21	6	44	25	13	4	8
Step 9	50	25	25	8	42	23	11	6	10
Step 10	23	10	13	7	16	8	3	8	4
Step 11	25	13	12	4	21	10	4	4	7

Note: This table displayed Demographics total frequencies and subgroup responses across gender, experience, and designation. Step 5 (Temporal Coordination) was universally agreed upon, whereas Steps 7-11 showed lower levels of faculty agreement, indicating weaker interdisciplinary implementation.

Some colleges (e.g., BKMC, KMC, NWSM, SMC, KBMC) showed relatively higher integration, while others (NMC, GMC, BMC, STMC) were lower. No single institution disproportionately drove these results (Table 2).

Table 2: Faculty-Reported Implementation of Integration Steps across Medical Colleges

Steps of Integration	BKMC (n=8)	BMC (n=6)	GMC (n=8)	KbMC (n=5)	KGMC (n=4)	KIMS (n=1)	KMC (n=16)	NMC (n=3)	NWSM (n=24)	PMC (n=7)	SMC (n=13)	STMC (n=2)	WMC (n=2)
Step 1	0	0	0	0	0	0	0	0	0	0	0	0	0
Step 2	4	5	8	1	0	1	7	3	7	2	7	1	2
Step 3	7	4	8	5	4	0	13	3	22	5	6	2	2
Step 4	7	4	8	5	4	0	11	2	20	6	8	1	2

Step 5	8	6	8	5	4	1	16	3	24	7	12	2	2
Step 6	4	0	0	1	3	0	5	0	11	4	6	0	1
Step 7	4	0	0	5	3	0	11	0	17	5	1	1	0
Step 8	5	0	0	5	3	0	9	0	20	5	2	1	0
Step 9	4	0	0	2	1	1	9	3	14	6	10	0	0
Step 10	3	0	0	1	0	0	4	2	4	1	8	0	0
Step 11	3	0	0	0	0	0	6	1	5	4	6	0	0

Note: This table shows the number of faculty members from each institution who reported implementation ("Yes") of the corresponding Step of integration according to Harden's Ladder (Steps 1-11). Step 5 (Temporal Coordination) showed universal agreement, whereas higher steps (7-11) revealed considerable variation between institutions. Bacha Khan Medical College (BKMC), Bannu Medical College (BMC), Gomal Medical College (GMC), Kabir Medical College (KbMC), Khyber Girls Medical College (KGMC), KMU Institute of Medical Sciences (KIMS), Khyber Medical College (KMC), Nowshera Medical College (NMC), Northwest School of Medicine (NWSM), Peshawar Medical College (PMC), Saidu Medical College (SMC), Swat Medical College (STMC), Women Medical College (WMC)

Experience influenced responses: faculty with >3 years' experience reported higher adoption of advanced steps (e.g., 52.5% vs. 42.1% at Step 9). Only Step 7 (correlation) differed significantly by experience ($\chi^2=4.221$, $p=0.045$) (Tables 1 and 3). Institutional variation was significant for several steps (2, 3, 7-11; all $p<0.050$). Designation also played a role: senior faculty (associate/full professors) endorsed more advanced integration. Steps 2 and 10 were significantly associated with academic rank ($p<0.050$), with associate professors particularly favoring interdisciplinary integration (Step 10) (Tables 1 and 3). Gender differences were minor: males reported higher agreement at Steps 7-8 (χ^2 for Step 7 = 4.339, $p=0.045$), whereas all female faculty reported Step 5. No significant gender differences were found for other steps (Tables 3).

Table 3: Summary of Chi-Square Test Results across Integration Steps by Faculty Demographics and Institutional Affiliation

Steps of Integration	Experience χ^2 / p	Gender χ^2 / p	Designation χ^2 / p	Institution χ^2 / p
1	0.240 / 1.000	1.164 / 0.465	1.031 / 1.000	11.491 / 0.465
2	0.162 / 0.800	0.468 / 0.549	8.559 / 0.036*	28.181 / 0.001*
3	2.837 / 0.092	0.508 / 0.603	2.805 / 0.361	24.124 / 0.037*
4	1.512 / 0.226	0.751 / 0.464	0.676 / 0.935	14.753 / 0.264
5	0.240 / 1.000	1.164 / 0.465	1.031 / 1.000	6.683 / 0.596
6	0.469 / 0.595	3.228 / 0.093	7.791 / 0.052	18.532 / 0.068
7	4.221 / 0.045*	4.339 / 0.045*	5.403 / 0.139	42.867 / <0.001*
8	3.369 / 0.078	5.404 / 0.027*	4.382 / 0.236	44.928 / <0.001*
9	0.664 / 0.454	0.508 / 0.547	1.659 / 0.650	31.450 / <0.001*
10	2.442 / 0.137	0.107 / 0.814	11.125 / 0.019*	22.694 / 0.039*
11	0.220 / 0.774	0.412 / 0.644	3.884 / 0.281	18.499 / 0.039*

Note: This table combines results from four separate cross-tabulation analyses to reduce visual clutter and enable direct comparison. Complete raw counts are available upon request

DISCUSSION

This study found that temporal coordination (Step 5) is fully implemented across KPK medical schools, whereas higher integration levels (Steps 7-11) are inconsistent. Senior and higher-ranked faculty reported greater integration, implying they may be more involved in curriculum planning

or have received relevant training. Junior faculty respondents reported lower agreement with higher integration, possibly due to limited involvement in curriculum design or access to training programs. This finding necessitates targeted training initiatives for junior faculty to bridge this gap. Institutional variation was significant, but not attributable to a single institution. Institutional variation was widespread, suggesting systemic challenges (policy gaps, interdepartmental collaboration) that likely affect implementation [13-15]. Our results align with previous findings: other studies have reported minimal isolation (Step 1) and dominant temporal coordination (Step 5) in Pakistani curricula [12]. The findings of this study align with those of this study. However, this study expands on this by analyzing faculty perceptions based on institution, experience, and gender, providing a more comprehensive evaluation of integration disparities across medical colleges in Khyber Pakhtunkhwa (KPK). The dominance of temporal coordination (Step 5) over advanced integration (Steps 7-11) in KPK mirrors. These findings align with the evolving landscape of medical education, where both faculty and students are adapting to innovative learning strategies. Recent insights from Pakistani faculty highlight a notable shift in teaching practices, emphasizing the need for active and student-centered approaches to improve engagement and learning outcomes [15]. Among these, Problem-Based Learning (PBL) has gained significant traction due to its demonstrated effectiveness in enhancing critical thinking, clinical reasoning, and knowledge retention. A scoping review by Trullàs et al., further supported the integration of PBL methodologies in undergraduate curricula, noting substantial improvements in educational outcomes across diverse settings [16]. Faculty development remains a critical component in overcoming the challenges associated with teaching in medical education. Shrivastava et al., emphasized that faculty often face multiple instructional barriers, including lack of training in modern pedagogical approaches and limited confidence in

implementing innovative methods. Their mixed-methods study demonstrates that medical education workshops play a significant role in enhancing teaching competencies, fostering a deeper understanding of effective educational strategies, and encouraging reflective teaching practices [17]. Curriculum integration is widely recognized as a cornerstone of modern medical education, aiming to create cohesive learning experiences that bridge basic and clinical sciences. Malik and Malik provide practical guidance for educators seeking to develop integrated curricula, emphasizing the importance of alignment, collaboration, and contextual relevance [18]. Further supporting this approach, Husain et al. highlighted how integration enhances learner engagement and facilitates better retention by reducing compartmentalized learning. However, the process is not without its challenges [19]. Achike underscored the complexities faced by institutions implementing integrated curricula, such as resistance to change, resource limitations, and the need for faculty development [20]. International studies from the Netherlands and South India regarding the integrated system report that students identify this system as enhancing engagement, critical thinking, and problem-solving [5-7]. However, these studies differed from this study in that they focused on students' perspectives, while this study reported faculty perspectives. Both emphasize gradual implementation (e.g., phased modules) and shared challenges: faculty resistance, resource constraints, and preserving disciplinary identity. Francis I. Achike described some of the challenges of integration in the modern medical curriculum, along with recommendations for each challenge [20]. Asad and Khaliq affirmed integration improves clinical reasoning but identified resource gaps and faculty resistance as critical barriers. This aligns with KPK's inconsistent advanced integration [21]. A strength of this study is the use of Harden's Ladder, a validated global framework, and the broad inclusion of KPK institutions. To our knowledge, it is the first assessment of curriculum integration in KPK following modular implementation. Limitations include reliance on self-reported data without triangulation through curriculum documents or direct observation, which may affect objectivity, and the use of convenience sampling. Future research should include curricular audits, student feedback, and qualitative interviews to explore barriers and strategies for improvement.

This study has several limitations that should be acknowledged. This study has several limitations that should be acknowledged. The findings are based on self-reported faculty perceptions, which may introduce response bias and may not fully reflect the actual curriculum implementation. Additionally, the study did not

include curriculum document analysis or direct classroom observation to validate reported integration levels. Future research should incorporate mixed-method approaches, including curriculum audits, student perspectives, and longitudinal evaluations, to provide a more comprehensive understanding of curriculum integration and guide effective educational reforms in medical colleges.

CONCLUSIONS

While temporal coordination (Step 5) is universal, higher integration (Steps 7-11) remains inconsistent, influenced by faculty experience, designation, and institutional factors. Critically, this gap may impede compliance with WFME accreditation standards, mandatory for graduates seeking US residencies, which require robust vertical-horizontal integration. Province-wide policy reforms, faculty development, and institutional support are urgently needed to meet these global benchmarks.

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Authors' Contribution

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Formal analysis: FA¹, QMYA, JN, RR

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All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Septoplasty in Focus: Clinical Outcomes and Complication Patterns in A Pakistani Cohort

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ABSTRACT

Septal deviation is a common cause of nasal obstruction, and septoplasty is the preferred corrective procedure. Despite its widespread use, septoplasty is associated with several intraoperative and postoperative complications, which remain underreported in the Pakistani population. **Objectives:** To determine the frequency and nature of complications following septal surgery at a tertiary care setting. **Methods:** An observational cohort study was conducted at the Department of Otorhinolaryngology, Civil Hospital Hyderabad and LUMHS Jamshoro from March 2020 to February 2021. A total of 174 patients undergoing septal surgery were enrolled using non-probability consecutive sampling. Data on demographics, presenting complaints, surgical procedures, and postoperative complications were collected using structured questionnaires. All patients were followed monthly for six months postoperatively. Data were analyzed using SPSS version 21.0. **Results:** The mean age of participants was 27.5 ± 5.2 years, with 62.1% being male. The most common intraoperative complication was hemorrhage, observed in 49 patients (28.2%). Postoperative complications included septal hematoma in 18 patients (10.3%), infection in 17 patients (9.8%), and septal perforation in 12 patients (6.9%). A statistically significant association was observed between resection of the deviated septum and both immediate and delayed complications ($p=0.035$), indicating that this procedure carried a higher risk compared to others. **Conclusions:** Septoplasty, particularly when involving resection of the deviated septum, was associated with a higher rate of both immediate and delayed complications. These findings highlight the need for careful surgical technique selection and structured postoperative monitoring to minimize morbidity and improve patient outcomes in clinical ENT practice.

INTRODUCTION

Nasal septal deviation (NSD) represents a displacement of the nasal septum affecting approximately 80% of the global population, although symptomatic cases are fewer [1]. This anatomical deformity often leads to chronic nasal obstruction, compromised ventilation, and reduced quality of life [2, 3]. When medical management such as nasal steroids or decongestants, fails, Septoplasty becomes the treatment of choice [4]. Despite its frequent application, septoplasty is associated with known complications, including hemorrhage, hematoma, perforation, infection, and adhesions [5, 6]. Recent refinements such as endoscopic techniques and quilting sutures have been

introduced to reduce these risks and enhance recovery [7, 8]. However, in Pakistan, systematic data on complication patterns following septoplasty remain limited. A few single-center studies have explored surgical approaches and postoperative outcomes, such as a comparative study from Lahore showing shorter operative times for endonasal septoplasty compared to external approaches [9], and the use of nasal splints significantly reducing adhesions [10-14]. Another evaluation from Jinnah Hospital endorsed endoscopic techniques for enhanced safety [11]. Yet, these findings remain fragmented, and standardized outcome monitoring across institutions is



lacking. Given this context, there is a clear need to generate robust, locally relevant data on the complications of septal surgery.

Nasal septal deviation is a common anatomical condition that frequently leads to nasal obstruction and reduced quality of life, with septoplasty being the standard surgical treatment. Although the procedure is widely performed, it is still associated with various intraoperative and postoperative complications that may affect surgical outcomes. While international studies have documented these complication patterns, limited systematic evidence is available from Pakistani clinical settings regarding the frequency and types of complications following septoplasty. This lack of comprehensive local data highlights the need for further investigation to guide safer surgical practices and improve postoperative patient management. This study aims to determine the frequency and types of complications associated with septoplasty at a tertiary care center in Hyderabad, with the goal of informing surgical practice and optimizing patient care.

METHODS

This observational cohort study was conducted in the Department of Otorhinolaryngology (ENT) at Liaquat University Hospital, Hyderabad, from March 2020 to February 2021. The hospital was a tertiary care teaching facility affiliated with Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro. A total of 174 patients undergoing septal surgery were included. The sample size was calculated using the OpenEpi sample size calculator, based on a hypothesized complication rate of 13% [6], with a 5% margin of error and a 95% confidence level. The study was approved by the Ethical Review Committee of LUMHS, Jamshoro (Approval Letter No. LUMHS/REC/-791). Informed written consent was obtained from all participants in Urdu or a local regional language, ensuring full comprehension of the study's nature, risks, and benefits. Patient confidentiality was maintained throughout the research process. Participants were enrolled through a non-probability consecutive sampling technique. The inclusion criteria comprised all patients of any age and gender who presented with nasal airway obstruction due to septal deviation and were scheduled for corrective septal surgery (septoplasty). Patients were excluded if they had a history of previous septal surgery, external nasal deformities, associated nasal pathologies such as nasal polyps or rhinoliths, or known hemostatic disorders. Data on demographic and clinical variables were collected using a structured, pre-tested questionnaire administered at the time of patient admission. Demographic data included age and gender. Clinical data included the primary presenting complaint, physical findings, the type of surgical procedure performed, and

complications encountered. All surgical procedures including Septoplasty, septal scoring, partial inferior turbinectomy, and combined techniques were performed by ENT surgeons with experience at least of 5 years, using standardized operative protocols. Septoplasty involved Killian's incision, elevation of mucoperichondrial flaps, resection or repositioning of deviated segments, and suturing with absorbable material. Scoring was performed in mild deviations without cartilage removal. Partial inferior turbinectomy was done using turbinate scissors or micro-debriders to reduce turbinate size. All patients received preoperative antibiotics, and hemostasis was achieved using cautery or Gelfoam. Postoperative care followed a uniform regimen, and postoperative complications were documented using a standardized follow-up proforma. Patients were followed for six months postoperatively, with clinical evaluations scheduled monthly at the ENT outpatient department. Assessments were conducted monthly up to 6 months after surgery, during which each patient underwent anterior rhinoscopy and nasal endoscopy to identify potential complications. Immediate complications were defined as those occurring intraoperatively or within 48 hours' post-surgery (e.g., hemorrhage, septal perforation), while delayed complications included those identified during any of the subsequent follow-up visits (e.g., hematoma, abscess, adhesions, anosmia, infection, or structural deformities). Data analysis was performed using SPSS version 21.0. Quantitative variables such as age were expressed as mean and standard deviation (Mean $\pm$ SD), while qualitative variables such as gender, surgical procedure type, and complications were summarized as frequencies and percentages (n, %). The Chi-square test was applied to determine the association between the type of surgical procedure and the incidence of complications. A p-value of less than 0.050 was considered statistically significant.

RESULTS

A total of 174 patients undergoing septal surgery were included in the study. The mean age of the participants was 27.54 ± 5.21 years, indicating a predominantly young adult population. There was a clear male predominance (62.1%) and a higher proportion of patients from urban areas (73%). Most patients belonged to the lower socioeconomic class, and nasal obstruction, either unilateral or bilateral, was the most common clinical presentation, followed by facial discomfort and headache (Table 1).

Table 1: Demographics and Clinical Profile of Patients Undergoing Septal Surgery (n=174)

Variable	Frequency (%), Mean $\pm$ SD
Mean Age (yrs)	27.54 $\pm$ 5.21
Gender	
Male	108 (62.1%)

Female	66 (37.9%)
Residence	
Urban	127 (73%)
Rural	47 (27%)
Presenting Complaint	
Facial Discomfort	18 (10.3%)
Unilateral Nasal Obstruction	51 (29.3%)
Bilateral Nasal Obstruction	66 (37.9%)
Frontal Headache	19 (10.9%)
Nose Bleeds	11 (6.3%)
Snoring	9 (5.2%)

With regard to postoperative outcomes, complications

Table 2: Incidence of Complications by Time of Onset (n=174)

Complications	During Surgery	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Hemorrhage	49 (28.2%)	-	-	-	-	-	-
Septal Hematoma	-	18 (10.3%)	11 (6.3%)	4 (2.3%)	1 (0.6%)	-	-
Adhesion	-	-	-	-	1 (0.6%)	3 (1.7%)	5 (2.9%)
Septal Perforation	12 (6.9%)	2 (1.1%)	-	-	-	-	-
Structural Deformity	-	9 (5.2%)	2 (1.1%)	-	-	-	-
Anosmia / Hyposmia	-	2 (1.1%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	-	1 (0.6%)
Infection	-	17 (9.8%)	12 (6.9%)	9 (5.2%)	-	-	-
Septal Abscess	-	1 (0.6%)	1 (0.6%)	2 (1.1%)	-	-	-

A comparative analysis of complication rates by type of surgical procedure revealed a statistically significant association between resection of the deviated septum and both immediate (9.8%) and delayed complications (16.7%) ($p=0.035$). In contrast, scoring of the septum, combined resection and scoring, and partial inferior turbinectomy were not significantly associated with complication frequency, despite having comparatively higher percentages in some cases ($p=0.410$, 0.270 , and 0.190 respectively). These findings suggest that resection alone may carry a higher risk of adverse outcomes compared to other techniques (Table 3).

Table 3: Type of Procedure Vs. Incidence of Complications (n=174)

Procedures	Immediate Complications (%)	Immediate CI (95%)	Delayed Complications (%)	Delayed CI (95%)	p-value
Resection of Deviated Septum					
Present	17 (9.8%)	6.2%-15.1%	29 (16.7%)	11.9%-22.9%	0.035
Absent	157 (90.2%)		145 (83.3%)		
Scoring of Septum					
Present	5 (2.9%)	1.2%-6.5%	9 (5.2%)	2.7%-9.5%	0.410
Absent	169 (97.1%)		165 (94.8%)		
Resection & Scoring of Nasal Septum					
Present	18 (10.3%)	6.6%-15.8%	31 (17.8%)	12.8%-24.2%	0.270
Absent	156 (89.7%)		143 (82.2%)		
Partial Inferior Turbinectomy					
Present	21 (12.1%)	8.0%-17.7%	35 (20.1%)	14.8%-26.7%	0.190
Absent	153 (87.9%)		139 (79.9%)		

DISCUSSION

This study evaluated 174 patients undergoing septal surgery and found that hemorrhage was the most frequent intraoperative complication (28.2%), while septal hematoma (10.3%), infection (9.8%), and septal perforation (6.9%) were the most commonly observed postoperative complications over six months of follow-up. Resection of the deviated septum was significantly associated with

were stratified by type and time of onset. The most common intraoperative complication was hemorrhage, reported in 28.2% of patients. Among early postoperative complications, septal hematoma was most frequent in the first month (10.3%), with rates decreasing in subsequent months. Septal perforation was reported in 6.9% intraoperatively, with a small number of new cases (1.1%) emerging within the first postoperative month. Structural deformities, anosmia/hyposmia, and infections were distributed across the follow-up period, while adhesions and septal abscesses tended to occur later, though at lower frequencies overall (Table 2).

higher complication rates ($p=0.035$), whereas other procedures, such as scoring or turbinectomy, did not show statistically significant associations. The mean age of the study cohort was 27.54 ± 5.21 years, with a male predominance (62.1%). The most common presenting complaint was nasal obstruction (56.3%), followed by frontal headache (24.7%) and facial discomfort (19.0%).

