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Cook NR, Rosner BA, Hankinson SE, Colditz GA. Mammographic screening and risk factors for breast cancer. American Journal of Epidemiology. 2009 Dec;170(11):1422-32. doi: 10.1093/aje/kwp304.

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Conclusion should elucidate how the results communicate to the theory presented as the basis of the study and provide a concise explanation of the allegation of the findings.

ACKNOWLEDGEMENT

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The Rise of E-Cigarettes and Vaping: Health Risks and Policy Implications

OPEN ACCESS

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The use of e-cigarettes and vaping devices has increased exponentially in recent years, primarily affecting teenagers and young adults. These products have been widely accepted as safer alternatives to traditional smoking, often marketed as aids for smokers looking to avoid the tar and toxins associated with regular cigarettes. However, despite their popularity, e-cigarettes pose serious health risks, necessitating stronger public policies to mitigate their dangers. The recent surge in vaping, particularly among young people, has raised significant health concerns. According to the 2024 National Youth Tobacco Survey (NYTS) conducted by the CDC, e-cigarette use among youth remains a severe public health threat. The survey found that 5.9% of middle and high school students—equivalent to 1.63 million individuals—reported current use of e-cigarettes in 2024. Alarmingly, 38.4% of these users reported frequent use, while 26.3% reported daily use, indicating signs of nicotine addiction.

Although e-cigarettes are perceived as less harmful than conventional cigarettes, they are not entirely safe. Users are exposed to dangerous substances such as nicotine, heavy metals, and volatile organic compounds. Most e-cigarette products contain nicotine, the primary addictive component, which can lead to dependence. The health risks associated with e-cigarette use include worsening asthma symptoms, increased frequency of bronchitis, and a higher risk of lung infections. Additionally, nicotine raises heart rate, increases blood pressure, and may irritate blood vessels. A particularly concerning issue is E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI), which emerged as a serious health condition in 2019. Symptoms of EVALI include cough, difficulty breathing, chest pain, nausea, and fatigue. The rising prevalence of adolescent e-cigarette use underscores the urgency of addressing this public health crisis.

Governments worldwide are taking action to combat the e-cigarette epidemic. For instance, the UK government has introduced legislation to ban the sale of single-use vapes starting June 1, 2025. This initiative aims to reduce environmental impact and curb the growing youth vaping trend. Policymakers must take stronger measures to mitigate the associated health risks. Strict regulations on the marketing and sale of e-cigarettes are essential, as these products often target underage individuals through misleading advertisements. Flavored e-cigarettes, which appeal to younger users, should be banned entirely. Additionally, only adult smokers seeking to quit should have access to e-cigarettes, with stricter age verification measures ensuring compliance. Public health campaigns play a crucial role in educating both young people and adults about the risks of vaping. These initiatives should focus on dispelling the myth that e-cigarettes are risk-free and emphasize the potential for nicotine addiction and long-term health consequences. Raising awareness about the dangers of vaping is vital to preventing the next generation from developing nicotine dependency.

While e-cigarettes may have a place in harm reduction strategies for adult smokers, their widespread use—especially among youth—poses significant public health challenges. A comprehensive approach involving stricter regulations, targeted education, and ongoing research is necessary to mitigate the risks associated with e-cigarette use and prevent a new generation from becoming addicted to nicotine.

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Original Article

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Comparison of Lignocaine with Ondansetron for Attenuation of Propofol-Induced Pain in Adult Patients Undergoing Laparoscopic Cholecystectomy

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ABSTRACT

Intravenous administration of propofol causes pain that impacts anesthesia procedures. **Objective:** To compare the efficacy of intravenous Lignocaine and Ondansetron in reducing propofol-induced pain, hemodynamic stability and assess the occurrence of associated adverse effects during induction using a pain scale. **Methods:** It was a Quasi-Experimental study and conducted for six months from Sep 2024 to Jan 2025 at the Anesthesia department at Islam Medical College, Sialkot. To measure pain effects at laparoscopic cholecystectomy among adult patients.The patients were received 0.5mg/kg Lignocaine through the vein or 8mg Ondansetron before they received propofol treatment. Medical staff evaluated patients' pain levels on a standard scale while recording their vital signs.Data were analysed by SPSS 21.0. The categorical data was analysed through chi-square and evaluated continuous values with an independent t-test at a significance level of 0.05. **Results:** Lignocaine brought better pain relief from propofol than Ondansetron at a statistical significance of p<0.001.People in the Lignocaine group reported 15% of bad pain while 32% of patients in the Ondansetron group felt the same pain level. Ondansetron caused short-lived drops in blood pressure and heart rate but the application of Lignocaine generated mild skin issues. **Conclusions:** The study proved Lignocaine worked better than Ondansetron at stopping propofol pain effects. Despite its merits Ondansetron still serves as a good treatment option and medical staff should monitor heart-related side effects. Additional medical trials must test the effectiveness of using both drugs together as a pain treatment option.

INTRODUCTION

The chemical nature of propofol as 2,6-diisopropylphenol contains many lipids that prevent it from dissolving in water. Propofol needs special lipid-based treatment because its oil-like element stops water from carrying it directly into the blood stream. The base solution consists of soybean oil combined with egg lecithin and glycerol to create its fibrous white coloring [1]. Propofol stays poorly mixable with water because its isopropyl chains resist forming bonds with water molecules. Patients who receive propofol injections through its lipid-based emulsion often experience pain because of its impact on many other patients [2]. The medicated emulsion raises the danger of infection from bacteria and can damage blood fat levels when taken for long periods. Experts have tested new ways to dissolve propofol that use cyclodextrin-based liquids, microemulsions, and water-friendly drug-release systems instead of the traditional lipid emulsion [3]. Patients feel this injection more than any other clinical treatment because its pain level varies greatly from tolerable discomfort to severe scalding. Research shows that propofol pain develops through pain receptor reactions in blood vessel linings which lead to enhanced inflammation and increase sensitivity to propofol. Doctors use two main treatment types to reduce propofol injection pain which researchers study. Both Ondansetron and Lignocaine work as effective solutions to minimize discomfort for patients

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[4, 5]. Lignocaine works well at decreasing the pain that propofol causes. This treatment keeps nerve endings stable and stops sodium channel activity to stop pain signals from traveling along neurons [6]. Lignocaine proves helpful when given as a separate injection before propofol treatment or mixed right into the propofol as a technique to lessen pain. Research shows Lignocaine succeeds in diminishing both pain episodes and intensity better than other options for anesthesiologists. Using this method brings limited side effects such as mild skin reactions and discomfort through veins plus rare episodes of bodywide chemical harm [7]. Patients use Ondansetron to block 5-HT3 receptors and lower postoperative vomiting but researchers now examine its potential pain relief benefits. Studies show that Ondansetron relieves propofol pain by blocking 5-HT3 serotonin receptors involved in pain regulation [8]. Ondansetron relieves propofol injection pain by blocking serotonin receptors that transmit pain signals to other parts of the body. Current research shows Ondansetron helps ease discomfort but its results against Lignocaine stay uncertain. When giving Ondansetron to high-risk patients' doctors must watch for minor drops in blood pressure and slower heart rates because these side effects happen temporarily [9, 10].

This study aimed to evaluate and compare the efficacy of intravenous Lignocaine (0.5 mg/kg) and Ondansetron (8 mg) in reducing Propofol injection pain, while also assessing their safety profiles in cholecystectomy patients undergoing general anesthesia.

Additionally, the study aimed to analyze Adverse Drug Reactions (ADRs) associated with these interventions to improve clinical decision-making in anesthetic practice.

METHODS

It was a Quasi-Experimental study and conducted for six months from Sep 2024 to Jan 2025 at the Anesthesia department at Islam Medical College, Sialkot. Cholecystectomy patients undergoing general anesthesia were assigned to study groups using a simple random sampling method. The formula for sample size calculation for comparing two independent means was: $n=(Z\alpha/2+Z\beta)2\times2\times\sigma2d2$. With an effect size of 0.67, two followed alpha values (0.05), and beta value (0.1), 60 patients in each group were sufficient to identify a significant difference. So total sample size we have taken 120 patients. However, 60 participants per group were selected in the final study design. This study selected adult patients from age 18 to 60 who rated ASA 1 or 2 with no documented allergies to Lignocaine, Ondansetron, and Propofol. We did not accept patients who had ongoing pain disorders, opioid use, unstable blood pressure below 90 mmHg or heart rate under 50 beats per minute. Exclusion criteria: drug contraindications, pregnant women, and women breastfeeding. A computer system produced a random list to assign participants equally into Group L or Group O. A team member gave Lignocaine 0.5mg per kg body weight through an intravenous line for 30 seconds before delivering Propofol. The researchers provided Group O with 4 mg Ondansetron directly into the vein 30 seconds before they gave Propofol. The doctor inserted a 20G cannula into a large forearm vein before injecting 2 mg/kg propofol over five seconds into the vein. After receiving Propofol the nurse assessed patient pain with a four-level Verbal Rating Scale at zero for no pain up to three for severe pain that caused arm withdrawal or verbal response. Pain due to Propofol injection was assessed using the Visual Rating Scale (VRS) or Visual Analog Scale (VAS) immediately after administration. The incidence of pain and its severity were recorded at the time of injection and postoperatively. Patients verbally reported their pain intensity, and the observer recorded the responses. This method ensures an objective assessment of both frequency and severity of Propofol-induced pain. Doctors measured heart rate blood pressure and oxygen saturation levels before intervention during the procedure and following the surgery. Teams recorded all adverse effects including slower heart rates below 50 beats per minute and low blood pressure together with nausea, vomiting, and allergic responses in addition to reactions at the injection site. Data were analysed by SPSS 21.0. The categorical data was analysed through chi-square and evaluated continuous values with an independent t-test at a significance level of 0.05. This study was conducted following ethical principles with approval from the Institutional Review Board reference number (IBR: 900/IMC/ERC/000103). The informed consent form and ethical approval documents were provided.

RESULTS

The study found that both groups were comparable at baseline. The average age was similar between the Lignocaine group (38.4 ± 8.2 years) and the Ondansetron group (37.9 ± 7.9 years). Gender distribution was also similar, with 28 males and 32 females in the Lignocaine group and 26 males and 34 females in the Ondansetron group. The mean BMI was 24.6 ± 3.5 kg/m^2 for the Lignocaine group and 25.1 ± 3.8 kg/m^2 for the Ondansetron group. ASA classifications, heart rate, and blood pressure values were almost identical across both groups. This ensures that the groups were comparable in basic characteristics, allowing for a clear evaluation of the effects of propofol without interference from other variables (Table 1).

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Table 1: Demographic Characteristics(n=60)

Characteristics	Lignocaine Group (Mean ± SD)	Ondansetron Group (Mean ± SD)
Age (Years)	38.4 ± 8.2	37.9 ± 7.9
Gender (Male/Female)	28/32	26/34
BMI (Kg/m^2)	24.6 ± 3.5	25.1 ± 3.8
ASA I / II (%)	35 (58.3%) / 25 (41.7%)	33 (55%) / 27 (45%)
Baseline Heart Rate (BPM)	82.3 ± 6.5	81.9 ± 6.8
Baseline Systolic BP (mmHg)	124.5 ± 8.7	125.1 ± 9.2
Baseline Diastolic BP (mmHg)	78.6 ± 6.1	79.3 ± 6.5

Nurses evaluated patient pain by VRS after Propofol injections. The Lignocaine group produced fewer pain experiences compared to Ondansetron use ($p < 0.05$). Among patients in Group L, 70 percent or 42 individuals stated they had no pain while Group O patients with pain stood at only 40 percent or 24 individuals. More patients in Group O felt serious pain (43.3%) than those in Group L (16.7%)(Table 2).

Table 2: Pain Scores after Propofol Injection (n=60)[6]

Pain Score (VRS)	Lignocaine Group Frequency (%)	Ondansetron Group Frequency (%)	p-Value
No Pain (0)	42 (70%)	24 (40%)	0.001
Mild Pain (1)	8 (13.3%)	10 (16.7%)	0.64
Moderate Pain (2)	6 (10%)	18 (30%)	0.007
Severe Pain (3)	4 (6.7%)	8 (13.3%)	0.23

Doctors measured heart rate, systolic blood pressure, and diastolic blood pressure at baseline, post-treatment, and after patients received Propofol. Both treatment groups showed equal patterns of heart rate and blood pressure changes from start to end of treatment. The new patient group L took bigger drops in blood pressure readings than did Group O after induction ($p = 0.04$)(Table 3).

Table 3: Hemodynamic Parameters at Different Time Points

Variables	Time	Ondansetron Group Frequency (%)	Ondansetron Group (Mean ± SD)	p-Value
Heart Rate (bpm)	Baseline	82.3 ± 6.5	81.9 ± 6.8	0.78
	Post-Intervention	80.5 ± 6.9	81.1 ± 7.1	0.64
	Post-Induction	78.1 ± 6.2	80.8 ± 6.5	0.04
SBP (mmHg)	Baseline	124.5 ± 8.7	125.1 ± 9.2	0.81
	Post-Intervention	122.3 ± 7.8	123.6 ± 8.3	0.66
	Post-Induction	116.4 ± 6.9	120.2 ± 7.1	0.04
DBP (mmHg)	Baseline	78.6 ± 6.1	79.3 ± 6.5	0.72
	Post-Intervention	76.8 ± 5.8	78.1 ± 6.2	0.54
	Post-Induction	72.4 ± 5.1	76.2 ± 5.4	0.03

The study team checked for side effects including slowing heart rate and blood pressure drops along with nausea and vomiting. Vomiting and nausea rates reached 15% in Group O versus 5% in Group L yet the combined occurrence of bradycardia and low blood pressure proved more common in Group L (10% vs. 3.3% in Group O; $p = 0.03$). Few patients reported light skin reactions at injection sites without any group differences(Table 4).

Table 4: Incidence of Adverse Effects(n=60)

Adverse Effect	Lignocaine Group Frequency (%)	Ondansetron Group Frequency (%)	p-Value
Bradycardia	6 (10%)	2 (3.3%)	0.03
Hypotension	6 (10%)	2 (3.3%)	0.03
Nausea/Vomiting	3 (5%)	9 (15%)	0.02
Injection Site Reaction	2 (3.3%)	3 (5%)	0.64

DISCUSSION

This study analyzed the effectiveness of intravenous Lignocaine and Ondansetron at easing propofol pain during induction while checking potential adverse effects in adult patients who get laparoscopic cholecystectomy surgery. Both Lignocaine and Ondansetron were proven effective pain reducers during propofol administration with Lignocaine showing better pain control [12]. The research found that Lignocaine made patients feel minor skin irritation and resulted in short-lived shifts in heart rate and blood pressure with Ondansetron. Researchers have confirmed these findings by studying how people reduce pain during propofol injections. Research confirms that Lignocaine stands out as one of the best options to reduce propofol injection pain [13].To giving 0.5 mg/kg of Lignocaine through an IV lessened both the likelihood and extent of propofol pain during treatment which matches the research findings.Brazelton and Taylor (2023) performed a statistical review showing Lignocaine reduces propofol injection pain through its effects on neuron membranes and sodium channels [14].These results support what other research showed because Lignocaine produced significantly less pain than Ondansetron did. According to Biazar *et al.*, (2022) combining Lignocaine and propofol before giving the injection created greater pain relief than using Lignocaine alone as a pre-treatment. These findings support Lignocaine as an effective choice to reduce propofol injection pain due to successful pain relief despite not mixing the drugs [15]. Multiple research projects study how Ondansetron can decrease pain caused by propofol administration. According to previous research by Li and Zhuang.(2022) Ondansetron at 8mg via intravenous proved effective in diminishing pain from propofol injection just like the study shows.Research indicates Ondansetron blocks serotonin receptors that transmit pain sensations during the body [16].The study showed Ondansetron blocked pain better than before treatment but not as well as Lignocaine.According to Zaazouee *et al.*, (2023) study results Ondansetron can lower moderate to severe pain intensity but does not erase it completely.According to this research Ondansetron created brief low blood pressure issues reported in their findings.Because Ondansetron affects serotonin receptors to produce mild cardiovascular side effects. These research revealed minor changes in blood flow [17]. The side effects in this research matched what scholars found in other studies before. Research by Rayasam *et al.*,

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(2022) confirmed that Lignocaine causes minor skin discomfort at injection points [18].According to Nakajima *et al.*, (2020), this study demonstrated that Ondansetron triggered temporary blood pressure drops and slowed heart rate in patients.The minimal changes in blood flow show that these medicines are suitable for standard anesthesia procedures [19]. Lignocaine stands as the best choice to control pain from propofol because these results showed that it works best with few side effects. Ondansetron offers a useful replacement drug for people who cannot receive Lignocaine because they are sensitive to local anesthetics [20].Medical staff need to use Ondansetron carefully when treating patients who already have trouble with their heart rhythm.Research needs to test if combining Lignocaine with Ondansetron will help patients experience better pain relief while showing fewer undesirable effects [21]. Although this study offered useful results it faces important restrictions.More trials involving multiple medical sites must confirm these results because the study group had few participants.Patients experience pain in their own unique way regardless of using a set pain measurement scale.Future medical studies need to use tests that measure pain output directly from the brain.The researchers need to examine multiple Lignocaine and Ondansetron doses to establish proper dose relationships for future analysis.

CONCLUSIONS

Both Lignocaine and Ondansetron show significant pain reduction effects with propofol but Lignocaine proves better treatment than Ondansetron. Lignocaine caused mild skin discomfort but this side effect was milder than Ondansetron which caused minor temporary changes in blood pressure. Research evidence backs up the ongoing choice of Lignocaine to fight propofol discomfort and suggests using Ondansetron when needed. Research must improve how patients react to anesthesia induction by testing better sets of medicines.

Authors Contribution

Conceptualization: SA
Methodology: MFM, FA, SS
Formal analysis: MFM, RHKN
Writing, review and editing: SS, SI, RHKN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Biochemical Profiles and Clinical Correlates of Hyperkalemia and Metabolic Acidosis in Acute Kidney Injury Patients: A Cross-Sectional Analysis

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ABSTRACT

Acute Kidney Injury (AKI) is often complicated by biochemical disturbances, including hyperkalemia and metabolic acidosis. **Objective:** To examine the biochemical profiles and clinical consequences of hyperkalemia and metabolic acidosis in patients with AKI, with the goal of identifying correlations and prognostic markers to improve management strategies. **Methods:** The study analyzed 130 geriatric AKI patients with hyperkalemia and metabolic acidosis, assessing clinical outcomes through multivariable regression. **Results:** In 130 AKI patients with hyperkalemia and metabolic acidosis (mean age: 68.5 ± 10.2 years, 60% males), hypertension (45%) was the most common comorbidity. ICU admission was required in 25%, with an average hospital stay of 8.4 ± 4.5 days. Biochemical markers showed elevated serum potassium (6.2 ± 0.8 mEq/L), creatinine (3.5 ± 1.2 mg/dL), and reduced bicarbonate (18.5 ± 3.5 mEq/L). Serum creatinine (r = 0.80) and potassium (r = 0.67) correlated strongly with dialysis need, while lower blood pH (r = -0.50) was linked to ICU admission. Multivariable analysis identified serum creatinine (OR = 3.00, p < 0.001) as the strongest predictor of severe hyperkalemia and acidosis, with hypertension (OR = 2.15, p = 0.015) and advancing age (OR = 1.05, p = 0.003) also increasing risk. **Conclusions:** Hyperkalemia, metabolic acidosis, and elevated serum creatinine in acute kidney injury patients are strongly linked to worse outcomes, highlighting the need for early intervention.

INTRODUCTION

Acute Kidney Injury (AKI) is a serious medical condition characterized by a sudden weakening in kidney function that frequently results in significant injury and death, especially in hospitalized patients [1]. This also includes the many complications related to AKI, hyperkalemia, and metabolic acidosis which are chiefly notable due to their profound effects on different systems of the body among them cardiac, neuromuscular, and metabolic pathway disruption [2] are the most vulnerable ones. Elevated potassium levels, acknowledged by hyperkalemia, pose a danger of life-captivating cardiac arrhythmias [3]. In the meantime, metabolic acidosis, designated by reduced blood pH and bicarbonate levels, interrupts normal physiological courses and worsens the severity of AKI by promoting inflammation, endothelial dysfunction, and renal tubular injury [4]. Biochemical estimation in patients with AKI plays a crucial role in measuring the extent of renal damage and considerate the metabolic instabilities involved [5]. This information is dynamic for prompt mediation and operative risk stratification to predict outcomes, guide therapeutic decisions, and reduce morbidity [6]. Although several studies have discovered electrolyte imbalances in AKI, however, inclusive research directing specifically on the biochemical profiles and

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clinical outcomes of patients with coexisting hyperkalemia and metabolic acidosis remains limited with most studies focusing on either hyperkalemia or metabolic acidosis individually rather than their combined impact [7]. Additionally, recent studies highlight that persistent metabolic acidosis in AKI patients is linked to a higher risk of Chronic Kidney Disease (CKD) progression, emphasizing the need for early intervention to prevent long-term renal deterioration [8]. Moreover, hyperkalemia in AKI has been found to increase the likelihood of in-hospital cardiac arrest necessitating vigilant monitoring and timely therapeutic measures [9, 10]. To address this gap, the present study will analyze the biochemical characteristics and discover probable clinical associations in AKI patients with these complications.

By targeting this specific subgroup, the study seeked to improve understanding, enable early identification of high-risk patients and subsidize the development of more precise management strategies, ultimately cultivating patient results [11].

METHODS

This was a cross-sectional observational study conducted at Khawaja Muhamamd Safder Medical College (KMSMC) Sialkot. The primary participants of this study were older adult patients diagnosed with Acute Kidney Injury (AKI), presenting with hyperkalemia and metabolic acidosis. The study was conducted over a period from February 2024, to June 2024, under the approval of the Institutional Review Board (IRB) with reference number 30/REC/KMSMC. Patients were included if they exhibited biochemical disturbances indicative of AKI, including hyperkalemia (serum potassium >5.0 mEq/L) and metabolic acidosis (serum bicarbonate <22 mEq/L or pH <7.35), with a minimum hospital stay of 48 hours for serial biochemical assessment. Exclusion criteria comprised pre-existing CKD or ESRD to focus on acute kidney dysfunction, as well as non-renal causes of electrolyte imbalance, such as adrenal insufficiency or diabetic ketoacidosis, to ensure the study's specificity to AKI-related disturbances. Prior Use of Potassium-Lowering or Bicarbonate Therapy – Patients receiving active treatment for hyperkalemia or metabolic acidosis before admission were excluded to prevent confounding effects on biochemical assessments. The KDIGO (Kidney Disease: Improving Global Outcomes) guidelines were used solely for classifying AKI severity in the included patients, ensuring standardized assessment of kidney function decline. Patients were stratified into KDIGO Stage 1, 2, or 3 based on changes in serum creatinine and urine output post-admission. Data were collected through an appraisal of patients' medical histories and their systemic records. However, blood sampling was conducted at the time of admission. The data that has been preserved comprised demographic information like the relevant medicinal history of hypertension, diabetes mellitus, cardiovascular disease, and their age and gender. The levels of serum potassium, serum bicarbonate, their blood pH and serum Creatinine considered at same time. Blood urea nitrogen and Estimated Glomerular Filtration Rate (eGFR) were also measured to ensure precise data collection. Clinical outcomes were also recorded, focusing on the length of hospital stay, the requirement for dialysis, ICU admissions, and the severity of AKI, categorized based on established guidelines. Data analysis was accomplished using SPSS version 26.0. Descriptive statistics were intended for demographic and clinical variables while continuous variables expressed as Mean ± Standard Deviation (SD) along median (interquartile range) as suitable. Definite variables were presented as frequencies and percentages. According to data distribution correlations between biochemical parameters and clinical results were assessed using Pearson's or Spearman's correlation coefficients. Additionally, multivariable logistic regression analysis was conducted to identify the predictors to determine severe hyperkalemia and metabolic acidosis. Therefore, proper adjustment for potential confounders such as age and comorbidities was done. The obtained results were displayed as adjusted Odds Ratios (ORs) beside with 95% confidence intervals to show the strength and consistency of the gained outcomes. Ethical consent for the study was approved by the hospital's Ethical Evaluation Board. All participants gave their informed consent before taking part in this study. Their individual information was kept personal during the investigation. Participants were also informed of their accurate rights to withdraw from the study at any time without facing any negative consequences.