These symptoms, which collectively affect patients' quality of life, have been consistently reported as the primary indications for septal surgery in both regional and international literature [15]. Analysis of septal deviation revealed varied presentations: unilateral nasal obstruction was noted in 29.3%, bilateral nasal obstruction in 37.9%, with lesser frequencies of other complaints such as facial discomfort (10.3%), frontal headache (10.9%), nosebleeds (6.3%), and snoring (5.2%). These clinical patterns support the necessity for individualized surgical approaches based on patient symptomatology and anatomical variations [6]. The incidence of complications following septal surgery was meticulously documented over a six-month follow-up period. Hemorrhage was the most common intraoperative event, comparable to previous Pakistani studies reporting similar rates between 25–30% [16]. Septal hematoma and infection were also frequent, particularly during the first month. Although complications such as adhesions, perforations, and anosmia were less prevalent, their potential impact on long-term surgical success underscores the importance of meticulous technique and postoperative care [17]. Current finding that resection of the deviated septum was significantly associated with complications aligns with studies suggesting that more invasive techniques increase tissue trauma and thus complication risk. For instance, similar associations have been reported in international literature, linking extensive resection with mucosal disruption and delayed healing [18, 19]. Moreover, current results concur with a recent European multicenter study, which emphasized that complication rates can be minimized through careful case selection and preference for minimally invasive techniques [20].

This study has certain limitations that should be considered while interpreting the findings. The research was conducted at a single tertiary care center using a non-probability sampling technique, which may limit the generalizability of the results. Additionally, the study focused mainly on short-term complications and did not evaluate long-term functional outcomes such as patient quality of life or symptom improvement. Future multicenter studies with larger sample sizes and longer follow-up periods are recommended to better assess the long-term safety and effectiveness of different septoplasty techniques and to establish standardized surgical protocols.

CONCLUSIONS

Septoplasty is effective for nasal obstruction but carries a risk of complications, especially with resection techniques. Hemorrhage, hematoma, and infection were common. Findings support careful surgical selection and structured follow-up to improve outcomes and guide clinical practice.

Authors' Contribution

Conceptualization: NY

Methodology: NY, SY, AAL, AA, FK

Formal analysis: AK, FK

Writing and Drafting: SY, AAL

Review and Editing: SY, AAL, NY, AK, FK

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Association of Serum Asprosin with the Risk Assessment of Diabetic Retinopathy

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ABSTRACT

Diabetic retinopathy (DR) is a microvascular complication of uncontrolled diabetes, resulting from impaired retinal blood circulation. Asprosin, a recently identified adipokine, exacerbates this condition by inducing inflammatory cytokines that enhance retinal inflammation and vascular permeability. **Objectives:** To investigate the association of serum Asprosin levels with the progression of diabetic retinopathy and its potential role as a biomarker for early diagnosis and disease monitoring. **Methods:** This cross-sectional analytical study was conducted from January to December 2023, involving 255 participants divided into three groups: diabetics with no retinopathy, diabetics with retinopathy, and non-diabetic controls (85 each). Serum Asprosin, fasting glucose, insulin, lipid profiles, and other relevant clinical features were evaluated. Statistical analyses were conducted using SPSS version 26, including One-Way ANOVA, the Bonferroni test, and Pearson's correlation. **Results:** The group with retinopathy showed the highest levels of Asprosin, insulin, fasting glucose, triglycerides, and LDL, while HDL was lowest in this group. The diabetic group showed intermediate levels, and controls showed the lowest levels across these variables. A strong positive correlation was observed between Asprosin and insulin resistance indicators such as HOMA-IR. **Conclusions:** Elevated serum Asprosin correlates with the presence and severity of diabetic retinopathy and aligns with dysregulated lipid and glycemic profiles. These findings support the potential of Asprosin as an early biomarker for DR risk and progression. Future longitudinal studies are necessary to determine its causal role and clinical applicability in diabetes-related retinal complications.

INTRODUCTION

Diabetes mellitus (DM) is one of the biggest health challenges we face today, marked by issues with insulin production or function that result in high blood sugar levels [1]. To date, most attention has been placed on Type 2 DM because of its increasing incidence and associated complications. If not controlled, high blood sugar can cause serious issues, including damage to the eyes, kidneys, and harm to the blood vessels and nerves [2]. One such major long-range complication is Diabetic Retinopathy (DR), which arises from blood flow inadequacy to the retina and can eventually result in impaired vision and

even blindness [3]. DR is the leading cause of global blindness, and the good news is that it is largely preventable with early detection and treatment [4]. It is important to manage this condition to enable blood sugar levels, hypertension, and cholesterol to stay under control [5]. While blood sugar levels remain elevated, it creates advanced glycation end products (AGEs) that damage the tiny blood vessels in the retina and lead to leaks, vitreous hemorrhage, and retinal detachment [6]. The diabetes-associated increased permeability of blood vessels, inflammation, endothelial cell damage, and high



concentration of inflammatory cytokines are responsible for DR in its advanced stages [7]. Asprosin, a peptide hormone discovered in 2016, has a significant role in regulating blood glucose through interactions with OLF734 receptors in various organs [8]. It is negatively associated with HOMA-B and positively with HOMA-IR, indicating its link with insulin resistance [9]. When Asprosin is high, as in diabetes, it leads to insulin resistance and persistent hyperglycemia, which worsens DR [10]. By increasing oxidative stress and inflammation in the retinal tissue, asprosin makes the situation worse by hastening the destruction to the retina's blood vessels and cells. Inflammatory cytokines are produced in response to it, and this can exacerbate retinal inflammation and increase vascular permeability [11]. As a result, the blood-retinal barrier breaks down, allowing fluids and blood to seep into the retina and resulting in macular edema [9]. Additionally, asprosin affects angiogenesis by modifying the expression of VEGF (vascular endothelial growth factor), which results in aberrant and delicate angiogenesis. These vessels are prone to bleeding, contributing to retinal hemorrhages and further visual impairment. Through enhanced oxidative stress and inflammation in the retinal tissues, Asprosin accelerates the devastation of retinal blood vessels and cells, weakening the blood retinal barrier. This leads to macular edema and eventual vision loss [10]. Given these multifaceted roles, asprosin represents a potential therapeutic target for treating diabetic retinopathy. Interventions aimed at reducing asprosin levels or blocking its activity may offer new avenues for preventing or slowing the progression of this vision-threatening condition [12]. Despite significant advances in the understanding of diabetic retinopathy (DR), identifying reliable biomarkers for its early detection and progression remains a major challenge. Recent studies have highlighted the metabolic hormone Asprosin as a potential regulator of glucose metabolism and insulin resistance. However, limited research has explored its association with retinal microvascular complications, particularly diabetic retinopathy. Furthermore, evidence regarding the relationship between serum Asprosin levels and DR risk in diverse populations remains scarce, creating a need for further investigation. This study aimed to investigate the connection between Asprosin levels and diabetic retinopathy (DR) in a varied group of participants.

METHODS

This cross-sectional analytical study was conducted in the Outpatient Departments of Diabetes and Ophthalmology between January and December 2023, after obtaining ethical approval from the IRB of Al-Ibrahim Eye Hospital, Isra Postgraduate Institute of Ophthalmology, Karachi, Pakistan (Letter No. REC/IPIO/2023/067). A total of 255

participants were enrolled and divided equally into three groups of 85 each: diabetics with diabetic retinopathy (DR), diabetics without DR, and healthy individuals. Patients with DR were diagnosed through fundus examination, following international clinical retinopathy guidelines. A purposive sampling method was employed with specific inclusion and exclusion criteria. Individuals with non-diabetic eye diseases, active inflammation, chronic infections, steroid use, or conditions affecting glucose metabolism and obesity were excluded. The minimum sample size was calculated using the online software OpenEpi, referencing a previous study ("Frequency of Diabetic Retinopathy in Karachi, Pakistan: A Hospital-Based Study," 2015). The prevalence of DR was taken as 6.5%, with a 95% confidence level, 5% margin of error, population size (N) of 100,000, and a design effect (DEFF) of 1. The formula applied was:

$$n = \frac{DEFF \times N \times p(1-p)}{\left(\frac{d^2}{Z_{1-\alpha/2}^2 \times (N-1)} \right) + p(1-p)}$$

where $Z_{1-\alpha/2} = 1.96$, $\{1-\alpha/2\} = 1.96$, $Z_{1-\alpha/2} = 1.96$. This yielded a minimum required sample size of 93. However, we recruited 255 participants to improve statistical power and subgroup analyses. All participants provided informed consent in their native language. A self-designed, pre-tested questionnaire was used to collect demographic details, lifestyle and dietary habits, medical history, and current or past treatments. Anthropometric measurements (including BMI) were recorded, along with blood pressure, pulse, respiratory rate, and pulse pressure. A fasting venous blood sample (5 ml) was collected, centrifuged, and the serum was stored at -20°C for analysis. Fasting blood glucose was measured using sodium fluoride vacutainers, while serum Asprosin and insulin levels were quantified using a human ELISA kit (Cat. No. E4095, sensitivity: 0.23 ng/ml; [Manufacturer, Country]). Data were analyzed using SPSS version 26.0. For normally distributed continuous data, one-way ANOVA with a Bonferroni post hoc test was applied. Pearson's correlation was used to evaluate relationships between anthropometric and biochemical parameters, with a particular focus on serum Asprosin levels.

RESULTS

Study results demonstrate significant differences in demographic measurements (age, weight, height, BMI, systolic and diastolic blood pressure, and pulse rate) across the control, diabetic, and retinopathy groups, with p-values around or close to <0.001 . These variations indicate distinct physiological profiles among the groups (Table 1).

Table 1: Demographic and General Physical Parameter Analysis of the Study Groups

Variables	Controls (N=85) Mean ± SD	Diabetics (N=85) Mean ± SD	Retinopathy (N=85) Mean ± SD	F-Value	p-Value
Age	40.37 ± 9.599	50.98 ± 7.543	51.84 ± 6.469	54.155	<0.001
Weight (kg)	67.65 ± 8.35	65.36 ± 8.76	67.64 ± 7.54	2.164	0.117
Height (cm)	167.35 ± 7.68	162.64 ± 10.27	165.64 ± 8.36	6.148	0.002
BMI (kg/m ²)	24.38 ± 2.62	25.05 ± 3.35	25.07 ± 2.72	1.513	0.222
Systolic BP (mmHg)	118.51 ± 7.67	117.88 ± 7.57	116.00 ± 8.27	2.350	0.097
Diastolic BP (mmHg)	75.10 ± 8.61	76.59 ± 6.82	74.47 ± 6.86	1.802	0.167
Pulse rate (b/min)	74.07 ± 3.73	75.29 ± 4.17	77.96 ± 5.33	16.828	<0.001
Pulse Pressure	42.74 ± 5.98	41.18 ± 3.75	41.82 ± 6.76	1.632	0.198
R/R (Breaths/min)	15.57 ± 2.17	16.06 ± 2.16	14.62 ± 2.16	9.651	<0.001

The analysis of biochemical markers demonstrated significant disparities among the groups. Lipid parameters (cholesterol, triglycerides, HDL, LDL, and VLDL), fasting blood sugar (FBS), fasting insulin, HOMA-IR, and serum Asprosin all had highly significant p-values of <0.001, suggesting notable differences in metabolic and lipid profiles between the groups. The biochemical analysis of serum Asprosin revealed significant differences between groups. Specifically, the Retinopathy group exhibited the highest Asprosin levels, followed by the Diabetic and Control groups (Table 2).

Table 2: Biochemical Analysis of the Study Groups

Variables	Controls (N=85) Mean ± SD	Diabetics (N=85) Mean ± SD	Retinopathy (N=85) Mean ± SD	F-Value	p-Value
Cholesterol	152.69 ± 9.59	177.32 ± 8.62	331.38 ± 4.35	85.90	<0.001
Triglycerides	157.25 ± 6.38	219.25 ± 1.27	449.10 ± 5.63	67.24	<0.001
HDL	63.42 ± 5.57	56.74 ± 18.33	33.79 ± 8.06	95.39	<0.001
LDL	70.19 ± 9.46	67.40 ± 34.77	207.89 ± 2.43	49.78	<0.001
VLDL	31.45 ± 13.28	43.85 ± 28.85	89.82 ± 50.53	67.24	<0.001
FBS	94.75 ± 7.10	124.34 ± 37.37	146.85 ± 7.90	48.48	<0.001
Fasting Insulin	0.71 ± 2.48	2.39 ± 9.29	7.02 ± 3.85	8.61	<0.001
HOMA-IR	0.17 ± 0.58	68 ± 2.69	2.70 ± 5.80	11.01	<0.001
Asprosin	19.99 ± 7.83	26.79 ± 8.67	47.30 ± 11.59	189.423	<0.001

Asprosin positively correlates with age, hypertension, diabetes status, and pulse rate, indicating higher levels in older individuals. A negative correlation with gender

suggests lower levels in males. Weak negative correlations were found with systolic and diastolic blood pressure, but no significant correlation was observed with weight, height, BMI, or pulse pressure. These findings suggest Asprosin's potential as a biomarker for age-related changes, hypertension, and diabetes (Table 3).

Table 3: Correlation of Asprosin with Demographic and General Physical Parameters

Variables	Pearson Correlation	p-Value
Age (in years)	0.317**	<0.001
Gender	-0.178**	0.004
Hypertension	0.222**	<0.001
Diabetes	0.581**	<0.001
Weight (kg)	0.006	0.930
Height (cm)	-0.019	0.759
BMI (kg/m ²)	0.036	0.570
Systolic BP (mmHg)	-0.128*	0.041
Diastolic BP (mmHg)	-0.136*	0.030
Pulse rate (beats/min)	0.279**	<0.001
Pulse pressure	-0.005	0.935
R/R (breaths/min)	-0.187**	0.003

**Correlation is significant at the 0.01 level (2-tailed). At a 95% confidence interval

*Correlation is significant at the 0.05 level (2-tailed). At a 95% confidence interval

BMI body mass index, blood pressure/R respiratory rate

The study found significant positive linear correlations between Asprosin and FBS, fasting insulin, HOMA-IR, cholesterol, triglycerides, LDL, and VLDL, indicating that higher Asprosin levels were associated with adverse metabolic profiles. In contrast, a significant negative correlation was observed between Asprosin and HDL, suggesting that elevated Asprosin levels may be linked to lower HDL levels, which are critical for cardiovascular and overall health (Table 4).

Table 4: Correlation of Asprosin with Biochemical Factors

Variables	Pearson Correlation (r)	p-Value
Cholesterol	0.481**	<0.001
Triglycerides	0.431**	<0.001
HDL	-0.586**	<0.001
LDL	0.483**	<0.001
VLDL	0.431**	<0.001
FBS	0.501**	<0.001
Fasting Insulin	0.315**	<0.001
HOMA-IR	0.321**	<0.001

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed).

HDL high high-density lipoprotein; LDL low density lipoprotein; VLDL: very low-density lipoprotein; FBS: fasting blood sugar; HOMA-IR: homeostatic assessment model of insulin resistance

DISCUSSION

When we compared the demographic and physical parameters, we noticed some significant differences among the groups we studied. The participants in the retinopathy group were older than those in the diabetic group, while the control group was notably younger than both. Ongoing hyperglycemia gradually weakens the retinal blood vessels, which play a role in diabetic retinopathy (DR), a condition that tends to be more severe in older individuals [13]. Previous research has also found a positive link between the prevalence of DR and the duration of diabetes, likely due to age-related changes in the retina that diminish macular blood flow and increase metabolic alterations. In comparison to the control group, both the diabetic and retinopathy groups showed higher BMI values, highlighting the connection between obesity, diabetes, and related complications. Earlier studies have similarly confirmed that a higher BMI is associated with diabetes, as excess body fat disrupts insulin metabolism through hormones and inflammatory markers, leading to insulin resistance and increased blood sugar levels [14]. The retinopathy group exhibited significantly altered lipid profiles compared to the diabetic group, while the control group maintained normal levels. Dyslipidemia can result in cholesterol buildup in the retina, which may lead to crystallization and contribute to DR, a finding that aligns with previous studies [15]. Current research revealed that the retinopathy group had higher levels of fasting blood sugar (FBS), fasting insulin (FI), and HOMA-IR compared to the other groups. In contrast, these parameters were within the normal range for the control group. Long-term high blood sugar can lead to various complications, including tissue inflammation, fluid imbalances, and damage to the retinal blood vessels, which aligns with findings from previous studies [16]. In the current study, serum Asprosin levels differed among the groups, peaking in the retinopathy group, followed by the diabetic group, and being the lowest in the control group. This peptide hormone is known to play a role in insulin sensitivity, appetite control, and energy balance, as highlighted in earlier research [17]. Interestingly, serum Asprosin levels tend to rise with age and prolonged diabetes, hinting at a link to metabolic issues like obesity and insulin resistance, which are more prevalent in older individuals. We observed some gender differences too, with females showing higher serum Asprosin levels than males, a finding that previous studies have also supported. This difference could be attributed to hormonal variations, body composition, and metabolic needs [18]. For instance, estrogen might boost Asprosin production, while testosterone could have the opposite effect, explaining these discrepancies. The severity of diabetes also plays a role in serum Asprosin

levels, with those experiencing poorly controlled diabetes showing higher levels compared to those with better control. Elevated Asprosin levels were positively correlated with fasting insulin, fasting blood glucose, HOMA-IR, LDL, and triglycerides, underscoring its involvement in disrupted glucose metabolism and diabetic complications [19]. Conversely, we found a negative correlation between Asprosin and HDL. Previous studies have further reinforced these connections, indicating that uncontrolled blood sugar levels can lead to complications like diabetic retinopathy [20].

The cross-sectional study design is one of the limitations of the study, as the patient sample was taken only once in the study. It was carried out at a single center setting, which may limit its generalizability to other clinical settings. Several factors, like the stage and severity of diabetic retinopathy (DR), duration of illness, medication usage, or patient compliance, were not accounted for in this study, which may limit the findings. Future studies should be conducted in compliance with the above limitations may produce profound effects on findings.

CONCLUSIONS

Higher levels of Asprosin might act as both diagnostic and prognostic indicators for DR, highlighting metabolic stress and inadequate glycemic control. This biomarker could be instrumental in pinpointing patients who are at a greater risk for DR, potentially allowing for timely interventions to prevent or slow down its progression. Asprosin shows great potential as a means for early detection and focused treatment of complications related to diabetic retinopathy. As it was a cross-sectional study, future longitudinal studies are needed to establish causality and determine its clinical utility.

Authors' Contribution

Conceptualization: AA, MUNI

Methodology: AS, MUNI

Formal analysis: AA, MUNI

Writing and Drafting: SS, SP, AS

Review and Editing: SS, SP, AS, MUNI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Correlation of Serum Ferritin Levels with Liver Iron Overload on Magnetic Resonance Imaging in Thalassemia Major Patients

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ABSTRACT

Blood transfusions are often necessary for people with thalassemia major, which causes iron buildup in critical organs. **Objectives:** To determine the correlation between Serum Ferritin and MRI-based liver iron levels. **Methods:** This cross-sectional analytical study was conducted on 101 beta thalassemia major patients visiting Shahida Islam Medical College and Hospital, Lodhran, in-between July 2024 to December 2024 using a non-probability consecutive sampling technique. Patients of Beta thalassemia major older than 15 years and dependent on blood transfusions were included in the study. Patients having any cardiac disease (valvular or congenital) or with any ongoing infection were excluded from the study. Patients who did not follow up regularly and did not consume chelation were also excluded. The association between serum ferritin concentrations and hepatic iron levels measured by T2 MRI was assessed using Spearman's correlation, with a p-value below 0.050 considered significant. **Results:** In this study of 101 thalassemia major patients, serum ferritin levels showed a significant negative correlation with liver iron overload measured by MRI ($r=-0.25$, $p=0.030$). Moderate hepatic iron overload was the most common finding (41.58%). Serum ferritin and AST levels increased significantly with worsening iron burden, while other liver function parameters showed no significant variation across groups. MRI proved more reliable than serum ferritin alone for assessing hepatic iron load. **Conclusions:** This study demonstrated a significant correlation between serum ferritin levels and hepatic iron overload evaluated through T2-weighted MRI in thalassemia major patients.