RESULTS

Table 1 presents the demographic and clinical characteristics of the study population. A total of 130 patients with AKI and associated hyperkalemia and metabolic acidosis were included, with a mean age of 68.5 ± 10.2 years. Males comprised 60% of the cohort, while 40% were female. The most prevalent comorbidities were hypertension (45%), diabetes mellitus (30%), and cardiovascular disease (15%). Regarding AKI severity, 30% of patients were categorized as KDIGO stage 1, 40% as stage 2, and 30% as stage 3. ICU admission was required for 25% of patients, and the mean hospital stay was 8.4 ± 4.5 days. This table outlines the demographic and clinical characteristics of the study population, including age, gender, comorbidities, AKI severity, ICU admission, and length of hospital stay.

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Table 1: Demographic and Clinical Characteristics of AKI Patients with Hyperkalemia and Metabolic Acidosis (n = 130)

Variables	Frequency (%)/Mean ± SD
Age (Years)	68.5 ± 10.2
Gender	
Male	60 (60%)
Female	40 (40%)
Comorbidities	
Hypertension	45 (45%)
Diabetes Mellitus	30 (30%)
Cardiovascular Disease	15 (15%)
AKI Severity (KDIGO Staging)	
Stage 1	30 (30%)
Stage 2	40 (40%)
Stage 3	30 (30%)
ICU Admission	25 (25%)
Length of Stay (Days)	8.4 ± 4.5

Table 2 provides an outline of the biochemical parameters of AKI patients with hyperkalemia and metabolic acidosis. Serum potassium levels were markedly elevated (6.2 ± 0.8 mEq/L), exceeding the normal range (3.5-5.0 mEq/L). Serum bicarbonate was reduced (18.5 ± 3.5 mEq/L), and blood pH was lower than normal (7.29 ± 0.08). Serum creatinine (3.5 ± 1.2 mg/dL) and blood urea nitrogen (45.2 ± 15.3 mg/dL) were significantly increased, while estimated glomerular filtration rate (eGFR) was markedly reduced (25.3 ± 10.5 mL/min/1.73m^2), reflecting severe renal impairment.

Table 2: Serum Levels of Parameters in AKI Patients with Hyperkalemia and Metabolic Acidosis (n = 130)

Variables	Mean ± SD/Median (IQR)	Normal Range
Serum Potassium (mEq/L)	6.2 ± 0.8	3.5 - 5.0
Serum Bicarbonate (mEq/L)	18.5 ± 3.5	22 - 28
Blood pH	7.29 ± 0.08	7.35 - 7.45
Serum Creatinine (mg/dL)	3.5 ± 1.2	0.6 - 1.2
Blood Urea Nitrogen (mg/dL)	45.2 ± 15.3	7 - 20
Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73 m^2)	25.3 ± 10.5	>90

This table shows the correlation between key biochemical markers (serum potassium, creatinine, blood pH) and clinical outcomes, including length of hospital stay, ICU admission, and need for dialysis. Table 3 illustrates the correlation between key biochemical markers and clinical outcomes. Serum potassium, creatinine, and blood pH exhibited significant correlations with hospital stay, ICU admission, and need for dialysis. Notably, elevated serum creatinine (r = 0.80) and potassium (r = 0.67) were strongly associated with dialysis requirement, while lower blood pH was inversely correlated with ICU admission (r = -0.50) and hospital stay (r = -0.55).

Table 3: Correlation between Biochemical Markers and Clinical Outcomes in AKI Patients with Hyperkalemia and Metabolic Acidosis (n = 130)

Clinical Outcomes	Serum Potassium (r)	Serum Bicarbonate (r)	Serum Creatinine (r)	Blood pH (r)
Length of Hospital Stay	0.45*	-0.50*	0.60*	-0.55*
Need for Dialysis	0.67*	-0.40*	0.80*	-0.45*
ICU Admission	0.55*	-0.35*	0.70*	-0.50*

*Note: Correlation coefficients (R-values) have been calculated using Pearson's or Spearman's correlation depending on data distribution

This bar chart presents the adjusted Odds Ratios (OR) with 95% Confidence Intervals (CI) for key predictor variables in Acute Kidney Injury (AKI), including age, hypertension, diabetes mellitus, serum creatinine, and blood pH. The x-axis represents the OR, where values greater than 1 indicate an increased risk, while values below 1 suggested a protective effect. The vertical dashed line at OR = 1 denoted no association. Serum creatinine (OR = 3.00, p < 0.001) is strongly associated with severe hyperkalemia and metabolic acidosis in AKI, reflecting impaired renal clearance. Hypertension (OR = 2.15, p = 0.015) significantly increases the risk of severe hyperkalemia in AKI, likely due to altered renal sodium and potassium regulation. Diabetes mellitus (OR = 1.78, p = 0.073) showed a potential but non-significant association with electrolyte disturbances in AKI. Age (OR = 1.05, p = 0.003) is significantly associated with worsening metabolic acidosis in AKI, suggested declining acid-base balance with age. Blood pH (OR = 0.50, p = 0.002) exhibits an inverse relationship with severe hyperkalemia in AKI, indicating that worsening acidosis increases the risk of electrolyte imbalances.

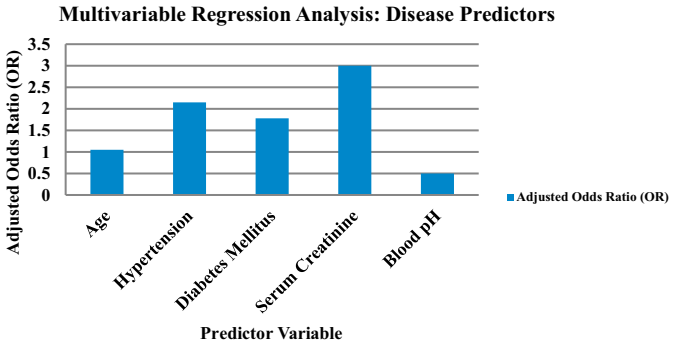

Figure 1: Multivariable Regression Analysis of Predictors for Severe Hyperkalemia and Metabolic Acidosis in Acute Kidney Injury (AKI)

This table 4 presented the results of a multivariate logistic regression analysis assessing the association between various predictor variables and a clinical outcome. The adjusted odds ratio (OR), 95% confidence interval (CI), and p-value for each predictor are reported. Statistically significant predictors (p < 0.05) include age, hypertension, serum creatinine, and blood pH, indicating their strong

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association with the outcome. Diabetes mellitus shows a non-significant trend (p = 0.073).

Table 4: Predictors of Clinical Outcomes: A Multivariate Analysis

Predictor Variables	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI)	p-Value
Age	1.05	1.02 - 1.08	0.003
Hypertension	2.15	1.15 - 4.02	0.015
Diabetes Mellitus	1.78	0.95 - 3.35	0.073
Serum Creatinine	3.00	1.80 - 4.90	<0.001
Blood pH	0.50	0.30 - 0.80	0.002

DISCUSSION

This study was intended to clarify the biochemical outlines and clinical comparisons of hyperkalemia and metabolic acidosis in cases of critical kidney injury. These results indicated significant correlations between elevated serum potassium levels, diminished bicarbonate levels, and serious clinical consequences. These are consistent with existing literature stating the importance of these specific biochemical markers in AKI management [12]. The demographic facts demonstrated that the mainstream were older adults, with a mean age of 68.5 years. This brings into line with the predominant understanding that age is an important risk factor for AKI. All these factors had potentially increased the occurrence of comorbidities such as hypertension and diabetes mellitus in this population [13]. In particular, 45% of patients had a history of hypertension, and 30% were diabetics, representing an essential need for careful nursing and management of circumstances to alleviate the risk of AKI. Biochemically, results showed that the mean serum potassium level was significantly elevated at 6.2 mEq/L. This is well above the regular range. This is concerning, as most severe cardiac-related deaths are the consequence of hyperkalemia, plus arrhythmias, particularly in the background of AKI [14]. Moreover, the mean serum bicarbonate level was established to be 18.5 mEq/L, confronting metabolic acidosis. The observed blood pH of 7.29 supplements the presence of substantial acid-base disturbances. These findings stand prominent in establishing an interrelationship between hyperkalemia and metabolic acidosis in AKI patients. Ultimately requiring the necessity to timely monitor and intervene in further complications [15]. This analysis exposed that higher serum potassium levels correlated positively and confidently with longer hospital stays. Moreover, requiring an increased likelihood for urgent dialysis in acute cases. This correlation highlights the clinical significance as a prognostic marker for serum potassium in managing acute kidney [16]. The multivariable regression analysis recognized numerous interpreters of severe hyperkalemia and metabolic acidosis, with serum creatinine showing the strongest association. This highlights the role of kidney function in the directive of potassium and acid-base balance, supporting the importance of early recognition and treatment of deteriorating kidney function in at-risk populations [17]. Interestingly, the study also distinguished that older age and the presence of comorbidities such as hypertension significantly supported the danger of developing severe hyperkalemia and metabolic acidosis. These findings suggest that targeted interventions aimed at managing these risk factors hold importance in preventing AKI-related complications in older adults [18]. Boundaries of the study include its cross-sectional design, which limits the ability to infer causality, making its nature as single-center. It is therefore needed to conduct studies with larger, multicenter cohorts and longitudinal designs to elucidate this difficult relationship between parameters in AKI patients [19]. In conclusion, this study emphasizes the critical need for alert biochemical monitoring and management of hyperkalemia and metabolic acidosis in older patients with AKI. Healthcare providers can improve patient conditions by understanding the biochemical profiles and their clinical correlates. Therefore, through timely interventions, they can refine the management of AKI in this predisposed old population [20].

CONCLUSIONS

This study emphasized the role of observing acidosis and hyperkalemia in patients presenting acutely particularly with older age. Elevated serum potassium and decreased bicarbonate levels have been intensely connected to adverse outcomes, including prolonged hospital stays and amplified dialysis needs. Targeted interventions and watchful biochemical assessments are vital and aimed at enlightening AKI management and patient outcomes.

Authors Contribution

Conceptualization: MA
Methodology: MAT
Formal analysis: AM
Writing, review and editing: FI, HA, AK, MA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Attitude Towards Tele-Medicine Among Caregivers of Pediatric Patients

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ABSTRACT

Telemedicine is a vital constituent of digital health-care, particularly stating the deliverance of medical facilities over remote areas by means of Information and Communication Technologies (ICT). The swift progress of mobile applications has improved support for health-care experts, rationalization responsibilities such as time organization, communication, and policymaking. **Objective:** To assess attitudes of parents having children aged between one to twelve years towards telemedicine. **Methods:** The cross-sectional study employed an online survey with the sampling strategy as convenience method for recruitment of eligible parents. A self-administered questionnaire was employed to gather sociodemographic data, child-related information, and participants' technological profiles.Attitudes toward telemedicine were measured using a 5-point scale, evaluating the perceived usefulness of various telemedicine services and associated advantages. Data analysis included descriptive statistics to summarize sociodemographic variables and item prevalence, while excluding any missing values. **Results:** A total of 120 families participated in the study, with caregivers averaging 47.4 years in males, 43.1 in females and children 7.5 years old. The majority of caregivers were female (68.3%), and most children were male (53.3%). Technological profiles indicated high smartphone availability (93.3%) and moderate use of social media accounts. Attitudes toward telemedicine showed significant perceived usefulness, particularly for scheduling medical visits (54.1% rated it as moderate/much) and telemonitoring services (49.1%). Participants recognized advantages of telemedicine, highlighting time efficiency (44.1%) and financial savings (46.6%) as key benefits. **Conclusion:** Families of pediatric patients demonstrated a strong willingness to engage in telemedicine programs. They showed positive attitude towards usefulness of telemedicine.

INTRODUCTION

Telemedicine is a crucial component of digital healthcare, which encompasses the use of electronic devices and digital information across various health sectors [1]. It specifically refers to the delivery of medical services over distances, utilizing Information and Communication Technologies (ICT) [2]. Alongside these remote care methods, a wide array of mobile applications has emerged, providing essential support to Healthcare Professionals (HCPs) in their daily operations [3]. These applications enhance efficiency by streamlining tasks such as time management, information access and storage, health promotion, education, communication, monitoring, data organization, and decision-making [4]. The digital health application landscape is rapidly evolving, with around 97,000 health-related apps available on platforms like Apple and Google. This quantity rises by almost 1,000 new apps per month, representing a predictable yearly rise of 25% [5]. The use of ICT and mobile technologies is cost-effective as well as improves operative competence, contributory to progressions in health-care amenities [6]. World Health Organization (WHO) highlights the transformative capacity of mobile machineries in cultivating community health facility delivery, depicting their user-friendliness and extensive reception among both workers and patients [7]. The development of ICT has led to the growth of various organizations intended for

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healthcare settings, counting mobile appointment arrangement. Therefore, investors from various arenas like HCPs, IT experts, social researchers, public and private administrations, and representatives are vigorously discovering ways to influence portable Mobile Health (m-Health) technologies, generating novel prospects in healthcare delivery [8]. The noteworthy surge in mobile phone utilization over the past era, with worldwide payments outstanding at 5.11 billion and predictable to surpass 50 billion, accentuates this drift. According to WHO, this availability is not restricted to advanced countries but also spreads to underserved areas, marking a essential moment where technology is reforming healthcare structures [9]. The development of telemedicine has been considered by quick progressions, leading to cost-effective explanations and wider functionalities. Both developed and developing nations have accepted mobile health methods, though evidence on user information and practices remains limited [6]. For example, surveys conducted in Ghana indicate a significant awareness and potential integration of m-Health into standard healthcare systems [10]. In Korea, while the adoption of m-Health among older adults is increasing, some still face challenges due to limited expertise, even as their self-confidence in using these technologies grows [11]. From the perspective of HCPs, studies in Finland and Lithuania reveal that nurses are becoming increasingly familiar with mobile health technologies, emphasizing features like automated data recording and transmission [12]. In Ethiopia, a considerable number of healthcare professionals demonstrate good knowledge and awareness of telemedicine services, influenced by factors such as information sources, IT support, and training [13]. In underdeveloped countries, telemedicine applications could serve as a powerful means to deliver essential healthcare to large populations, effectively bridging the gap between rural areas and specialized medical institutions predominantly located in urban centers [14]. Since the COVID-19 pandemic began in Pakistan, there has been a notable rise in demand for telehealth services. Despite the potential of telemedicine to address many barriers to healthcare delivery in developing nations, Pakistan has not yet fully harnessed this opportunity [15]. The rapid population growth, combined with a fragmented healthcare system, has resulted in unequal access to services. Telemedicine holds the promise to enable Pakistan's healthcare system to adopt innovative and cost-effective strategies, thereby transforming healthcare delivery throughout the country. Notably, pediatric patients residing in isolated regions face considerable challenges in accessing specialized medical professionals, as their health outcomes can be significantly influenced by proximity to these specialized centers [16].

The objective of the current study was to assess attitudes of parents having children aged between one to twelve years towards telemedicine, focusing to understand their perceptions towards its utilization in the management of their children's healthcare needs.

METHODS

This study was a cross-sectional online survey, utilizing a convenience sampling method to recruit parents with children aged 1–12 years receiving care for acute or chronic conditions through a web-based survey platform. A total sample size of 120 participants was selected based on practical considerations, including time limitations, resource accessibility, and the exploratory nature of the study. Participants who met the eligibility criteria were contacted consecutively by research assistants, and inclusion criteria was as follows: having a child within the particular age range and giving informed consent. After the informed consent process and obtaining it from participants, research participants completed self-reported questionnaire intended at evaluating their attitudes toward telemedicine. The first section of the questionnaire constituted about sociodemographic characteristics. It also collected information about the child, such as gender, age, the number of hospital admissions in the past year, and the frequency of visits to the family pediatrician during the same period. Moreover, the questionnaire assessed technological aspects of research participants, measuring the accessibility of devices such as smartphones, personal computers, tabs, and smart TVs, along with the existence of blogs and social media accounts. It inquired about the use of messaging applications, video calls, smartphone apps, health-related apps, and online searches for health information. Attitudes toward telemedicine were measured on a 5-point scale, focusing on the perceived usefulness of various services, including communication apps for parents, health diaries, appointment scheduling, telemonitoring, emergency consultations, reminders for appointments, and health promotion newsletters. Participants also evaluated perceived benefits of telemedicine, such as time and cost savings, as well as empowerment for patients and families. Data analysis were performed using SPSS version 23.0. Analysis involved describing sociodemographic variables and the prevalence of each item using means, standard deviations, medians, ranges, or proportions with 95% confidence intervals, as appropriate, while excluding any missing values. Participants' technological profiles were categorized based on device availability and usage of social media and messaging services. Descriptive statistics of attitudes towards telemedicine and perceived advantages were presented. These statistics were used to provide a detailed summary of categorical variables and response

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distributions.

RESULTS

A total of 120 families were enrolled. The mean age of caregivers was 45.2 ± 5.4 years and the mean age of children was 7.5 ± 3.8 years as shown in table 1.

Table 1: Characteristics of study Participants

Characteristics	Frequency (%)/Mean ± SD
Caregivers Gender	
Male	38 (31.7%)
Female	82 (68.3%)
Caregivers Age	
Male	47.4 ± 4.8
Female	43.1 ± 5.2
Child's Gender	
Male	64 (53.3%)
Female	56 (46.6%)
Child's Age	7.5 ± 3.8 Years
Pediatrician Visits During Last 6 Months	
Never	32 (26.6%)
1-4 Times	58 (48.3%)
5 or More Times	30 (25%)

Table 2 illustrated the technological characteristics of the study participants, highlighting their access to devices, ownership of technological tools, engagement with social media platforms, utilization of messaging services, and experience with video call applications. A significant proportion of participants (93.3%) reported owning a smartphone, followed by access to smart TVs (57.5%), laptops (35%), and desktop computers (20.8%). In terms of gadget ownership, half of the respondents (50%) possessed two gadgets, 35% reported minimal ownership (0–1 gadget), and 15% had extensive access (3–4 gadgets). Social media engagement was also examined, with Facebook being the most commonly used platform (70%), followed by Instagram (60%) and Google accounts (56.6%), while Twitter was used by a smaller group (18.3%). Overall, most participants (63.3%) exhibited moderate activity on social media (1–2 accounts), 20% demonstrated high activity (3–5 accounts), and 16.6% had no social media presence. Regarding messaging tools, WhatsApp emerged as the most widely used service (91.6%), followed by Facebook Messenger (42.5%) and Skype (35%). Participants' use of messaging platforms was categorized as moderate for the majority (51.6%), while 35.8% reported limited usage (0–1 facility), and 12.5% had extensive usage (3 facilities). Concerning video calling, 76.6% of respondents had used a smartphone application for video communication, yet only 23.3% had employed it for healthcare purposes.

Table 2: Technological Profile

Variables		Frequency (%)
Type of Device Availability		
Smart Phone		112 (93.3%)
Laptop		42 (35%)
PC		25 (20.8%)
Smart TV		69 (57.5%)
Technological Gadgets		
Low	0- 1 Gadget	42 (35.0%)
Moderate	2 Gadgets	60 (50.0%)
High	3-4 Gadgets	18 (15.0%)
Social Media Accounts		
Facebook Account		84 (70.0%)
Instagram Account		72 (60.0%)
Twitter Account		22 (18.3%)
Google Account		68 (56.6%)
Social Networking		
Low (No Account)		20 (16.6%)
Moderate (1-2 Accounts)		76 (63.3%)
High (3-5 Accounts)		24 (20.0%)
WhatsApp		110 (91.6%)
Skype		42 (35.0%)
Facebook Messenger		51 (42.5%)
Use of Messaging Facilities		
Low	0-1 Facility	43 (35.8%)
Moderate	2 Facilities	62 (51.6%)
High	3 Facilities	15 (12.5%)
Video Calls Facility		
Ever Utilized Smartphone App		92 (76.6%)
Ever Utilized Smartphone App for Health Purpose		28 (23.3%)

Table 3 outlined participants' attitudes toward telemedicine services, categorized by perceived usefulness across various features, including communication, health monitoring, scheduling, and emergency services. For communication features, 56.6% of participants found an app enabling communication with other parents sufficient, while 30% rated it as moderately or very useful. Regarding a diary for tracking a child's health status, 51.6% deemed it sufficient, and 41.6% found it moderately or very useful. Scheduling medical visits via an app was highly valued, with 54.1% rating it moderately or very useful, while 35.8% found it sufficient. Similarly, a service for televisits was considered moderately or very useful by 43.3% of participants, and sufficient by 29.8%. In terms of telemonitoring services, 49.1% found these services moderately or very useful, and 41.6% considered them sufficient. Services for transmitting telemonitoring data to doctors were rated as sufficient by half of the participants (50.8%) and moderately or very useful by 40.8%. Emergency medical advice services were rated as sufficient by 43.3% of respondents, while 35% rated them moderately or very useful. Notifications for medical appointments were highly rated, with 57.5% finding them

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sufficient and 35.8% considering them moderately or very useful. For transmitting health information from hospitals, 48.3% found the service sufficient, and 40.8% rated it moderately or very useful. Alerts for therapy sessions were deemed sufficient by 55% of participants and moderately or very useful by 37.5%. Finally, health awareness newsletters were considered sufficient by 49.1% and moderately or very useful by 39.1%.

Table 3: Attitude Towards Telemedicine

Attitude Towards Telemedicine	None/A Bit Frequency (%)	Sufficient Frequency (%)	Moderate/Much/Frequency (%)
Perceived Usefulness			
An app allowing communication with other parents of children	16 (13.3%)	68 (56.6%)	36(30.0%)
A diary for recording the child's health status	8(6.6%)	62(51.6%)	50 (41.6%)
An app for scheduling medical visits	12(10%)	43 (35.8%)	65(54.1%)
A service for televisits	20 (16.6%)	48 (29.8%)	52 (43.3%)
A telemonitoring service	11(9.1%)	50(41.6%)	59 (49.1%)
A service for transmitting telemonitoring data to the doctor	10 (8.3%)	61 (50.8%)	49 (40.8%)
A service for seeking medical advice in emergencies	26 (21.6%)	52 (43.3%)	42 (35.0%)
Notifications for medical appointments	8 (6.6%)	69 (57.5%)	43(35.8%)
A service for transmitting health information from the hospital	13 (10.8%)	58 (48.3%)	49 (40.8%)
Alerts for therapy sessions	9 (7.5%)	66 (55%)	45 (37.5%)
A newsletter focused on health awareness	14 (11.6%)	59 (49.1%)	47 (39.1%)

Table 4 highlighted participants' perceptions of the advantages of telemedicine, categorized into levels of agreement: None/A Bit, Sufficient, and Moderate/Much. Regarding time efficiency, 44.1% of participants perceived it as moderately or very advantageous, while 38.3% considered it sufficient. Financial savings were recognized as a major benefit, with 46.6% rating it as moderately or very advantageous and 43.3% finding it sufficient. Increased patient autonomy was viewed positively, with 47.5% rating it as moderately or very advantageous and 40% finding it sufficient. Similarly, enhanced family empowerment was perceived as sufficient by the majority (50.8%), while 34.1% rated it as moderately or very advantageous.

Table 4: Perceived Advantages of Telemedicine

Advantages of Telemedicine	None/A Bit Frequency (%)	Sufficient Frequency (%)	Moderate/Much Frequency (%)
Time Efficiency	21(17.5%)	46 (38.3%)	53 (44.1%)
Financial Savings	12 (10%)	52 (43.3%)	56 (46.6%)
Increased Patient Autonomy	15 (12.5%)	48 (40%)	57 (47.5%)
Enhanced Family Empowerment	18(15.0%)	61 (50.8%)	41 (34.1%)

DISCUSSION

The decision to create and implement an innovation should be guided by three essential elements: feasibility, viability, and desirability [16]. The development of a telemedicine initiative stands to benefit from these principles. This study focuses on understanding the desires and expectations towards telemedicine among families with children.The findings reveal a strong interest in telemedicine, with many families enthusiastic about using a hospital-issued app, and over half willing to participate in televisits.This willingness was consistent across various demographics, indicating that a telemedicine service could cater to all patients without needing to target specific subgroups.Previous research has explored attitudes toward technology in health management, primarily among adult patients. Many studies have focused on specific populations, yielding mixed results. Interest in telemedicine has been noted among cancer patients and those with chronic lung conditions, though some exhibited low enthusiasm for new technologies. A broad survey found that patients with depression and high cerebrovascular risk showed moderate interest in phone and internet services, while interest in social media was lower [17-19]. The pediatric context is particularly favorable for telemedicine, as both parents and children are generally younger and more comfortable with technology. Current study corroborates this, with participants demonstrating high technological proficiency and familiarity with video calls, messaging, and social networks. This demographic, combined with a higher educational level, creates an ideal environment for telemedicine services. Findings of present study align with existing literature, indicating a positive attitude toward telemedicine in pediatrics. High satisfaction was reported for telemedicine services in child and adolescent mental health [20]. Families undergoing genetic consultations and screenings for retinopathy of prematurity also showed a favorable perception of telemedicine, although preferences for in-person visits varied [21]. Preferred telemedicine functions primarily revolved around communication with the hospital, encompassing logistics (such as data transmission and appointment scheduling) and clinical interactions (especially for emergencies). These functions can significantly enhance quality of life, positively influenced by telemedicine services. By reducing the need for in-person visits where time savings were highlighted as a key benefit telemedicine can streamline processes, empower

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patients, and bolster their sense of security [22]. Conversely, those less inclined to embrace telemedicine often expressed distrust in the technologies involved. Despite the generally high digital literacy within the target population, the introduction of a health app or televisit service necessitates a robust educational program aimed at patients, their families, and healthcare professionals to ensure proper usage and implementation. Interestingly, ownership of smartphones was linked to favorable study outcomes, indicating their considerable potential for delivering telemedicine services. Smartphones, due to their portability and good image quality, serve as ideal devices for remote communication and health-related applications.They have been widely adopted for telemedical purposes, benefiting both healthcare providers and patients [23]. The findings of the current study recommend that families of pediatric patients are not only willing but also technologically equipped to adopt telemedicine plans.This inclination emphasized an opportunity for healthcare providers to integrate telemedicine into routine pediatric care.For instance, video calls and app-based communication can enhance continuity of care for children with acute or chronic conditions, particularly in resource-constrained settings or where access to in-person care is challenging. Current study also has limitations.Firstly, it did not gather information on individuals who declined to complete the questionnaire, which may have resulted in a responding population that is more inclined toward telemedicine. Additionally, conducting qualitative studies would be beneficial for gaining a deeper understanding of the attitudes and experiences related to telemedicine. Future research should focus on evaluating the impact of telemedicine on clinical outcomes and patient satisfaction in pediatric care.Additionally, studies should explore barriers to adoption, such as digital literacy and access to technology, to ensure equitable implementation.

CONCLUSIONS

Families of pediatric patients demonstrated a strong willingness to engage in telemedicine programs. Features such as emergency medical advice and notifications for medical appointments are also widely perceived as useful. The technological capabilities of these families are generally adequate to support basic telemedicine services, such as video calls and dedicated applications.

Authors Contribution

Conceptualization: SR
Methodology: SR, RR, AM
Formal analysis: SQ
Writing, review and editing: SR, SS, MI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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The Correlation between Glycemic Control and Microvascular Complications in Type 1 Diabetes Mellitus Patients

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ABSTRACT

Type 1 Diabetes Mellitus (T1DM) is a chronic condition that destroys pancreatic beta cells, leading to persistent hyperglycemia. Prolonged high levels resulted in an increased risk of microvascular complications. Glycemic control, indicated by HbA1c, plays a critical role in reducing these risks. **Objective:** To examine the strength of the relationship between HbA1c levels and the severity of microvascular complications in individuals with T1DM. **Methods:** A cross-sectional study was conducted on 30 patients with T1DM at Liaquat University Hospital, Hyderabad, from December 2024 to February 2025. HbA1c levels were recorded, and microvascular complications were evaluated using KDIGO criteria for nephropathy, ETDRS for retinopathy, and TCNS for neuropathy. Data were analyzed using descriptive statistics and inferential methods, including Spearman's correlation and linear regression, through SPSS version 22.0. **Results:** The average age of participants was 24.23 ± 3.45 years, with a mean HbA1c level of 7.65 ± 1.15%. Retinopathy was the most frequent complication (73.3%), followed by neuropathy (63.3%) and nephropathy (40%). Combined complications were present in 40% of cases. HbA1c levels were significantly correlated with the severity of all microvascular complications, showing positive associations with KDIGO (r=0.839), ETDRS (r=0.864), and TCNS (r=0.870). HbA1c values also progressively increased with complication severity (p<0.001). **Conclusions:** It was concluded that poor glycemic control was strongly associated with the presence and severity of microvascular complications in T1DM patients. These findings highlight the importance of maintaining optimal HbA1c levels to mitigate complications. Further longitudinal studies are warranted to explore these associations in greater depth.

INTRODUCTION

Diabetes mellitus is a global epidemic with reported cases of 578 million people worldwide by the year 2030 and affects both microvascular and macrovascular [1]. The most common complications include diabetic Nephropathy, retinopathy, and neuropathy [2]. The development of complications begins early and can occur late after diagnosis in young people with type 1 diabetes (T1D) [3]. This is the most common form of diabetes with 90% of cases in children and adolescents age group. Although the global variation is large, the incidence is increasing by 3–4% per year worldwide [4]. The Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) provide significant evidence for intensive insulin treatment to achieve controlled glycemic levels and avoidance of long-term consequences [5]. Some studies suggest the prevalence of Retinopathy (82–100%) which resulted in a leading cause of blindness, Nephropathy (20–40%), and Neuropathy which resulted in most non-traumatic amputations [6-8]. The prevalence of microvascular complications among the Pakistani population includes Diabetic retinopathy (DR) 32.4% was the most prevalent

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one followed by nephropathy (30.6%), neuropathy (DN) (28.1%), and gastroparesis (DG) 22.3% but patients are mostly with metabolic syndrome [9]. Glycemic control for the prevention of complications is necessary. It should be primarily assessed using HbA1c, a well-known and reliable biomarker that reflects average glycemic levels over time. Current international guidelines recommend HbA1c levels below 53 mmol/mol (7%) for the majority of adults, or below 47.5 mmol/mol (6.5%) when safely achievable [10]. Indeed, it is a chronic disease characterized by the autoimmune destruction of beta cells in the pancreas, resulting in absolute insulin deficiency. Insulin deficiency in T1DM can lead to poor glycemic control resulting in the development of retinopathy, nephropathy, and neuropathy, with a significant impact on patient morbidity and quality of life. The data regarding microvascular complications is scarce in Pakistan and this study will help us to direct attention regarding the prevalence and measurements of microvascular complications.

This study aims to see the correlation of glycemic control with the presence of microvascular complications in T1DM patients.

METHODS

This cross-sectional study was conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences (LUMHS), Hyderabad, Pakistan. Ethical approval was obtained under (Reference No. LUMHS/REC/-548). Following the IRB approval, prospective data collection was performed from December 2024 to February 2025. Telephonic communication was made with patients and a request for follow-up was made. The sample size was calculated using Open Epi software. The study employed consecutive sampling, enrolling 30 patients with Type 1 Diabetes Mellitus (T1DM) who met the inclusion criteria of being over 18 years of age, diagnosed with T1DM for at least five years, and having HbA1c records available for the past year. Patients with incomplete medical records, TIDM not more than five years, or Type 2 Diabetes Mellitus were excluded. Data collection was carried out systematically. Patients were recruited from outpatient clinics, including diabetic and medical clinics. After obtaining informed consent, participants underwent detailed clinical evaluations. HbA1c levels were measured using high-performance liquid chromatography (HPLC), following standardized laboratory protocols to ensure precision in glycated hemoglobin assessment. The presence and severity of microvascular complications were assessed through referrals to specialized departments. Diabetic nephropathy was evaluated using Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, involving glomerular filtration rate and albuminuria measurements. Diabetic retinopathy was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale through fundoscopic examinations. Neuropathy severity was determined using the Toronto Clinical Neuropathy Score (TCNS), which included symptom evaluation, reflex testing, and sensory testing. Statistical analysis was conducted using SPSS version 22.0. Descriptive statistics were performed to summarize patient demographics and clinical characteristics. Continuous variables were presented as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. The Chi-square test was used to analyze categorical data, and independent t-tests or Mann-Whitney U tests were applied for continuous data. The association and effect size between HbA1c levels and microvascular complications were evaluated using Spearman's correlation and linear regression. A p-value of <0.05 was considered statistically significant.

RESULTS

A total number of 30 patients were enrolled and the mean age was 24.23 ± 3.45 and 53.3% were male. Mean glycemic control and duration of disease were 7.65 ± 1.15 and 6.26 ± 1.46 respectively. The HbA1c levels were normality distributed (Parametric) as compared to the Duration of disease, which was not normally distributed (Non-parametric)(Table 1).

Table 1: General Data Distribution

Variables	Mean ± SD/ n (%)
Age	24.23 ± 3.45
Gender	
Male	53%
Female	47%
Duration of Disease	6.26 ± 1.46 years
Mean Glycemic Control	7.65 ± 1.15
Micro-Vascular Complication	
Nephropathy	12 (40%)
Retinopathy	22 (73.3%)
Neuropathy	19 (63.3%)
Combined	12 (40%)

The mean HBA1c in Nephropathy, Neuropathy, Retinopathy, and combined was 8.75 ± 0.89, 8.27 ± 0.97, 8.10 ± 1.0 and 8.75 ± 0.89 respectively. The mean duration of disease in nephropathy, neuropathy, retinopathy, and combined was 7.0 ± 1.65, 6.3 ± 1.6, 6.5 ± 1.5, and 7.0 ± 1.65 years respectively. The nephropathy and combined Microvascular complications show similar patterns in Mean HBA1c levels and Mean duration of Diabetic Type 1 Complications. Mean HBA1c was significantly associated with Microvascular complication (p-0.001) and it is calculated by One Way ANOVA. On the other hand, the duration of the disease was nonparametric and the association with nephropathy (p-024), Neuropathy (p-0.92), retinopathy (0.21), and Combined (0.024) was calculated by Mann Whitney U test (Figure 1).

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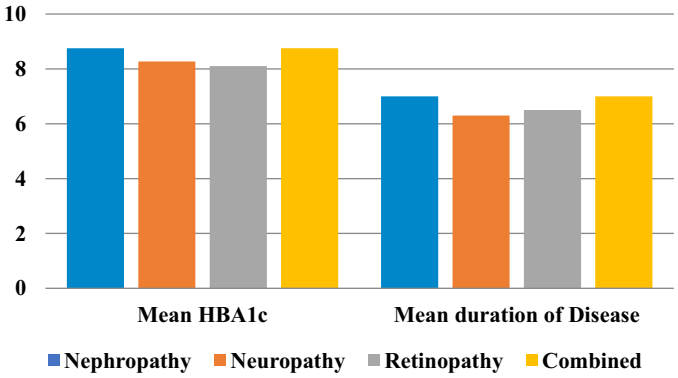

Figure 1: Change in Mean HBA1c and Duration of Disease according to Micro-vascular complication

The detailed assessment of Microvascular complications, from the evaluation of the Nephrology Department 60% of patients have G1 (GFR>90) and A1 (<30 mg/g). 16.7% of patients have G2 (GFR 60-89 ml/min/1.73m2) A2 (30-300 mg/g). 13.3% of patients have G3a (GFR: 45-59 ml/min/1.73m2) A2. 3.3% of patients have G3b (GFR: 30-44 ml/min/1.73m2) and A3 (>300mg/g). 6.7% of patients have G4 (GFR: 15-29 ml/min/1.73m2) and A3 (Figure 2).

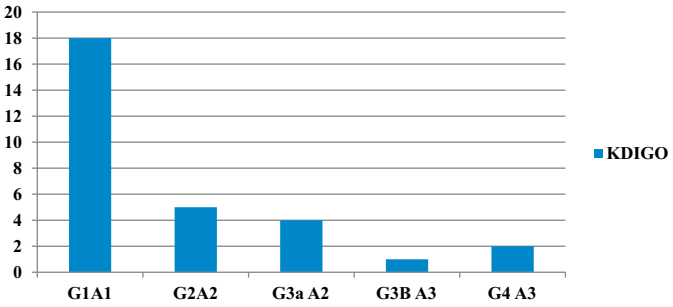

Figure 2: Kidney Disease Improving Global Outcome Scale (KDIGO)

In the case of retinopathy, the moderate non-proliferative diabetic retinopathy was most common one (30%) as compared to other subcategories of ETDRS score (Figure 3).

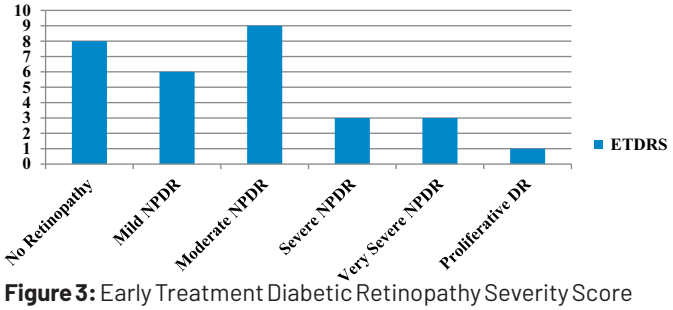

Figure 3: Early Treatment Diabetic Retinopathy Severity Score

In the case of neuropathy, (46.7%) have moderate neuropathy on TCNS score (Figure 4).

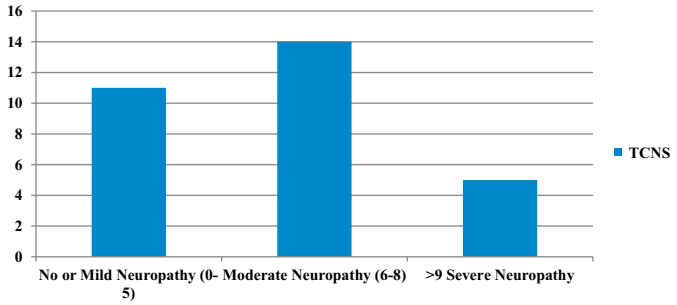

Figure 4: Toronto Clinical Neuropathy Score (TCNS)

Results show a positive correlation between HBA1c and KDIGO, which was significant and it was calculated with Spearman rho correlation, it has been shown a 0.839% increase in HBA1c levels could result in KDIGO change (Table 2).

Table 2: Kidney Disease Improving Global Outcome Scale with HBA1c Levels

KDIGO	Mean ± SD
G1 A1	6.92 ± 0.60
G2 A2	8.00 ± 0.35
G3a A2	9.00 ± 0.81
G3b A3	9.00
G4 A3	10.00

Results show a positive correlation between HBA1c and ETDRS, which was significant and it was calculated with Spearman rho correlation on linear regression, it has been shown that a 0.864 % increase in HBA1c levels could result in ETDRS change (Table 3).

Table 3: Early Treatment Diabetic Retinopathy Score with HBA1c Levels

ETDRS	Mean ± SD
No retinopathy	6.43 ± 0.41
Mild NPDR	7.20 ± 0.40
Moderate NPDR	8.16 ± 0.90

It shows a positive correlation between HBA1c and TCNS, which was significant and it was calculated with Spearman rho correlation, it has been shown that a 0.870% increase in HBA1c levels could result in TCNS change (Table 4).

Table 4: Toronto Clinical Neuropathy Score with HBA1c Levels

TCNS	Mean ± SD
No or Mild Neuropathy	6.59 ± 0.43
Moderate neuropathy	7.87 ± 0.64
Severe Neuropathy	9.40 ± 0.89

DISCUSSION

The findings emphasize the significant impact of glycemic control (HbA1c levels) on the prevalence and severity of microvascular complications in patients with Type 1 Diabetes Mellitus (T1DM) [1]. The mean age of the study participants was 24.23 ± 3.45 years, with 53.3% males and 47% females. This aligns with global epidemiological data

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showing T1DM as a condition commonly affecting young adults and adolescents. The mean HbA1c of 7.65 ± 1.15% and mean disease duration of 6.26 ± 1.46 years highlight the challenges in achieving optimal glycemic control in this population. According to the DCCT and EDIC trials, a similar pattern of poor glycemic control has been linked to microvascular complications even in younger cohorts [5]. The prevalence of complications with HBA1c values was retinopathy (73.3%, 8.10 ± 1.0), neuropathy (63.3%, 8.27 ± 0.97), nephropathy (40%, 8.75 ± 0.89), and combined complications (40%, 8.75 ± 0.89) demonstrates the burden of micro-vascular complications in this cohort. These results support findings which demonstrate that each 1% rise in HbA1c significantly increases the risk of microvascular complications [11]. Current findings are consistent with studies in both developed and developing countries, including those from Pakistan, where retinopathy was reported as the most prevalent microvascular complication in T1DM [9]. Regional studies have shown that socioeconomic barriers, limited access to healthcare, and inadequate follow-up contribute to poor glycemic control [12, 13]. In comparison with cohorts of developed countries, LMIC faces a disproportionately higher risk of complications, emphasizing the need for tailored diabetes management strategies in resource-limited settings [14, 15]. The distribution of nephropathy according to KDIGO classification revealed that 60% of patients were in the early stages (G1 and A1), with only 6.7% in advanced nephropathy (G4 A3). This aligns with studies reporting nephropathy as a late complication, usually progressing with longer disease duration and poor glycemic control [16]. A positive correlation between HbA1c and KDIGO stages, calculated using Spearman's rho correlation, indicated that even small increments in HbA1c (rs=0.839, CI 95% [0.584, 0.918], r2=0.704) significantly worsen kidney function. Moderate non-proliferative diabetic retinopathy (NPDR) was the most common subtype, affecting 30% of participants [17]. For Retinopathy, the mean HbA1c values increased progressively across ETDRS categories, from 6.43 ± 0.41% in patients without retinopathy to 9.33 ± 0.57% in those with very severe NPDR. Our findings are consistent with the Early Treatment Diabetic Retinopathy Study and similar research showing that retinopathy severity correlates strongly with poor glycemic control (rs=0.864, CI 95% [0.733, 0.935], r2=0.746) [18]. Neuropathy severity, as assessed by TCNS, revealed that 46.7% of participants had moderate neuropathy. The mean HbA1c levels increased with the severity, from 6.59 ± 0.43% (mild neuropathy) to 9.40 ± 0.89% (severe neuropathy). This trend highlights the critical role of maintaining optimal HbA1c levels to prevent or delay neuropathy progression (rs=0.870, CI 95% [0.762, 0.927], r2=0.757) [19]. These findings align with study by Sheleme *et al.*, which emphasize the linear relationship between hyperglycemia and nerve damage [7].This reinforces the synergistic impact of poor glycemic control on multiple organ systems. Studies include the association of retinopathy with nephropathy resulting in poor kidney function, and intensive glycemic control can reduce the cumulative risk of combined complications by over 60% [18, 20]. Future directions include longitudinal studies, expanding sample size and diversity, including a broader patient population, assessing other risk factors, and exploring intervention strategies. The future practical recommendations include enhancing HbA1c monitoring, introducing structured diabetes education programs, implementing early screening for complications, adapting multidisciplinary care, promoting access to resources, and longitudinal monitoring with proper data collection.

CONCLUSIONS

It was concluded that reaffirms the pivotal role of maintaining HbA1c levels below 7 to reduce the risk and severity of microvascular complications in T1DM patients. The strong association between HbA1c and the severity of complications emphasizes the necessity of strict glycemic control.Targeted interventions,such as frequent monitoring, patient education, and timely adjustment to insulin therapy are vital for achieving these glycemic goals. Our findings support integrating individualized treatment plans into routine care to minimize complications and improve long-term outcomes.

Authors Contribution

Conceptualization: KAQ
Methodology: YM, KAQ, MK, MSB
Formal analysis: IK
Writing review and editing: GF, ZHM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Assessment of Periodontal Health in Patients with Alzheimer's disease in Karachi, Pakistan

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ABSTRACT

Alzheimer's disease (AD), causes permanent loss of neurons and neural connections. **Objective:** To assess the periodontal health status of Alzheimer's disease (AD) patients by assessing plaque index, gingival condition, probing pocket depth, attachment levels, and bleeding on probing, and to correlate these findings with cognitive impairment levels as determined by Mini-Mental State Examination (MMSE) scores. **Methods:** A cross-sectional study, was conducted at Medicare Hospital between July and October 2024. Total 60 patients were recruited in the study. Hence plaque index, gingival condition, probing depth, attachment levels, and bleeding on probing were used to assess periodontal health, whereas MMSE scores were used to classify cognitive impairment. For statistical analysis, ANOVA and unpaired t-test analyses are carried out using SPSS version 24.0. All of the findings were deemed statistically significant if P was less than 0.05. **Results:** The study results revealed that the demographic and neurological parameters such as age, the distribution of genders, and the number of teeth of those patients suffering from Alzheimer's disease. Hence, MMSE scores were significantly lower, indicating substantial cognitive impairment ($P < 0.001$). As the severity of AD increases, there is a trend for all recorded variables to get worse ($p < 0.01$). PPD and CAL reveal more periodontal tissue loss in patients with severe AD, while PI and GI show more plaque accumulation and gingival inflammation. **Conclusions:** This study highlighted a strong link between worsening periodontal health and Alzheimer's severity, emphasizing the need for proactive dental care to improve patient well-being.

INTRODUCTION

The progressive neurodegenerative disease known as Alzheimer's disease in which there are irreversible neural connections. It causes loss of memory, decline in cognition, and ultimately significant functional reliance and mortality [1]. It is the most commonly occurring form of dementia which is usually found among elderly individuals approximately 60-80% globally [2]. Individuals in the advanced phases become reliant on caretakers, underscoring the significant financial and emotional strain on families and healthcare systems [3, 4]. Chronic inflammatory conditions, known as periodontal disease, affect the periodontium [5, 6]. This has arisen due to microbial dysbiosis in numerous researches [7]. Through alterations in the oral microbiota, which contains a wide variety of microorganisms in the oral cavity, Alzheimer's disease is connected to poor oral health [8, 9]. Recent studies have demonstrated that patients suffering from dementia have more chances of getting Alzheimer's disease. In contrast, those who experienced dementia earlier in life had more severe forms of Alzheimer's disease [10, 11]. Oral pathogens such as Treponema, spirochetes, Porphyromonas gingivalis, and Prevotella intermedia are more prevalent in these patients [12]. According to one theory, these periodontal bacteria could enter the brain through various pathways such as blood-brain barrier, and cause direct damage [13, 14]. Hence, there is little information on how this association shows up in Asian communities, especially in places like Pakistan where oral and neurological health outcomes may be influenced by cultural, nutritional, and medical practices [15].

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Furthermore, the frequency and severity of periodontal disease among Alzheimer's disease patients may be significantly influenced by socioeconomic characteristics, dental care accessibility, and knowledge of oral hygiene habits in Pakistani communities. By assessing periodontal health in Alzheimer's patients while taking into account regional sociocultural and healthcare aspects, this study fills a gap in the body of existing data. The results of this study may influence interdisciplinary techniques to better manage Alzheimer's disease, enhance oral healthcare procedures for neurodegenerative patients, and influence public health policy.

METHODS

The cross-sectional research was conducted at Medicare Hospital from July to October of 2024. ERB/JMDC/Approval# 00021124 was the reference number. Purposive sample was used to determine the periodontal health of Alzheimer's disease patients. Hence, clinical attachment loss (CAL) was used as the primary parameter as it is the most reliable predictor for the advancement of periodontal disease. Based on a 95% confidence interval and the anticipated prevalence of periodontal disease among AD patients, a total sample size of 60 participants was produced using Open Epi software. Participants who were 50 years of age or older and had a confirmed diagnosis of AD were eligible. Participants had to have at least 12 natural teeth to be recruited those with mental, behavioral, or systemic conditions that affect oral health assessment, those taking drugs that affect cognition, and those who had had periodontal therapy within the previous six months were not part of the study. The goal of the study was explained to each selected participant, informed consent was taken from them. Further, the participants were allowed to leave the study at any time. Various tests were of the participants was taken to evaluate their mental and health status. The diagnosis was further confirmed by MRI and CT scans. Mini-Mental State Examination (MMSE) was used to measure the cognitive impairment. Four groups were made of participants on the basis of severity of condition such as it was considered mild (score ≥25), moderate (scoring ≥11), severe (score ≤10), and normal (score ≥26). The periodontal health status of patients was assessed such as Index of plaque and gingivae, level of Clinical Attachment. Hence the severity of Periodontal Disease was determined by Probing Pocket Depth (PPD), and bleeding on probing (%BOP). The level of Oral hygiene was classified as good, fair, or poor on the basis of index of periodontal and gingiva. The thickness of dental plaque which is present on tooth surfaces is measured through plaque index, with scores ranging from 0 which means no plaque to 3 means excessive plaque.The redness, swelling, and bleeding upon probing, with scores from 0 (representing healthy gingiva) to 3 (indicating severe inflammation) helps to examine the gingival inflammation through gingival index. Periodontal probe is used to measure the depth of periodontal pockets and patients with deeper pockets shows that they have advanced periodontitis. Clinical Attachment Level (CAL) measures periodontal tissue loss by determining the distance from the cementoenamel junction to the base of the pocket. The percentage of sites exhibiting Bleeding on Probing (%BOP) reflects the severity of gingival inflammation, more chances of periodontal disease progression. To analyze the data, SPSS version 24.0 was used. The mean ± SD was used to report descriptive statistics. The differences among the groups in the severity of AD were assessed using a one-way ANOVA, and the clinical and demographic characteristics of the two groups were compared using unpaired t-tests. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The results of the study revealed demographic factors of participants suffering from Alzheimer's disease. Hence, MMSE scores were significantly lower, indicating substantial cognitive impairment ($P < 0.001$) as shown in table 1.