INTRODUCTION

Thalassemia represents a genetic disorder transmitted in an autosomal recessive pattern, in which hemoglobin formation is significantly impaired [1]. In the majority of patients, especially those with the major type of thalassemia, blood transfusions are frequently required, leading to iron accumulation in multiple organs [2]. The liver, heart, and endocrine systems are the organs where iron builds up the most often. The first organ to be loaded with iron is the liver [3]. In the initial phase of iron

accumulation, binding of transferrin takes place with an excess of iron. When transferrin surpasses the capacity to bind iron, then free iron starts appearing and accumulating in organs [4]. Iron, in its free state, is toxic to cells, leading to damage to tissues, causing significant mortality and morbidity. It may result in life-threatening complications, which include arrhythmia, liver fibrosis, heart failure, etc. [5]. Humans lack an active system for eliminating excess iron. Nearly all thalassemia major patients who receive



regular blood transfusions tend to slowly accumulate toxic amounts of iron over the years and show symptoms by age 10 years or so, sometimes even earlier [6]. By the time they reach early adolescence, they tend to have potentially lethal levels of iron in their body. If left untreated or if treatment is delayed, thalassemia-associated iron toxicity is regarded as the single most common factor causing organ damage [7]. Chelation therapy tends to remain the most effective method for alleviating excess iron overload. Therefore, it is vital to accurately assess the exact quantity of iron overload to manage chelation in beta thalassemia patients receiving transfusions [8]. Adjusting doses of iron chelation is of utmost importance in managing patients' extent of iron overload. Various known methods are available for measuring the overload of iron. Serum ferritin is often used indicator of iron overload, but it is also known to be an acute-phase protein; therefore, multiple factors can influence its levels, such as chelation, vitamin C levels, inflammation, infection, and damage to the liver [9]. On a clinical basis, levels of serum ferritin (SF) reflect the liver stores of iron. Even though a broad correlation exists in-between liver stores of iron and SF, predicting iron overloading from SF levels tends to remain unreliable [10]. In individuals with thalassemia major, serum ferritin is frequently utilized as a surrogate biomarker to measure body iron reserves. It is inexpensive and widely available; however, its reliability can be limited due to fluctuations influenced by inflammation, infection, or liver dysfunction. In contrast, Magnetic Resonance Imaging (MRI), particularly T2 or R2 techniques, is a more precise method of evaluating iron overload since it enables the direct and non-invasive measurement of liver iron content. Studies have shown that while there is often a correlation between serum ferritin and liver iron load measured by MRI, the strength of this association can vary. Thus, MRI serves as a confirmatory method to validate elevated serum ferritin levels and to guide iron chelation therapy more precisely [11]. Liver biopsies were the gold standard for detecting iron excess until recently. However, due to its invasiveness, it was linked with multiple complications [12]. Additionally, iron's distribution within liver cells is uneven, and so it's difficult to attain the best specimen for biopsy [13]. At present, biopsy is increasingly being replaced by Magnetic Resonance Imaging (MRI). A T2 MRI can reliably measure iron concentration in liver cells as well as the heart. It has the benefit of being non-invasive and beneficial for chelation therapy for individual patients [14]. Studies have shown a lack of correlation in-between the iron content of the liver and the iron content of the myocardium. Previously, SF levels were thought to be correlated with iron load in various organs. Recently, studies have demonstrated that other conditions, such as infection, inflammation, and chronic disorders, also influence SF

levels [15]. MRI, a reproducible and highly sensitive technique, detects the iron content of tissues. Its ability to enhance tissue's susceptibility towards MR intracellular makes it the recommended choice for measuring excess iron overload. It can help detect increased iron levels even before the occurrence of symptoms [16]. The iron load in thalassemia patients has been evaluated in the literature using techniques such as total iron binding capacity, serum ferritin, serum iron, echocardiography, liver biopsy, and T2 MRI [17]. There has been a mixed association between ferritin levels and iron buildup in organs. However, its levels may be affected by infection, inflammation, or any chronic/malignant condition. As a result, MRI with gradient echo T2 is the gold standard technique for non-invasive iron detection [18].

Regular blood transfusions in patients with beta thalassemia major lead to progressive iron accumulation in vital organs, particularly the liver, resulting in serious complications if not monitored properly. Although serum ferritin is widely used as a convenient and inexpensive biomarker to estimate body iron stores, its reliability is limited because it can be influenced by inflammation, infection, and liver dysfunction. Magnetic Resonance Imaging (MRI), especially T2-weighted techniques, provides a more accurate and non-invasive assessment of hepatic iron concentration. However, limited local studies have evaluated the correlation between serum ferritin levels and MRI-based liver iron overload in thalassemia patients, highlighting the need for further investigation. This study aimed to determine the correlation between biochemical markers of iron overload and MRI-based liver iron levels.

METHODS

This cross-sectional study was conducted on 101 beta thalassemia major patients at Shahida Islam Medical College and Hospital, Lodhran, from July to December 2024, with approval from the Institutional Review Board (IRB No. SIMC/ET.C./00031/24). A total of 140 patients were initially recruited through a non-probability consecutive sampling technique from the hospital's wards and outpatient department. Patients older than 15 years with a confirmed diagnosis of beta thalassemia major requiring blood transfusions were included, while those with cardiac disease (valvular or congenital), ongoing infections, irregular follow-up, or poor compliance with chelation therapy were excluded. The required sample size was calculated using the OpenEpi online tool with the formula $n = [DEFF \times Np(1-p)] / [(d^2/Z^2(1-\alpha/2 \times (N-1) + p(1-p))]$. Based on a hypothesized prevalence of 7% in Pakistan, with a 95% confidence level, 5% margin of error, a population size of 1,000,000, and a design effect of 1, the minimum sample size was estimated at 101 participants. After obtaining

informed consent, data were collected on a structured proforma, including baseline demographics, biochemical measurements, and MRI findings. Liver enzymes (ALT, AST, and SGPT) were measured using commercial colorimetric kits (Randox, Crumlin, UK). Hemoglobin levels were estimated by the cyanmethemoglobin method, considered the gold standard: 20 µL of blood was mixed with Drabkin's reagent (potassium ferricyanide and potassium cyanide), allowed to react at room temperature for 5 minutes, and absorbance was measured at 540 nm using a spectrophotometer against a standard calibration curve. Ferritin levels were quantified with a human ELISA kit (EH300RB, Thermo Fisher, Lithuania), and optical density was measured at 450 nm using a Stat Fax 2100 reader (USA). Hepatic iron status was evaluated by magnetic resonance imaging on a 1.5 Tesla Siemens scanner (Germany). T2 relaxation times were processed with CMR Tools (London, UK), and patients were classified as normal ($T_2 > 6.3$ ms), mildly overloaded (2.8–6.3 ms), moderately overloaded (1.4–2.8 ms), or severely overloaded (<1.4 ms) [19]. Data management and statistical testing were performed with SPSS version 23.0. The Shapiro–Wilk test analyzed variables distribution. Relationships between MRI-derived iron levels and biochemical markers (ALT, AST, SGPT, and serum ferritin) were assessed using Spearman's rank correlation, and group differences across iron overload categories were compared using the Kruskal–Wallis test. A p-value below 0.050 was considered statistically significant.

RESULTS

There were 101 individuals with beta thalassemia major in the research. Participants' median age was 21 years (IQR: 19–26 years). Among them, 63 (62.38%) were male and 38 (37.62%) were female. Diabetes mellitus was present in 24 (23.76%) patients. The median serum ferritin level was 3550 ng/ml (IQR: 2275–5950). Hepatic iron overload, assessed by MRI, was found to be moderate in 42 (41.58%) patients, while 26 (25.74%) each had normal or mild overload, and 7 (6.93%) had severe overload. The median ALT, AST, and ALP values for liver function were 42 U/L (IQR: 21–69), 39 U/L (IQR: 25–52), and 328 U/L (IQR: 200–495), respectively. The median levels of direct and total bilirubin were 0.32 mg/dL (IQR: 0.23–0.45) and 2.3 mg/dL (IQR: 1.7–3.8), respectively (Table 1).

Table 1: Baseline Demographics of Patients Included in the Study (N=257)

Variables		Median (IQR) / Frequency (%)	p-Value
Age (Years)		21 (19–26)	—
Gender	Male	63 (62.38 %)	0.180
	Female	38 (37.62 %)	

Diabetic status		24 (23.76 %)	—
Serum Ferritin (ng/ml)		3550 (2275–5950)	—
Hepatic Iron Load (T2 MRI)	Normal	26 (25.74 %)	<0.002
	Mild Overload	26 (25.74 %)	
	Moderate Overload	42 (41.58 %)	
	Severe Overload	07 (6.93 %)	
Liver Function Tests	ALT (u/L)	42 (21–69)	<0.001
	AST (u/L)	39 (25–52)	
	ALP (u/L)	328 (200–495)	
	Total Bilirubin (mg/dl)	2.3 (1.7–3.8)	
	Direct Bilirubin (mg/dl)	0.32 (0.23–0.45)	

*Chi-square and Kruskal–Wallis test applied

Across different grades of hepatic iron overload, T2' MRI values showed a marked decline with rising iron accumulation ($p < 0.001$). Gender distribution and diabetes status did not differ significantly among the groups ($p = 0.210$ and $p = 0.320$, respectively). Hemoglobin levels tended to decrease with higher iron load, although the change was not statistically significant ($p = 0.080$). Serum ferritin levels increased significantly with worsening iron overload, rising from 2275 ± 1825 ng/ml in the normal group to 5950 ± 3150 ng/ml in the severe group ($p < 0.001$). Among liver enzymes, AST showed a significant elevation ($p = 0.02$), while ALT, ALP, total bilirubin, and direct bilirubin remained statistically unchanged across the groups (Table 2).

Table 2: Comparison of Various Variables with Different Iron Deposition Levels on T2 Hepatic MRI (N=101)

Variables		Hepatic Iron Load				p-Value
		Normal (n=26)	Mild (n=26)	Moderate (n=42)	Severe (n=7)	
T2' MRI		8.2 (6.8–14.2)	3.8 (3.4–5.0)	2.3 (1.7–2.5)	1.1 (0.8–1.3)	<0.001*
Gender	Male	14 (13.86 %)	22 (21.78 %)	22 (21.78 %)	05 (4.95 %)	0.210
	Female	12 (11.88 %)	04 (3.96 %)	20 (19.8 %)	02 (1.98 %)	
Diabetes	Yes	03 (2.97 %)	06 (5.94 %)	08 (7.92 %)	07 (6.93 %)	0.320
	No	23 (22.77 %)	20 (19.8 %)	34 (33.66 %)	0	
Hemoglobin (mg/dl)		10.1 ± 1.1	9.8 ± 0.9	9.7 ± 1.0	8.9 ± 0.9	0.080
Serum Ferritin (ng/ml)		2275 ± 1825	2870 ± 1275	4250 ± 2875	5950 ± 3150	<0.001*
ALT (u/L)		25 (21–38)	31 (26–40)	36 (29–46)	42 (25–69)	0.080
AST (u/L)		28.5 (25.2–29.5)	32 (28.4–36.5)	39.5 (31.2–44.5)	42.5 (38.5–52)	0.020
ALP (u/L)		270 (200–325)	385 (252–430)	327 (280–410)	426 (325–495)	0.310
Total Bilirubin (mg/dl)		1.7 (1.4–2.0)	2.8 (2.1–3.1)	2.6 (3.5–4.1)	3.0 (2.9–3.6)	0.220
Direct Bilirubin (mg/dl)		0.28 (0.2–0.32)	0.32 (0.26–0.35)	0.39 (0.24–0.43)	0.34 (0.33–0.45)	0.380

*Chi-square and Kruskal–Wallis test applied

A correlation analysis revealed that serum ferritin levels were inversely related to hepatic iron load on MRI, showing statistical significance ($r = -0.25$, $p = 0.030$) (Figure 1).

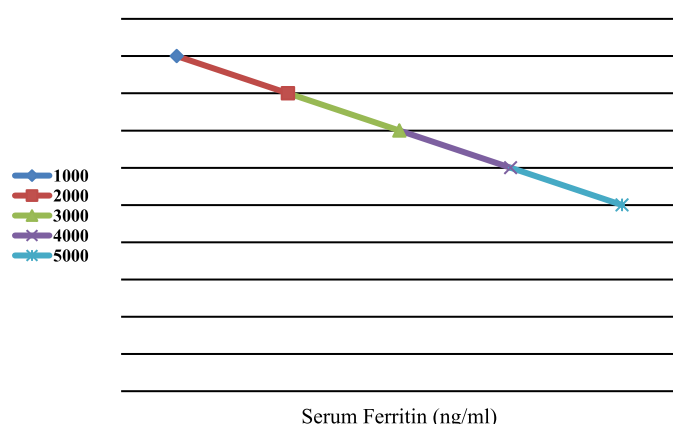


Figure 1: Correlation of Serum Ferritin with Liver Iron Load [Spearman Correlation Applied] ($r=-0.25$, $p=0.030$)

DISCUSSION

The study demonstrated a strong association between serum ferritin (SF) levels and hepatic iron accumulation in patients with beta thalassemia major, as measured by T2 MRI. Significant iron overload was observed in seven patients (6.93%). Patients with severe hepatic iron deposition exhibited higher AST and ALT levels compared to those with normal, mild, or moderate iron overload. However, a statistically significant association was observed only with AST levels. T2 MRI was preferred for iron quantification because it is non-invasive, safe, rapid, and reproducible, providing an indirect measure inversely correlated with intracellular iron deposition [20]. Consequently, T2 MRI is regarded as the gold standard for diagnosing and monitoring iron status in thalassemia major patients [21]. Consistent with our findings, Voskaridou et al. reported a substantial correlation between heart and liver T2 values and SF levels [22], while Fischer et al. observed similar results. Unlike our study, their research included cardiac iron assessment; due to financial constraints, cardiac T2 MRI was not evaluated in our study [23]. Other studies also reported significant correlations between SF levels and liver T2 MRI but found no significant association with cardiac T2 values [24]. Although SF is commonly used to estimate body iron stores in beta thalassemia major, its reliability is limited by co-existing clinical conditions such as inflammation, liver disease, or infection, which can alter SF levels [25]. Liver diseases are frequent in thalassemia major and are typically reflected by elevated AST and ALT levels. Our findings are in line with previous studies, including Mohammad et al., who reported a significant positive correlation between ALT and SF levels [26]. In contrast, current study observed a significant correlation only with AST. Despite evaluating both SF levels and hepatic MRI for iron load, this study has limitations, including a small sample size, single-center design, and cross-sectional nature, which restricted patient follow-up and assessment of chelation therapy

effectiveness. Future multi-center, longitudinal studies are warranted to validate these findings. Integration of MRI-based T2* assessments into routine clinical protocols could provide a reliable, non-invasive estimate of hepatic iron concentration, overcoming the limitations of SF measurements influenced by inflammation or liver dysfunction. Wider adoption of these imaging techniques may allow early detection of iron overload, timely optimization of chelation therapy, and reduced risk of iron-related complications. Establishing population-specific reference ranges and cost-effective imaging protocols could further enhance the feasibility of MRI-guided monitoring, particularly in resource-limited clinical settings.

This study has several limitations that should be considered while interpreting the findings. The research was conducted at a single center with a relatively small sample size, which may limit the generalizability of the results to the wider thalassemia population. In addition, the cross-sectional design did not allow long-term follow-up to evaluate changes in iron overload or response to chelation therapy. Future multicenter longitudinal studies with larger cohorts are recommended to further validate the relationship between serum ferritin and MRI-based iron assessment and to optimize monitoring strategies for thalassemia patients.

CONCLUSIONS

This study demonstrated a statistically significant correlation between serum ferritin levels and hepatic iron overload, as assessed by T2-weighted MRI, in patients with thalassemia major. Although serum ferritin remains a convenient and accessible biomarker for monitoring iron status, its variability can limit its accuracy in reflecting true liver iron overload. MRI-based assessment offers a more precise evaluation of hepatic iron overload and should be integrated into routine monitoring protocols, particularly in patients receiving regular transfusions.

Authors' Contribution

Conceptualization: MYK

Methodology: NM

Formal analysis: SA, NN

Writing and Drafting: SA, NN, KA, SI

Review and Editing: SA, NN, KA, SI, NM, MYK

All authors approved the final manuscript and take responsibility for the integrity of the work

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Original Article



Evaluation of Factors Leading to the Development of Acute Pancreatitis at Tertiary Care Hospital, Karachi

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ABSTRACT

Acute pancreatitis (AP) involves pancreatic inflammation that may extend to surrounding tissues. Clinical outcomes can be predicted through assessment of disease-specific prognostic markers. **Objectives:** To evaluate the prevalence of etiological factors for AP among patients at a tertiary healthcare center in Karachi. **Methods:** A descriptive cross-sectional design, this six-month study was conducted in the Medicine Department of Civil Hospital, Karachi, from 06-08-2022 to 05-02-2023. Participants were selected through convenience sampling (a non-probability approach). Data processing was done by SPSS version 26.0. Chi-square test was applied by taking a p-value of ≤ 0.050 , which is significant. **Results:** The research cohort comprised 135 eligible participants with a mean age of 46.71 ± 6.82 years. Gender distribution showed 55 male patients (40.7%) and 80 female patients (59.3%). Out of the 135 patients, 43.7% had cholelithiasis, 11.1% had alcohol induced pancreatitis, 17.8% had post-ERCP pancreatitis, 14.8% had hypertriglyceridemia, and 10.4% had IgG4-mediated pancreatitis. **Conclusions:** Acute pancreatitis is a multi-factorial pathology of different severity and outcomes. Gallstones were found to be the most prevalent cause of the condition.

INTRODUCTION

Acute pancreatitis (AP) is a form of inflammation of the pancreas. Although it has a mild course in most cases and does not cause serious complications in about 80% of cases, it may cause serious complications, and up to 20% may also succumb to it in some individuals [1]. A patient with acute epigastric pain that radiates to the back, nausea and vomiting must also be urgently examined to exclude several potentially fatal illnesses, among which there are

myocardial infarction, rupture or aortic aneurysm, peptic ulcer disease and its complications of hemorrhage or penetrating injury, and acute pancreatitis [2]. The patient's history should guide the clinician, who should conduct a physical inspection to assess specific issues and review the results of appropriate diagnostic tests to establish a proper treatment plan by narrowing the range of potential diagnoses [3, 4]. The prevalence of risk factors is known to

vary geographically and demographically, which is one reason the causes and incidence of acute pancreatitis differ across geographic regions [5]. Common etiological factors include alcoholic pancreatitis with higher overall acute pancreatitis incidence in certain countries as compared to countries with predominantly gallstone pancreatitis, as it is reported differently in various countries in terms of incidence curve [6]. Hospital visits in emergency departments due to acute pancreatitis have been on the rise. In 2012, the emergency visits rate for AP was 105 per 100,000 population, and the general mortality rate was approximately 1%. Death is more likely to occur when age increases, the presence of comorbidity and greater severity of diseases, especially caused by infected pancreatic necrosis and multiorgan failure [7]. Gallstones are the most prevalent causative factor of acute pancreatitis, whereas alcohol is more prominent among middle-aged men. The unknown cause known as idiopathic cases causes 20% to 34% of the cases, with no difference in their rates of occurrence among men and women [8-10]. The rate of idiopathic pancreatitis may vary depending on the clinician's diligence in seeking the underlying cause of the condition, as reported by patients [11]. Autoimmune pancreatitis (AIP) is an infrequent nonneoplastic disease, which is considered a different manifestation of pancreatic ductal adenocarcinoma (PDAC). The level of serum immunoglobulin G4 (IgG4) is useful for distinguishing between these disorders, as elevated IgG4 is a characteristic feature of AIP but not observed in PDAC patients [12]. Hameed et al., reported the etiologic distribution of acute pancreatitis (AP) in their cohort: 74% cholelithiasis, 2.6% alcohol-induced pancreatitis, 4.5% post-ERCP pancreatitis, and 0.6% hypertriglyceridemia with IgG4-mediated pancreatitis [13]. Efficient prevention measures and treatment regimens are still important interventions recommended to be adopted globally to limit the morbidity and deaths due to acute pancreatitis. Although significant progress has been made in the pathophysiological understanding of this condition over the last fifteen years, it remains challenging for clinicians to manage its multifactorial aetiology and complex clinical manifestations [14]. There are also changes in lifestyle, demographic shifts, socioeconomic status, and morbidities that continue to evolve. These factors should be acknowledged in the prevention of the onset of irreversible chronic pancreatitis, as the most valuable measures to prevent its occurrence must have been established previously [15]. Ultimately, understanding the various causes that contribute to the development of acute pancreatitis is crucial for effectively managing and preventing the condition. This study provides a benchmark that can be shared with other healthcare facilities, which

will be the study's key result. Finally, there is a need to understand the factors leading to the development of acute pancreatitis for its better management and prevention. Hence, the results from this study form the benchmark that is shared with other healthcare facilities. The findings of this study are expected to provide valuable insights into the unique clinical profile of acute pancreatitis in this population, enabling the development of targeted interventions and enhancing the overall management of this challenging condition.

Acute pancreatitis is a common gastrointestinal emergency with diverse etiological factors such as gallstones, alcohol consumption, metabolic disorders, and post-procedural complications. The distribution of these risk factors varies across different populations due to demographic, lifestyle, and healthcare differences. In Pakistan, particularly in tertiary care hospitals, limited local data are available regarding the relative prevalence of these etiological factors among patients presenting with acute pancreatitis. This lack of region-specific evidence creates a gap in understanding the dominant causes and limits the development of targeted preventive and management strategies. This study aims to evaluate the prevalence of etiological factors for AP among patients at a tertiary healthcare center in Karachi.