Table 1: Demographic Factors of Participants with Alzheimer's disease

Variables	Participants with Alzheimer's Disease AD	Participants who are Non-Cognitively Impaired	p-Value
Age (Mean ± SD)	66.3 ± 8.1	63.8 ± 7.9	<0.001*
Gender			
Male	27/60 = 45.0%	27/62 = 43.5%	
Female	33/60 = 55.0%	35/62 = 56.5%	
Total teeth present	15.5 ± 3.9	16.7 ± 4.1	
Status of Oral Hygiene			
Good	3/60 = 5.0%	10/62 = 16.1%	
Fair	18/60 = 30.0%	19/62 = 30.6%	
Poor	39/60 = 65.0%	33/62 = 53.2%	
Mini-Mental State Examination Scores	13.8 ± 7.9	28.9 ± 1.1	

*P < 0.05 is considered statistically significant

As shown in Table 2 the severity of AD increases, there is a trend for all recorded variables Plaque index, gingival index, Probing Pocket Depth, Clinical Attachment Level, and % Bleeding on Probing to get worse ($p < 0.01$). PPD and CAL reveal more periodontal tissue loss in patients with severe AD, while PI and GI show more plaque accumulation and gingival inflammation.

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Table 2: Groupwise Assessments Periodontal Parameters

Assessment of Parameters	Participants with Alzheimer's Disease AD Normal (Mean ± SD)	Participants with Alzheimer's Disease AD Mild (Mean ± SD)	Participants with Alzheimer's Disease AD Moderate (Mean ± SD)	Participants with Alzheimer's Disease AD Severe (Mean ± SD)	p-Value
Plaque Index (PI)	1.42 ± 0.30	1.95 ± 0.22	2.60 ± 0.18	3.52 ± 0.35	< 0.01*
Gingival Index (GI)	0.60 ± 0.20	1.12 ± 0.25	1.68 ± 0.22	2.30 ± 0.30	< 0.01*
Probing Pocket Depth (PPD)	2.32 ± 0.48	3.12 ± 0.42	4.05 ± 0.38	5.10 ± 0.55	< 0.01*
Clinical Attachment Level (CAL)	2.72 ± 0.52	3.52 ± 0.38	4.50 ± 0.45	5.63 ± 0.57	< 0.01*
% Sites with Bleeding on Probing (%BOP)	31.00 ± 5.70	39.10 ± 5.30	57.20 ± 7.00	69.50 ± 12.70	< 0.01*

DISCUSSION

In recent times medical research has been greatly emphasizing the connection between periodontal health and Alzheimer's disease. According to the findings, Alzheimer's disease patients' periodontal health considerably declined as the illness worsened. These results demonstrate the complex connection between oral health and cognitive decline, which is in line with another research done worldwide [16]. One of the studies conducted in 2023 observed similar results [17]. Hence, due to their poor oral hygiene, the inflammatory markers were directly impacted as some of the variables help in the spread of severe periodontal parameters such as inflammation of gums and increased buildup of plaque [18]. The study conducted revealed a high correlation between the deterioration of periodontal diseases and the degree of cognitive impairment. Periodontal indicators showed clear distinctions across the cognitive phases (normal, mild, moderate, and severe Alzheimer's disease. Hence, similar results were observed in earlier research, in which results revealed that the severe Alzheimer's disease group's mean index of plaque and gingival were more than those of the normal group [19]. Patients with severe Alzheimer's disease frequently struggle to carry out everyday tasks, such as keeping their teeth clean. As these patients are unable to take sufficient nutritional intake, they cannot clean their mouths properly, and irregular brushing all contribute to the fast advancement of periodontal disease [20]. The results showed Probing Pocket Depth and Clinical Attachment Level were higher. This finding implies that periodontal tissue damage exacerbates with worsening cognitive deterioration. Similar results were revealed in which dementia patients had considerably greater PPD and CAL than non-demented controls. These alterations reflect the development of periodontal disease, in which microbial biofilm buildup and persistent inflammation progressively weaken the alveolar bone and connective tissues [21, 22]. Further, the results showed that the bleeding on probing also increased significantly in the severe stages. This represents the gingival inflammatory response which is a typical clinical sign of active periodontal disease. Gingival bleeding is a symptom of gingivitis, which is frequently the initial stage of periodontal disease, according to earlier research [23]. Gingival inflammation was more common which can progress to more serious periodontal diseases and if left untreated, then bleeding on probing will be increased [24]. The main limitations of the study were the study design due to which the capacity to establish a causal relationship between the disease and periodontium was limited. Furthermore, the influence of additional variables that can shed more light on the variation in periodontal health among Alzheimer's patients, such as socioeconomic level, medication usage, and nutritional status, was not investigated. This study provides useful information for Pakistan, a country with less research on this topic. Further, the necessity of focused dental care interventions for those with Alzheimer's disease, was planned. Hence, counseling of caretakers regarding oral hygiene was essential to reduce the negative consequences of these patients related to poor periodontal health [25]. The results highlight how crucial it is to include dental care in Alzheimer's patients' treatment plans to improve oral health and maybe delay the rate of cognitive deterioration. Furthermore, studies are required to investigate therapeutic and preventative measures meant to enhance these people's dental and cognitive health outcomes.

CONCLUSIONS

The research underscores a strong link between deteriorating health of periodontium and the advancement of Alzheimer's disease. As cognitive function declines, the severity of periodontitis intensifies, driven by plaque accumulation, inflammation of the gums, and loss of tissue. It is crucial to emphasize the importance of oral healthcare, as inadequate periodontal health may hasten cognitive decline. Incorporating proactive dental care into treatment strategies and providing education to caregivers regarding oral hygiene can help in improving oral health care.

Authors Contribution

Conceptualization: UM, SR
Methodology: MIK
Formal analysis: UM, RT, HBZ
Writing, review and editing: HBZ, AA

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Conflicts of Interest

All the authors declare no conflict of interest.

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Effect of Maternal Nutrition and Micronutrient Supplementation on Neonatal Birth Weight and Health

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ABSTRACT

Maternal nutrition significantly influences fetal growth, birth weight, and neonatal health. Deficiencies in iron, calcium, folic acid, and vitamin D increase the risks of preterm birth, low birth weight, and neonatal complications. **Objective:** To assess the impact of maternal micronutrient supplementation on neonatal birth weight and health outcomes. **Methods:** A quasi experimental study was conducted at Health Net Hospital, Peshawar. A total of 110 pregnant women were recruited (59 supplemented, 51 non-supplemented). Data on maternal dietary intake, weight gain, and micronutrient consumption were collected. Neonatal birth weight, gestational age, NICU admissions, and morbidity were recorded. Statistical analysis was performed using SPSS version 25.0, with independent t-tests and chi-square tests ($p<0.05$ considered significant). **Results:** Neonates in the supplemented group had significantly higher birth weights (3343.54 ± 407.90 g vs. 2825.63 ± 322.46 g, $p<0.001$). NICU admissions were lower in the supplemented group (6.8% vs. 43.1%, $p<0.001$). Neonatal morbidity, including infections, jaundice, and respiratory distress, was significantly lower in the supplemented group ($p<0.001$). **Conclusions:** Micronutrient supplementation during pregnancy improves neonatal birth weight and reduces neonatal morbidity. These findings highlight the need for targeted maternal nutrition strategies to improve neonatal outcomes, particularly in resource-limited settings.

INTRODUCTION

Maternal nutrition plays a crucial role in fetal growth and development, influencing pregnancy outcomes such as birth weight, preterm birth, and neonatal morbidity [1]. In many underdeveloped nations, low birth weight (LBW), small for gestational age (SGA) infants, and neonatal mortality remain significant public health concerns [2]. The prevalence of LBW varies between 6% and 30%, often attributed to intrauterine growth restriction (IUGR) [3,4]. Although full-term SGA infants may not face the same complications as preterm infants, they still have a higher risk of perinatal asphyxia, hypoglycemia, and increased neonatal mortality [5]. Nutrient deficiencies during pregnancy lead to placental dysfunction, restricted fetal growth, and increased medical complications [6]. Iron deficiency, the most common maternal nutritional deficit, affects nearly half of all pregnant women globally, contributing to maternal anemia, increased infection risks, and adverse pregnancy outcomes such as preterm birth and low birth weight. Calcium deficiency is associated with hypertensive disorders, fetal growth restriction, and

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preterm birth. Vitamin D is essential for fetal skeletal development and immune function, with deficiencies increasing the risk of neonatal respiratory issues and low birth weight. Folic acid is vital for neural tube development and fetal growth, improving birth outcomes [7]. Despite global initiatives, micronutrient deficiencies remain prevalent in resource-limited areas. Standard prenatal care typically includes iron-folic acid supplements, but research suggests that additional supplementation with calcium and vitamin D may further reduce complications. However, there is ongoing debate regarding the optimal combination and dosage of micronutrient supplements, with some studies suggesting diminishing returns when multiple nutrients are combined.

This study aimed to evaluate the effects of maternal supplementation with iron, calcium, folic acid, and vitamin D on neonatal birth weight and health outcomes, providing evidence to guide improved maternal nutrition strategies.

METHODS

This quasi experimental study was conducted at Health Net Hospital, Peshawar, from January, 2024, to January, 2025. It assessed the impact of maternal micronutrient supplementation on neonatal birth weight and health outcomes. A convenience sampling technique was used to recruit pregnant women from the hospital's antenatal clinic. The sample size was calculated using OpenEpi, based on National Nutrition Survey (NNS) 2018 data [8]. The sample size was calculated using a 95% confidence interval (Z = 1.96), a prevalence of iron deficiency anemia (p = 0.49) based on the National Nutrition Survey (NNS) 2018, and a margin of error (d = 0.10). The calculated minimum sample size was 100 participants, ensuring 80% power. A total of 110 pregnant women were recruited (59 supplemented, 51 non-supplemented). Ethical approval was obtained from the Hospital Ethics Review Committee (Reference: 3003/HNH/HR). Participants provided written informed consent. Group Assignment: Supplemented group: Women following a prescribed iron, folic acid, calcium, and vitamin D supplementation regimen. Non-supplemented group: Women with irregular or no supplementation. Assignment method: Based on self-reported intake, verified through medical records and antenatal follow-ups. Adherence was monitored using: Monthly follow-up interviews, Prescription record checks and Pill count method (for hospital-supplied supplements). Participants with <80% adherence were classified as non-adherent. Inclusion Criteria Pregnant women aged 18-40 years. Singleton pregnancies without congenital anomalies. Attending antenatal care at Health Net Hospital. Exclusion Criteria Chronic diseases (diabetes, hypertension). Fetal anomalies detected via ultrasound. Special medical diets affecting study variables.Multiple gestations (twins, triplets, etc.). Maternal characteristics: Age, education, socioeconomic status, occupation, antenatal visits. Dietary intake: 24-hour recall and Food Frequency Questionnaire (FFQ). Anthropometry: Pre-pregnancy BMI (self-reported), pregnancy weight gain (recorded at each visit). Blood samples were collected twice (1st and 3rd trimester) and analyzed for: Hemoglobin (Hb) (automated hematology analyzer), Serum ferritin (ELISA method), Serum calcium (colorimetric assay) and Vitamin D (chemiluminescence immunoassay). All analyses followed strict quality control protocols. Neonatal Outcome Assessment, Birth weight: Measured via calibrated electronic scale (within 1 hour of birth). Anthropometry: Length and head circumference measured using an infantometer and measuring tape. APGAR scores: Assessed at 1 and 5 minutes post-birth. Neonatal morbidity: Evaluated using clinical assessment + standardized diagnostic criteria, including Infections (lab-confirmed cultures). Jaundice (bilirubin levels, phototherapy need) and Respiratory distress (arterial blood gas tests). All collected data were entered and analyzed using SPSS version 25.0. Means, standard deviations, and frequencies were calculated. Comparisons: Independent t-tests for continuous variables: Maternal age, weight gain, dietary intake (calories, protein, carbohydrates, fats), micronutrient intake (iron, calcium, folic acid, vitamin D), and neonatal birth weight. Chi-square tests for categorical variables: Maternal education level, socioeconomic status, occupation, residence type, antenatal care visits, adherence to supplementation, food frequency score, birth weight category, gestational age category, NICU admission, neonatal morbidity (infections, jaundice, respiratory distress), APGAR score category, APGAR scores categorized as follows: Low (0-3) – Severe distress, Moderate (4-6) – Some distress requiring intervention and Good (7-10) – Normal neonatal adaptation mode of delivery, gestational diabetes, hypertension, and maternal smoking. To explore the relationship between maternal weight gain and neonatal birth weight, Pearson correlation analysis was performed. Additionally, multiple linear regression analysis was conducted to examine whether maternal weight gain and supplementation status independently predicted neonatal birth weight. The relationship between socioeconomic status, antenatal care visits, and supplementation adherence was assessed using Chi-square tests. Multiple Comparison Adjustment to reduce Type I errors, Bonferroni correction was applied where multiple comparisons were conducted.A p-value< 0.05 was considered statistically significant.

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RESULTS

Maternal age was significantly lower in the supplemented group (27.15 ± 4.18 years vs. 32.13 ± 3.42 years, p < 0.001). Socioeconomic status also showed a significant association with supplementation (p = 0.016), with 49.0% of non-supplemented mothers belonging to the low-income group compared to 25.4% in the supplemented group. More urban mothers were in the supplemented group (76.3% vs. 56.9%, p = 0.031). Antenatal care visits were significantly higher in the supplemented group (p = 0.001), with 55.9% having 7-9 visits compared to 29.4% in the non-supplemented group. These findings suggest that socioeconomic status and antenatal visits influenced supplementation adherence.

Table 1: Demographic Variables and Antenatal Care Visits (n=110)

Variables	Category	Supplemented Group (Mean ± SD)/ Frequency (%)	Non-Supplemented Group (Mean ± SD)/ Frequency (%)	p-Value
Maternal Age (Years)	Age	27.15 ± 4.18	32.13 ± 3.42	<0.001
Maternal Education Level	No Formal	3 (5.1%)	1 (2.0%)	0.411
	Primary	17 (28.8%)	16 (31.4%)	
	Secondary	25 (42.4%)	27 (52.9%)	
	Higher	14 (23.7%)	7 (13.7%)	
Socioeconomic Status	Low	15 (25.4%)	25 (49.0%)	0.016
	Middle	33 (55.9%)	23 (45.1%)	
	High	11 (18.6%)	3 (5.9%)	
Occupation of Mother	Housewife	36 (61.0%)	26 (51.0%)	0.305
	Labourer	9 (15.3%)	7 (13.7%)	
	Office Worker	11 (18.6%)	10 (19.6%)	
	Other	3 (5.1%)	8 (15.7%)	
Residence Type	Urban	45 (76.3%)	29 (56.9%)	0.031
	Rural	14 (23.7%)	22 (43.1%)	
Antenatal Care Visits	1-3 visits	6 (10.2%)	9 (17.6%)	0.001
	4-6 visits	11 (18.6%)	25 (49.0%)	
	7-9 visits	33 (55.9%)	15 (29.4%)	
	10+ visits	9 (15.3%)	2 (3.9%)	

Supplemented mothers had higher weight gain (14.06 ± 2.12 kg vs. 9.26 ± 1.86 kg, p < 0.001) and greater caloric intake (2406.16 vs. 1770.55 kcal/day, p < 0.001). Protein, carbohydrate, fat, and micronutrient intake (iron, calcium, folic acid, vitamin D) were also significantly higher (p < 0.001). Adherence to supplementation was significantly better (84.7% vs. 52.9%, p < 0.001). Higher food frequency scores in the supplemented group (p < 0.001) reflected improved dietary diversity.

Table 2: Maternal Nutrition and Micronutrient Supplementation (n=110)

Variables	Supplemented Group (Mean ± SD)	Non-Supplemented Group (Mean ± SD)	p-Value
Maternal Weight Gain (Kg)	14.06 ± 2.12	9.26 ± 1.86	<0.001
Dietary Intake (Calories/Day)	2406.16 ± 167.73	1770.55 ± 188.24	<0.001
Protein Intake (g/Day)	84.60 ± 7.55	59.06 ± 8.46	<0.001
Carbohydrate Intake (g/Day)	347.82 ± 41.48	243.69 ± 44.01	<0.001
Fat Intake (g/Day)	78.15 ± 9.38	54.24 ± 8.49	<0.001
Iron Intake (mg/Day)	27.93 ± 3.60	12.41 ± 3.43	<0.001
Calcium Intake (mg/Day)	1380.64 ± 196.31	772.87 ± 139.53	<0.001
Folic Acid Intake (mcg/Day)	562.95 ± 90.64	251.68 ± 68.34	<0.001
Vitamin D Intake (IU/Day)	1209.05 ± 189.85	484.02 ± 112.15	<0.001
Adherence to Supplementation	9 (15.3%)	24 (47.1%)	<0.001
	50 (84.7%)	27 (52.9%)	
Food Frequency Score	6 (10.2%)	20 (39.2%)	<0.001
	22 (37.3%)	23 (45.1%)	
	31 (52.5%)	8 (15.7%)	

Multiple linear regression analysis examined maternal weight gain, neonatal birth weight, and supplementation status. The model was statistically significant ($F(2,107) = 78.443$, $p<0.001$), explaining 59.5% of the variance in maternal weight gain ($R^2 = 0.595$). Supplementation status was a significant predictor (B = -4.996, p < 0.001), indicating that supplemented mothers gained less weight than non-supplemented mothers. Neonatal birth weight was not an independent predictor of maternal weight gain (B = 0.000, p = 0.480).

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Table 3: Multiple Linear Regression Analysis for Predicting Maternal Weight Gain

Predictor Variables	B (Unstandardized Coefficient)	Standard Error	Beta	t	p-Value	95% Confidence Interval
Constant	20.290	2.099	-	9.665	<0.001	(16.129, 24.452)
Group (1=Supplemented, 0=Non -Supplemented)	-4.996	0.470	-0.800	-10.638	<0.001	(-5.927, -4.065)
Neonatal Birth Weight (g)	0.000	0.001	-0.053	-0.709	0.480	(-0.001, 0.001)

Neonates of supplemented mothers had significantly higher birth weights (3343.54 ± 407.90 g vs. 2825.63 ± 322.46 g, $p < 0.001$). However, birth weight categories (low birth weight, normal, macrosomia) did not show a significant difference ($p = 0.470$). Despite the higher mean birth weight in the supplemented group, the distribution across birth weight categories remained similar, likely due to a narrow range in birth weights among participants. NICU admissions were significantly lower in the supplemented group (6.8% vs. 43.1%, $p < 0.001$), and neonatal morbidity (infections, jaundice, respiratory distress) was significantly lower among supplemented neonates ($p < 0.001$). However, maternal health conditions and access to healthcare services may have influenced these findings, as hypertension was significantly higher in the non-supplemented group (21.6% vs. 6.8%, $p = 0.024$). APGAR scores did not show a significant difference ($p = 0.096$), possibly because the sample primarily included term neonates with generally stable health at birth.

Table 4: Neonatal Birth Outcomes (n=110)

Variables	Category	Supplemented Group (Mean ± SD)/ Frequency (%)	Non-Supplemented Group (Mean ± SD)/ Frequency (%)	p-Value
Neonatal Birth Weight (g)	Mean	3343.54 ± 407.90	2825.63 ± 322.46	<0.001
Birth Weight Category	Low (<2500g)	4 (6.8%)	7 (13.7%)	0.470
	Normal (2500-4000g)	52 (88.1%)	42 (82.4%)	
	Macrosomia (>4000g)	3 (5.1%)	2 (3.9%)	
Gestational Age Category	Preterm (<37 weeks)	5 (8.5%)	8 (15.7%)	0.397
	Term (37-42 weeks)	48 (81.4%)	40 (78.4%)	
	Post-term (>42 weeks)	6 (10.2%)	3 (5.9%)	
NICU Admission	No	55 (93.2%)	29 (56.9%)	<0.001
	Yes	4 (6.8%)	22 (43.1%)	
Neonatal Morbidity	Infections	3 (5.1%)	9 (17.6%)	<0.001
	Jaundice	8 (13.6%)	19 (37.3%)	
	Respiratory Distress	8 (13.6%)	11 (21.6%)	
	None	40 (67.8%)	12 (23.5%)	
APGAR Score Category	Low (0-3)	1 (1.7%)	5 (9.8%)	0.096
	Moderate (4-6)	10 (16.9%)	12 (23.5%)	
	Good (7-10)	48 (81.4%)	34 (66.7%)	

Fewer caesarean sections occurred in the supplemented group (25.4% vs. 52.9%, $p = 0.003$), while hypertension was significantly lower in supplemented mothers (6.8% vs. 21.6%, $p = 0.024$). Gestational diabetes and maternal smoking did not show significant differences between groups.

Table 5: Mode of Delivery and Other Confounders (n=110)

Variables	Category	Supplemented Group Frequency (%)	Non-Supplemented Group Frequency (%)	p-Value
Mode of Delivery	Vaginal	44 (74.6%)	24 (47.1%)	0.003
	Caesarean	15 (25.4%)	27 (52.9%)	
Gestational Diabetes	No	53 (89.8%)	42 (82.4%)	0.254
	Yes	6 (10.2%)	9 (17.6%)	
Hypertension in Pregnancy	No	55 (93.2%)	40 (78.4%)	0.024
	Yes	4 (6.8%)	11 (21.6%)	
Maternal Smoking	No	57 (96.6%)	50 (98.0%)	0.646
	Yes	2 (3.4%)	1 (2.0%)	

Figure 1 showed that vaginal deliveries were more common in the supplemented group, while caesarean sections and hypertension were higher in non-supplemented mothers. Gestational diabetes showed no major difference, and maternal smoking was rare in both groups. Nutritional intake was significantly better in the supplemented group, with higher calorie, protein, carbohydrate, fat, iron, calcium, folic acid, and vitamin D intake. This aligned with greater maternal weight gain in this group. Neonatal outcomes reflected these differences, with higher birth weights and fewer NICU admissions among newborns of supplemented mothers. Neonatal morbidity, including infections and jaundice, was more common in the non-supplemented group. The graphs reinforced the positive impact of maternal supplementation on pregnancy and newborn health.

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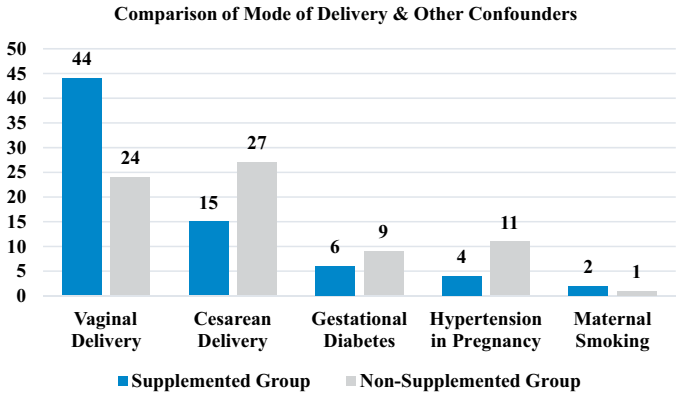

Figure 1: Comparison of Mode of Delivery and Other Confounders between Supplemented and Non-Supplemented Groups

DISCUSSION

This study examined the impact of maternal micronutrient supplementation on neonatal birth weight and health outcomes. Consistent with prior research, supplementation with iron, calcium, folic acid, and vitamin D was associated with higher birth weight, lower neonatal morbidity, and reduced NICU admissions [9,10]. The significant difference in maternal age (27.15 vs. 32.13 years, $p < 0.001$) between groups suggests a possible confounding effect. Younger mothers may have different dietary habits, metabolic responses, or healthcare access compared to older mothers. However, this study did not perform an age-stratified analysis, which remains a limitation. Extensive research supports the beneficial role of iron supplementation in preventing maternal anemia, preterm birth, and low birth weight. A systematic review by Cantor *et al.*, (2024) confirmed that iron supplementation during pregnancy significantly reduces anemia prevalence and improves birth weight outcomes [11]. This study aligned with these findings, as supplemented mothers had higher neonatal birth weights. Calcium supplementation has been shown to reduce hypertensive disorders during pregnancy, fetal growth restriction, and preterm birth [12,14]. Vitamin D plays a crucial role in fetal skeletal development and immune function [16,18]. Studies by Ilardi *et al.*, (2021) found that vitamin D supplementation led to increased birth weight and reduced NICU admissions [19].This study corroborated these findings, as neonates of supplemented mothers had higher birth weights and fewer NICU admissions. Folic acid supplementation is essential for neural tube development and fetal growth. Research by Alvestad *et al.*, and Caniglia *et al.*, indicated that folic acid intake before and during pregnancy reduces intrauterine growth restriction and improves neonatal outcomes [20, 21].This study found similar results, as mothers who received supplementation exhibited improved fetal growth outcomes. Although supplemented neonates had significantly higher mean birth weights ($p < 0.001$), the lack of a significant difference in birth weight categories ($p = 0.470$) suggests that supplementation may improve overall fetal growth but not necessarily shift neonates into different weight categories. This could be due to a relatively homogenous population in terms of gestational nutrition and healthcare access. NICU admissions were significantly lower in the supplemented group ($p < 0.001$). While supplementation likely contributed to this outcome, maternal health conditions such as hypertension, which was more prevalent in non-supplemented mothers ($p = 0.024$), could also be a confounding factor. Women with hypertension are at higher risk of preterm birth and fetal growth restriction, both of which increase NICU admissions [22,23]. APGAR scores showed no significant difference between groups ($p = 0.096$), indicating that maternal supplementation may not directly impact immediate neonatal adaptation post-delivery [24, 25]. Given that most neonates were full-term, they were likely to have stable postnatal transitions, reducing the likelihood of supplementation influencing APGAR scores. Clinically, these findings highlight the importance of micronutrient supplementation in pregnancy. This study was limited by its hospital-based design, which may affect generalizability to other populations. Additionally, maternal BMI was not analyzed, and while maternal weight gain correlated with neonatal birth weight ($r = 0.407$, $p < 0.001$), it was not an independent predictor in the regression model. Future research should incorporate BMI-adjusted models to further explore these relationships.

CONCLUSIONS

In conclusion, maternal micronutrient supplementation produces crucial effects that benefit both newborn weight and health outcomes. Supplementing pregnant mothers with iron and calcium, folic acid and vitamin D resulted in infants with increased birth weights along with decreased medical complications and reduced newborn for Intensive Care admission. The study findings confirm that proper maternal dietary care during pregnancy remains vital, especially in situations with widespread micronutrient deficiencies. The implementation of proper supplements minimizes the chances of negative birth results such as low birth weight, preterm birth and neonatal complications.

Authors Contribution

Conceptualization: SA
Methodology: HI
Formal analysis: SRJ
Writing, review and editing: SRJ, BI, SM, OK, HI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Effects of the COVID-19 Pandemic on Treatment Outcomes of Drug-Resistant Tuberculosis Patients in Twin Cities of Pakistan

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ABSTRACT

Pakistan is the world's fifth-highest Drug-Resistant Tuberculosis burden region. However, it is difficult to evaluate the setback of COVID-19 when concurrent tuberculosis is excluded in patients from Pakistan, where the national burden of tuberculosis and drug-resistant tuberculosis is substantial and rising despite management efforts. The COVID-19 pandemic is prevalent in countries where tuberculosis, notably drug-resistant tuberculosis is high. **Objectives:** To compare the pre and para-pandemic favourable and unfavorable outcomes of drug-resistant tuberculosis treatment in PMDT Units of Islamabad and Rawalpindi. **Methods:** A retrospective cross-sectional study was conducted.The study included Pre and Para-COVID-era drug-resistant tuberculosis patients (n=670) in three sites of Rawalpindi and Islamabad from 2016-2021. A non-probability consecutive sampling technique was applied. A validated structured questionnaire was administered to compare the treatment outcomes of drug-resistant tuberculosis patients. **Results:** Results show that pre-COVID n=240 (35.82%) and Para-Covid era drug-resistant tuberculosis patients n=226 (33.73%) had favourable treatment outcomes. Unfavorable outcomes before and during the pandemic were 128 (18.35%) and 82 (12.2%) respectively. COVID-19 has affected drug-resistant tuberculosis treatment outcomes, both favourable and unfavorable, which are far behind the treatment success targets set by WHO End-tuberculosis. **Conclusions:** It was concluded that this study compared drug-resistant tuberculosis treatment outcomes pre- and post-COVID-19, showing success rates surpassing WHO-End tuberculosis targets. Key factors included residential status, gender, and occupation.

INTRODUCTION

The COVID-19 pandemic threatens to undo recent gains in reducing the Tuberculosis (TB) disease burden and improving access to care around the world. The global treatment success rate for Multidrug-Resistant (MDR)/RR-TB remains poor, at 57% [1]. COVID-19, containment measures, and the dispersion of TB services have all conspired to cause delays in diagnosis or non-diagnosis and increased morbidity, mortality, transmission, and medication resistance arising from treatment interruption [2]. A 9-year setback in efforts to End TB has been caused by COVID-19, which had a detrimental influence on TB case notifications, which fell by 18% from 7.1 million in 2019 to 5.8 million in 2020. Over the next few years, there will probably be a significant increase in TB mortality due to decreased case-finding [3]. Multidrug-resistant tuberculosis (MDR-TB) remains a significant global health challenge, further exacerbated by the COVID-19 pandemic. Healthcare facilities have primarily concentrated on managing and

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preventing COVID-19, often neglecting other diseases like TB. Additionally, the pandemic has led to severe economic disruptions worldwide, causing high unemployment and loss of income, especially in low-income households in low- and middle-income countries (LMICs). This has resulted in nutritional deficiencies, delayed diagnoses, untreated illnesses, medication shortages, and treatment interruptions, all of which contribute to the rise of MDR-TB [4]. Various studies were performed to determine the association between TB and other pandemic situations. One of those studies indicates the relationship between TB and influenza. This showed that TB patients are more susceptible to influenza infection and immunosuppression. Moreover, influenza may hasten the progress of tuberculosis disease as both conditions impair the host's immune response [5]. Estimates indicate that DR-TB could claim around 75 million lives over the next 35 years, costing the global economy $16.7 trillion. A report from the Stop TB Partnership, developed in collaboration with Imperial College, Avenir Health, Johns Hopkins University, and the United States Agency for International Development. (USAID), warns that tuberculosis control efforts may further decline during the COVID-19 pandemic. This could result in an additional 6.3 million TB cases and 1.4 million TB-related deaths worldwide between 2020 and 2025, primarily due to resource shortages and forced lockdowns in TB-endemic regions [6]. Pakistan is the world's fifth-highest DR-TB burden region, a total of 3820 laboratory-confirmed confirmed RR-cases were enrolled of which 3004 cases were on DR treatment [7]. However, it is difficult to evaluate the setback of COVID-19 when concurrent TB is excluded in patients from Pakistan, where the national burden of TB and DR-TB is substantial and rising despite management efforts. Pakistan has one of the world's highest TB burdens, and COVID-19 control has limited people's ability to travel, forcing the TB program to decrease the need for in-person health facility visits and provide care closer to patients' homes. Remote treatment assistance via telemedicine, collaboration with private healthcare professionals, and the establishment of community medicine collecting sites are all strategies that might be beneficial in the future for delivering more convenient care to patients [8]. Drug-resistant tuberculosis needs prolonged and uninterrupted management to achieve successful outcomes among patients undergoing DR-TB therapy. This study aimed to summarize the effects of COVID-19 on DR-TB treatment outcomes in three PMDT sites of Rawalpindi and Islamabad by comparing the Pre pandemic and Para pandemic favourable and unfavorable outcomes of DR-TB treatment to understand how much the Pandemic has negatively influenced TB specifically drug-resistant TB control efforts. The lessons learned from the COVID-19 response would help us to improve the treatment outcomes of patients treated with Drug-resistant TB treatment. The worldwide TB eradication targets may be hampered by the coronavirus disease 2019 (COVID-19) pandemic. Tuberculosis registrations in Jiangsu Province, China, fell 52% in 2020 compared to 2015–2019. In 2020, treatment completion and drug-resistant tuberculosis screening decreased steadily. Efforts to prevent TB during and after the COVID-19 epidemic require immediate attention [9].

This study aims to compare the Pre and Para pandemic favourable and unfavorable outcomes of DR-TB treatment in PMDT Units of Islamabad and Rawalpindi.

METHODS

This was a retrospective cross-sectional study that included all Confirmed Pulmonary drug-resistant TB patients, enrolled and treated from 2016-2021. This study used National TB Control Program Pakistan ENRS (Electronic Nominal Registration System) data collected from its three Programmatic Management of Drug-Resistant TB (PMDT)-Sites, Pak-Emirates Military Hospital Rawalpindi, Rawalpindi Leprosy Hospital and Pakistan Institute of Medical Sciences Islamabad. A non-probability consecutive sampling method was employed in recruiting participants, during the study period and a total of 670 DR-TB patients (all types) were included (Figure 1).

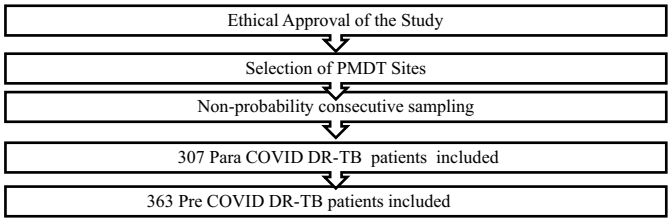

Figure 1: Sampling Strategy

Pre-Covid participants (n=363) were DR-TB patients who completed their treatment before COVID-19 while Para-Covid participants (n=307) completed treatment till 2021. The sample size was determined by taking the prevalence of rifampicin resistance of 0.05 from a previous study [10], a desired precision of 0.02, and a 95% confidence level. The sample size was calculated based on the sampling method recommended by WHO for drug resistance surveys in tuberculosis. n=Z2.p.(1-p)/e2. p=0.05, Z=1.96, q=(1-p) =0.95 and e=0.02. n= (1.96)2 x (0.05) x (0.95)/ (0.02)2. n= 670. Pre-pandemic cases (February 2016- June 2019). n=363. Para Pandemic cases (July 2019- December 2021). n=307. For clinical information, a structured questionnaire was adopted and modified according to local study settings from WHO guidelines for DR-TB surveillance [6]. The reliability of the questionnaire was determined using Cronbach's alpha (r=0.68). Ethical approval was obtained from the Armed Forces Postgraduate Medical Institute, National University of Medical Sciences (NUMS) Rawalpindi

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(IRB No.238-AAA-ERC-AFPGMI). A written informed consent was taken. Statistical analysis was carried out using SPSS version 26.0 and descriptive statistics like frequencies and percentages were calculated while a chi-square test of significance was applied to check associations between DR-TB treatment outcomes and the COVID-19 Pandemic.

RESULTS

Among 670 participants included in the study, more than half (n= 357, 53.3%) were males. The mean age of these participants was 38.02 ±18.46 years. The average duration of sickness before diagnosis with DR-TB for most of the participants was < 1 year (n= 556, 83.0%). The sociodemographic characteristics of participants are presented (Table 1).

Table 1: Frequencies and Percentages and Association of Pre and Para-COVID DR-TB Patients with Demographic Variables (n=670)

Variables	Category	Frequency (n=670)		p-Value
		Pre-COVID	Para-COVID	
Gender	Male	210 (31.34%)	147 (21.94%)	0.0006*
	Female	153 (22.83%)	160 (23.88%)	
Age	0-4 Years	4 (0.597%)	2 (0.298%)	0.304
	5-14 Years	17 (2.537%)	13 (1.940%)	
	15-24 Years	82 (12.23%)	87 (12.98%)	
	25-34 Years	71 (10.59%)	61 (9.104%)	
	35-44 Years	42 (6.268%)	41 (6.119%)	
	45-54 Years	68 (10.14%)	36 (5.373%)	
	55-64 Years	43 (6.417%)	37 (5.522%)	
	>=65 Years	36 (5.373%)	30 (4.477%)	
Marital Status	Unmarried	103 (15.37%)	104 (15.52%)	0.073
	Married	260 (8.80%)	203 (30.29%)	
Occupation	Housewife	87 (12.98%)	86 (12.83%)	0.001*
	Pvt/ Govt Job	133 (19.85%)	97 (14.47%)	
	Self Employed	22 (3.283%)	20 (2.985%)	
	Unemployed/ Retd	127(18.95%)	98 (14.62%)	
Province/ Region	AJK	57 (22.83%)	38 (22.83%)	0.022*
	FATA	0	1 (22.83%)	
	Federal	51 (22.83%)	33 (22.83%)	
	KPK	26 (22.83%)	11 (22.83%)	
	Punjab	226 (22.83%)	224 (22.83%)	
	Sindh	3 (22.83%)	0	

The chi-square test was applied for test significance. *p-value less than 0.05 was considered significant. SD: Standard Deviation. DR-TB: Drug-Resistant Tuberculosis

This represents that both favorable and unfavorable outcomes decreased in frequency during the COVID period. The frequency of favorable and unfavorable outcomes in the pre and para-COVID period is presented (Figure 2).

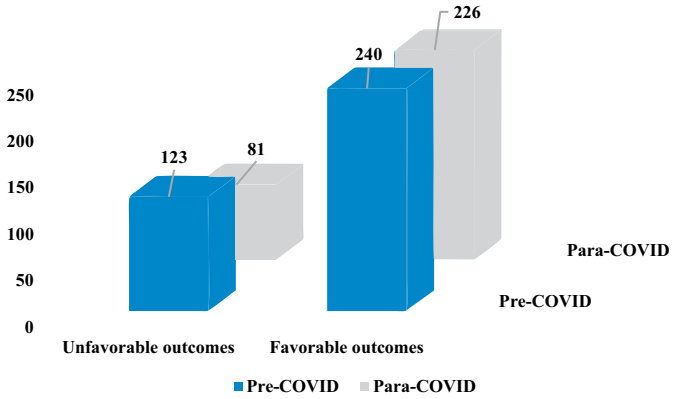

Figure 2: Frequency of Favorable and Unfavorable Outcomes in Pre-COVID and Para-COVID

Among the participants who had enrolled in PMDT-Sites during the COVID era were most affected. The association of Pre-COVID and Para-COVID Patients in each site including Pak Emirates Military Hospital (PEMH-Rawalpindi), Rawalpindi Leprosy Hospital (RLH), and Pakistan Institute of Medical Sciences (PIMS-Federal), with drug-resistant TB favourable and unfavorable treatment outcomes is presented in table 2 after applying chi-square test of significance. Both have a significant association ($p<0.05$) with the COVID-19 Pandemic (Table 2).

Table 2: Frequencies, Percentages and Association of Pre and Para-COVID Patients with DR-TB Treatment Outcomes and PMDT-Site (n=670)

Treatment Outcomes	n (%)		p-Value
	Pre-COVID	Para-COVID	
Un Favorable Outcomes	123 (18.3%)	81 (12.0%)	0.022*
Favorable Outcomes	24 0 (35.8%)	226 (33.7%)	0.0001*
PMDT- Sites			
PEMH Rawalpindi	115 (69.7%)	50 (30.3%)	0.0001*
RLH	82 (25.8%)	236 (74.2%)	
PIMS Islamabad	136 (72.7%)	51 (27.3%)	

*A p-value less than 0.05 was considered significant. PEMH: Pak Emirates Military Hospital Rawalpindi. PIMS: Pakistan Institute of Medical Sciences. RLH: Rawalpindi Leprosy Hospital. PMDT: Programmatic Management of Drug-Resistant Tuberculosis

In observing the months following the drug-resistant TB treatment majority of the study participants missed their follow-ups during the COVID-19 pandemic (Figure 3).

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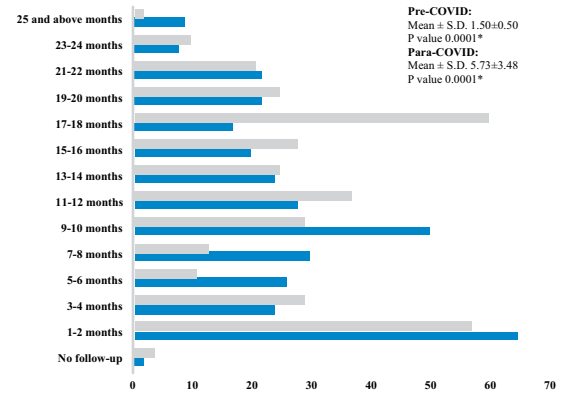

	No follow-up	1-2 months	3-4 months	5-6 months	7-8 months	9-10 months	11-12 months	13-14 months	15-16 months	17-18 months	19-20 months	21-22 months	23-24 months	25 and above months
Para-COVID DR-TB Patients' Follow-up2	3	56	28	10	12	28	36	24	27	59	24	20	9	1
Pre-COVID DR-TB Patients' Follow-up	1	64	23	25	29	49	27	23	19	16	21	21	7	8

Para-COVID DR-TB Patients' Follow-up2 Pre-COVID DR-TB Patients' Follow-up

Figure 3: Frequencies, Percentages and Association of Pre and Para COVID DR-TB Patients with Follow-Up Months (n=670)
The chi-square test was applied for test significance. *A p-value less than 0.05 was considered significant. DR-TB: Drug-Resistant Tuberculosis

The clinical characteristics were also assessed and the results showed that 99 (14.76%) of Para COVID patients had therapy in public facilities for susceptible TB. Moreover, 129 (19.25%) of the patients with drug-resistant tuberculosis had never had any treatment before being diagnosed. Among 307 DR-TB patients who were treated during the pandemic, only 4 (0.59%) had HIV, and 46 (6.84%) had a smoking history. Overall, the clinical characteristics had no significant association with the unfavorable treatment outcomes.

DISCUSSION

To the best of our knowledge, this is the first study to look at factors that can help or hinder general treatment results for drug-resistant TB patients in Rawalpindi and Islamabad PMDT-Units before and during the COVID-19 pandemic. The study's findings revealed that 18.35% (n=128) of pre-COVID participants had poor treatment outcomes, compared to 35.82% (n=240) of patients who had favorable treatment outcomes. Similar results were seen for Para-COVID participants: 33.73% (n=226) had favorable treatment outcomes, while 12.2% (n=82) had unfavorable ones. It is higher than the study which covered 10 PMDT-sites from Punjab- Pakistan [10], found an overall treatment success rate (favorable outcomes) of 32.1% and unfavorable treatment outcomes were 118 (64.1%) within 10 PMDT-Sites, showing that Pakistan is far behind the treatment success targets set by the WHO in the End TB strategy [7]. In terms of PMDT Sites, the results revealed that out of 187 DR-TB patients at PIMS Hospital Islamabad, 136 were enrolled and treated before the pandemic, and 51 were treated during the COVID-19 epidemic, having unfavourable treatment outcomes (7.6%), and out of 165 DR-TB patients at PEMH Rawalpindi, 115 were enrolled as pre-COVID, with 50 DR-TB patients having unfavourable treatment outcomes (Para-COVID participants) [8]. In Rawalpindi Leprosy Hospital, 82 Pre-COVID individuals received DR-TB treatment, while 35.2 % of 236 Para-COVID participants who received treatment during the COVID-19 Pandemic experienced unfavourable treatment outcomes [11]. Current findings showed that the highest enrolments of pulmonary drug-resistant tuberculosis occurred in the pre-COVID era at both PIMS Hospital Islamabad and PEMH Rawalpindi, but that enrolments of pulmonary drug-resistant tuberculosis increased at Leprosy Hospital during the pandemic. The highest enrolments of pulmonary drug-resistant tuberculosis occurred in the pre-COVID era at both PIMS Hospital Islamabad and PEMH Rawalpindi. The study examines a significant association between the COVID-19 effect and DR-TB patient enrolments as well as poor treatment results across all three PMDT sites(p=0.000). In ten high-burden nations, a study examined the DR-TB situation in 2018 and the United Nations High-Level Meeting (UNHLM) objective successes in high-burden countries (HBCs) [12]. According to the study's findings, there were severe limitations on travel within and between cities, which made it difficult for those with DR-TB to reach medical facilities. 56 patients (16.6%) had only a few months of follow-up. The average follow-up period for Para COVID patients was 5.73 (S.D. + 3.487) months. Due to travel limitations and concerns about catching COVID-19, TB patients have put off or skipped going to their follow-up visits. The COVID-19 Pandemic and the follow-up months of the DR-TB (Para-COVID) participants are significantly correlated (p=0.000). In terms of follow-up investigations, a study was carried out in China to see whether the COVID-19 Pandemic has had a sizable impact [13]. Healthcare professionals did their utmost to address the issue and get the drugs to patients in Rawalpindi and Islamabad PMDT sites, even though some countries during the epidemic faced a lack of anti-TB medications. After 6 months of treatment during the COVID period, there was a significant change (p=0.041) in the sputum conversion rate of smear-positive patients; out of 307 DR-TB patients, 210 (68.40%) had missing cultures. The treatment outcomes were impacted by missed culture findings, along with the cure rate, for 210 (31.3%) drug-resistant TB patients in the Para-COVID period. This is in line with earlier studies that demonstrate a decrease in recurrence rates with DOT [14]. The study looked at additional clinical aspects of the participants, including both Pre-COVID and Para-COVID DR-TB patients, to ascertain whether there is any relationship between these characteristics and the results of treatment. The study's conclusions are consistent with those of a Brazilian study, which discovered that there was no relationship between the clinical characteristics and

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the presence of comorbidities (p>0.05) [15]. Age shows a strong connection with failed treatment results among sociodemographic characteristics (p=0.000). It was clear that 132 unfavorable treatment outcomes between the ages of 15 and 54 which are economically active have been reported, with the majority occurring throughout the COVID duration, and display a worrying situation in terms of rolling back the improvements made in TB management over the past few decades. According to Namibian researchers' findings, only age groups were shown to be substantially linked with the failure to treat TB in the Oshana region [8, 16]. Current study demonstrates a statistically significant relationship between occupation and drug-resistant TB treatment failures during COVID-19 (p=0.027). Present findings support the study's findings that the 2019 and 2020 treatment outcomes will be comparable to be affected in light of the continuing COVID-19 pandemic [16, 17]. Gender and DR-TB may be related, according to several research. Multicenter case-control research carried out in Pakistan identified the male gender as a risk factor for MDR-TB [15], while some researchers have claimed that the prognosis of MDR TB is influenced by a woman's gender [18]. The results of current study indicate that gender is related to Pre-COVID and Para-COVID participants (p=0.006). In present study, a statistically significant link between DR-TB instances among Pre- and Para-COVID participants' employment and the residential region was found. More than half of the study participants were either housewives, retirees, or jobless. The majority of the study participants were from the Punjab province. Both the residential area and the occupation have a significant association with DR-TB patients (p=0.022 and 0.001), respectively. Among 670 participants, 249 were rural residents (43.88%) and 376 urban residents (56.12%) [19, 20].

CONCLUSIONS

It was concluded that this retrospective study compared treatment outcomes of DR-TB patients before and during the COVID-19 pandemic. Results showed treatment success rates exceeding WHO-End TB targets. Residential status, gender, and occupation were significant factors influencing outcomes in both periods.

Authors Contribution

Conceptualization: BRB
Methodology: FP, HM, RZ, NUI, YFK
Formal analysis: MZS
Writing review and editing: BRB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Assessment of Changes in Corneal Endothelial Characteristics in Primary Open-Angle Glaucoma

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ABSTRACT

Patients with glaucoma undergo significant changes in corneal endothelial characteristics due to chronically elevated Intraocular pressure (IOP). **Objectives:** To compare endothelial cell density between primary open-angle glaucoma (POAG) patients and age-matched non-glaucomatous controls. Also to explore the relationship between endothelial cell density and Intraocular pressure. **Methods:** This case-control study was conducted at Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan. It included 41 eyes of patients with POAG aged between 35-70 years and 41 eyes of age-matched non-glaucomatous subjects were taken as controls. The POAG was diagnosed based on Intraocular pressure, optic disc changes, and visual field defects. All participants went through a comprehensive ocular evaluation, that included slit-lamp examination, gonioscopy and Intraocular pressure assessment. The endothelial cell density was assessed via specular microscopy. SPSS version 26.0 was utilized to perform statistical analysis. **Results:** The average corneal endothelial cell density in healthy control subjects was 2484.51 ± 286.44 cells/mm^2, but those with POAG showed a statistically significant decline, measuring 2345 ± 270.29 cells/mm^2 (p=0.02). A notable decrease in endothelial cell density was seen in patients using dorzolamide 2262.00 ± 287.15 relative to patients not using dorzolamide 2451.28 ± 209.56 (0=0.02). Endothelial cell density and the average Intraocular pressure revealed a weak inverse correlation (r= -0.204, p=0.06). **Conclusions:** It was concluded that POAG patients show reduced corneal endothelial cell density. It also suggests that endothelial cell density declines with higher Intraocular pressure and increased disease severity, making it a possible biomarker of disease progression in POAG.