METHODS

A descriptive cross-sectional study was conducted at the Department of Medicine, Civil Hospital, Karachi, from 06-08-2022 to 05-02-2023 after getting ethical approval from the CPSP research evaluation unit (Ref No: CPSP/REU/MED-2019-183-15622) and written informed consent was obtained from the patients. Using the WHO sample size calculator with a 4.5% post-ERCP incidence rate [13], 3.5% margin of error, and 95% confidence interval, we calculated a required sample of 135 subjects. A design effect (DEFF) of 1 was applied to account for a simple random sampling design. The total population size was estimated at 20,000. The study utilized a non-probability consecutive sampling methodology. Inclusion criteria was confined on newly diagnosed patients with acute pancreatitis presenting within 24 hours, either gender, patients having age of 30-60 years were included and patients with history of hepatitis B, C and HIV, patients with history of malignancy, pregnant women, patients with history of asthma, COPD, stroke, congestive heart failure, Patients with chronic liver disease and chronic kidney disease were excluded from the study. The patient's history was taken in detail, and they underwent a clinical examination upon admission. The researcher also examined possible causes of acute pancreatitis development, such as cholelithiasis (diagnosed with the help of an abdominal ultrasound), alcohol abuse, post-

ERCP surgery, hypertriglyceridemia (a lipid profile), and IgG4-related pancreatitis (a sample of IgG4). A quantitative research design was employed in this study; participants' age was treated as a continuous variable. Qualitative variables were gender, residential status, type 2 diabetes mellitus, hypertension, smoking status and the risk factors of acute pancreatitis. The data analysis was conducted using the SPSS version 26.0. Means were calculated as the mean value $\pm$ standard deviation (SD) in cases of normally distributed quantitative variables. Qualitative variables, including gender, residence status, type II diabetes mellitus, hypertension, smoking status, and all factors related to acute pancreatitis (cholelithiasis, alcohol consumption, post-ERCP, hypertriglyceridemia, and IgG4-mediated pancreatitis), were calculated in terms of frequency and percentages. To measure the modification effect of the factors, stratification was based on the attributes of age, gender, residence status, type 2 diabetes mellitus, hypertension, and smoking status. This enabled them to be evaluated regarding their effects on the outcome variables. Following stratification of the data, statistical analysis was conducted using chi-square or Fisher's exact tests, where a p-value ≤ 0.050 denoted significance.

RESULTS

This research analyzed 135 patients treated at the Civil Hospital Karachi's Department of Medicine, Pakistan, who met the study's inclusion and exclusion criteria. The participants' ages varied from 30 to 60 years, with a mean age of 46.71 ± 6.82 years. Regarding the gender distribution, 55 (40.7%) were male and 80 (59.3%) were female. Regarding the status of residence, 43 (31.9%) were residing in urban locations, while 92 (68.1%) were in rural locations. Regarding hospital stay, most of the patients stay for ≤ 5 days (66.67%) (Table 1).

Table 1: Demographic, Clinical, and Biochemical Characteristics of Patients

Variables	Frequency (%)	Mean ± SD
Age (Years)		
30-45	103 (76.30%)	46.71 ± 6.82
46-60	32 (23.70%)	
Gender		
Male	55 (40.70%)	-
Female	80 (59.30%)	
Residence		
Urban	43 (31.90%)	-
Rural	92 (68.10%)	
Length of Hospital Stay		
≤5	90 (66.67%)	-
>5	45 (33.33%)	

Findings demonstrate risk factors causing pancreatitis.

Out of 135 patients, 59 (43.7%) and 76 (56.3%) had and did not have cholelithiasis, respectively. Out of 135 patients, 15 (11.10%) had alcohol, and 120 (88.90%) did not have respectively. Out of 135 patients, 24 (17.8%) had post-ERCP, and 111 (82.2%) did not have post-ERCP, respectively. Out of 135 patients, 20 (14.8%) had hypertriglyceridemia, and 115 (85.2%) did not have hypertriglyceridemia, respectively. Out of 135 patients, 14 (10.4%) had IgG4-mediated disease, and 121 (89.6%) did not have IgG4-mediated disease, respectively, where chi-square results indicate a p-value of 0.001 (Table 2).

Table 2: Risk Factors Causing Pancreatitis

Variables	Frequency (%)	p-Value
Cholilithiasis	59 (43.70%)	0.001
Alcohol	15 (11.10%)	0.001
Post ERCP	24 (17.80%)	0.002
Hypertriglyceridemia	20 (14.8%)	0.002
IgG4 mediated	14 (10.4%)	0.003

Results shows the associated factors causing pancreatitis. Frequency distribution on diabetes mellitus type II showed that out of 135 patients, 97 (71.90%) had diabetes mellitus type II while 38 (28.10%) did not have diabetes mellitus type II respectively. In the case of hypertension, 46 (34.1%) patients were dominated by hypertension, whereas 89 (65.9%) were non-hypertensive. About smoking status, 15 (11.1%) patients were smokers, while 88.9% of patients were non-smokers (Table 3).

Table 3: Associated Factors

Variables	Frequency (%)
Diabetes Mellitus Type II	
Yes	97 (71.90%)
No	38 (28.10%)
Hypertension	
Yes	46 (34.10%)
No	89 (65.90%)
Smoking	
Yes	15 (11.10%)
No	112 (88.90%)

An age and gender stratification of cholelithiasis revealed that among individuals aged 30-45 years, 45 (43.7%) had cholelithiasis, while 58 (56.3%) did not. In the 46-60 years age group, cholelithiasis was exhibited in 14 (43.8%), whereas most had no such occurrence (18, 56.2%). The relationship between cholelithiasis and age was not statistically significant, with a p-value of 0.990. In the stratification by gender, 15 (27.3%) out of the total of males had cholelithiasis, whereas 40 (72.7%) were found to possess none. Among the female patients, 44 (55%) had cholelithiasis, while 36 (45%) did not. The p-value was large ($p=0.010$), indicating a significant association (Table 4).

Table 4: Stratification for Age and Gender with Respect to Cholelithiasis

Variables	Cholelithiasis		p-Value
	Yes	No	
Age (Years)			
30-45	45 (43.7%)	58 (56.3%)	0.990
46-60	14 (43.8%)	18 (56.2%)	
Gender			
Male	15 (27.3%)	40 (72.7%)	0.010
Female	44 (55%)	36 (45%)	

DISCUSSION

Acute pancreatitis is an interesting disease, categorized by the inflammation of pancreatic tissue, parenchyma oedema, and necrosis due to auto-digestion of the glandular enzymes, which can cause multi-organ failure or even death [16]. Gallstones represent the most common etiology of acute pancreatitis in Pakistan, whereas alcohol-related cases are relatively less frequent. In daily routine practice, drug-induced acute pancreatitis is not very common [17]. Over the last several decades, the intensive care of patients with AP has improved significantly because of its connection with high morbidity and mortality rates. The aetiology of the disease must be determined to effectively handle and prevent further occurrences of the disease. Two of the most frequent etiological factors, i.e. alcohol and gallstones, account for a total of 80%, and alcoholic pancreatitis is by far much more prevalent [18]. According to the recent recommendations, the current aetiology of AP must be determined in at least 80% of cases, and not more than 20% can be seen as idiopathic. The management and administration of care to AP should be planned according to the knowledge of the equivalence as well as the aetiology of the disease [19]. According to the study done by Hameed *et al.* out of the 154 patients, 59.1% were women [13]. The most frequent aetiology encountered was gallstones (74%), followed by idiopathic (13%). A cholecystectomy performed on 44.7% of gallstone pancreatitis patients is called a same-admission cholecystectomy. Upon admission, 14.9% of patients had serum amylase levels within three times the upper normal limit, while 29 (18.8%) exhibited serum lipase levels within the same range. A greater score on the Ranson and modified CT severity index translated to a greater triage and death percentage. The rate of complications was 21.4 % with a mortality rate to be 7.1%. There were two hundred and twelve (212) patients in a research study conducted by Patel *et al.*, [20], with 88 men (73.33%) and 32 women (26.66%). The average age of the participants was 36.96 years, with a standard deviation of 13.44 years. The most frequent presenting symptom was abdominal pain, and then came vomiting. Alcohol use was the major cause of acute pancreatitis, as it was the cause in 85 patients

(70.8 per cent). The cause was identified in 25 patients (20.8%), and in five patients (4.1%), it was unknown. There were three deaths as a result of severe pancreatitis among the patients (2.5%). Additionally, a body mass index (BMI) of 25 kg/m² or higher, a hematocrit (HCT) of 44 % or more, and a C-reactive protein (CRP) level of more than 150 mg/L were associated with a higher risk of developing severe acute pancreatitis. Datta *et al.*, used a sample of 40 patients with acute pancreatitis, comprising 20 male and 20 female, with an average age of 44.3 ± 2.7 years [21]. Out of the 40 cases, 26 patients (65%) received a diagnosis of moderate to severe acute pancreatitis.. Certain clinical parameters, such as ascites or pleural effusion, were not identified to have significant correlations with the severity of the illness. 62.5% of the cases displayed gallstones and metabolic conditions such as hypertriglyceridemia and hypercalcemia; however, none of them could be, in any way, significantly associated with the severity of the disease.

This study was conducted at a single tertiary care center with a relatively limited sample size and utilized convenience sampling, which may affect the generalizability of the findings. Additionally, the cross-sectional design restricts the ability to establish causal relationships between risk factors and the development of acute pancreatitis. Long-term clinical outcomes and recurrence rates were not assessed. Future multicenter prospective studies with larger sample sizes and extended follow-up are recommended to better understand etiological patterns and improve preventive and therapeutic strategies for acute pancreatitis.

CONCLUSIONS

AP is still a typical diagnosis that causes hospitalization. Gallstones are the most frequent cause, and post-ERCP comes next. It has a great influence on institutional costs, hospitalization and death. The disease severity may be mild or severe and entails a risk of having systemic complications. The main points of management are timely fluid resuscitation, adequate nutrition support, and management of complications at the moment they occur. Patients with mild acute pancreatitis due to gallstones are normally recommended to undergo cholecystectomy before their release to avoid any recurrence. A multidisciplinary approach is encouraged when looking at moderate to severe cases of acute pancreatitis, especially with local and systemic complications.

Authors' Contribution

Conceptualization: MA

Methodology: MA, AWS, RS, AZ

Formal analysis: MA

Writing and Drafting: FT¹, FT², AWS, AZ

Review and Editing: FT¹, FT², AWS, AZ, MA, RS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Original Article



The Effect of Ferulic Acid on Inflammation in a Myocardial Ischemia-Reperfusion Experimental Model

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ABSTRACT

Cardiovascular disease is a leading cause of death globally, with ischemia-reperfusion injury (IRI) causing tissue damage through oxidative stress and inflammation. Interleukin-6 (IL-6) plays a role in IRI-related myocardial damage. Ferulic acid, a plant-derived phenolic compound, shows potential as an anti-inflammatory and antioxidant therapy to reduce IRI. **Objectives:** To investigate the dose-dependent protective effect of ferulic acid in an experimental myocardial ischemia-reperfusion injury model, focusing on its impact on serum IL-6 levels. **Methods:** This experimental study was conducted over 6 months by the Department of Pharmacology at Rehman College of Dentistry, Peshawar, Pakistan, utilizing healthy male Sprague Dawley rats weighing 300–350 grams (g). Rats showing signs of illness were excluded from the study. Twenty rats were randomly allocated to control (n=10) and treatment (n=10) groups. Preceding the induction of ischemia-reperfusion injury, the treatment group was administered oral ferulic acid for 15 days; controls were untreated. Data were analyzed using SPSS version 23.0. Results are presented as mean ± standard deviation, and the mean difference was compared by an independent sample t-test, taking $p < 0.050$. **Results:** IL-6 levels in serum were measured using ELISA, with control rats showing higher IL-6 (66–80 ng/l) than ferulic acid-treated rats (46–55 ng/l). There was a significant reduction in IL-6 levels in the treated group. This indicates ferulic acid lowers inflammation in myocardial ischemia-reperfusion injury. **Conclusions:** It was concluded that the ability to lower the IL-6 level and modulate oxidative-inflammatory pathways, ferulic acid can be a promising therapeutic agent to attenuate myocardial inflammatory responses and reperfusion injury.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death in Southeast Asia as well as globally [1,2]. Myocardial infarction (MI), which afflicts over a million people per year in the United States alone [3], frequently results in ischemia-reperfusion injury (IRI) an unexpected tissue injury caused by the reinstatement of blood flow to ischemic myocardium [4, 5]. IRI is a complex process in which oxidative stress, mitochondrial injury, calcium overload, apoptosis, and substantial inflammation are implicated [6, 7]. Inflammation is closely involved in the

process of IRI. For pro-inflammatory cytokines, interleukin-6 (IL-6) is particularly relevant because of its association with myocardial dysfunction, infarct expansion, and adverse remodeling [8–10]. Increased concentration of IL-6 has been associated with acute coronary syndromes, heart failure, and poor cardiac outcomes [11]. In addition, IL-6 stimulates C-reactive protein (CRP) production and thus exacerbates the inflammatory cascade [12]. Modulation of the inflammatory response during reperfusion is important for



enhancing recovery of the heart. Novel therapies now include anti-inflammatory and antioxidant treatments to alleviate IRI [13]. Of these, ferulic acid (FA) has demonstrated potential as a phenolic compound found in plant sources such as rice bran, sweet corn, and tomatoes. FA has a significant antioxidant and anti-inflammatory capacity against free radicals, initial inhibition of NF- κ B, and reduced expression of IL-6, TNF- α , and COX-2 [14, 15]. Along with the antioxidant effects of Ferulic Acid, FA also provides neuroprotective, hepatoprotective, cardioprotective, and antidiabetic actions, hence making it a pleiotropic compound as compared to more narrowly acting phenolics [16].

Myocardial ischemia-reperfusion injury (IRI) remains a major contributor to cardiac morbidity and mortality, primarily due to oxidative stress and heightened inflammatory responses, particularly elevated IL-6 levels. Although several antioxidant and anti-inflammatory agents have been explored, the therapeutic potential of naturally occurring polyphenols like ferulic acid in attenuating IRI-induced inflammation is not fully elucidated. Limited experimental evidence exists on the dose-dependent effects of ferulic acid specifically on IL-6 modulation in myocardial IRI, highlighting a critical gap in understanding its cardioprotective efficacy. This study aims to investigate the dose-dependent protective effect of ferulic acid in an experimental myocardial ischemia-reperfusion injury model, focusing specifically on its impact on serum IL-6 levels using a rat ELISA assay.

METHODS

This experimental study was conducted at the Department of Pharmacology, Rehman College of Dentistry, Rehman Medical Institute, Peshawar, Pakistan. All experimental procedures were conducted in compliance with institutional ethical guidelines, and ethical consent was obtained from the Institutional Review Board of Rehman Medical College of Dentistry, Peshawar, Pakistan (Ref. No. RCD-09-22-1135). The study was conducted over six months, from January to June 2023. The first two months were dedicated to randomization and intervention, followed by the next two months, during which intervention and laboratory analysis were carried out alongside preliminary statistical analysis. The fifth and sixth months were focused on data handling, detailed statistical analysis, and preparation of the final report. This study consisted of 2 major experimental phases that included the dose-response activity of ferulic acid as well as its protective effect against myocardial ischemia/reperfusion in rats. Male Sprague Dawley (SD) rats (300–350 g) were used in the present study. The healthy adult male rats that were negative for infection or pre-existing disease were selected as the inclusion criteria. Rats that displayed

altered behavior, including signs of disease or body weight outside the ideal range, were not included in the study. Ferulic acid and Rat IL-6 Enzyme-linked immunosorbent assay (ELISA) Kit were purchased from Sigma-Aldrich® RAB0114. Eppendorf Tubes® and square Petri dishes (120 mm × 120 mm) were obtained from Thermo Scientific™, and the Eppendorf pipette used in the experiment was from RochG*Power 3.1. was used to determine the sample size. For the dose-response phase ($n = 5$ per group): For a one-way ANOVA with $\alpha = 0.05$, power $(1 - \beta) = 0.80$, and $k = 4$ –5 groups, $n = 5$ per group provides 80% power to detect a large effect size (Cohen's $f \approx 0.78$ –0.84; $\eta^2 \approx 0.38$ –0.41). Treatment phase ($n = 10$ per group): For a two-sample comparison (two-tailed t-test, $\alpha = 0.05$, power = 0.80), $n = 10$ per group provides 80% power to detect a large effect size (Cohen's $d \approx 1.32$). Our pilot data for IL-6 indicated an expected effect size of $d \approx 1.6$, exceeding this threshold. Randomization was carried out by using a simple random number generator to avoid selection bias. To determine the optimal dose of ferulic acid, 30 rats were randomly divided into six groups of five rats each. Group 1 received only a standard rat diet, while the other groups received ferulic acid orally at doses of 10, 20, 30, 40, and 50 mg/kg diluted in water for 15 days, five times per week. The animals were kept in cages under a controlled environment with a constant temperature of 22–24 °C and were given pellet diets ad libitum. After one hour of oral administration on the final dosing day, 0.5 mL of blood was collected from the lateral tail vein of each rat into sterile anticoagulated tubes and stored at –80 °C. Samples were centrifuged at 3500 rpm for 15 minutes. The concentration of ferulic acid in the serum was measured using HPLC at a UV wavelength of 320 nm. To induce ischemia-reperfusion injury, 20 rats were randomly assigned to either a control group ($n = 10$) or a treatment group ($n = 10$). The treatment group received the optimized dose of ferulic acid orally for 15 days, while the control group received no treatment. Anesthesia was induced using 5% isoflurane in 50% oxygen via a facial mask and maintained with 2% isoflurane during the procedure. The left anterior descending (LAD) coronary artery was ligated for 30 minutes, followed by 120 minutes of reperfusion to simulate ischemia-reperfusion injury. After completion of the reperfusion period, 1 mL of blood was collected via cardiac puncture using a 23G1 needle and a 5 mL syringe. Serum IL-6 levels were quantified using the Rat IL-6 ELISA kit to assess inflammation. Data were analyzed using SPSS version 23.0. Data were expressed as mean $\pm$ standard deviation (SD). Normality of IL-6 values was assessed using the Shapiro-Wilk test. For comparison between groups: If normally distributed, the independent-samples t-test (two-tailed) was applied. If not normal, the Mann-Whitney U test was used. For Effect sizes, the

Parametric: Cohen's d with 95% confidence intervals (CI) was used. The confidence intervals for mean differences were calculated by using SD and the t-distribution. The Significance was set at $\alpha=0.05$. Exact p-values are reported; $p<0.001$.

RESULTS

This research analyzed 135 patients treated at the Civil Hospital Karachi's Department of Medicine, Pakistan, who met the study's inclusion and exclusion criteria. The participants' ages varied from 30 to 60 years, with a mean age of 46.71 ± 6.82 years. Regarding the gender distribution, 55 (40.7%) were male and 80 (59.3%) were female. Regarding the status of residence, 43 (31.9%) were residing in urban locations, while 92 (68.1%) were in rural locations. Regarding hospital stay, most of the patients stay for ≤ 5 days (66.67%) (Table 1).

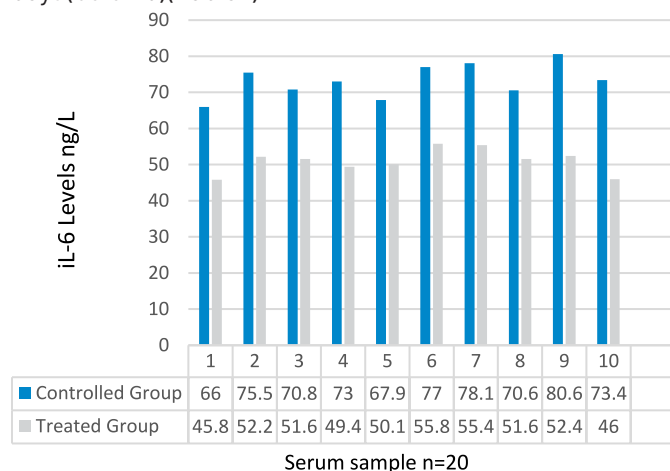


Figure 1: Comparison of IL Levels Between the Treated and Control Groups

Descriptive statistics, the Shapiro-Wilk test indicated that IL-6 values in both the groups were normally distributed (Control: $W=0.96$, $p=0.610$; and Treatment group: $W=0.94$, $p=0.480$) (Table 1).

Table 1: Descriptive Statistics and Normality Testing of IL-6 Concentrations

Groups	Number (n)	Mean $\pm$ SD (ng/L)	95% CI (ng/L)	Shapiro-Wilk W (p)
Control	10	71.2 $\pm$ 3.2	68.9–73.5	0.960 ($p=0.61$)
Treatment	10	49.2 $\pm$ 2.1	47.7–50.7	0.940 ($p=0.48$)

The treatment group demonstrated a significant decrease in IL-6 as compared with the Control, with a mean difference of 22.0 ng/L (95% CI: 19.0–25.0), $p<0.001$. The standardized effect size was Cohen's $d=8.18$ (95% CI: 5.10–11.25), which reflected a large treatment effect. Serum IL-6 levels between the control group and the ferulic acid-treated group following myocardial ischemia-reperfusion injury. The control group showed significantly higher IL-6 levels (mean 71.2 ± 3.2 ng/L) compared to the treated group (mean 49.2 ± 2.12 ng/L). Statistical analysis revealed a

significant difference between the 2 groups ($p<0.001$). This indicates that ferulic acid administration effectively reduced IL-6 levels, suggesting a potent anti-inflammatory effect in the experimental model. These findings support the role of ferulic acid in attenuating inflammation associated with ischemia-reperfusion injury (Table 2).