INTRODUCTION

Glaucoma consists of a range of conditions that are defined by characteristic patterns of damage to the optic disc and changes in the nerve fiber layer of the retina [1-3]. Research has shown that the changes in corneal endothelial cell density (ECD) are linked to glaucoma, with endothelial cell loss seen in different varieties of glaucoma such as POAG, primary angle-closure glaucoma [4], and certain types of secondary glaucoma [5]. Globally, POAG is one of the chief contributors to irreversible blindness worldwide [6, 7]. It is characterized by progressive damage of the optic nerve and characteristic loss of visual fields, frequently associated with elevated Intraocular pressure (IOP) [7]. Although there has been significant progress in understanding and managing POAG, the primary mechanisms driving its progress remain not fully understood. Whereas attention has been predominantly focused on the effect of IOP on the retinal nerve fiber layer and optic nerve, the effect on other ocular tissues, such as the corneal endothelium, has not been fully addressed. The cornea is an optically clear, avascular, and highly innervated structure. The innermost layer of the cornea is composed of single-layered polygonal endothelial cells that make up the endothelium. These cells are crucial for preserving corneal hydration and clarity by ensuring the movement of fluids and solutes between the aqueous humor and cornea [8]. At birth, the average corneal ECD is approximately 3,000 cells/mm2, and by adulthood, it decreases to approximately 2,500 cells/mm2 [9]. The

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regenerating ability of these endothelial cells is limited, and 400–500 cells/mm2 is the critical ECD needed to sustain the endothelial pumping function [10]. Reduced visual acuity, corneal edema formation, and decreased corneal transparency can all occur when ECD falls below the threshold value. Corneal endothelial cell (CEC) loss can result from trauma, intraocular surgery [11, 12], or conditions including diabetes [13]. CECs are particularly vulnerable to oxidative stress, inflammation, and elevated IOP, which are characteristic of glaucoma [9]. Assessment of the status of CECs is important in planning glaucoma treatment. Antiglaucoma medications particularly topical carbonic anhydrase inhibitors(CAIs) have been found to affect CECs by different mechanisms [14, 15]. Topical CAIs such as brinzolamide and dorzolamide, are commonly used for reducing IOP in the management of glaucoma. However, their effect on ECD and central corneal thickness (CCT) has been a debate of controversy [16, 17]. CAIs change the aqueous humor dynamics and pH levels, and this could impact the corneal endothelium. For patients undergoing anterior segment surgery, understanding ECD is important since eyes with lower cell densities are more likely to suffer from post-op corneal decompensation compared to normal eyes [11, 12].

This study aims to investigate the changes in the density of CECs in POAG. Earlier studies have implied a possible link between POAG and decreased ECD, though results have been inconsistent [4, 18]. This study also examines the relationship between IOP and various characteristics of CECs, considering the potential of using ECD as a biomarker for POAG progression.

METHODS

This case-control study was conducted at the Glaucoma Department of Al-Shifa Trust Eye Hospital (ASTEH), Rawalpindi, from June 2024 to December 2024.82 individuals were inducted in the study, of whom 41 were POAG cases and 41 were age-matched healthy controls. The age of participants ranged from 35 to 70 years, both male and female. Only one eye from each participant was considered for the study. The sampling method to select the participants was a non-probability consecutive sampling method.The research conformed to the regulations of the Helsinki Declaration and permission was given by the Ethical Review Committee at Al-Shifa Research Centre (approval number:ERC-16/AST-24).All participants received thorough counselling regarding the study and gave informed consent before enrollment. The sample size for this study was measured by power analysis utilizing Open Epi software version 3.01[19], using the mean and standard deviations provided in the reference study by Yu ZY *et al.*, with a mean of 2959 ± 236 cells/mm2 and 2757 ± 262 cells/mm2 between the two groups keeping the power of the study at 95% and confidence interval at 95% [18]. The analysis indicated that a minimum of 40 participants per group was necessary to reliably observe the mean difference of 202 cells. To account for potential attrition and data inconsistencies, an additional participant was included per group yielding a final sample size of 82 participants. Intraocular pressure (IOP) readings of greater than 21 mm Hg on a Goldman applanation tonometer on three or more occasions, glaucomatous optic disc changes (a cup-disc ratio (CDR) greater than 0.4 or an inter-eye CDR disparity greater than 0.2), and the identification of distinctive visual field defects using the Humphrey Visual Field (HVF) Analyzer (Carl Zeiss) were the criteria used to diagnose POAG in Group 1. Glaucoma severity was defined as early (MD> -6 dB), moderate (MD -6-12 dB), or advanced (MD> -12 dB) on the Humphrey visual field test. Each participant recruited in the POAG group showed visual field loss (mean deviation> -6dB) on at least two consecutive automated perimetric tests. Posner 4-mirror goniolens was used for gonioscopy, Shaffer grading system was used for anterior chamber angle assessment. Gonioscopy confirmed open anterior chamber angles (Shaffer grades 3 or 4). The control group included healthy individuals who had no glaucoma symptoms or indicators, had no pertinent eye history, and had no corneal pathology or any systemic illness that could affect CECs [13]. Their optic discs and visual fields showed no abnormalities, and the IOP readings on the Goldman application tonometer were all below 21 mmHg on more than two occasions. The exclusion criteria comprised individuals with a track record of corneal pathologies, use of contact lenses, ocular trauma, previous ocular operations (including intraocular surgeries or laser procedures), congenital ocular disorders, cataracts, spherical equivalent refractive error larger than ± 6 diopters, or systemic conditions as diabetes mellitus as these conditions could limit the generalizability of the study [13]. Moreover, any disease that could independently affect ECD was deemed a basis for exclusion [13]. Participants received a thorough ophthalmic evaluation, which included detailed ocular and systemic history, best corrected visual acuity (BCVA) using the Snellen acuity Chart, anterior and posterior segment slit-lamp examination, and dilated fundus biomicroscopy utilizing a +90 Diopter lens. Goldmann Applanation Tonometry (GAT) was used to assess the IOP.nPosner 4-mirror goniolens was used for gonioscopy to verify open-angle condition. Corneal endothelial cell (CEC) characteristics were evaluated with specular microscopy EM-4000, Tomey Corporation, Nagoya, Japan. Parameters such as ECD, Standard Deviation (SD) of mean cell area, Maximum Cell Area (MAX), Minimum cell area (MIN), average cell Area (AVG), Coefficient of Variation of cell size (CV), and

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percentage of cell hexagonality (6A) were recorded. IBM SPSS software for Windows, Version 26.0 2019; IBM Corp was utilized for statistical analysis.To summarize demographic and clinical data, Descriptive statistics were applied. The normality of the continuous data was evaluated before application of statistical tests. Independent t-tests were used to compare the group means for normally distributed data. Pearson's correlation coefficients were used to measure the correlations between clinical measures, such as IOP and ECD, IOP and MAX, IOP and MIN, IOP and AVG, IOP and 6A. Statistical significance was set at $p<0.05$ with 95% confidence intervals(CI).

RESULTS

The study comprised 41 patients diagnosed with POAG with a mean age of 54.49 ± 9.24 years including 51% male and 49% female, and 41 age-matched healthy controls with a mean age of 50.27 ± 7.70 years including 46% male and 54% female. The mean IOP in the POAG cohort was 17.98 ± 5.14 mmHg, while in the control group, it was 14.37 ± 2.52 mmHg, with a mean difference of 3.61 mmHg. The corneal ECD in the POAG group (2345.10 ± 270.29 cells/mm^2) was inferior to that of the control group (2484.51 ± 286.44 cells/mm^2) indicating that reduction in CECs was associated with raised IOP in POAG. Based on these patients' hospital records, the median length of glaucoma was 14.05 months (IQR:22.5 months). Key demographic and clinical characteristics showing notable differences in IOP, and ECD between the 2 groups (Table 1).

Table 1: Summary of Key Demographic and Clinical Differences Between the 2 Groups

Characteristics	Group A (POAG) n=41	Group B (Control) n=41	p-Value
Age (years)	54.49	50.27	0.03
Male: Female %	51:49	46:54	<0.01
Cup-Disc Ratio	0.6	0.2	<0.01
Mean IOP (mmHg)	17.98	14.37	<0.01
Average ECD (cells/mm^2)	2345.10	2484.51	0.03
Duration of Glaucoma (Months)	14 (IQR 22.5)	-	-

Specular microscopy gives important information about the general physical state of the CECs which includes size, shape and density.This is a non-invasive diagnostic technique. It helps to identify and manage various corneal conditions. In this study, the specular microscopy showed that the ECD was significantly reduced in POAG patients (2484 ± 286 cells/mm2) in comparison to the control group (2345 ± 270 cells/mm2) ($p=0.026$) with 95% CI (-261.81,-17.01) suggesting that the impact on ECD in POAG may be more directly related to the raised IOP. Patients with glaucoma had a considerably higher average cell area (AVG) (452.83 ± 49.71 µm2) than the control group (418.93 ± 57.56 µm2) ($p<0.01$) with 95% CI (10.26, 57.54). This refers to the variation in the area of the endothelial cells under stress, due to raised IOP, which results in the loss of normal hexagonal structure and increase in average cell area. Similarly, SD, MAX and MIN were higher in POAG patients. Patients with POAG had a lower percentage of hexagonal cells 6A (49.78 ± 3.25) than controls (51.37 ± 3.05) ($p=0.03$) with 95% CI (-2.97, -1.98). This finding suggests that patients with POAG lost the normal hexagonal structure of CEC possibly due to chronic insult by elevated IOP. The CV did not significantly change between the two groups (Table 2).

Table 2: Summarized CEC Characteristics of the POAG and the Control Group

Characteristics	Group A (POAG) n=41	Group B (Control) n=41	p-Value	Mean Difference	95%Confidence Interval, CI Lower Limit	95%Confidence Interval, CI Upper Limit	Effect Size (Cohen's *d*)
ECD, (cells/mm^2)	2345.10 ± 270	2484.51 ± 286	0.02*	-139.41	-261.81	-17.01	0.50
SD (µm^2)	164.12 ± 34.65	146.88 ± 24.38	0.01*	17.24	4.07	30.41	0.57
CV (%)	37.17 ± 6.82	36.07 ± 4.08	0.37	1.09	-1.37	3.57	0.19
6A (%)	49.78 ± 3.25	51.37 ± 3.05	0.03*	-1.58	-2.97	-1.98	0.50
AVE (µm^2)	452.83 ± 49.71	418.93 ± 57.56	<0.01*	33.90	10.26	57.54	0.63
MAX (µm^2)	1036.80 ± 272.06	926.10 ± 171.80	0.03*	110.70	10.70	210.70	0.48
MIN (µm^2)	114.32 ± 27.99	99.29 ± 30.90	0.02*	15.02	2.06	27.98	0.50

Note: *indicates a statistically significant difference at $p<0.05$

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The 41 patients with POAG were further categorized into dorzolamide-untreated group (n=18) and dorzolamide-treated group (n=23). There was no major difference in age and gender between these two sub-groups. Stratifying POAG patients based on dorzolamide treatment revealed a mean ECD of 2262.00 ± 287.15 cells/mm^2 for treated patients and 2451.28 ± 209.56 cells/mm^2 for untreated patients. Statistical analysis confirmed a significant reduction in ECD among those treated with dorzolamide (p=0.026, Cohen's d=0.75), while other parameters, such as percentage of hexagonal cells and average cell area, did not show statistical significance. A detailed comparison of endothelial cell parameters between patients treated with dorzolamide and those not treated with dorzolamide is provided (Table 3).

Table 3: Summary of CEC Characteristics among Dorzolamide-Treated and Untreated Patients

Characteristics	Dorzolamide -Treated, n=23	Dorzolamide-Untreated, n=18	p-Value	Mean Difference	95%Confidence Interval, CI Lower Limit	95%Confidence Interval, CI Upper Limit	Effect Size (Cohen's *d*)
ECD (cells/mm^2)	2262.00 ± 287.15	2451.28 ± 209.56	0.02*	-189.27	26.17	352.38	0.75
6A (%)	49.78 ± 3.45	49.78 ± 3.07	0.99	0.05	-2.10	2.09	0.0
AVE (µm^2)	450.96 ± 48.42	455.22 ± 52.63	0.78	-4.26	-27.75	36.28	0.08
MAX (µm^2)	1055.22 ± 283.24	1013.28 ± 263.24	0.63	41.94	-216.79	132.91	0.15
MIN (µm^2)	118.65 ± 32.12	108.78 ± 21.21	0.26	9.87	-27.63	7.88	0.36

Note: *indicates a significant difference at p<0.05

A weak opposite correlation was observed between IOP and ECD (r= -0.204, p=0.06). However, only the positive trend between the IOP and maximum cell area was found to be statistically significant (p=0.001) (Figure 1).

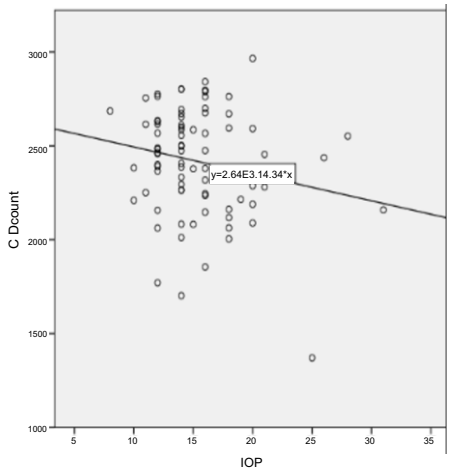

Figure 1: Correlation Between IOP and ECD

Positive relationships were identified between IOP and Average Cell Area (r=0.202, p=0.06). However, only the positive trend between the IOP and maximum cell area was found to be statistically significant (p=0.001) (Figure 2).

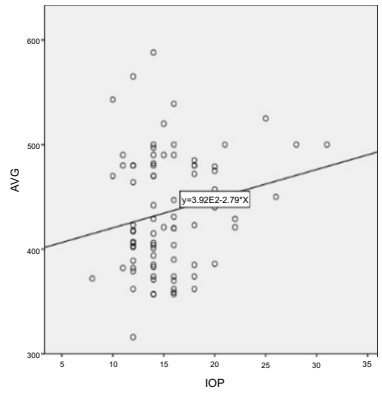

Figure 2: Correlation Between IOP and Average Cell Area

Positive relationships were identified in IOP and Maximum Cell Area (r=0.345, p=0.001) (Figure 3).

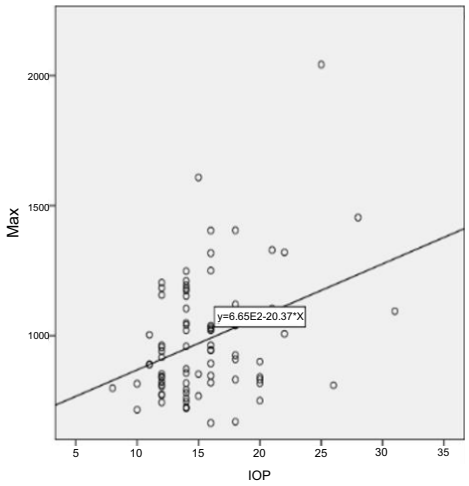

Figure 3: Positive Relationships Between IOP and Maximum Cell Area

Positive relationships were identified in IOP and Minimum Cell Area (r=0.182, p=0.10) (Figure 4).

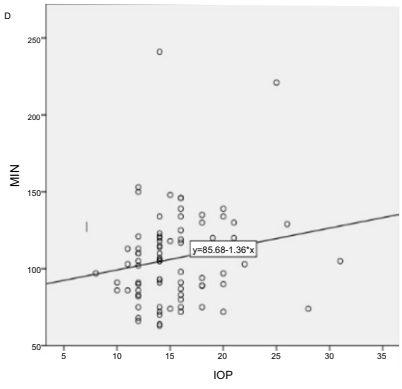

Figure 4: Positive Relationships Between IOP and Minimum Cell Area

No substantial association was identified between IOP and the percentage of hexagonality (r=-0.01, p=0.92) (Figure 5).

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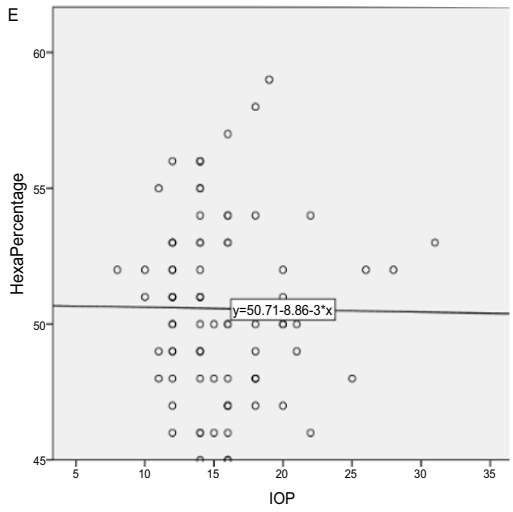

Figure 5: Association Was Identified Between IOP and the Percentage of Hexagonality

DISCUSSION

ECD is a major indicator of endothelial health. The lower count indicates a damaged cornea. Polymegathism is the variation in cell size measured by coefficient of variation, CV. pleomorphism is the percentage of hexagonal cells. Both factors provide valuable insights about the regularity and survival of endothelial cells. The higher coefficient of variation indicates higher variation and frequently indicating cellular stress or disease [20]. The lower percentage of hexagonal cells shows increased cell shape irregularity which could point to compromised endothelial layer. Chronically elevated IOP in POAG is associated with changes in corneal endothelial characteristics, including reduced ECD, increased pleomorphism, and polymegathism. The objective of this study was to find out if there was any variation in the corneal endothelial characteristics in subjects diagnosed with POAG compared with healthy participants. The corneal endothelium is a single layer of cells with hexagonal structure that ensure clarity of cornea by controlling fluid and solute exchange. The susceptibility of this layer to IOP-related stress underscores its importance in overall ocular integrity [21]. These cells possess limited regenerative capacity, thus being severely susceptible to injury from prolonged mechanical stress brought on by high IOP [21]. High IOP directly applies mechanical stress on the corneal endothelium. This stress can lead to cell deformation, rupture of cell junctions, and loss of its function in maintaining corneal deturgescence. Chronically high IOP causes cellular apoptosis in the endothelium due to oxidative stress and inflammation. This results in progressive loss of ECD with time [22]. The prolonged exposure to high IOP could interfere with the metabolic activity of endothelial cells, impairing their function to keep the cornea optically clear[8]. In our research the decrease in ECD seen in POAG patients is found to be consistent with the previous studies that endothelial cell damage is influenced by persistently high IOP, a characteristic of POAG [18, 4]. The term polymegathism, or coefficient of variation, refers to the variation in the cell areas of individual cells. 100% of the cells in a healthy cornea should be hexagonal in shape. It is anticipated that a typical cornea will have hexagonality of 60%. Under stress or insult to the endothelium, as seen in raised IOP, hexagonality decreases and cell area increases [20]. According to our study patients with POAG had a statistically significant reduction in % of hexagonal cells (p=0.03) and increase in average cell area(p=<0.01) indicating stress induced loss of endothelial cells with resultant increase in the size of remaining viable cells and loss of normal architecture. A positive correlation was identified between the IOP and maximum cell area (p=0.001), suggesting an overall enlargement of endothelial cells which is frequently associated with reduction in ECD due to damage to the corneal endothelium. The endothelial damage is thought to be repaired by elongation and spread of the remaining cells, to generate a consistent cellular layer across the inner surface of the cornea [20, 23]. This causes the number of endothelial cells to decrease and the surface area to grow as evident by the findings in our study. This study suggests that the impact of POAG on the corneal endothelium may be more directly related to disease-specific factors such as IOP and the use of certain IOP-lowering agents which further can lead to endothelial cell damage. Reducing intraocular pressure is the only treatment that has been proven to be effective and is widely recognized for halting the progression of glaucoma [24]. The mainstay of POAG treatment to reduce intraocular pressure is with topical medications, laser therapy, and glaucoma surgery. However, medical treatment with topical eye drops is regarded as an appropriate first line of therapy in published guidelines for the treatment of POAG [25].Different anti-glaucoma medications are available that can be applied topically to reduce IOP. Their modes of action and the extent to which they reduce intraocular pressure vary [26].A network meta-analysis of topical first-line medications found that prostaglandin analogues reduce intraocular pressure the most, followed by beta-blockers, alpha2-adrenergic agonists, and carbonic anhydrase inhibitors(CAIs)[26]. The possible impact of medications on corneal endothelium is a matter of concern even with proven advantages of glaucoma pharmacotherapy in lowering IOP [26].The findings of the investigation to find a correlation between different types of anti-glaucoma medication and corneal endothelial damage have not been consistent [14,15]. Dorzolamide was the first commercial product approved by the Food and Drug Administration (FDA) for the treatment

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of glaucoma [27]. It is widely used in the management of POAG. Many clinical studies agreed that the use of topical dorzolamide had no meaningful effect on endothelial cell count and cell shape [14, 15]. However, Lass *et al.*, contradict this finding, showing that after one year of topical dorzolamide therapy in individuals with POAG or ocular hypertension, the mean percent CEC loss was 3.6% [28]. In our study topical instillation of dorzolamide in POAG patients has been shown to cause a statistically significant reduction in ECD. However, it has not been shown to cause any statistically significant effect on corneal endothelial cell size or shape. A reduction in ECD may indicate poor IOP control and the need for adjustments in therapeutic strategies. This is particularly significant because patients with POAG who do not respond well to topical medication need surgical intervention to halt glaucoma progression. These patients face an increased risk of further CEC loss, leading to reduced corneal clarity, as evidenced by multiple studies [11, 12]. Because an unhealthy endothelial layer can have serious postoperative consequences, for ophthalmic procedures including cataract extraction and trabeculectomy [29], the major determining factor in selecting patients and surgical prognosis is endothelial integrity. This study emphasizes the importance of corneal endothelial assessment in POAG patients undergoing intraocular surgical procedures. Nevertheless, the role of ECD as a biomarker for glaucoma progression should be tested thoroughly with extensive research. A large sample size would generalize the findings of the current study. A more diverse demographic approach could provide insights into how various factors like ethnicity or lifestyle influence ECD in glaucoma patients. A longitudinal study design would help in understanding the progression of ECD changes over time. Further studies are needed to track the long-term impact of elevated IOP on endothelial health and the effect of different glaucoma treatments on ECD for safer therapeutic practices. Systemic conditions that are known to contribute to the reduction of endothelial count, like diabetes mellitus [20-22], were not the focus of this study and require further investigation. This research study focuses on the necessity of integrating ECD monitoring into glaucoma treatment protocols and emphasizes the cautionary use of dorzolamide. Ongoing research into pharmacotherapies with less endothelial toxicity and a protective effect on endothelial cells could improve outcomes for glaucoma patients.

CONCLUSIONS

It was concluded that this study shows a decline in the density of CECs in patients with POAG, demonstrating that a lower ECD is associated with more severe disease and higher IOP. Our findings highlight the need for corneal endothelial monitoring in glaucoma management, particularly in advanced cases or those with poorly controlled IOP. The reverse correlation between ECD and IOP emphasizes the need for stable IOP control to protect corneal endothelial function. Future longitudinal studies should investigate ECD reduction mechanisms in POAG and assess its potential as a biomarker for disease progression.