Table 2: Comparison of Serum IL-6 Levels between Control and Ferulic Acid-Treated Groups in Myocardial Ischemia-Reperfusion Injury Model

Comparison	Mean differences (95% CI)	Statistical Test	Effect Size (Cohen's d, 95% CI)	p-Value
Control vs Treatment Group	22.0 (19.0 – 25.0)	Independent t-test	8.18 (5.10 – 11.25)	<0.001

DISCUSSION

Plant polyphenol ferulic acid is effective at inhibiting inflammation triggered by myocardial I/R injury in rats. Serum interleukin-6 (IL-6) levels were significantly lower in the treated group compared to the controls, suggesting that ferulic acid had a potential protective effect on the attenuation of inflammation damage post-reperfusion. IL-6 is a major pro-inflammatory cytokine involved in tissue edema, neutrophil infiltration, and oxidative injury; hence, its inhibition is good evidence for its anti-inflammatory action. Multiple earlier studies validate these findings. Aneja *et al.* noted that epigallocatechin-3-gallate (EGCG) mitigated myocardial injury by blocking the NF- κ B and AP-1 signaling pathways, which resulted in decreased IL-6 and neutrophil activity during I/R injury in rats [17]. Likewise, Chen *et al.* found that rosmarinic acid lessened cardiomyocyte apoptosis and improved heart function by activating PPAR γ and suppressing inflammation via NF- κ B [18]. Lv *et al.* reported that total flavones of *Abelmoschus manihot* lowered serum IL-6 and TNF- α and reduced oxidative stress (MDA), while increasing antioxidant enzymes (SOD), thus conserving myocardial tissue from I/R injury [19]. Furthermore, Zhao *et al.* identified a synergistic drug combination from traditional Chinese medicine, including ferulic acid that effectively reduced IL-6, TNF- α , and oxidative markers, and enhanced myocardial structure and antioxidant defenses [20]. Their mechanistic findings highlighted activation of PPAR γ and inhibition of NF- κ B and Akt signaling, consistent with polyphenols' known bioactivity. Additional work by Sahu *et al.* emphasized the therapeutic role of polyphenols such as quercetin and ferulic acid in cardio protection by reducing inflammatory cytokines, inhibiting neutrophil activation, and attenuating oxidative stress following I/R injury [21]. In another animal study, Luo *et al.* demonstrated that ferulic acid significantly decreased infarct size and myocardial inflammatory infiltration, associated with downregulation of IL-6, IL-1 β , and TNF- α , and upregulation of SOD and catalase activity [22]. Oxidative stress and inflammation are correlated in

the pathophysiology of I/R injury. During reperfusion, excessive production of reactive oxygen species (ROS) exacerbates myocardial damage and promotes cytokine release. Polyphenols like ferulic acid act as free radical scavengers, modulate transcription factors (e.g., NF- κ B), and enhance endogenous antioxidant systems such as SOD and catalase, thereby mitigating both oxidative and inflammatory injury [22]. Moreover, the narrow standard deviation may be because all rats were approximately the same age and weight (300–350 g), kept under standardized environmental conditions, and all the selected rats were free from infection, which likely had reduced biological variability. Also, serum IL-6 measurements were performed using a high-sensitivity ELISA kit with technical replicates, which might have contributed to consistency in the readings. Despite the results, several limitations must be considered. The study had a relatively small sample size, which limited the generalizability and statistical reliability. Since only male rats were used in the study, the study excluded sex-based responses to ferulic acid. Moreover, the treatment duration was short, which may not reflect long-term efficacy or safety. Finally, a comparative reference group using standard antioxidants or anti-inflammatory drugs was not included, which limits the ability to position the effects of ferulic acid relative to established therapies.

This study was limited by a small sample size, use of only male rats, and a short treatment duration, which may restrict the generalizability of the findings. Future research should include both sexes, larger cohorts, and extended treatment periods to assess long-term effects. Additionally, comparative studies with standard anti-inflammatory and antioxidant therapies are warranted to establish the relative efficacy of ferulic acid and clarify its mechanisms in myocardial protection.

CONCLUSIONS

In conclusion, the current study aligns with a growing body of evidence suggesting that ferulic acid has significant cardioprotective effects in the context of I/R injury. By reducing IL-6 levels and modulating oxidative-inflammatory pathways, ferulic acid may serve as a valuable therapeutic agent to attenuate myocardial inflammation and limit reperfusion injury. Future studies are needed to address the gaps by including both male and female rats, increasing the sample sizes, and experimenting with ferulic acid in relevant disease models. Increasing the duration of treatments and dose-response studies will further help to clarify the mechanisms of action. Comparative trials with other standard antioxidants or anti-inflammatory agents are also recommended to establish its relative efficacy.

Authors' Contribution

Conceptualization: NA,

Methodology: NA, AIQ, MZY

Formal analysis: MT, MS

Writing and Drafting: AIQ, MZY, MT, MS

Review and Editing: AIQ, MZY, MT, MS, NA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Neutrophil-Lymphocyte Ratio as a Prognostic Marker for Inflammatory Status Among Patients with Diabetes Mellitus

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder associated with systemic inflammation and multiple vascular complications. Identifying accessible and cost-effective biomarkers for inflammation can improve the management and prognosis of diabetic patients. **Objectives:** To evaluate the neutrophil to lymphocyte ratio (NLR) as a prognostic marker for inflammatory status in patients with diabetes mellitus. **Methods:** This cross-sectional analytical study included 212 diabetic patients recruited from Liaquat University Hospital, Hyderabad. Data were collected on demographics, clinical history, complications, and comorbidities. Blood samples were analyzed for complete blood count and C-reactive protein (CRP) to calculate NLR. Patients were categorized based on normal (≤ 3) or raised (> 3) NLR. Statistical analysis was performed using SPSS version 21.0, with $p < 0.050$ considered significant. **Results:** Of the 212 participants, 52.8% were female and 81.1% had Type 2 diabetes. Raised NLR was observed in 24.1% and elevated CRP in 40.1%. Neuropathy (34.4%) and nephropathy (24.5%) were the most frequent complications. Raised NLR was significantly associated with elevated CRP ($p = 0.012$), diabetic nephropathy ($p = 0.030$), and diabetic retinopathy ($p = 0.040$), while no significant association was observed with gender, duration of diabetes, or hypertension. **Conclusions:** NLR is a cost-effective, readily available marker significantly associated with systemic inflammation and microvascular complications in diabetes. It holds promise for routine inflammatory screening in clinical settings.

INTRODUCTION

Chronic inflammation is increasingly recognized as a central mechanism in the pathogenesis of type 2 diabetes mellitus (T2DM) and its complications [1, 2]. The neutrophil-to-lymphocyte ratio (NLR), a simple calculation from routine complete blood count (CBC) has emerged as a reliable, cost-effective surrogate marker of systemic inflammatory status [3]. Physiologically, NLR elevation reflects the dual shift in immune response during chronic inflammation. Neutrophilia occurs due to increased bone marrow stimulation by pro-inflammatory cytokines (such as IL-6 and TNF- α), while lymphopenia results from stress-induced cortisol release and apoptosis of lymphocytes,

collectively contributing to a raised NLR [4]. Several recent meta-analyses and cohort studies have confirmed NLR's association with poor glycemic control (HbA1c elevations), diabetic nephropathy, retinopathy, and cardiovascular disease outcomes among T2DM patients [5, 6]. Despite its global relevance, the utilization of NLR in Pakistan has only recently begun to be validated through local research. [7] A notable retrospective cohort study at Aga Khan University Hospital in Karachi assessed 130 patients hospitalized with diabetic foot ulcers and found that an NLR greater than 4 was significantly associated with higher ulcer grades, increased rates of major amputation, greater



postoperative complications ($p < 0.001$), and elevated in-hospital and 1-year mortality ($p = 0.008$ and $p = 0.010$ respectively). This finding supports the role of NLR as a sensitive and economically feasible prognostic biomarker for severe diabetic complications in Pakistan [8]. Globally, T2DM continues to rise. Data from the International Diabetes Federation indicate that in 2021, there were approximately 537 million adults (20–79 years) with diabetes, the majority type 2, with projections exceeding 700 million by 2045 [9]. Specifically, in South Asia, and Pakistan in particular, prevalence remained high, approximately 17% among adults by 2019, with diabetes ranking among the top causes of morbidity and mortality [10]. Chronic low-grade inflammation in T2DM underpins the vascular complications that contribute heavily to Pakistan's healthcare burden [11]. While cytokine profiling remains the gold standard, its limited feasibility underscores the utility of simpler alternatives. In resource-limited settings like Pakistan, NLR's advantages are efficiency, affordability, and integration into routine diagnostics, making it a highly attractive tool. While advanced inflammatory markers (e.g., serum cytokines IL-6, TNF- α) are costly and not widely available, NLR provides a pragmatic alternative for early risk stratification and monitoring [12].

Diabetes mellitus is increasingly recognized as a chronic inflammatory condition that contributes to the development of microvascular and macrovascular complications. Although several inflammatory biomarkers have been studied, many of them are expensive and not readily available in routine clinical practice, particularly in resource-limited settings. The neutrophil-to-lymphocyte ratio (NLR), derived from a simple complete blood count, has emerged as a potential surrogate marker of systemic inflammation; however, evidence regarding its clinical significance among diabetic patients in Pakistan remains limited. This highlights the need to evaluate the prognostic value of NLR in assessing inflammatory status and related complications in diabetic populations. This study aims to evaluate the prognostic value of the neutrophil-lymphocyte ratio in assessing the inflammatory status of patients with diabetes mellitus, offering a potentially valuable approach to early detection and improved clinical management.

METHODS

This cross-sectional analytical study was conducted at the Diagnostic and Research Laboratory, Liaquat University of Medical and Health Sciences (LUMHS), Hyderabad, in collaboration with the Department of Medicine at Liaquat University Hospital, Hyderabad. The study spanned six months, from December 2024 to May 2025, after obtaining ethical approval from the Ethical Review Committee of

LUMHS, Jamshoro (Ref. No. LUMHS/REC/-545). A total of 212 participants were recruited through non-probability consecutive sampling. The sample size was determined using the WHO OpenEpi calculator, considering a 26.7% prevalence of diabetes mellitus in Pakistan (2022), a 5% margin of error, and a 90% confidence level. The calculation was based on the formula: $n = [DEFF \times Np(1-p)] / [(d^2/Z^2(1-\alpha/2 \times (N-1) + p(1-p)))]$ [13]. Patients aged 18 years and above with a confirmed diagnosis of Type 1 or Type 2 diabetes mellitus for at least one year were included. Individuals with recent infections, chronic inflammatory or autoimmune diseases, those on immunosuppressive therapy, or with known malignancies or hematologic disorders affecting neutrophil or lymphocyte counts were excluded. After obtaining informed consent, demographic and clinical data were collected using a structured questionnaire. Blood samples (5 cc) were drawn to assess complete blood counts (CBC) using the Siemens ADVIA 2120i automated hematology analyzer. Neutrophil counts were considered normal between $2.0-7.5 \times 10^9/L$ (40–75% of total WBCs), while lymphocyte counts ranged from $1.0-3.5 \times 10^9/L$ (20–45%). The neutrophil-to-lymphocyte ratio (NLR) was calculated from complete blood count (CBC) results, and C-reactive protein (CRP) levels were recorded as a supplementary marker of inflammation. NLR values were categorized as normal (1–3) or elevated (>3). Data were analyzed using SPSS version 26.0. Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize patient characteristics. Independent t-tests were applied to compare NLR values across groups. Chi-square test was used to examine associations between NLR status and diabetes duration, and treatment status. All statistical tests were conducted using a 95% confidence interval, and a p-value < 0.050 was considered statistically significant.

RESULTS

The study comprised 212 diabetic patients, with a slight female predominance (52.8%). The majority (81.1%) had Type 2 diabetes, and 53.3% reported a positive family history of diabetes. The mean duration of diabetes was 11.8 ± 8.3 years, indicating a chronic disease course in most participants (Table 1).

Table 1: Demographics, Clinical History

Variables		Frequency (%)
Gender	Female	112 (52.8)
	Male	100 (47.2)
Type of Diabetes	Type 2	172 (81.1)
	Type 1	40 (18.9)
Family History of DM	Yes	113 (53.3)
	No	99 (46.7)
Duration of Diabetes		11.8 ± 8.3 years

Regarding inflammatory markers, 24.1% of patients exhibited elevated neutrophil-to-lymphocyte ratio (NLR), while 40.1% had raised C-reactive protein (CRP) levels. This suggests that a notable proportion of diabetic patients may be undergoing active systemic inflammation, even in the absence of overt clinical signs (Figure 1)

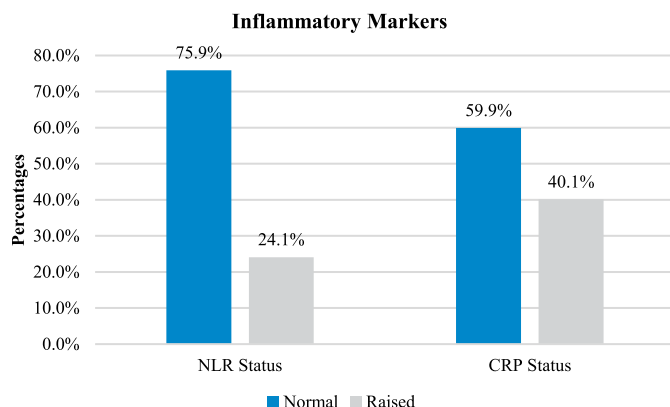


Figure 1: Status of Inflammatory Markers

Among complications and comorbidities, neuropathy (34.4%) and nephropathy (24.5%) were the most common microvascular complications, while retinopathy was present in 19.8% of patients. Cardiovascular disease was observed in 20.8%, and nearly half of the participants had hypertension (46.2%) and dyslipidemia (46.2%). Obesity was present in 47.2%, and chronic kidney disease in 11.3%, indicating a high burden of coexisting conditions (Table 2).

Table 2: Complications and Comorbidities

Variables		Frequency (%)
Nephropathy	Absent	160 (75.5)
	Present	52 (24.5)
Retinopathy	Absent	170 (80.2)
	Present	42 (19.8)
Neuropathy	Absent	139 (65.6)
	Present	73 (34.4)
Cardiovascular Disease	Absent	168 (79.2)
	Present	44 (20.8)
Hypertension	Absent	114 (53.8)
	Present	98 (46.2)
Dyslipidemia	Absent	114 (53.8)
	Present	98 (46.2)
Obesity	Absent	112 (52.8)
	Present	100 (47.2)
Chronic Kidney Disease	Absent	188 (88.7)
	Present	24 (11.3)

Among 212 patients with type 2 diabetes, 161 had normal NLR and 51 had raised NLR. Gender distribution was comparable between the groups, with 48.4% males in the normal NLR group versus 43.1% in the raised NLR group (95% CI: 13.6% to 22.1%, $p=0.520$). The mean duration of diabetes was longer in the raised NLR group (13.2 ± 6.9

years) compared to the normal NLR group (10.5 ± 7.4 years), though this difference was not statistically significant (95% CI: 1.9 to 7.2 years, $p=0.240$). Raised CRP was significantly more frequent in patients with elevated NLR (60.8%) than in those with normal NLR (33.5%) (95% CI: 6.4% to 44.6%, $p=0.012$). Likewise, diabetic nephropathy was more prevalent in patients with raised NLR (41.2% vs. 19.3%) with a significant difference (95% CI: 2.1% to 40.2%, $p=0.030$). Similarly, diabetic retinopathy occurred in 31.4% of patients with raised NLR compared to 16.1% with normal NLR (95% CI: 1.7% to 28.5%, $p=0.040$). Hypertension was more frequent among those with raised NLR (64.7% vs. 40.4%); however, this was not statistically significant (95% CI: 2.8% to 37.0%, $p=0.260$) (Table 3).

Table 3: Comparison of Clinical and Laboratory Variables by NLR Status

Variables	NLR Normal (N=161) N (%)	NLR Raised (N=51) N (%)	95% CI	P-Value
Gender (Male)	78 (48.4)	22 (43.1)	13.6% to 22.1%	0.520
Duration of Diabetes (years)	10.5 + 7.4	13.2 + 6.9	1.9 to 7.2 years	0.240
Type 2 Diabetes	129 (80.1)	43 (84.3)	9.8% to 17.3%	0.530
CRP Raised	54 (33.5)	31 (60.8)	6.4% to 44.6%	0.012*
Diabetic Nephropathy	31 (19.3)	21 (41.2)	2.1% to 40.2%	0.030*
Diabetic Retinopathy	26 (16.1)	16 (31.4)	1.7% to 28.5%	0.040*
Hypertension	65 (40.4)	33 (64.7)	2.8% to 37.0%	0.260

*Statistical significance: $p < 0.050$

DISCUSSION

The findings yielded a notable association between elevated NLR levels and the presence of microvascular complications, particularly diabetic nephropathy and retinopathy. Among the 212 diabetic patients evaluated, 24.1% exhibited elevated NLR values (>3), while 40.1% had increased C-reactive protein (CRP) levels. The significant correlation between raised NLR and CRP underscores the utility of NLR as a surrogate inflammatory marker in diabetic individuals [14]. These findings are consistent with the work of Liu *et al.* (2017), who reported a positive relation in elevated NLR and increased CRP and IL-6 levels among patients with Type 2 DM, emphasizing NLR's potential as a cost-effective and readily available inflammatory indicator [15]. The current study also demonstrated a statistically significant association between raised NLR and diabetic nephropathy. This is in line with the study by Li *et al.* in China, which found that diabetic patients with nephropathy had significantly higher NLR values compared to those without renal involvement [16]. Further supporting this, Tang *et al.* in China concluded that elevated NLR was independently associated not only with the presence but also the severity of diabetic kidney disease, suggesting its relevance in disease stratification [17]. Moreover, our data showed a significant relationship

between raised NLR and diabetic retinopathy. This observation resonates with a 2023 study-analysis by El-Tawab et al., which affirmed a strong association between high NLR levels and the risk of diabetic retinopathy, particularly its proliferative forms. [18] While hypertension and obesity were prevalent among our participants, no statistically significant association was found between NLR and these comorbidities. These findings partially contrast with a study by Zhang et al., who reported a mild but significant relationship between elevated NLR and hypertension in diabetic patients [19]. However, differences in sample size, population characteristics, and the control of confounding factors could account for this discrepancy. The prevalence of diabetic neuropathy in our study (34.4%) was notably high, but it did not reach statistical significance when associated with raised NLR. This contrasts with results from the study by Rezaei Shahrabi et al., who identified NLR as a potential marker for diabetic peripheral neuropathy severity [20]. However, differences in diagnostic criteria and neuropathy grading may explain these variations. The use of NLR as a prognostic biomarker is advantageous due to its accessibility, cost-effectiveness, and correlation with well-established inflammatory parameters. In contrast, cytokine assays (e.g., IL-6, TNF- α) are not feasible in most routine clinical setups due to cost and technical limitations. This positions NLR as a practical tool for primary screening, particularly in low-resource settings like Pakistan. Our findings support recommendations by the ADA and recent literature advocating for inflammatory profiling in the management of diabetic patients to prevent complications [21]. Integrating NLR into routine assessments may facilitate early identification of patients at risk for vascular complications, enabling timely interventions.

This study was limited by its single-center cross-sectional design, which restricts the ability to establish causal relationships between elevated NLR and diabetic complications. Additionally, the use of consecutive sampling and the absence of longitudinal follow-up may limit the generalizability of the findings. Advanced inflammatory markers and glycemic control indicators such as HbA1c were not extensively analyzed for correlation with NLR. Future multicenter longitudinal studies with larger sample sizes and comprehensive inflammatory profiling are recommended to further validate NLR as a reliable prognostic biomarker in diabetic patients.

CONCLUSIONS

Elevated NLR showed a significant association with increased CRP levels and microvascular complications, including diabetic nephropathy and retinopathy, highlighting its value as a convenient and cost-effective marker.

Authors' Contribution

Conceptualization: SN,

Methodology: SN, IDU, SK, SM, AR

Formal analysis: IS,

Writing and Drafting: SN, IDU, SK, SM, IS, AR

Review and Editing: SN, IDU, SK, SM, IS, AR

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Circumcision of Infants with Gomco Clamp - An Effective and Safe Method, in A Tertiary Care Setting

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ABSTRACT

Circumcision is among the most commonly performed pediatric surgical procedures. The Gomco clamp is widely used due to its simplicity and safety profile. However, variations in clamp size may influence postoperative outcomes. **Objectives:** To evaluate the safety, efficacy, and complication rates of Gomco clamp circumcision in neonates and infants, with a focus on the association of clamp size with key outcomes. **Methods:** This prospective observational study was conducted at Baqai Medical University from March 2022 to February 2024. Male neonates and infants up to one year undergoing elective Gomco clamp circumcision were enrolled. Data on age, weight, clamp size, procedure duration, and complications were recorded. Follow-ups were conducted at days 3-5, days 7-10, and at 2 months to assess early and delayed complications and cosmetic outcomes. **Results:** Early complications were mild and infrequent. Surgical site infection (4.2%), meatal stenosis (4.2%), and adhesions (8.3%) were rare. Bleeding requiring intervention occurred in 6.2% of cases, and cosmetic outcomes were excellent or good in 85.4%. Significant associations were found between clamp size and bleeding ($p=0.041$), as well as cosmetic outcome ($p=0.027$). **Conclusions:** Gomco clamp circumcision is a safe and effective method for neonates and infants. However, careful selection of clamp size is crucial for minimizing complications and optimizing cosmetic results.

INTRODUCTION

Male circumcision is one of the oldest and most commonly performed surgical procedures worldwide, particularly during the neonatal and infantile period. It is practiced for religious, cultural, hygienic, and occasionally medical reasons in many countries, including Pakistan, where it is routinely performed in infancy as part of cultural and religious tradition [1, 2]. Globally, it is estimated that more than one-third of males are circumcised, with rates exceeding 90% in Muslim-majority countries like Pakistan [3]. The neonatal period is considered optimal for circumcision due to anatomical simplicity, faster healing,

and lower rates of complications [4]. Compared to circumcision performed in older children or adults, neonatal circumcision is associated with reduced procedural risks, minimal discomfort, and faster wound healing [5]. In Pakistan, neonatal and infant circumcision is mostly carried out in outpatient settings by general practitioners, pediatricians, or trained surgical staff, often without standardized techniques or anesthesia [6]. This unregulated practice of circumcision increases the risk of avoidable complications. The complications include bleeding, infection, meatal stenosis, and unsatisfactory



cosmetic results [7]. Multiple techniques have been described for infant circumcision, including the Plastibell device, Mogen clamp, and Gomco clamp. Among these, the Gomco clamp is one of the most widely used and time-tested instruments, particularly in the United States and parts of South Asia [8]. It works by crushing the foreskin between a metal bell and a clamp plate, minimizing bleeding while allowing precise excision. Studies have shown that the Gomco clamp is safe, efficient, and associated with excellent cosmetic outcomes when performed under appropriate aseptic and anesthetic conditions [9]. Despite its advantages, the technique's effectiveness is influenced by factors such as clamp size selection, operator skill, and postoperative care. Complication rates for Gomco circumcision vary between 1% and 5%, with bleeding being the most common adverse event [10]. A 2019 RCT confirmed that when performed by experienced hands, Gomco circumcision in neonates had lower complication rates and superior cosmetic satisfaction compared to Plastibell and Mogen methods [11]. In Pakistan, however, limited published data evaluate the safety and efficacy of the Gomco clamp technique in neonates and infants under controlled clinical settings. Most circumcisions are carried out in non-standardized environments without uniform protocols for anesthesia, clamp size selection, or postoperative follow-up [12].

Despite the widespread practice of neonatal and infant circumcision in Pakistan, most procedures are performed in non-standardized settings without uniform protocols for anesthesia, clamp size selection, or postoperative follow-up. Limited local data exist evaluating the safety, efficacy, and complication profile of the Gomco clamp in controlled clinical environments. This lack of evidence underscores the need for systematic assessment to guide safer and more effective circumcision practices. This research aimed to address this gap by systematically evaluating the complication profile, cosmetic outcomes, and procedural efficiency of Gomco clamp circumcision among neonates and infants in a tertiary care setup. Understanding these factors can guide policy and training initiatives to promote safer practices in both urban and rural clinical settings. This study aimed to evaluate the safety, efficacy, and complication profile of Gomco clamp circumcision among neonates and infants undergoing elective circumcision.

METHODS

This prospective observational study was conducted at the Department of Pediatric Surgery, Baqai Medical University, Karachi, from March 2022 to February 2024. The study was initiated after obtaining approval from the institutional ethical review committee (BMU-EC/01-2022). All consecutive male neonates and infants up to one year of age undergoing elective circumcision by a single

experienced pediatric surgeon were enrolled from the outpatient clinic. Infants with low birth weight (<2.5 kg), significant jaundice, bleeding disorders, pustular groin rash, or penile anomalies (e.g., hypospadias) were excluded. A coagulation profile was performed preoperatively in all cases. Informed written consent was obtained from parents or guardians, and data were recorded using a standardized proforma. The sample size was calculated via the Open Epi sample size calculator by taking the incidence of mild bleeding as an early procedure-related complication in 3.2% boys with 5 % Margin of Error and a 95% Confidence Interval [13]. Each circumcision was performed using the Gomco clamp technique by a trained surgical team under sterile conditions. The majority of procedures were conducted in a minor operating theatre under local anesthesia, using a dorsal penile nerve block with 1% lidocaine. Clamp sizes were selected based on the diameter of the glans and included 1.1 cm, 1.3 cm, and 1.45 cm clamps. The duration of each procedure was recorded from the time of clamp application to the removal and completion of dressing. All infants were observed for one hour postoperatively for immediate complications and discharged with postoperative care instructions. Follow-up was scheduled at three intervals: day 3–5 (to assess early complications such as bleeding, urination difficulty, or infection), day 7–10 (to monitor healing progress), and at two months' post-procedure (to evaluate delayed complications such as surgical site infection, meatal stenosis, adhesions, and cosmetic outcome). Complications were categorized as early (within the first two weeks) or delayed (after two weeks up to two months). Bleeding requiring intervention was defined as any hemorrhage requiring re-clamping, suturing, or pharmacological hemostasis. The cosmetic outcome was self-reported by parents using a 4-point scale (Excellent, Good, Acceptable, Poor), adapted from a previously published study [14]. Surgeons also assessed cosmetic results independently to ensure clinical evaluation. Data were collected using a standardized proforma developed by the research team, which captured age at circumcision (in weeks), weight at the time of procedure (kg), type of analgesia, clamp size, procedure duration, and clinical outcomes. The proforma included sections on patient demographics, procedural details, complications, and parent-reported cosmetic outcomes (adapted from a previously published scale [14]). The data collection proforma was developed by the research team and subsequently pre-validated by 12 independent surgeons (pediatric, general and urologists) to ensure content clarity, relevance, and completeness. Each item was assessed for clarity, necessity, and ease of interpretation. Content Validity Index (CVI) for individual

items (I-CVI) was 0.91, indicating strong content validity. Internal consistency reliability was tested using Cronbach's alpha, which was 0.87, reflecting good reliability of the tool. Safety variables included the presence and severity of bleeding, need for re-intervention, and use of postoperative antibiotics. Efficacy was evaluated based on intraoperative complications and the overall cosmetic outcome. All data were entered and analyzed using SPSS version 25.0, and descriptive statistics were reported as means $\pm$ standard deviations for quantitative variables, and frequencies and percentages for categorical variables. Associations between clamp size and categorical outcomes (e.g., bleeding, antibiotic use, cosmetic grade, and re-intervention) were analyzed using the Chi-square test, and a p -value < 0.050 was considered statistically significant.

RESULTS

Among the 48 neonates and infants who underwent Gomco clamp circumcision, the mean age at circumcision was 6.4 ± 3.1 weeks, and the average weight was 4.5 ± 0.5 kg. The majority (85.4%) received local anesthesia, while general anesthesia and no analgesia were used in 10.4% and 4.2% of cases, respectively. The most commonly used clamp size was 1.1 cm (47.9%), followed by 1.3 cm and 1.45 cm. The average procedure duration was 12.1 ± 2.4 minutes, suggesting this method is quick and efficiently performed in this age group (Table 1).

Table 1: Demographic and Procedural Characteristics (n=48)

Variables	Frequency (%)
Age	
At Circumcision	6.4 ± 3.1 Weeks
Weight	
At Procedure	4.5 ± 0.5 kg
Analgesia Used	
Local	41 (85.4%)
General	5 (10.4%)
None	2 (4.2%)
Clamp Size Used	
1.1 cm	23 (47.9%)
1.3 cm	17 (35.5%)
1.45 cm	8 (16.6%)
Procedure Duration	
Minutes	12.1 ± 2.4

Early complications were infrequent, with bleeding mostly mild or moderate, and only one case (2.1%) categorized as severe. Urination difficulty was reported in 10.4% of cases. Delayed complications such as surgical site infection, meatal stenosis, and adhesions were rare, occurring in $\leq 8.3\%$ of the participants, indicating favourable short- and medium-term safety (Table 2).

Table 2: Postoperative Complications (n=48)

Variables		Frequency (%)
Early Complications		
Bleeding	None	36 (75.0%)
	Mild	7 (14.6%)
	Moderate	4 (8.3%)
	Severe	1 (2.1%)
Urination Difficulty	Yes	5 (10.4%)
	No	43 (89.6%)
Delayed Complications		
Surgical Site Infection	Yes	2 (4.2%)
	No	46 (95.8%)
Meatal Stenosis	Yes	2 (4.2%)
	No	46 (95.8%)
Adhesions	Yes	4 (8.3%)
	No	44 (91.7%)

Safety outcomes showed that only 6.2% of participants required intervention for bleeding, and just 2.1% needed re-intervention. Antibiotic use postoperatively was limited (14.6%), supporting the low infection rate. In terms of efficacy, cosmetic results were highly favorable, with 56.2% rated excellent and none rated poor (Table 3).

Table 3: Safety and Efficacy Outcomes (n=48)

Outcomes	Frequency (%)
Bleeding Requiring Intervention	
Yes	3 (6.2%)
No	45 (93.8%)
Re-intervention Required	
Yes	1 (2.1%)
No	47 (97.9%)
Antibiotic Use	
Yes	7 (14.6%)
No	41 (85.4%)
Cosmetic Outcome	
Excellent	27 (56.2%)
Good	14 (29.2%)
Acceptable	7 (14.6%)
Poor	0 (0.0%)

Clamp size was significantly associated with bleeding requiring intervention ($p=0.041$) and cosmetic outcome ($p=0.027$). Smaller clamp sizes (1.1 cm) were linked to slightly higher bleeding rates and acceptable cosmetic scores, suggesting clamp size selection may influence clinical outcomes (Table 4).

Table 3: Safety and Efficacy Outcomes (n=48)

Outcomes	1.1 cm (n=23)	1.3 cm (n=17)	1.45 cm (n=8)	95% CI	p-value
Bleeding Requiring Intervention					
Yes	2 (8.7%)	1 (5.9%)	0 (0.0%)	0.5%-24.1%	0.041*
No	21 (91.3%)	16 (94.1%)	8 (100.0%)		

Antibiotic Use					
Yes	5 (21.7%)	1 (5.9%)	1 (12.5%)	6.5%–35.7%	0.103
No	18 (78.3%)	16 (94.1%)	7 (87.5%)		
Cosmetic Outcome					
Excellent	13 (56.5%)	10 (58.8%)	4 (50.0%)	42.4%–70.3%	0.027*
Good	6 (26.1%)	6 (35.3%)	2 (25.0%)		
Acceptable	4 (17.4%)	1 (5.9%)	2 (25.0%)		
Poor	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Re-intervention Required					
Yes	1 (4.3%)	0 (0.0%)	0 (0.0%)	0.1%–16.3%	0.158
No	22 (95.7%)	17 (100.0%)	8 (100.0%)		

DISCUSSION

The present study evaluated the safety and efficacy of Gomco clamp circumcision in neonates and infants, with particular attention to the impact of clamp size on postoperative outcomes. The findings reaffirm the Gomco clamp as a safe and effective technique when used by trained personnel in a sterile clinical setting. The mean age and weight at the time of circumcision in this study were 6.4 ± 3.1 weeks and 4.5 ± 0.5 kg, respectively. These figures align with global recommendations supporting early infant circumcision due to faster healing and lower risk of complications compared to older children [15]. Early complications were infrequent in our sample, with 75% experiencing no bleeding and only 2.1% classified as severe. This is consistent with a study done in Punjab, where the Gomco clamp showed a significantly lower bleeding rate than the Mogen technique [16]. Urination difficulty occurred in 10.4% of participants, but resolved without intervention, consistent with findings by Saeedi et al. who reported transient dysuria in 8–12% of Gomco cases [17]. Delayed complications like surgical site infection (4.2%), meatal stenosis (4.2%), and adhesions (8.3%) were rare in our cohort. These rates are notably lower than those seen in circumcisions performed with Plastibell, which has been associated with up to 10–15% risk of delayed complications [5]. Safety outcomes in Gomco circumcision were favourable: bleeding requiring intervention was noted in only 6.2% of cases, and only one infant (2.1%) required re-intervention. Antibiotic use was limited to 14.6%, further supporting the low rate of infectious complications. These results are comparable to a Canadian retrospective review that reported an overall complication rate of 6.4% for Gomco procedures in infants under 3 months of age [18]. Cosmetic outcomes were excellent or good in 85.4% of cases, and none were rated poor. This aligns with findings by Freeman et al. who concluded that the Gomco clamp yielded the highest cosmetic satisfaction among circumcision techniques [14]. Importantly, our study identified statistically significant associations between the clamp size of the Gomco clamp and two key outcomes: bleeding requiring

intervention ($p=0.041$) and cosmetic outcome ($p=0.027$). Smaller clamp sizes (particularly 1.1 cm) were associated with higher bleeding rates and more acceptable rather than excellent cosmetic grades. These findings are supported by research from Michigan, USA, where improper bell size selection was a leading factor for both bleeding and suboptimal cosmetic results [19]. This emphasizes the critical need for precise preoperative assessment and appropriate bell selection. A recent study also highlighted that over-tightening or improper Gomco clamp bell size selection could cause increased tissue trauma, leading to bleeding and delayed wound healing. Moreover, operator training has been shown to significantly impact complication rates, underscoring the need for standardized training protocols [20]. The low rate of re-intervention (2.1%) in our study is consistent with literature from high-income settings where structured follow-up and proper technique were applied [21].

This study was limited by its single-center design and relatively small sample size, which may affect generalizability. Future research should include multicenter trials with larger cohorts and long-term follow-up to evaluate delayed complications and refine guidelines for clamp size selection and standardized circumcision protocols.

CONCLUSIONS

Gomco clamp circumcision in neonates and infants was found to be a safe and effective procedure with minimal complications and high cosmetic satisfaction. Early and delayed complications were rare. A significant association was observed between clamp size and both bleeding requiring intervention and cosmetic outcome, highlighting the importance of appropriate clamp selection. The technique remains a reliable option when performed by trained professionals under sterile conditions.

Authors' Contribution

Conceptualization: BAS

Methodology: BAS, AGA, SA, SQ, KA

Formal analysis: SMAB, KA

Writing and Drafting: AGA, SA, SQ

Review and Editing: AGA, SA, SQ, SMAB, KA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Frequency of Alveolar Osteitis (Dry Socket) in Smokers after Mandibular Molar Extraction

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ABSTRACT

Alveolar osteitis (AO) is the infection of the alveolar bone of the maxilla or mandible. Alveolar osteitis is a frequent and delayed complication, causing extreme pain with disruption in social life, sleep and work. **Objectives:** To determine the smoking status and prevalence of dry socket in patients undergoing mandibular molar extraction. **Methods:** A prospective observational cohort study was undertaken in the Department of Oral and Maxillofacial Surgery at LUMHS, Jamshoro, Pakistan. Data acquisition was completed over a duration of six months using a non-probability convenience sampling strategy. Statistical evaluation was conducted through SPSS software version 26.0. The Chi-square test was utilized to determine associations between variables, with a p-value of less than 0.050 regarded as statistically significant. **Results:** Patients were 32.91 ± 8.61 years old on average. There were 59.6% male and 40.94% female. The frequency of dry socket in patients presenting for mandibular molar extraction at 7 days was 10.4% (31/298). The rate of dry socket was significantly high in smokers (61.1%) and ex-smokers (80%) cases compared to non-smokers (0.4%) patients. **Conclusions:** In individuals having their mandibular molars extracted, there was a significant correlation between smoking status and the occurrence of dry socket ($p=0.001$). These results highlight how important quitting smoking is for lowering the chance of this excruciating side effect and enhancing recovery after surgery.

INTRODUCTION

The inflammation of the bone in the alveolar region, or the alveolar process of the maxilla or mandible, is designated as alveolar osteitis, or dry socket [1]. Typically, it happens after exodontia. Extreme pain, poor healing, foul-tasting, inflammation, and a disrupted clot that leaves the socket unfilled are the hallmarks of this post-extraction problem [2]. This moderate to severe pain might spread to other areas of the head, including the neck, temple, eye, and ear. Usually beginning on the second or fourth day following the

extraction, the pain might linger for 10 to 14 days [3]. Numerous preventive strategies have been developed as a result of recent developments in the pathophysiology of dry sockets. For example, using antimicrobials such as chlorhexidine has become a viable method of reducing the incidence of dry sockets. It functions by inhibiting bacterial development during extraction, which lessens the risk of infection and the blood clot's eventual disintegration [4]. Immunosuppression and diabetes are typical systemic



illnesses that have been linked to an increased risk of postoperative sequelae like dry socket. Often, the etiology of dry socket is not clearly understood but seems to be multifactorial. Such factors include use of oral contraceptives, smoking, traumatic extractions, poor oral hygiene, and excessive local anesthetic vasoconstrictor use [5]. The routine procedure performed by oral and maxillofacial surgeons, involving a lot of post-operative complications, is the surgical removal of the impacted lower third molar. The most common signs and symptoms of complications are pain, swelling and trismus, which are affected to a certain degree by the severity of many factors and variables [6]. The body reacts by forming a blood clot in the alveolar socket immediately after tooth extraction. Studies have shown that smoking slows the healing of wounds, influences bone remodeling and impairs the reaction to healing [7]. A comprehensive systematic review published in 2022 that analyzed eleven studies meeting inclusion criteria found that tobacco smokers had a more than three-fold increase in the odds of developing dry socket compared to non-smokers ($OR > 3.0$) [8]. The combined incidence of AO was approximately 13.2% in smokers compared to only 3.8% in non-smokers, indicating that smoking substantially elevates the risk of this painful complication [9]. In another study, smokers had a dry socket incidence of 12%, versus 4% in non-smokers [10]. Another study in Chile highlighted that tobacco smoking after extraction increased the odds of dry socket with an odds ratio of 3.5 (95% CI: 1.3–9.0) [11]. A cross-sectional observational study in Northern Saudi Arabia found 62.6% of dry socket cases occurred in cigarette smokers. The overall incidence of alveolar osteitis in their sample was 15.7%, suggesting a substantial association [12]. A study conducted at Peshawar, Pakistan, reports that among 356 patients, 89 (25.0%) patients had dry socket [13]. Tobacco contains cotinine, hydrogen cyanide, carbon monoxide, and nicotine, all of which are cytotoxic to different types of cells and prevent wounds from healing. Nicotine, which is the primary component of tobacco smoke, makes platelets stickier, raising the risk of tissue ischaemia and thrombotic microvascular occlusion. Moreover, it prevents macrophage and fibroblast growth [14].

Alveolar osteitis (dry socket) is one of the most common and painful complications following tooth extraction, particularly after mandibular molar removal. Several risk factors such as smoking, poor oral hygiene, and traumatic extraction have been reported; however, the magnitude of this association varies across different populations. Despite the high prevalence of smoking in many regions, limited local evidence is available regarding the frequency of dry socket among smokers compared with non-smokers following mandibular molar extraction. Therefore, further

investigation is required to better understand this relationship and guide preventive strategies in clinical practice. Identifying the gaps in the literature in this domain showed that the frequency of alveolar osteitis in smokers vs. non-smokers after mandibular molar extraction is crucial for guiding future research and improving patient outcomes. Recognizing the connection between dry socket among smokers and non-smokers is essential for crafting comprehensive treatment plans for individuals undergoing dental extractions. This study aimed to determine the smoking status and prevalence of dry socket in patients undergoing mandibular molar extraction.