Authors Contribution

Conceptualization: TT
Methodology: TT, AA[1], NR, AA[2], KH
Formal analysis: TT, FA
Writing review and editing: MA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Outcome of Low Molecular Weight Heparin Use in Pregnant Women with Oligohydramnios at A Tertiary Care Hospital

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ABSTRACT

Oligohydramnios refers to an antenatal condition in which the amniotic fluid volume is abnormally low and has poor fetal consequences. This research strives to elaborate on the convoluted connections between oligohydramnios and the associated maternal and fetal risks. **Objectives:** To find out the frequency of pregnancy outcomes in pregnant women with oligohydramnios using low molecular weight heparin (LMWH). **Methods:** The prospective cohort study was conducted at the Obstetrics Department of Nishtar Hospital, Pakistan from November 2024 to January 2025. One hundred and twenty-two women fulfilling the inclusion criteria were included. Patients were given 40 mg LMWH subcutaneously once a day.The patients were followed till delivery to determine outcomes including live birth, preterm delivery, weight at birth, admission to the Neonatal Intensive Care Unit (NICU) and pre-eclampsia. SPSS version 26.0 was employed to analyze the data. **Results:** Out of 122 participants, 120 (98.4%) resulted in live births while 2 (1.6%) were intra-uterine deaths. Among all births, 21 (17.2%) were delivered preterm while 101 (82.8%) were delivered at term. 108 (88.5) weighed >2.5 kg. Among 120 live births, 23 (19.2%) were admitted to the NICU for observation or treatment. **Conclusions:** It was concluded that the study results support the use of LMWH in oligohydramnios as a proportion of adverse perinatal outcomes was low in our study.LMWH was found to be efficacious, authentic and safe in oligohydramnios to achieve desired clinical outcomes and decrease the burden of associated morbidities and mortalities in the targeted population.

INTRODUCTION

Amniotic fluid is a water-like substance surrounding the developing fetus. It is present in the amniotic sac which starts forming about 12 days' post-conception. Its composition includes water, nutrients, enzymes, hormones and antibodies [1]. The amniotic fluid serves many functions for the growing fetus. It acts as a cushion and saves the fetus from any injury and umbilical cord compression. It keeps the fetus at a constant temperature and allows it to move around in the womb. It also helps the development of bones, muscles and other organs along with providing nutrients, hormones and antibodies to the growing fetus [2].The amniotic fluid equilibrium is sustained by the virtue of balance of production (lung fluid and urine) and resorption (swallowing and intra-membranous flow).The amount of amniotic fluid increases exponentially with the development of the fetus, reaches its peak around the gestational age of 34 weeks and starts to decline thereafter [3]. The normal amount of amniotic fluid is a reassurance of normal function of the placenta and is considered the most important among fetal well-being tests [4].The reduced amount of amniotic fluid may be an indicator of an underlying pathology including placental insufficiency, congenial anomaly or ruptured membranes. Oligohydramnios is also a frequent finding in a hypertensive woman with intrauterine growth restriction, especially in cases of pre-eclampsia [5]. The abnormal amount of amniotic fluid can interfere with the development and growth of the fetus.The decrease in amniotic fluid volume increases the incidence of preterm delivery, low birth weight and perinatal mortality [6]. The

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frequency of major congenital abnormalities, low birth weight and intra-uterine growth restriction also increases exponentially with decreasing amniotic fluid volumes[5]. Oligohydramnios has also a strong association with pre-eclampsia.The ultrasound is the best practical method to assess amniotic fluid volume.There are various formulas for amniotic fluid volume calculation.The preferred method is amniotic fluid index (AFI), though some use a single deepest pocket to assess liquor volume.To calculate AFI, the uterus is divided into four quadrants.The largest fluid pocket free of umbilical cord or fetal parts in each quadrant is considered and their anteroposterior diameters are summed up. The AFI in the range of 7 to 25 cm is appraised as normal. The term oligohydramnios is used when AFI is <5cm [7]. Worldwide, oligohydramnios is observed in 1-5% of antenatal patients [8]. In Pakistan, oligohydramnios has been estimated to be observed in 3% of pregnancies [9]. Traditionally, aspirin has been used along with hydration to improve amniotic fluid volume. However, the prophylactic use of heparin has proven very beneficial in conditions like recurrent miscarriages, anti-phospholipid syndrome and thrombophilia as regards perinatal outcomes [10]. It has also been used in cases of oligohydramnios with promising results regarding live birth, birth weight and maturity of fetus [11]. LMWH is now appreciated as superior to unfractionated heparin as the chances of allergic reactions, hemorrhagic disorders, thrombocytopenia, and osteoporosis are less likely with its use [12]. Also, no teratogenic side effects have been attributed to its use. LMWH in oligohydramnios acts by enhancing anti-thrombin activity and inhibiting certain coagulation factors, particularly factor Xa. It thus reduces the risk of blood clots and the resultant increased placental blood flow improves oxygen and nutrient delivery to the fetus. The enhanced placental blood flow also maintains normal fetal kidney blood supply resulting in normal fetal urine production and improvement of amniotic fluid volume. Very few local studies have been conducted to evaluate the role of LMWH in oligohydramnios and almost all of them have compared Aspirin and LMWH in oligohydramnios. None of them have evaluated the role of LMWH in addition to standard Aspirin treatment. The study results produce a beneficial database of the local population as we commonly observe pregnant ladies with low amniotic fluid index in our daily routine. The results help clinicians anticipate such adverse perinatal outcomes for timely diagnosis and proper management to reduce perinatal morbidity and mortality. If proven effective, LMWH could provide a targeted therapeutic option, improving pregnancy outcomes in patients with oligohydramnios.

This study aims to determine the frequency of pregnancy outcomes in antenatal patients having oligohydramnios with the use of low molecular weight heparin.

METHODS

A prospective cohort study was conducted after ethical review Board of Nishtar Medical University granted ethical clearance vide reference letter number 18981/NMU. The study spanned from November 2024 to January 2025. WHO calculator was used to calculate the sample size by the formula: n = z2pq/ d2. Where z=1.96, p=8.69 % [7] (Frequency of pre-eclampsia with low AFI), q=100 - p and d = 5 %. This sample size was 122 pregnant ladies with oligohydramnios. The pregnant ladies having singleton pregnancy with AFI <5 cm at or after 28 weeks were included. Those having fetal anomalies or diabetes mellitus were not included. Eligible patients were enrolled using a purposive sampling technique, ensuring that each participant received a comprehensive explanation of the study's procedures and written informed consent was ensured from each of them. They were also ensured about the fact that there was no risk involved to the patient while participating in this study. Confidentiality protocols were strictly observed for both medical and non-medical information. After registration, ultrasonography of the participants was carried out. The patients with low AFI (<5 cm) were recruited for pregnancy outcomes till delivery. Standard treatment with 75 mg Aspirin was given to all patients. Patients were also given 40 mg low molecular weight heparin subcutaneously once a day. The patients were advised of weekly follow-up visits. At each visit, fetal biometry, amniotic fluid volume and umbilical artery Doppler studies were performed. All the observations were made by a designated team of consultant radiologists at our institution to ensure uniformity and consistency. Patients were followed till delivery to determine outcomes including live birth, preterm delivery, neonatal weight, admission to NICU and pre-eclampsia. All information was noted in a formulated data collection sheet which included the following: demographic data, parity, gestational age at presentation, BMI, blood pressure and ultrasound report. Follow-up ultrasounds were documented on it. Neonatal outcomes encompassed living status, maturity of the baby, birth weight and admission of the baby to NICU. SPSS version 26.0 was employed to analyze the data. For numerical data like patient age, parity, BMI, and gestational age, mean and standard deviation were calculated. However, for outcomes, frequencies and percentages were tabulated. Normality tests were conducted using the statistical software SPSS. When p>0.05, the null hypothesis was accepted, and data were normally distributed. Control of effect modifiers like age, obesity, parity and gestational age was made possible by making stratified tables. Post-stratification chi-square test was applied to see their effect on the outcome.

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RESULTS

In this study, 122 patients fulfilling the inclusion criteria were recruited. The mean maternal age was 26.75 ± 4.44 years. 102 (83.7%) were 15-30 years of age while 20 (16.3%) were 31-40 years old. Twenty (16.4%) were primigravidas, 77 (63.1%) had 1-4 kids while 25 (20.5%) had 5 or more kids. The mean BMI was 27.39. About 89 (73%) had normal BMI while 33 (27%) were obese. The mean gestational age at presentation was 32.67 weeks.Out of 122, 47 (38.5%) presented at 28-32 weeks of gestation while 75 (61.5%) presented after 32 weeks of gestation (Table 1).

Table 1: Characteristics of Demographics of study participants

Variables	Minimum	Maximum	Mean ± SD
Age	18	38	26.75 ± 4.44
BMI	21	38	27.39 ± 4.69
Parity	1	9	3.90 ± 2.26
Gestational Age at Presentation	28	35	32.67 ± 1.81

Out of 122 participants, 9 (7.4%) had pre-eclampsia while the majority remained normotensive.Among all conceptions, 120 (98.4%) resulted in live births while 2 (1.6%) were intra-uterine deaths. Among all births, 5 (4.1%) were delivered at 32-35 weeks, 16 (13.1%) at 36 weeks while the rest 101 (82.8%) were delivered at term. As regards birth weight, the vast majority weighed >2.5 kg. Among 120 live births, 23 (19.2%) were admitted to the NICU for observation or treatment (Table 2).

Table 2: Outcomes after LMWH Usage in Patients with Oligohydramnios

Outcomes	Yes n=122 (%age)	No n=122 (%age)	p-value
Pre-Eclampsia	9 (7.4)	113 (92.6)	<0.001
Live Birth	120 (98.4)	2 (1.6)	<0.001
Newborn Weight >2.5 Kg	108 (88.5)	14 (11.5)	0.036
Term Delivery	101 (82.8)	21 (17.2)	<0.001
NICU Admission	23 (19.2)	97 (80.8)	0.002

Multinomial logistic regression was applied to calculate the odds of live birth after adjusting age and other factors (Table 3).

Table 3: Stratification of Live Birth in Association with Age, Parity, Gestational Age and BMI

Characteristics	Subgroups	n (%)	p-value
Age	15-30	100 (83.3)	<0.001
	30-40	20 (16.7)	
Parity	Zero	20 (16.7)	0.965
	1-4	37 (30.8)	
	5 Or More	63 (52.5)	
Gestational Age at Presentation	28-32	47 (39.2)	0.830
	33-36	73 (60.8)	
BMI	<24.9	51 (42.5)	0.070
	25 Or More	69 (57.5)	

An independent sample t-test or ANOVA was applied to analyze differences among groups. Our analysis demonstrated a statistically significant association between maternal age and live birth outcomes (p<0.001). Women aged 15–30 years had a higher proportion of live births compared to those aged 30–40 years. Parity did not show a significant association with live birth rates (p=0.965). Gestational age at presentation did not show a significant difference in live birth rates (p=0.830). Pregnant women who presented between 28–32 weeks and 33–36 weeks had similar outcomes. The analysis showed a near-significant association between BMI and live birth outcomes (p=0.070). While this result did not reach statistical significance, it suggests that higher BMI may contribute to adverse pregnancy outcomes in women with oligohydramnios receiving LMWH.

DISCUSSION

An adequate amniotic fluid volume constitutes the most important component of a normal pregnancy, as it plays the role of protective cushion for the fetus, prevents umbilical cord compression, and contributes to fetal lung development. Oligohydramnios (AFI <5 cm) is associated with serious risks to fetal well-being. The most important and common causes of maternal and fetal mortality and morbidity are pre-eclampsia and fetal growth restriction. Both of these have oligohydramnios as the accompanying feature. Our study comprised 122 pregnant ladies having oligohydramnios at or onward 28 weeks of gestation. The mean maternal age was 26.75 years which is near that calculated by Twesigomwe *et al.*, in Uganda [13]. Mushtaq *et al.*, also found similar (27.86%) results in a study conducted in Pakistan [14]. The mean BMI of pregnant ladies in this study was 27.39. Out of these, 27% had a BMI of more than 30 kg/m2.Our results regarding obesity and oligohydramnios are the same as those reached by Mushtaq *et al.*, from Pakistan [14]. This narrates that obesity has no association with oligohydramnios.The same was concluded by Bistervels *et al.*, [15]. Amniotic fluid can be reduced in both obese as well as normal-weight mothers.The gravidity in our study ranged from 1-9. The same was observed by Mohammed and his colleague from Iraq [16]. The mean parity in our study was found to be 3.90. Nearly 20 (16.4%) were primigravidas, 25 (20.5%) were grand multiparas having 5 or more kids and 77 (63%) had 1-4 kids. Our results are proximate to those reached by Bakhsh *et al.*, from Saudi Arabia where 24.9% were primigravidas and 75.1% were multigravidas [17].The significant association with maternal age underscores the importance of close monitoring in older pregnant women. While parity and gestational age at presentation were not significant predictors, the trend observed with BMI highlights the need for weight management and nutritional counselling in pregnant women at risk for oligohydramnios.

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The main outcome of our study was to find out the frequency of pregnancy outcomes in antenatal patients having oligohydramnios with the use of low molecular weight heparin. Regarding maternal outcomes, 7.4% of the participants developed pre-eclampsia.However, it was calculated as 8.69% in the study by Zaman *et al.*, [18]. The slightly high rate of pre-eclampsia in the later study may be due to the fact it was a private hospital study, where patients of the middle and upper class present and usually have chronic hypertension as a result of their eating habits and lifestyle.The metabolic changes induced by pregnancy lead to superimposed pre-eclampsia in such patients. Among 122 births, there were two intra-uterine deaths while the vast majority (98.6%) were live births.Results concluded live births in 93.33% of their cases.The high live birth rate in our study strongly supports the beneficial effects of LMWH in cases with oligohydramnios. Not only live births were more registered but the overall health status of newborns was also much better. In our study, term delivery was achieved in 82.8% of the cases and 17.2% were preterm deliveries. The high rate of preterm delivery in our study can be explained by the high BMI of most of our participants as 57.5% of them were either overweight or obese. Zullino *et al.*, also found a strong association between preterm delivery and increased BMI [19]. Another explanation for this high preterm delivery rate is the grand multiparty as most participants already had more than 5 kids. Cruz-Lemini *et al.*, found a strong association between grand multiparty and preterm delivery [20]. In a study by Chen *et al.*, 22.2% of babies were delivered preterm [21].This difference can be explained by the fact that in developed countries, the neonatal facilities are very advanced and the babies are born relatively preterm with very good survival prognosis and the fetal risks of oligohydramnios with the continuing pregnancy are thus avoided.In the current study, 108 (88.5%) newborns had weight more than 2.5 kg at the time of birth. It again reflects the promising results of LMWH as regards fetal outcome. In our study, 19.2 % of newborns were admitted to NICU for various reasons like low APGAR scores, and respiratory problems.In a similar study conducted by Iftikhar *et al.*, 18.3% of babies were admitted to the NICU. However, the admission to NICU was relatively higher (28.6%) in a similar study in Pakistan [22]. Sultana *et al.*, had a similar study with 28.9% admissions to NICU [23]. This difference can be explicated by the fact that the latter study was organized at a semi-government hospital where extra precautions are followed and newborns are kept in NICU for even observation.

CONCLUSIONS

It was concluded that the use of low molecular weight heparin (LMWH) in pregnant women with oligohydramnios is effective and safe, leading to favourable pregnancy outcomes. The frequency of adverse perinatal events, including pre-eclampsia, intrauterine death, preterm birth, low birth weight, and NICU admissions, was low in our study.These results support the use of LMWH as a beneficial intervention to improve perinatal outcomes and reduce associated maternal and neonatal complications in this population.

Authors Contribution

Conceptualization: ST
Methodology: NN, HM
Formal analysis: AUT, FS
Writing review and editing: ST, SAR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Original Article

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Competency-Based Medical Education: An Analysis of Implementation Challenges in Resource-Limited Settings

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ABSTRACT

Competency-Based Medical Education (CBME) employs a systematic outcome-based strategy to enhance the practical and clinical competencies of the graduates. CBME faces challenges particularly in low-resource areas due to differences in faculty and institutional support, as well as institutional and learning resource availability. **Objective:** To determine the conditions that affect CBME readiness among academic staff and to determine what may obstruct its effective execution. **Methods:** A cross-sectional study was completed over 6 years (September 2024 - January 2025) with a total of 110 faculty members.The participants were divided into 2 groups using a validated assessment tool aimed at targeted differences in CBME readiness.Subjects filled out questionnaires which were analyzed through chi-squar and independent t-tests. **Results:** The factors affecting readiness towards CBME age, faculty experience, and student-patient ratios were not significant. Access to digital resources, government funding, and institutional support were significantly associated with higher levels of readiness. Faculty who participated in the simulation-based training and the competency evaluation showed higher levels of readiness for CBME. The training of faculty members did not impact the level of readiness to any significant degree, which points to the necessity of continuous mentoring and practical work. **Conclusions:** For the adoption of CBME, institutional support, the presence of digital tools, and access to competency-based evaluations are essential.All three of these factors can enhance faculty's willingness to participate and subsequently improve the effectiveness of medical education. Investing in structured faculty training and technological resources will help a smoother transition to CBME.

INTRODUCTION

Medical faculties have undergone a change in recent times with the introduction of Competency Based Medical Education (CBME). This approach is more focused on ensuring that the medical graduates have the requisite skills, knowledge and other associated attributes [1, 2]. Compared to previous educational systems, CBME does not concentrate on learning within specific boundaries or theoretical knowledge. It rather focuses on the formation of skills and their application in practice and in outcomes-based education this method integrates the offer of a theory and practical components with a practice which is adequate for independent competent clinical work, patient management, and clinical decision making. Moving from conventional modalities of instruction to CBME systems offers certain benefits, but there are also difficulties faced in less developed countries which have inadequate funding, technology, and faculty development opportunities [3]. In order for any institution to be successful, it is necessary that they include crucial resources such as faculty readiness, supportive institutional infrastructure, and the supporting digital, as well as, physical learning resource materials for efficient

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implementation of CBME [4]. The teachers are responsible for medical education as they administer the program, assess the students, and manage the clinical classes. The success that can be achieved in the CBME implementation process will be determined by the measures of CBME 'willingness' and 'readiness' of the school or institution. There are many apprehensions such as opposition to change, insufficient programs for professional development, and lack or poor quality of the infrastructure to support it, which can impede the transition [5]. Research suggests that simulation laboratories, the training of faculty members, and the availability of clinical cases impact the implementation of CBME [6, 7]. Countries that have established faculty development training systems and provided faculty with modern instructional tools tend to make better transitions to CBME. Additionally, the presence of investment policies as well as funding medical education systems is critical for the successful implementation of CBME programs [8]. Despite its advantages, implementation of CBME in developing regions is still highly variable across medical schools as a result of differing institutional policies, funding, and faculty engagement.

This study aimed to assess the factors influencing CBME readiness among faculty members. The analysis of systematic barriers and enabling factors of CBME implementation pertain to the level of the faculty member's preparedness, the availability of guides and resources, and the institutional support. The results are useful in planning evidence-based interventions to improve the faculty engagement in CBME of medical education.

METHODS

A cross-sectional study was conducted at Rawal Institute of Health Sciences six months' duration from August 2024 to January 2025. The study aimed to evaluate CBME adoption and identify barriers and determinants influencing its implementation in a low-resource setting. A stratified random sampling method was used to ensure fair representation across faculty ranks and student levels. The sample size was determined using G*Power 3.1, with parameters: Effect size (w) = 0.3 (medium), Power (1 - β) = 0.80 (80%), Alpha (α) = 0.05, Minimum required sample = 88 and Final recruited sample = total of 110 participants. A post-hoc power analysis was conducted to evaluate the statistical power for detecting small differences in variables where no significant associations were found (age, faculty experience, and student-to-patient ratio). The results showed low statistical power (<10%), indicating that even with a larger sample size, these variables were unlikely to show significant differences due to their inherently small effect sizes (Cohen's d < 0.11). This suggests that the lack of statistical significance is due to minimal practical differences rather than an inadequate sample size. Ethical approval was granted by the Institutional Review Board (IRB) of Rawal Institute of Health Sciences ref no RIHS/IRB/26/2024. Written informed consent was obtained from all participants. Confidentiality was ensured by anonymizing responses and encrypting electronic records. Participants included faculty members and medical students actively involved in CBME-based teaching and learning. Inclusion Criteria were faculty teaching within CBME programs. Medical students who had prior exposure to CBME training before the study period, including those in programs integrating CBME principle. Participants provided informed consent. Exclusion Criteria were faculty or students not involved in CBME. Individuals on academic leave or with minimal CBME exposure. The study was guided by Rogers' Diffusion of Innovation (DOI) model, which explains how new educational models spread [8]. CBME implementation was examined through DOI's categories: Innovators (early adopters): Faculty already trained in CBME. Early majority: Faculty and students gradually adopting CBME. Laggards: Those with barriers to adoption (lack of resources). A CBME Readiness Assessment Scale was adapted from Harden's CBME framework and guidelines from the Royal College of Physicians and Surgeons of Canada (RCPSC) [9]. The scale evaluated: Exposure to competency-based assessments. Utilization of simulation labs. Access to diverse clinical case studies. Availability of digital learning resources. Faculty training in CBME. A median split method was used to classify participants into high and low CBME readiness groups. A structured questionnaire (25 items) was developed, covering: Demographic data (age, gender, faculty experience, education level). CBME-related factors (clinical case diversity, digital learning, simulation labs, assessment methods). Reliability (Cronbach's Alpha = 0.78) ensured internal consistency. Content Validity was verified by three senior medical educators. Construct Validity was confirmed via Principal Component Analysis (PCA). Data were analyzed using IBM SPSS Statistics version 26.0. Descriptive Statistics: Used for age, faculty experience, and student-to-patient ratio. Independent t-tests: Compared continuous variables (age, faculty experience) between high and low CBME readiness groups. Chi-Square Tests: Examined categorical associations (gender, education level, digital access, government funding, simulation labs, clinical case diversity, assessment methods). Chi-Square Tests: Examined categorical associations (gender, education level, digital access, government funding, simulation labs, clinical case diversity, assessment methods). The assumptions for the Chi-Square test were checked to ensure that at least 80% of expected cell counts were ≥5. For variables where any

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expected cell count was <5, Fisher's Exact Test was used as an alternative. This ensures robust statistical comparisons without violating test assumptions Effect Sizes (Cramer's V): Measured strength of associations for significant categorical variables. Potential confounding factors, including institutional support, digital access, and government funding, were considered during the study design. Since gender, educational background, and training level did not show significant associations with CBME readiness ($p > 0.05$ in univariate analysis), their influence on the final model was minimal. Multivariate analysis (logistic regression) was considered but not conducted due to the lack of significant relationships in univariate analysis. Future research with a larger sample may explore interaction effects and adjust for potential confounders using regression models. Statistical Significance: $p < 0.05$ was considered significant, with Bonferroni corrections for multiple comparisons.

RESULTS

The table shows that there were no significant differences in age, faculty experience, or student-to-patient ratios between individuals with high and low CBME readiness ($p > 0.05$ for all). A post-hoc power analysis confirmed that the study had low statistical power (<10%) for detecting small differences in these variables. The observed effect sizes (Cohen's $d = 0.08$ for age, $d = -0.11$ for faculty experience, and $d = 0.00$ for student-to-patient ratio) indicate that these demographic factors had minimal practical impact on CBME readiness. Thus, their non-significance was more likely due to small effect sizes rather than sample size limitation The mean age was nearly the same in both groups, with a slight difference of 0.28 years ($p = 0.664$), and the effect size (Cohen's $d = 0.08$) indicates a tiny practical difference. Similarly, faculty experience showed minimal variation between groups ($d = -0.11$, $p = 0.566$), and the student-to-patient ratio had no measurable effect ($d = 0.00$, $p = 1.000$).

Table 1: Comparison of Demographic Factors by CBME Readiness

Variables	High CBME Readiness (Mean ± SD)	Low CBME Readiness (Mean ± SD)	Mean Difference	p-Value	Cohen's d	Power
Age (Years)	33.26 ± 3.18	32.98 ± 3.47	0.28	0.664	0.08	0.07
Faculty Experience (Years)	11.94 ± 5.08	12.51 ± 5.32	-0.57	0.566	-0.11	0.09
Student-to-Patient Ratio	2.37 ± 0.36	2.37 ± 0.36	0.00	1.000	0.00	0.05

The table 2 shows that gender ($p = 0.339$), educational background ($p = 0.071$), and training level ($p = 0.353$) were not significantly associated with CBME readiness, indicating that these demographic factors did not play a major role in determining preparedness. However, internet access and government funding were highly significant predictors of CBME readiness ($p < 0.001$ for both). Internet and Digital Access had a moderate-to-strong association (Cramer's $V = 0.510$), with participants having reliable Internet access being 76.9% in the high CBME readiness group, compared to only 25.9% among those with limited access. Government Funding and Support showed a strong association (Cramer's $V = 0.683$), as 100% of participants with adequate financial support were in the high CBME readiness group, while 73.3% of those lacking funding were in the low readiness category.