METHODS

A prospective observational cohort study was conducted at the Department of Oral and Maxillofacial Surgery of Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro. Data were collected from October 19, 2022, to April 18, 2023, using a non-probability consecutive sampling method. The Research Ethics Committee granted ethical permission for the project (Reference No LUMHS/REC/165). All participating patients provided written informed consent before being included in the study. Calculation of Sample size was done by the Raosoft sample size calculator, taking the proportion of dry socket in 20% [15], 98% confidence interval, level of significance 6% and 4% was added as non-responses and unfilled questionnaires, so the calculated sample size was 298. The term smoker in this study indicates the person who has been a smoker of cigarettes for the last three years, a non-smoker identifies the person who has never smoked in the past 10 years, and an ex-smoker shows the person who has quit smoking in 1 past year. Patients between the ages of 20 and 60, those having their mandibular molar extracted, and healthy individuals not on medication were included in the study. Patients who were allergic to local anaesthetics at the time of procedure, antibiotics, pregnant women, patients with cardiovascular disease, or patients with any systemic disease or systemic pathology were excluded from the study. Patients' demographic information, including age and gender, was collected on a proforma. On preoperative assessment, they were asked about smoking status (smoking status indicates persons who were using cigarettes only). Smoking status was classified based on the smoke duration mentioned above in the paragraph. Smokers were operated under local anesthesia by the principal investigator. After the extraction surgical site was irrigated with normal saline using a conventional syringe, and pressure gauze was placed. The diagnosis of dry socket (alveolar osteitis) was primarily based on clinical criteria including the presence of intense postoperative pain that increased after the third day following extraction,

exposed alveolar bone within the socket, and absence of suppuration. A periapical radiograph was taken after extraction if conditions like a root left behind post-extraction, any chance of periapical lesion, a soft tissue lesion, food stagnation or any clinical symptoms associated with these conditions were examined and patients were evaluated in terms of pain and healing through visual analogue scale VAS [15] healing index, halitosis and erythema on 1st 4th and 7th postoperative day. Healing Scale, halitosis scale and erythema scales were used to assess the dry socket. The healing index in the context of a dry socket (alveolar osteitis) refers to a clinical tool used to evaluate the progress of healing after a tooth extraction, particularly when complications like dry socket occur. Clinical uses of a Healing Index in Dry Socket indicate monitoring recovery after treatment, evaluating treatment efficacy, assessing Pain Reduction over time, documenting healing progress in clinical notes, and guiding decisions for re-treatment or follow-up. Halitosis was noted as present or absent. Patients with dry socket often present with foul odor from the mouth and bad taste, due to tissue breakdown and bacterial colonization in the exposed socket. This makes halitosis a supporting symptom for diagnosing dry socket. Although not quantified formally, more pronounced halitosis could reflect more extensive tissue necrosis or infection, possibly indicating a more severe or advanced socket condition. The erythema scale measures redness around the socket, indicating inflammation. Erythema scale was assessed by visual inspection and by the palpation method, and its grading demonstrates grade 0 for no ulceration and grade 4 indicates hemorrhage, ulceration and necrosis of tissue. SPSS version 26.0 was used to input and analyze the data. Age and pain score were among the quantitative variables that were displayed as the standard deviation and mean. The qualitative information was displayed as frequency and percentages for the following conditions: erythema, dry socket, halitosis, smoking status, gender, occupation, and healing index. The relationship between a dry socket and smoking history was examined using the chi-square test. The p-values < 0.050 were considered significant.

RESULTS

Results demonstrate demographic characteristics of patients, where the Mean $\pm$ SD of age was 32.91 ± 8.61 years. The gender breakdown showed that 176 people (59.06%) of the total were male and 122 people (40.94%) were female. On the seventh day, the mean $\pm$ standard deviation of the visual analogue pain score was 1.55 ± 1.61 , and the median was 1.00 (Table 1).

Table 1: Demographic Information of Patients

Variables	Mean $\pm$ SD
Age	32.91 $\pm$ 8.61 Years
Gender	
Male	176 (59.06%)
Female	122 (40.94%)

The terms of smoking status and dry socket association show that 252 patients (84.66%) were non-smokers, 36 patients (12.08%) were smokers, and 10 patients (3.36%) were previous smokers (who had left smoking for 1 year), and a significant association was documented (p-value=0.001). The rate of dry socket was significantly high in smokers (61.1%) and ex-smokers (80%) cases compared to non-smokers (0.4%) patients (Figure 1).

Association of dry socket & smoking status of patients

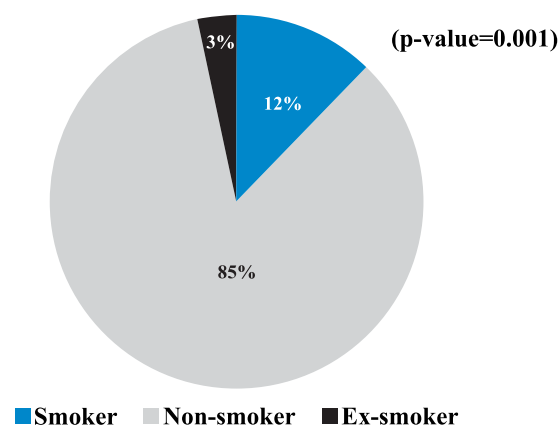


Figure 1: Smoking Status of Patients

Assessment of healing index, halitosis and erythema with respect to time was reported. The stratification analysis revealed a strong correlation between the rate of dry socket and the healing index (p-value=0.012) and a substantial correlation between gender, halitosis, and erythema (p-value=0.001) (Table 2).

Table 2: Assessment of Healing Index, Halitosis and Erythema with Respect to Time

Variables		1 st Day n (%)	4 th Day n (%)	7 th Day n (%)	p- Value
Healing Index	Very Poor	1(0.3%)	0(0%)	0(0%)	0.001
	Poor	80(26.8%)	22(7.4%)	28(9.4%)	
	Good	124(41.6%)	183(61.4%)	6(2%)	
	Very Good	93(31.2%)	93(31.2%)	40(13.4%)	
	Excellent	0(0%)	0(0%)	224(75.2%)	
Halitosis	Yes	6(2%)	60(20.1%)	23(7.7%)	0.001
	No	292(98%)	238(79.9%)	275(92.3%)	
Erythema	Yes	7(2.3%)	43(14.4%)	25(8.4%)	0.001
	No	291(97.7%)	255(85.6%)	273(91.6%)	

Association between dry socket and smoking status in patients with mandibular molar extraction stratified by age groups and gender, and a slightly significant association for

age groups and female gender (p -value=0.019) and for male gender (p -value=0.001) (Table 3).

Table 3: Association of Dry Socket Stratified by Age Groups and Gender

Variables		A0-Dry socket		p-Value
		Yes, n (%)	No, n (%)	
Age Groups (Years)	20-25	14 (17.1%)	68 (82.9%)	0.019
	26-35	5 (4.2%)	115 (95.8%)	
	36-45	8 (11.1%)	64 (88.9%)	
	46-60	4 (16.7%)	20 (83.3%)	
Gender	Male	28 (15.9%)	148 (84.1%)	0.001
	Female	3 (2.5%)	119 (97.5%)	0.019

DISCUSSION

The participants in our study were 32.91 ± 8.61 years old on average. The cohort comprised 59.6% male and 40.94% female. Analysis of smoking habits revealed that 84.66% of individuals were non-smokers, 15.4% were current smokers, and 3.36% were former smokers. Our study concludes 10.4% of dry sockets in extracted teeth. Similarly, Sharma *et al.* evaluated 580 patients, among whom 230 were male and 350 were female, identifying dry socket in 5.1% of extracted teeth [16]. In a study by Singh *et al.* among 86 patients (46 male and 40 female), dry socket developed in 5 male and 4 female [17]. Chhabra *et al.* documented 293 third molar extractions in patients aged 18 to 45 years, reporting a dry socket incidence of 4.09% (12 cases out of 178 extractions) [18]. A higher prevalence was observed among smokers (8 cases) compared to non-smokers (4 cases). There was no discernible gender bias in the majority of dry socket cases, which were linked to the excision of mandibular third molars. Interestingly, smokers had a greater incidence after having their mandibular third molars surgically extracted. Their study reported a 10.4% dry socket incidence at 7 days' post-extraction. Current research showed a statistically significant correlation ($p=0.001$) involving cigarette consumption and the occurrence of dry socket after mandible molar removal. That result is critical for patient management and reinforces the necessity of preoperative education regarding potential post-extraction complications. Nusair YM and Younis MH reported 42% female participants and 58% male participants [19]. The mean age of their patients was 35.4 ± 14.95 years, with a range of 10 to 73 years. Additionally, they reported that smokers had a much greater frequency of dry socket (12%) than non-smokers (4%), and that there was a significant correlation between the prevalence of dry socket and the amount of tobacco used ($p=0.002$), which is in line with the findings of our study. Our study further highlighted that smokers exhibited a dry socket rate of 61.1%, while ex-smokers demonstrated an even higher rate of 80%, compared to a mere 0.4% among non-smokers. These findings strongly reaffirm the

established link between tobacco use and increased risk of alveolar osteitis following molar extraction. A prior study that included 4000 removed through surgery third molars found that those who smoked half a pack of cigarettes per day had a four to five times higher incidence of alveolar osteitis (12%) than those who did not smoke (2.6%). Furthermore, the risk increased to more than 20% for patients who smoked a full pack every day and to as much as 40% for those who smoked the day of surgery [20]. Whether this elevated risk is attributable to systemic influences or direct local effects such as thermal injury or suction-induced disturbance at the extraction site remains to be fully elucidated [20]. The notable difference in the prevalence of dry socket between those who smoke and people who do not smoke, however, highlights the substantial influence of smoking on the healing process. Several mechanisms may explain this association. Firstly, toxic substances in tobacco smoke, including nicotine and various chemical agents, impair vascularization and tissue repair, both of which are essential for optimal socket healing. Smoking disrupts blood clot formation and hampers oxygen and nutrient delivery to the healing tissues, contributing to the development of dry socket [21, 22]. Apart from smoking, Nilesch and Pisal and Åström *et al.* found that female patients who used oral contraceptives had almost double the risk (16.66%) of alveolar osteitis as compared to both male and non-contraceptive female patients [23, 24]. The combined results of these studies highlight how crucial it is to put smoking cessation programs into place to reduce the likelihood of postoperative problems like dry socket as well as to enhance general health. Oral health practitioners should actively educate patients on the detrimental impact of smoking on surgical outcomes and provide necessary support for cessation. It is particularly vital to counsel patients who are active or former smokers about their heightened risk and encourage them to quit smoking before undergoing molar extractions or other invasive dental procedures.

This study has certain limitations that should be considered while interpreting the findings. The research was conducted at a single institution using a convenience sampling technique, which may limit the generalizability of the results to the broader population. In addition, other potential risk factors such as oral hygiene practices, extraction difficulty, and postoperative patient compliance were not extensively evaluated. Future multicenter studies with larger sample sizes and consideration of additional clinical variables are recommended to better understand the multifactorial causes of alveolar osteitis and improve preventive and management strategies.

CONCLUSIONS

Our study finds a substantial correlation (p -value=0.001) between smoking status and the occurrence of dry socket in patients undergoing extraction of their mandibular molars. Dry sockets can be less common with appropriate prevention and control strategies, improving overall oral health and results.

Authors' Contribution

Conceptualization: ZK, MAS

Methodology: ZK, BL, NZ, RK

Formal analysis: ZK

Writing and Drafting: SM, AK, NZ, RK

Review and Editing: SM, AK, NZ, RK, ZK, BL, MAS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Sensorineural Hearing Loss in Patients with Persistent Chronic Otitis Media in Terms of Duration and Type of Tympanic Membrane Perforation

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ABSTRACT

The World Health Organization (WHO) estimated that worldwide, around 65-330 million people suffer from chronic otitis media, of which as high as 50 % suffer impairment in their hearing.

Objectives: To determine the association between Sensorineural Hearing Loss (SNHL) in patients with chronic suppurative otitis media (CSOM) in terms of duration of CSOM and type of tympanic membrane perforation. **Methods:** This multicenter study was conducted at Hamdard University, Karachi, Fatima Jinnah Medical College, Lahore, and Loralai Medical College, Loralai, between March 2024 and February 2025, on patients diagnosed with active chronic otitis media. Patients with a history of meningitis, head trauma, tympano-mastoid surgery, congenital or acquired sudden hearing loss, or post-traumatic tympanic membrane perforation were excluded. Data were analyzed using SPSS version 23.0. Pearson correlation and one-way ANOVA were applied, with a p-value of less than 0.050 considered statistically significant. **Results:** Most patients were between 12 and 30 years of age. Mean duration of CSOM was 14.85 ± 9.1 months. The most common perforation of the tympanic membrane was marginal, in 204 (50.5%) patients. A significant moderate positive correlation was found between CSOM duration and SNHL ($r=0.43$, $p=0.002$). Patients with subtotal perforations ($n=32$) had the highest mean SNHL (37.1 ± 6.9 dB). The most frequent symptoms were ear discharge (88.1%) and hearing loss (94%). **Conclusions:** Both the duration of CSOM and the type of tympanic membrane perforation were significantly associated with sensorineural hearing loss. Prolonged disease, marginal perforations and subtotal perforations contributed to greater hearing loss, underscoring the need for early intervention.

INTRODUCTION

It is still a major debate whether chronic inflammatory conditions such as otitis media can lead to Sensorineural hearing loss (SNHL) [1]. Impairment of hearing in patients having chronic suppurative otitis media (CSOM) in general has been shown to cause a rise in air conduction thresholds but bone conduction within normal thresholds [2]. Nonetheless, various researchers have observed persistent CSOM causing cochlear dysfunction as a commonly reported sequel; therefore, the possibility of

CSOM causing SNHL cannot be ruled out [3]. The World Health Organization (WHO) estimated that worldwide, around 65-330 million people suffer from chronic otitis media, of which as high as 50 % suffer impairment in their hearing [4]. The variety of CSOM occurs in two types: the squamosal and the mucosal type. It causes mild to moderate loss of hearing in almost half of the cases [5]. Impairment in hearing is generally reported to increase thresholds of air conduction, resulting in hearing loss of a



conductive variety. Commonly observed risk factors influencing loss of hearing include defects of the tympanic membrane, impaired ossicular chain and status of the middle ear [6]. According to estimations, 13.8 to 36.2 % of patients from the developing population with impaired hearing are associated with chronic otitis media [7]. This leads to impairment of speech development among the pediatric populations, while in adults, it leads to psychosocial issues. CSOM, causing conductive loss of hearing, is frequently reported in studies. Various studies have evaluated CSOM leading to loss of function of the cochlea and therefore SNHL, termed as CSOM sequel [8]. The majority of the speech sounds fall within the range of 500 to 4000 Hz. High frequency sounds show most hearing loss, where most patients find it challenging to understand consonants like F, H, S, CH and SH [9]. CSOM has also been reported to lead to transient shifts of thresholds or sometimes even permanent shifts in thresholds by passage of inflammatory pathogens via the round window, which could spread in an apical fashion and then be measurable even on routine audiometry [10]. Chronic otitis media with effusion (persistent) occurs when continuous negative pressure persists in the middle ear for long periods of time [11]. In such cases, effusion tends to become trapped in the middle ear cavity because of its unique anatomy. This leads to impairment of the mucociliary system coupled with impaired pumping action of the eustachian tube's opening as well as closure [12]. Published literature has demonstrated controversial results, with some studies observing positive associations while others observing negative associations between CSOM and SNHL. Confusion also persists with regard to the association of SNHL in terms of age of patient, duration of disease (CSOM) and any possible relation with the opposite normal ear [13]. Even though the prevalence of CSOM worldwide is reported to be high, there remains a gap and uncertainty in the literature with regard to the effect of CSOM on SNHL (in the inner ear) [14]. Whilst conductive loss of hearing can be surgically corrected, SNHL continues to be a permanent effect. The only management with SNHL is the use of a hearing aid [15].

Chronic suppurative otitis media (CSOM) is a common otological condition in developing countries and is frequently associated with conductive hearing loss. However, the potential relationship between CSOM and the development of sensorineural hearing loss (SNHL) remains controversial in existing literature. While some studies suggest that chronic middle ear inflammation may lead to cochlear damage, evidence regarding the role of disease duration and the type of tympanic membrane perforation in SNHL is still limited and inconsistent. Therefore, further investigation is needed to clarify this association and provide evidence for early clinical intervention. This study

aims to determine the association between Sensorineural Hearing Loss (SNHL) in patients with chronic suppurative otitis media (CSOM).

METHODS

This cross-sectional, multicenter study was conducted at Hamdard University, Karachi; Fatima Jinnah Medical College, Lahore; and Loralai Medical College, Loralai, from March 2024 to February 2025. After obtaining ethical approval from the Institutional Ethical Review Committee (Ref No. ERB 2024-15) of Hamdard University, data collection was initiated. Informed consent was taken from each patient after explaining the purpose of the research and ensuring the confidentiality and anonymity of their data. The sample size of the study was calculated using the OpenEpi online software. Based on a hypothesized frequency of sensorineural hearing loss (SNHL) in chronic suppurative otitis media (CSOM) of 7%, as reported in a recent local study by Anwar et al. [16], and using a 95% confidence level with 5% confidence limits, the required sample size was calculated to be 404 (see Table 1).

Table 1: Sample Size for Frequency in a Population and for Various Confidence Levels

Sample Size for Frequency in a Population	
Variables	Values
Population size (for finite population correction factor or fpc)(N):	1000000
Hypothesized % frequency of outcome factor in the population (p):	7% +/- 5
Confidence limits as % of 100 (absolute +/- %)(d):	5%
Design effect (for cluster surveys-DEFF):	1
Sample Size (n) for Various Confidence Levels	
Confidence	Sample Size
95%	404

Equation Sample size (n) = (DEFF*Np(1-p)) / ((d²/Z²1-α/2*(N-1) + p*(1-p))

The sample size was calculated using OpenEpi, Version 3 (SSPropor calculator). After obtaining ethical approval and informed consent, patients between 12 and 60 years of age with active chronic otitis media (COM) were recruited. COM was defined as a disease duration of at least three months. Patients presenting with unilateral otorrhea and a persistent tympanic membrane perforation for at least three months, while having a normal tympanic membrane in the contralateral ear, were included in the study. Patients with a history of meningitis, head trauma, tympano-mastoid surgery, ototoxic drug use, family history of acquired or congenital sudden hearing loss, or post-traumatic tympanic membrane perforation were excluded. The contralateral ear of each patient served as a control to rule out disorders such as presbycusis, metabolic diseases, noise-induced trauma, and ototoxicity. In cases where presbycusis was suspected, audiometric

correction was applied to minimize confounding. A non-probability consecutive sampling technique was used. Following informed consent, eligible patients were enrolled after an explanation of the study's purpose and procedures. Demographic details, medical history, and complete ENT examination were recorded on a pre-designed proforma. The examination was performed using a Welch Allyn otoscope. Patients presenting with active ear discharge were prescribed systemic and topical antibiotics for one week and were reassessed after the discharge had subsided. Audiometric evaluation was carried out in a soundproof room by a trained audiologist using a clinical audiometer, according to ISO standards. The frequencies tested were 500, 1000, 2000, and 4000 Hz. A total of 404 patients were finally included in the analysis of sensorineural hearing loss (SNHL) parameters. A bone conduction threshold of 20 dB was used to define SNHL in order to improve the sensitivity of the study. Data analysis was performed using SPSS version 23.0. Categorical variables were expressed as frequencies and percentages, while continuous variables were reported as mean and standard deviation after testing for normality with the Shapiro-Wilk test. For group comparisons, independent t-test and one-way ANOVA were applied after adjustment for confounding variables. A p-value of less than 0.050 was considered statistically significant.

RESULTS

A total of 404 patients with persistent chronic suppurative otitis media (CSOM) were included, comprising 228 male and 176 females. Among male, the most prevalent age group was 12–20 years (64, 28.07%), followed by 21–30 years (52, 22.81%) and 31–40 years (48, 21.05%). In female, the most common age group was 41–50 years (44, 25%), followed by 12–20 years (40, 22.73%) and 51–60 years (32, 18.18%). The mean duration of CSOM was 14.46 ± 9.7 months in male and 15.24 ± 8.5 months in female. Regarding the type of tympanic membrane perforation, marginal perforations were most frequently observed in both 112 (49.12%) male and 92 (52.27%) female, followed by central perforations in 96 (42.11%) male and in 72 (40.91%) female. Subtotal perforations were the least common, occurring in 20 (8.77%) male and 12 (6.82%) female (Table 2).

Table 2: CSOM Patients Distribution According to Various Demographics (n=404)

Age Groups	Male (%), (n=228)	Female (%), (n=176)
12-20 Years	64 (28.07%)	40 (22.73%)
21-30 Years	52 (22.81%)	32 (18.18%)
31-40 Years	48 (21.05%)	28 (15.91%)
41-50 Years	36 (15.79%)	44 (25%)
51-60 Years	28 (12.28%)	32 (18.18%)
Mean Duration of CSOM (Months)	14.46 ± 9.7	15.24 ± 8.5

Type of Tympanic Membrane Perforation		
Central	96 (42.11%)	72 (40.91%)
Marginal	112 (49.12%)	92 (52.27%)
Subtotal	20 (8.77%)	12 (6.82%)

This study illustrated the frequency of key clinical features observed in patients with chronic suppurative otitis media (CSOM). The most commonly reported symptom was ear discharge, seen in 356 (88.1%) patients, followed by hearing loss in 300 (74.3%) and earache in 168 (41.6 %) cases. Tinnitus was reported by 112 (27.7%) participants, and vertigo was the least frequent symptom, affecting 60 (14.9%) individuals (Figure 1).

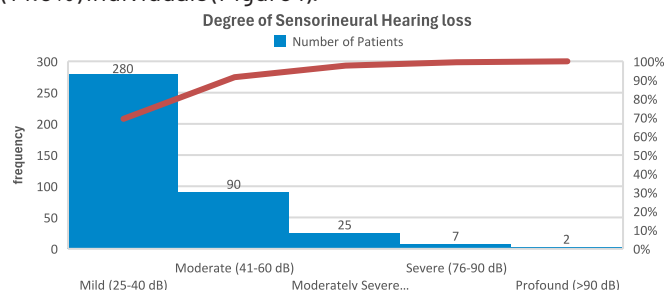


Figure 1: Representation of Clinical Features Associated with CSOM (n=404)

In tuning fork testing, Weber's test showed lateralization to the right in 164 (40.59%), to the left in 148 (36.63%), and was central in 92 (22.77%). Rinne's test was negative on the left in 172 (40.19%), on the right in 132 (36.27%), and positive bilaterally in 100 (22.55%). The differences were not statistically significant (Weber's test $\chi^2 = 1.77$, $p > 0.050$; Rinne's test $\chi^2 = 1.95$, $p > 0.050$) (Table 3).

Table 3: Results of Tuning Fork Testing in CSOM Patients (n=404)

Weber's Test	Frequency (%)	Rinne's Test	Frequency (%)
Shifted + Left	148 (36.63%)	Right -ve test	132 (36.27%)
Shifted + Right	164 (40.59%)	Left -ve test	172 (40.19%)
Central	92 (22.77%)	Right + Left +ve test	100 (22.55%)

*Weber's test $\chi^2 = 1.77$, $p > 0.050$. *Rinne's test $\chi^2 = 1.95$, $p > 0.050$

The analysis of 404 patients establishes a quantifiable link between chronic otitis media and sensorineural deterioration. The moderate positive correlation ($r = 0.49$, $p < 0.001$) indicates that for every unit increase in disease duration, the severity of SNHL increases, with the duration of illness accounting for 24% ($r^2 = 0.24$) of the variation in hearing loss. Furthermore, the type of tympanic membrane perforation has a significant impact ($p = 0.010$), with mean SNHL severity escalating from 29.5 ± 6.3 dB in central perforations, to 32.6 ± 5.8 dB in marginal perforations, and peaking at 37.1 ± 6.9 dB in subtotal perforations. This clear gradient demonstrates that larger, more anatomically significant perforations pose a greater risk to cochlear function, underscoring that CSOM is a progressive condition requiring timely intervention to prevent permanent inner ear damage.

Table 4: Association of Duration and Type of Tympanic Membrane Perforation with Sensorineural Hearing Loss (SNHL) (n=404)

Variables	Frequency / Mean	Mean SNHL (dB ± SD)	Test Applied	p-Value	Effect Size
Duration of CSOM (Months)	14.85 ± 9.1	29.5 ± 6.3	Pearson Correlation	<0.001	$r = 0.49$, $r^2 = 0.24$
Type of Tympanic Membrane Perforation	-	-	One-way ANOVA	0.010	$\eta^2 = 0.09$
Central	(n=168)	29.5 ± 6.3	-	-	-
Marginal	(n=204)	32.6 ± 5.8	-	-	-
Subtotal	(n=32)	37.1 ± 6.9	-	-	-

DISCUSSION

The results of the study showed that the duration of CSOM was positively correlated with SNHL. A similar type of tympanic membrane perforation was also significantly associated ($p=0.01$) with SNHL. However, on tuning fork testing, both Rinne's and Weber's tests showed an insignificant difference between the ears. In otorhinolaryngological practice, CSOM is one of the commonly observed conditions [17]. Although some researchers have reported associations between CSOM and SNHL, a difference of opinion persists in terms of the significance of the concept [18]. Even though literature demonstrates that at present, there is no consensus regarding the pathogenesis of SNHL because of CSOM, consistent reports of increasing damage made clinicians believe that the pathogenicity of CSOM passing through the round window membrane is the most probable hypothesis for causing SNHL [19]. The most frequent age groups in our study were patients between 12 and 20 years, followed by the 21-30 years' age group. As the age increased, the frequency of patients showed a decline, with the 51-60 years' age group reporting the least common age group. The mean duration of CSOM was slightly higher in female (15.24 ± 8.5 months) as compared to male (14.46 ± 9.7 months). The most common type of tympanic membrane perforation was marginal, in 204 (50.5%), central in 168 (41.58%) and subtotal in 32 (7.92%) patients. Similarly, other studies have also reported similar age groups and types of tympanic membrane perforation [20]. For instance, a study by Rasouli et al. reported a mean age of 21.93 in patients with CSOM [21]. Another study by Nahata et al. reported a maximum patient age between 15 and 24 years, i.e. 24 (38 %) patients [22]. Likewise, Naveen et al. also observed that most patients included in the study were between 11 and 30 years, i.e. 66 (66 %) [23]. This shows that the trend of SNHL in CSOM occurs mostly in the younger ages. Our study observed that the duration of CSOM was significantly associated with SNHL. In line with our study findings, Naveen et al. also observed that as the duration of CSOM increased, the incidence of SNHL also increased [23].

Nahata et al. reported that the majority of patients in their study (69) were found to have a central type of tympanic membrane perforation, followed by posterior in 16 and anterior in 15 (together they constitute the marginal type of perforation) [22]. As observed in this study, other researchers have also documented that perforations in the tympanic membrane have been associated with conductive loss of hearing with varying degrees. Similar to our study, the larger the perforation (subtotal) of the tympanic membrane, the greater the loss in decibels of hearing has been observed [24]. Perforations are more commonly observed in the posterior (marginal) quadrants of the tympanic membrane. This was in line with our study as well. This shows that the locality of perforations also has a direct impact on hearing loss severity. Numerous researchers have also observed contradicting impacts of the type and location of perforation on the degree of SNHL. However, anatomically, any perforation in the margins (anterior or posterior) may lead to worsening of hearing since the round window is in direct approximation to sound [25].

This study has certain limitations, including its cross-sectional design, which restricts the ability to establish a causal relationship between CSOM and sensorineural hearing loss. Additionally, other potential confounding factors such as environmental noise exposure and socioeconomic influences were not extensively evaluated. The study also relied on hospital-based sampling, which may limit the generalizability of the findings to the wider population. Future longitudinal and multicenter studies with detailed audiological follow-up are recommended to better understand the long-term impact of CSOM on cochlear function and to guide preventive strategies.

CONCLUSIONS

The study concluded that both the duration of chronic suppurative otitis media (CSOM) and the type of tympanic membrane perforation were significantly associated with sensorineural hearing loss. A longer duration of disease and marginal perforations showed a strong association with Sensorineural Hearing Loss (SNHL), while subtotal perforations were also found to contribute to greater overall hearing loss. These findings highlight the importance of early detection and management of CSOM to prevent progression to irreversible cochlear damage.

Authors' Contribution

Conceptualization: SA

Methodology: TGA

Formal analysis: SA, MMUK, MA

Writing and Drafting: SA, TGA, MA, NA, NI

Review and Editing: SA, TGA, MA, NA, NI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article



Gynecological Adverse effects of Tamoxifen Treatment to Hormone Receptor Positive Breast Cancer Female Patients

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ABSTRACT

Tamoxifen, an oral synthetic selective estrogen modulator, has been widely used as an anti-cancer drug for over 50 years. Tamoxifen increases disease free survival and overall survival rates, when given as an adjuvant but many patients experience side effects which reduces quality of life. The present study investigates the adverse effects of tamoxifen in hormone receptor-positive breast cancer patients. **Objectives:** To investigate the Adverse effect of tamoxifen treatment on hormone receptor positive breast cancer patient. **Methods:** The longitudinal cohort study was conducted at Al-Tibri Medical College with collaboration of Liaquat National Hospital Karachi from March 2019 to Sep 2023. The study included 135 premenopausal women with hormone receptor-positive breast cancer. After surgery and chemotherapy, all received tamoxifen 20 mg/day for five years and were evaluated every six months for four years. **Results:** A total of 135 premenopausal hormone receptor-positive breast cancer patients were studied. Mean age was 44.6 years, and 79% had children. Endometrial thickness increased from 5.0 mm before treatment to 9.3 mm after 48 months of Tamoxifen ($p < 0.050$). Common adverse effects included vaginal discharge (36%), hot flashes (19%), and rash pigmentation (14%). D and C and Pap smear showed mostly benign or inflammatory changes. Long-term Tamoxifen use was linked to increased endometrial thickness and mild gynecological side effects. **Conclusion:** Tamoxifen showed mild, tolerable side effects and histopathological changes but effectively reduced metastasis, supporting its use with regular endometrial monitoring.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide and remains one of the main causes of cancer-related deaths. Almost 70% of breast cancers are hormone receptor positive, showing the presence of estrogen and/or progesterone receptors that help tumor cells grow under hormonal influence [1]. The use of endocrine therapy, mainly tamoxifen, a selective estrogen receptor modulator [SERM], has improved

survival and reduced recurrence in such patients [2]. Tamoxifen works as an estrogen blocker in breast tissue but shows partial estrogen-like effects on other organs like the uterus, bones, and liver [3]. Although tamoxifen has proven effective in controlling disease progression, its long-term use is linked with several gynecological side effects [4]. These include endometrial thickening, hyperplasia, polyps, cystic changes, and in rare cases, even



endometrial carcinoma [5]. In premenopausal women, it can also cause ovarian cysts, irregular menstruation, vaginal discharge, and uterine bleeding, which may affect the patient's overall quality of life [6]. The chances of these effects usually increase with the duration of therapy and higher cumulative doses [7]. Globally, different studies have examined the gynecological impact of tamoxifen, but most of the evidence comes from Western or postmenopausal groups [8, 9]. The biological response in premenopausal women can be different due to active ovarian function and higher estrogen levels that may change the drug's metabolism and tissue response [10]. Moreover, genetic, nutritional, and socioeconomic factors could also influence the safety and tolerability of tamoxifen in South Asian populations, particularly among Pakistani women [11]. In Pakistan, breast cancer often appears at a younger age and is mostly diagnosed at a later stage. However, there is still limited data regarding the long-term gynecological safety of tamoxifen in premenopausal patients [12]. Evaluating these side effects is essential for better patient monitoring, early identification of endometrial abnormalities, and to improve treatment compliance.

Tamoxifen is widely prescribed as an adjuvant endocrine therapy for hormone receptor-positive breast cancer because of its proven ability to reduce recurrence and improve survival. However, due to its partial estrogenic effects on the female reproductive system, long-term use may lead to various gynecological complications such as endometrial thickening, polyps, and menstrual irregularities. Although several international studies have reported these adverse effects, limited data are available regarding the long-term gynecological impact of tamoxifen among premenopausal breast cancer patients in the Pakistani population. Therefore, evaluating these effects is important to improve patient monitoring and ensure safe long-term therapy. This study aims to assess the gynecological adverse effects and endometrial changes associated with tamoxifen therapy in premenopausal hormone receptor-positive breast cancer patients in the Pakistani population.

METHODS

This longitudinal cohort study was conducted on 135 premenopausal women already diagnosed with hormone receptor positive infiltrating ductal carcinoma of breast, admitted in the Oncology Ward of Liaquat National Hospital, Karachi from March 2019 to Sep 2023. Ethical approval was obtained from the Ethical Review Committee of Al-Tibri Medical College (Ref. No. IREC/ATMC/22/19). A total of 152 patients were initially screened, out of which 17 were excluded 7 due to metastatic disease, 5 using hormonal contraceptives, and 5 lost to follow-up before

baseline evaluation. Written consent was taken from all participants. The sample size of 135 patients was calculated using a single-proportion formula, assuming a 30% prevalence of gynecological adverse effects, a 95% confidence level, and an 8% margin of error. After adjusting for a 10% loss to follow-up, 135 participants provided adequate power to detect significant changes in endometrial thickness and the frequency of adverse effects during tamoxifen therapy. Finally, 135 patients were enrolled and followed up for a period of four years. Patients were selected through non-probability purposive sampling based on inclusion criteria which included premenopausal women between 25 to 50 years of age, having histopathological confirmed primary infiltrating ductal carcinoma in one breast only, positive for estrogen and/or progesterone receptors, and non-metastatic at the time of diagnosis. Postmenopausal patients, had bilateral or metastatic breast cancer, were taking oral contraceptives or hormone replacement therapy, or had any previous gynecological malignancy or severe systemic illness were excluded from the study. Physical and clinical evaluations of patients were carried out by an oncologist, and information regarding tumor size, grade, axillary lymph node involvement and hormone receptor profile was noted. After surgical removal of tumor, adjuvant therapy was given according to tumor histopathology including chemotherapy with various combinations of 5-Fluorouracil, Adriamycin, and Cyclophosphamide, Methotrexate, and Paclitaxel, along with hormonal therapy of Tamoxifen 20 mg per day for five years. All patients were evaluated before the start of treatment and then followed up every six months for four years (48 months). During each visit, patients underwent clinical and gynecological examination, clinical outcomes and adverse effects were clearly defined before data collection. "Rash pigmentation" referred to any noticeable discoloration or skin rash observed during follow-up and confirmed by a clinician. "Pelvic inflammation" denoted findings of tenderness or inflammation confirmed by gynecological examination or Pap smear. All other symptoms, such as vaginal discharge, irregular menses, and gastrointestinal disturbance, were recorded based on patient complaint and verified through clinical evaluation. SPSS version 22.0 used for the statistical analysis; paired t test was applied to test the mean analysis at 95% confidence interval.

RESULTS

A total of 135 premenopausal hormone receptor-positive breast cancer patients were included in the study. The mean age of the patients was 44.60 ± 0.82 years, and the mean age at marriage was 20.44 ± 0.50 years. Among them, 79.01% (n=106) had children, while 54.1% (n=73) reported a history of abortion (Table 1).

Table 1: Age and Children Status of Hormone Receptor Positive Patient

Control	Age (Years) Mean $\pm$ SD	Age at Marriage (Year) Mean $\pm$ SD	Percentage of Subject having Children (N) %	Percentage of Subject Having Abortions (N) %
Hormone receptor positive breast cancer female patient.	44.60 $\pm$ 0.82	20.44 $\pm$ 0.50	79.01 (106%)	54.1 (73%)

Family history assessment revealed that 20.74% (n=28) of the patients had a family history of cancer, while 13.33% (n=18) had hypertension, 11.11% (n=15) diabetes, 2.96% (n=4) jaundice, and 5.18% (n=7) arthritis (Table 2).

Table 2: Family History of Hormone Receptor Positive Breast Cancer Female Patient

Control	Family History of Cancer (N) %	Hypertension (N) %	Diabetes (N) %	Jaundice (N) %	Arthritis (N) %
Hormone receptor positive breast cancer female patient (135)	20.74 (28%)	13.33 (18%)	11.11 (15%)	2.96 (4%)	5.18 (7%)

Endometrial evaluation showed a significant increase in thickness following tamoxifen therapy. The mean endometrial thickness increased from 5.0 ± 0.01 mm before treatment to 7.3 ± 0.2 mm after 24 months and 9.3 ± 0.3 mm after 48 months ($p < 0.05$) (Table 3).

Table 3: Endometrium Thickness Before and After Tamoxifen Treatment

Endometrium Thickness (mm)	Before Treatment	After 24 Months	After 48 Months
Mean $\pm$ S.D	5.0 ± 0.10 (135)	7.3 ± 0.2 (135)*	9.3 ± 0.3 (135)*

Paired t test was applied, $p < 0.05$ as compare to before tamoxifen treatment

Regarding treatment-related toxicities, the most commonly reported adverse effects were vaginal discharge (36.3%), hot flashes (19.2%), rash pigmentation (14.1%), and gastrointestinal disturbances (14.1%), whereas irregular menses were observed in 3.7% of patients. Dilation and curettage (D&C) findings revealed benign endometrium (7.4%), stroma proliferation (5.2%), polyps (2.9%), and cystic hyperplastic ovarian cysts (3.7%). Pap smear results demonstrated atrophic vaginitis (5.9%), pelvic inflammation (16.3%), and bacillary background (8.9%), with few cases of metaplastic cells (2.9%) and reactive cellular changes (0.7%) (Table 4).

Table 4: Toxicities Developed After Tamoxifen Treatment

Overall effect (N) %	Dilation and Curettage D and C (N) %	Pap Smear Finding (N) %
Vaginal Discharge	36.3 (46%)	Endometrium Carcinoma – Atrophic Vaginitis 5.9 (8%)

Rash Pigmentation	14.1 (19%)	Endometrium Stroma	5.2 (7%)	Pelvic Inflammation	16.3 (22%)
Hot Flashes	19.2 (26%)	Benign Endometrium	7.4 (10)	Bacillary Background	8.9 (12%)
Gastrointestinal Disturbance (Anorexia)	14.1 (19%)	Polyp	2.9 (4%)	Reactive Cellular Changes	0.7 (1%)
Irregular Menses	3.7 (5%)	Cystic Hyperplastic Ovarian Cyst	3.7 (5%)	Metaplastic Cells	2.9 (4%)

DISCUSSION

The study included pre-diagnosed hormone receptor-positive breast cancer patients, who were already treated with either surgery, chemotherapy, or radiotherapy. In the present study, tamoxifen 20 mg/day was given to hormone receptor-positive patients as an adjuvant treatment for 5 years. Tamoxifen acts as an antiestrogen agent, decreasing the risk of recurrence of cancer in hormone receptor-positive patients, but it also exerts estrogenic effects in the endometrium and is associated with various uterine pathologies such as endometrial polyp, hyperplasia, and uterine cancer [13]. Endometrial thickness was noted before starting tamoxifen treatment by transabdominal ultrasound. After 24 and 48 months of tamoxifen treatment, endometrial thickness increased with the passage of treatment. According to previous studies, long-term tamoxifen treatment increases endometrial thickness and can be used as a predictor of developing endometrial carcinoma due to mild estrogenic effects on the endometrium. Young breast cancer survivors with tamoxifen-related endometrial diseases are at higher risk of developing endometrial cancer [14, 15]. In the present study, no case of endometrial cancer was observed. In premenopausal breast cancer patients treated with tamoxifen, abnormal uterine bleeding and increased endometrial thickness were noted in 32.7% of patients, which was not related to age, BMI, or duration of tamoxifen use [16]. In another study, age, body mass index, and menopausal status were not associated with endometrial pathology, whereas parity, endometrial thickness, and the presence of abnormal vaginal bleeding were associated with endometrial pathology during tamoxifen treatment in breast cancer women [17]. In the present study, tamoxifen-treated patients showed polyps, hyperplasia, and ovarian cysts, as found by previous researchers [18, 19]. When women take tamoxifen as an adjuvant treatment for breast cancer, some experience a relapse or new invasive breast cancer, indicating that some cells have become resistant to tamoxifen. In the endometrium of women, preventive tamoxifen on long-term exposure (>2 years) is likely to offer a growth advantage to endometrial cells with pre-existing mutations. The association between tamoxifen and

endometrial changes remained significant [20, 21]. The overall effects of tamoxifen in breast cancer patients include vaginal discharge, hot flashes, and gastrointestinal symptoms. Pelvic inflammation and atrophic vaginitis were also observed, whereas no abnormal histological changes in the cervix were reported on gynecological examination [22]. It is concluded that tamoxifen, which is used for prevention of breast cancer recurrence, causes some adverse effects such as vaginal discharge, pigmentation, hot flashes, and irregular menses. On dilation and curettage (D and C), polyps, endometrial stroma, and ovarian cysts were also seen. The main Pap smear findings are pelvic inflammation, so gynecological surveillance for the risk of endometrial disease in young breast cancer survivors is recommended for early detection and to avoid unnecessary procedures. The female genital system has a proliferative input on the endometrium, cervix, and vaginal epithelium. Therefore, it is important to perform a thorough examination of the cervix, vagina, and endometrial epithelium for any pathophysiological alterations due to tamoxifen treatment. This study has some limitations, including its single-center design, small sample size, and use of purposive sampling, which may limit generalization. Adverse effects were self-reported without standardized grading, introducing possible bias, but the findings still provide useful insight into tamoxifen's gynecological effects in premenopausal women.

This study has certain limitations that should be considered while interpreting the findings. The research was conducted at a single center with a relatively small sample size and purposive sampling, which may limit the generalizability of the results. Additionally, some adverse effects were based on patient-reported symptoms rather than standardized grading scales. Future multicenter studies with larger populations and longer follow-up periods are recommended to better evaluate the long-term gynecological safety of tamoxifen and to establish clearer monitoring guidelines for breast cancer patients receiving hormonal therapy.

CONCLUSIONS

Tamoxifen therapy in premenopausal hormone receptor-positive breast cancer patients showed mild gynecological changes, including increased endometrial thickness and benign histopathological findings. The drug was generally well tolerated, though regular gynecological monitoring is advised to detect early endometrial alterations and ensure safe long-term use.

Authors' Contribution

Conceptualization: UR, AS

Methodology: UR, AI

Formal analysis: AS

Writing and Drafting: AK, AS, SR, AS

Review and Editing: AK, AS, SR, AS, UR, AI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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