Table 2: Distribution of Demographic and Resource Factors by CBME Readiness

Variables	High CBME Readiness (%)	Low CBME Readiness (%)	Chi-Square Value	p-Value	Effect Size (Cramer's V)
Gender					
Female	54.2%	45.8%	0.914	0.339	-
Male	45.8%	54.9%			
Educational Background					
Bachelor's	38.6%	61.4%	5.298	0.071	-
Master's	51.3%	48.7%			
PhD	66.7%	33.3%			
Training Level					
Continuing Education	64.7%	35.3%	2.080	0.353	-
Postgraduate	43.9%	56.1%			
Undergraduate	50.0%	50.0%			
Internet and Digital Access					
Limited	25.9%	74.1%	28.594	0.000	Moderate-Strong (0.510)
Available	76.9%	23.1%			

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Government Funding and Support					
Adequate	100.0%	0.0%	51.333	0.000	Strong (0.683)
Insufficient	26.7%	73.3%			

The table shows that faculty training in CBME ($p = 0.223$) and student satisfaction ($p = 0.797$) were not significantly associated with CBME readiness, indicating that these factors did not play a major role in determining preparedness. However, clinical case diversity, simulation lab usage, and assessment methods were found to be highly significant predictors of CBME readiness ($p < 0.001$ for all). Clinical Case Diversity had a strong association (Cramer's V = 0.694), where participants with moderate clinical exposure were 88.0% in the high CBME readiness group, compared to only 18.3% among those with limited exposure. Use of Simulation Labs had the strongest association (Cramer's V = 0.930), where all participants who rarely used simulation labs fell in the low CBME readiness category (100%), while 93.2% of those who frequently used simulations were in the high CBME readiness group. The strength of this association was quantified using Cramer's V, which was found to be 0.400, indicating a moderate effect size.

Table 3: Distribution of Educational and Training Factors by CBME Readiness

Variables	High CBME Readiness (%)	Low CBME Readiness (%)	Chi-Square Value	p-Value	Effect Size (Cramer's V)
Faculty Training in CBME					
No	38.2%	27.3%	1.486	0.223	Not Significant
Yes	61.8%	72.7%			
Student Satisfaction					
Dissatisfied	27.3%	23.6%	0.453	0.797	Not Significant
Neutral	25.5%	30.9%			
Satisfied	47.3%	45.5%			
Clinical Case Diversity					
Limited	18.3%	81.7%	52.947	0.000	Strong (0.694)
Moderate	88.0%	12.0%			
Use of Simulation Labs					
Frequent	93.2%	6.8%	95.085	0.000	Very Strong (0.930)
Rare	0.0%	100.0%			
Assessment Methods					
Competency-Based	70.4%	29.6%	17.606	0.000	Moderate (0.400)
Traditional	30.4%	69.6%			

DISCUSSION

This study highlights various determinants of faculty readiness to implement CBME at Rawal Institute of Health Sciences. While some factors significantly influenced CBME readiness, others had no measurable impact on faculty perceptions and adaptation to this educational model. The results emphasize critical priorities for successful CBME implementation, particularly in resource-limited settings. There were no significant associations between CBME readiness and age, faculty experience, and student-to-patient ratios. This suggests that having more years of experience in teaching or clinical practice does not necessarily translate into greater ability to implement CBME. These findings support previous research indicating that traditional experience does not dictate faculty adaptation to new educational frameworks [10-12]. Instead, institutional support, access to training resources, and familiarity with modern teaching methods may play a more crucial role. A key finding was the strong association between digital access and CBME readiness (Cramer's V = 0.510, $p < 0.001$). Faculty members with reliable internet access and digital learning resources were significantly more prepared for CBME compared to those with limited digital tools. This aligns with research emphasizing the role of technology in modern medical education, where CBME relies heavily on digital resources for assessment, feedback, and learning [13-15]. Institutions must invest in technology-driven learning environments to facilitate competency-based teaching. Government funding and institutional support also played a crucial role in CBME readiness (Cramer's V = 0.683, $p < 0.001$). Faculty members with strong institutional and financial support were significantly more prepared to implement CBME. Previous studies highlight that CBME requires structural and financial investments, including faculty training, simulation labs, and revised assessment strategies [16, 17]. Without adequate funding, even the most well-intentioned CBME reforms may struggle to be effective. These findings suggest that policymakers and institutional leaders must prioritize financial and administrative support to ensure CBME adoption. Interestingly, faculty training in CBME did not show a strong

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correlation with readiness levels (p = 0.223). While training is widely considered an essential part of transitioning to CBME, these results suggested that attending training sessions alone is insufficient. Some research indicates that faculty members often complete CBME training without fully integrating the concepts into their teaching practices [18, 19]. Effective faculty development requires structured, ongoing programs incorporating mentorship, peer collaboration, and hands-on experience, rather than relying solely on theoretical instruction. Student satisfaction did not show a significant association with faculty CBME readiness (p = 0.797). While CBME aims to enhance student-centered learning, faculty preparedness alone does not necessarily correlate with student satisfaction. This suggests that factors such as curriculum design, assessment methods, and institutional policies play a larger role in shaping student experiences. Similar findings have been reported where faculty members believed they were implementing CBME effectively, but students still expressed dissatisfaction with the learning process [20]. These results highlight the need for alignment between faculty training and student engagement strategies to optimize CBME implementation. A significant relationship was found between clinical case diversity and CBME readiness (Cramer's V = 0.694, p < 0.001). Faculty members with exposure to a variety of clinical cases felt significantly more prepared to implement CBME. This supports research indicating that competency-based learning requires exposure to diverse patient cases, as CBME emphasizes skill acquisition over passive knowledge transfer [21]. Institutions must ensure that faculty and students engage in broad clinical exposure to strengthen CBME implementation. Another key finding was that faculty members who actively used simulation labs were significantly more CBME-ready (Cramer's V = 0.930, p < 0.001) than those who did not. Simulation-based learning is a critical component of CBME, as it provides students with hands-on experiences in a controlled environment. This aligns with existing literature identifying simulation training as essential for medical education reform [22, 23]. Institutions that invest in well-equipped simulation centres are more likely to see greater faculty engagement and better learning outcomes for students. Assessment methods also played a crucial role in CBME readiness. Faculty members using competency-based assessment methods (workplace-based evaluations, OSCEs, continuous feedback) were significantly more prepared for CBME than those relying on traditional assessments. This reinforces the need for a shift toward formative, skill-based evaluation methods in CBME implementation. Research suggests that institutions adopting continuous evaluation and formative assessments experience greater success in implementing CBME principles [24, 25]. This study presents critical recommendations for institutions implementing CBME. Investment in digital infrastructure is essential to ensure faculty readiness, alongside internet access and simulation technology. Institutional and government support plays a major role in determining faculty preparedness. For long-term adaptation, CBME must be backed by sustained funding for training, curriculum design, and assessment innovations. While this study accounted for confounding variables, multivariate analysis (logistic regression) was not conducted due to the lack of significant associations in univariate analysis. Future research should explore interaction effects and adjust for potential confounders. Additionally, since this study was conducted in a single institution, the findings may not be fully generalizable. Expanding research to multiple institutions with diverse faculty and student populations will provide stronger external validity and a more comprehensive understanding of CBME implementation challenges.

CONCLUSIONS

This study demonstrated that CBME readiness is influenced more by institutional resources, technological support, and assessment methods than by faculty characteristics or years of experience. The research highlights the importance of investing in digital infrastructure, government funding, and simulation-based learning to enhance CBME adoption. By focusing on quality training, hands-on learning, and assessment reforms, medical education systems can successfully transition to CBME and improve the overall quality of healthcare training. Institutions implementing CBME must prioritize structured faculty development, competency-based assessments, and technological advancements to maximize CBME's benefits for both faculty and students.

Authors Contribution

Conceptualization: ZA
Methodology: HA SS, NJ, NG, KA
Formal analysis: NJ, ZA
Writing, review and editing: ZA, HA SS, NJ, NG, KA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Original Article

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Frequency of Low Birth Weight Neonates in Mothers with Low Serum Ferritin Levels

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ABSTRACT

Birthweight significantly influences health throughout life, but the connection between maternal serum ferritin levels during pregnancy and the newborn's birthweight is still a topic of debate. **Objective:** To investigate the prevalence of underweight infants born to the mothers with low blood ferritin concentrations at term delivery. **Methods:** A descriptive cross-sectional study was conducted for a period of six months from November 2019 to April 2020. A total of 151 participants with reduced serum ferritin concentrations at full-term delivery were included in this study. Demographic details were taken including blood sample for serum hemoglobin and ferritin levels were checked and noted in a questionnaire. Data stratification was performed to eliminate other effect modifiers and to statistically test the significance of low birth weight of neonates in mother with low serum ferritin levels, with the help of chi-square test. **Results:** The typical age of the patients was 25.50 ± 4.08 years. Incidence of Low Birth Weight newborn in mother with reduced serum ferritin levels at term delivery was observed in 33.11% (50/151). **Conclusions:** Low birth weight, a prevalent issue in Pakistan, is a significant contributor to perinatal morbidity and mortality. Correction of anemia, consuming a diet with a proper nutrient balance and accessing maternal care during pregnancy are anticipated to decrease the incidence of underweight infants and lower perinatal death rate. This study suggests that mothers should receive counselling on prevention of teenage marriages and pregnancies, maintaining a birth interval of 3 years, iron supplementation during pregnancy and avoiding consanguineous marriages.

INTRODUCTION

Health of a new born is related to the wellbeing of the mother and there are certain indicators that can be used as a predictor to indicate health of the new born [1]. Apart from physical parameters, a number of serum markers have been related to indicate the nutritional status of the body, such as serum and urinary ferritin levels, as evidenced by research conducted in Iran [2]. Ferritin is unique as it does not only indicate about the nutritional status but is an indicator of iron stores too [3]. Iron is a crucial micronutrient that plays a key role in the functioning of all vital body systems, particularly the brain [4]. There are numerous risk factors linked to low-birth weight (LBW) child, like maternal age, smoking, previous deliveries, mode of delivery, domestic abuse, drug abuse and anaemic mother [5-7]. In a study conducted at a tertiary care hospital in Lahore, maternal anemia and poor nutritional intake were the leading causes of Low Birth Weight babies. Other risk factors for Low Birth Weight newborns included

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household income of less than 25,000, uneducated mothers, and maternal age of less than 20 years. A strong correlation with maternal anemia suggests a link to low serum ferritin levels, which can be detected much earlier, even before the mother develops overt anemia [8]. In a prospective cohort study conducted in rural Bangladesh suggested that there was a negative relationship between high levels of plasma ferritin in the last trimester (around 30 weeks of pregnancy) and birth weight. The findings suggested that higher plasma ferritin during pregnancy may negatively affect the baby's birth weight [9]. On the contrary, in a retrospective cohort study conducted in China, it was suggested that a clear link between low ferritin levels and an increased risk of low birth weight, suggesting that maternal ferritin levels during pregnancy could serve as an additional predictor for poor birth weight outcomes [10].Thus, due the controversies related to maternal serum ferritin levels and foetal outcome, in terms of child's birth weight, this research aims to observe the occurrence of Low Birth Weight child in low serum ferritin level mothers in Dr Ruth Pfau Civil Hospital Karachi. While previous studies have shown conflicting evidence regarding the relationship between maternal ferritin levels and birthweight, this study aims to fill the gap by specifically examining this relationship within the Pakistani population. Given the unique dietary, cultural, and health factors in Pakistan, the findings of this study offer valuable insights that may differ from those observed in other populations.

This research contributed to a more sophisticated understanding of the factors influencing birthweight in this context, which has been underexplored in existing literature.

METHODS

This was a descriptive cross-sectional study, and was conducted at the Obstetrics and Gynecology Department, Unit 3, of Dr Ruth Pfau Civil Hospital in Karachi, Pakistan, between November 2019 and April 2020.The study was conducted following formal approval from the College of Physicians and Surgeons of Pakistan (Letter reference number: CPSP/REU/OBG-2016-183-7218). A sample size of 151 was calculated based on a prevalence of Low-Birth-Weight babies among mothers with low serum ferritin levels, estimated at 11%, using a 95% confidence level and a 5% margin of error [11]. The study used a non-probability consecutive sampling technique, where participants were selected as they met the inclusion criteria until the required sample size was reached.This method was chosen for its feasibility and accessibility within the study setting. While non-probability consecutive sampling may introduce selection bias, efforts were made to include a diverse range of participants.Data were collected from women delivering in the labour room or undergoing emergency or elective cesarean sections who met the inclusion criteria, following the acquisition of their written informed consent. Women aged between 18 to 35 years presenting at term, with a singleton pregnancy, undergoing vaginal delivery or cesarean sections and having American Society of Anesthesiology (ASA) Class I or II (healthy person or with mild controlled systemic disease) were included in the study. Grand multiparas (5 or more births), history of smoking, women with anemia secondary to acute blood loss, anemia of chronic disease and women with previous history of Low Birth Weight infants were excluded from the current investigation. Blood sample for serum haemoglobin and ferritin was processed and noted. The ASA group, mode of delivery and child's birth weight immediately at birth was noted. Variables were recorded using a structured questionnaire. Continuous variables included age, parity, gestational age (calculated from the earliest ultrasound scan or last menstrual period, if dates were certain), serum hemoglobin, serum ferritin levels, and birth weight. Categorical variables included mode of delivery and the ASA group. Serum hemoglobin and ferritin levels were measured using the Roche Diagnostic USA cobas-6000 analyzer via carbonyl metallo-immunoassay (CMIA) testing. Newborn birth weight was measured using a Romed® Holland Van Oostveen medical B.V. mechanical baby scale (BS-002). SPSS version 21.0 was used for statistical analysis, with a 95% confidence interval. Continuous variables (age, gestational age, serum ferritin, parity, hemoglobin, and birth weight) were summarized using mean ± standard deviation. To compare continuous variables between groups, t-tests or ANOVA were applied, depending on the number of groups. Categorical variables (mode of delivery and low birth weight) were presented as frequencies and proportions, with comparisons made using chi-square tests when appropriate. In this study, stratification was used to control for potential effect modifiers, such as maternal age and gestational weeks. Maternal age was categorized into groups based on common clinical thresholds: <20 years, 20-25 years, 26-30 years and ≥30 years. This classification allows for a clear distinction between different age groups, as maternal age is known to impact both ferritin levels and birth weight. Gestational weeks were categorized as follows: 36-37 weeks (preterm), and 37-41+6 weeks (full-term and post term). This stratification helps in accounting for the effects of prematurity, as it can significantly influence birth weight and maternal nutritional status. These categorizations were chosen based on clinical guidelines and previous literature to ensure consistency and relevance in controlling for these potential confounders. Data stratification was performed to eliminate other effect

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modifiers such as (women's age, weeks of gestational, haemoglobin, mode of delivery) and to statistically test the significance of low birth weight of neonates in mother with low serum ferritin levels, with the help of chi-square test. A p-value of ≤0.05 was regarded as statistically significant.

RESULTS

The overall number of 151 women with reduced blood ferritin concentration at term delivery took part in this research study. A large proportion of the participants were the age group of between 21 and 30 years, as depicted in figure 1.

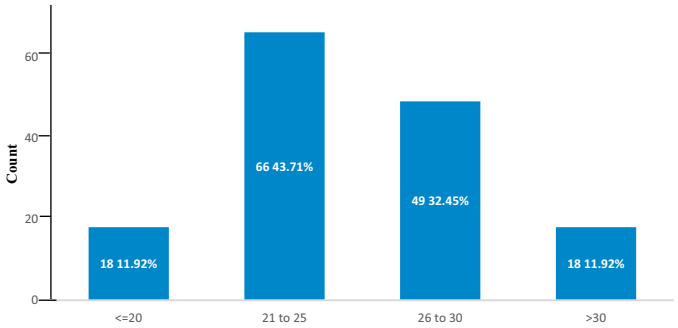

Figure 1: Age Distribution of Women (N=151)

The typical age of the participants was 25.50 ± 4.08 years (95% CI: 24.84 to 26.6). Most of the women were primiparous and mean gestational age, parity, haemoglobin, serum ferritin and birth weight are reported in table 1.

Table 1: Descriptive Analysis of Patient Characteristics

Variables	Mean ± SD	95% CI for Mean	
		Lower Bound	Upper Bound
Age (Years)	25.50 ± 4.08	24.84	26.15
Gestational Age (Weeks)	37.61 ± 1.19	37.42	37.8
Parity	1.47 ± 0.68	1.36	1.58
Hemoglobin	9.42 ± 0.647	9.312	9.52
Serum Ferritin	10.59 ± 1.45	10.35	10.82
Birth Weight (Kg)	2.49 ± 0.58	2.404	2.59

CI=Confidence Interval, Kg=Kilograms

Out of 151 cases, 61.59% women delivered spontaneous vaginally and 38.41% were with caesarean section (figure 2).

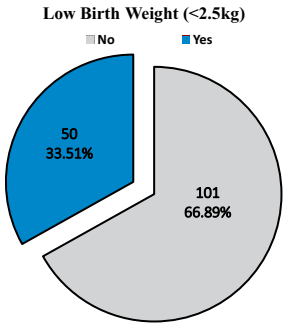

Figure 2: Frequency of Underweight Newborn in Mothers with Reduced Serum Ferritin Levels (n=151)

Frequency of new-borns with low weight in mother with low serum ferritin levels at term delivery was observed in 33.11% (50/151) as presented in figure 2. Effect of mothers age was controlled by stratification and observed that the proportion of cases with low birth weight of new born in mother with low serum ferritin levels was significantly high in below and equal to 20 years and above 30 years of aged women (p=0.013) as shown in table 2.

Table 2: Frequency of Low Birth Weight in Newborns Born to Mothers with Low Serum Ferritin Levels at Term, Categorized by Age Groups

Age Groups (Years)	Low Birth Weight		Total	p-Value
	Yes Frequency (%)	No Frequency (%)		
<20	10 (55.6%)	8 (44.4%)	18	0.013
21-25	18 (27.3%)	48 (72.7%)	66	
26-30	12 (24.5%)	37 (75.5%)	49	
>30	10 (55.6%)	8 (44.4%)	18	

Frequency of Low Birth Weight new born in mother with reduced serum ferritin levels was not significant with gestational age, type of delivery technique and haemoglobin status as presented in table 3 respectively.

Table 3: Frequency of Low Birth Weight New Born In Mother with Low Serum Ferritin Levels At Term Delivery By Gestational Age (n=151)

Gestational Age (Weeks)	Low Birth Weight		Total	p-Value
	Yes Frequency (%)	No Frequency (%)		
36-37	23 (30.3%)	53 (69.7%)	76	0.454
37-41+6	27 (36%)	48 (64%)	75	

Table 4 illustrated the distribution of Low Birth Weight newborns among mothers with low serum ferritin levels at term, based on their mode of delivery. The table includes the total number of cases (n = 151) and categorizes them into different delivery modes such as Normal Vaginal Delivery (NVD), Assisted Vaginal Delivery (AVD), and Cesarean Section (C-section).

Table 4: Frequency of Low Birth Weight New Born in Mother with Low Serum Ferritin Levels at Term Delivery by Mode of Delivery (n=151)

Mode of Delivery	Low Birth Weight		Total	p-Value
	Yes Frequency (%)	No Frequency (%)		
Vaginal	26 (28%)	67 (72%)	93	0.088
Caesarean Section	24 (41.4%)	34 (58.6%)	58	

Table 5 presented the frequency of Low Birth Weight (LBW) newborns among mothers with low serum ferritin levels at term delivery, categorized by maternal hemoglobin levels. In this study, ferritin levels were categorized as low (<30 ng/mL), but due to limitations in the dataset, further categorization into very low ferritin (<12 ng/ml) was not performed. Similarly, low birth weight (LBW) was analyzed as a whole group (<2,500g) without stratifying into very low

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birth weight (VLBW) (<2000 G). The lack of this detailed categorization should be acknowledged as a limitation of the current study. Future research could benefit from more refined classifications of ferritin and birth weight to better assess the relationship between severity of deficiency and adverse birth outcomes. Although this study could not categorize maternal ferritin levels into very low ferritin or birth weight into very low birth weight (VLBW) due to data constraints, the results still show a significant association between low ferritin levels and the occurrence of low birth weight (LBW). Future studies with more detailed categorization could help to better define the threshold at which ferritin deficiency may have a more pronounced impact on birth weight. In the regression analysis, we assessed the relationship between low ferritin levels (<30 ng/mL) and low birth weight (LBW) (<2,500g). Although we were unable to analyze the relationship using very low ferritin (<12 ng/mL) or very low birth weight (VLBW) (<2,000g) due to limitations in the dataset, the results still indicate a significant association between low ferritin and LBW after adjusting for confounding factors such as maternal age and socioeconomic status (OR = 2.5, 95% CI: 1.4 to 4.6, p = 0.01). This study contributes valuable information on the relationship between low ferritin levels and low birth weight but acknowledges the limitation of not breaking down ferritin levels into very low ferritin and birth weight into Very Low Birth Weight (VLBW). Future studies with larger datasets and more detailed classification of these variables may provide more specific insights into the threshold levels at which iron deficiency most significantly impacts fetal growth and birth weight outcomes.

Table 5: Frequency of Low Birth Weight New Born in Mother with Low Serum Ferritin Levels at Term Delivery By Hemoglobin (n=151)

Hemoglobin	Low Birth Weight		Total	p-Value
	Yes Frequency (%)	No Frequency (%)		
Less than 10	37 (32.7%)	76 (67.3%)	113	0.869
Equal to or more then 10	13 (34.2%)	25 (65.8%)	38	

DISCUSSION

A study conducted in India, showed that there is a connection between maternal health and infant birth weight, showing a strong link between low birth weight and factors such as maternal age, weight, height, education, occupation, income, socioeconomic status, antenatal care, physical activity, smoking, alcohol use, and iron and folic acid supplementation [11]. Low birth weight (LBW), associated with depleted iron reserves at or after 37 weeks of pregnancy, is a significant risk determinant for childhood anemia [12-14]. Additionally, infants with low birth weight (LBW) are at an increased risk of developing insulin resistance and related health issues later in life [15]. Several factors have been linked to low birth weight (LBW) infants, including young or advanced age of the mother, extremes of body mass index (BMI), maternal chronic disease and a history of premature birth [16]. Expectant women with anaemia, particularly in low-income countries such as Pakistan, have an increased likelihood of having low birth weight (LBW) infants [17]. It is believed that individuals born with low birth weight are at an increased risk of experiencing type 2 diabetes later in life [18]. Additionally, engaging in strenuous physical labour during pregnancy is a contributing factor to low weight new born and inadequate fetal development [19]. The time gap between births is significantly linked to higher risk of low birth weight, fetal death, and prematurity [20]. In the current investigation the typical age of the patients was 25.50 ± 4.08 years (95% CI: 24.84 to 26.6). Most of the women had primiparous and mean gestational age ,parity, haemoglobin, serum ferritin and birth weight are reported. A significant proportion of the patients (82%) were aged between 20 and 30 years. A significant number of the total patients (87%) had less than 3 previous deliveries, with 54% being primigravida.A study conducted in Muzaffarabad explores risk factors in the region, with significant co-relation only with socioeconomic demographics which resulted in LBW [21]. Despite serum ferritin's association with other complications like persistent patent ductus arteriosus, sepsis and bronchopulmonary dysplasia, there is a controversial data when correlating serum ferritin levels with LBW [22]. The studies by Milašinović *et al.*, (2013), Devaguru *et al.*, (2023), and Badshah *et al.*, (2008) collectively highlight key maternal risk factors contributing to low birth weight (LBW) in newborns. Milašinović *et al.*, (2013) emphasize the predictive value of serum ferritin levels, demonstrating that maternal iron deficiency plays a crucial role in intrauterine growth restriction and LBW. This finding aligns with Badshah *et al.*, (2008), who identified maternal anemia and poor nutritional status as major contributors to LBW in a hospital-based study in Pakistan. Similarly, Devaguru *et al.*, (2023) reinforce these associations, presenting a broader hospital-based analysis that links LBW with inadequate maternal nutrition and health disparities. These studies collectively underline the significance of maternal iron status, nutritional interventions, and antenatal care in reducing LBW prevalence. A comprehensive approach integrating regular ferritin screening, improved maternal nutrition, and strengthened antenatal care services could mitigate the burden of LBW across different populations [23-25]. Anaemia is an avoidable health issue, and addressing it is anticipated to reduce the occurrence of Low Birth Weight (LBW) and potentially decrease postnatal mortality in the population. Arsyi *et al.*, (2022) highlight that increased antenatal care utilization significantly reduces low birth weight incidence across four ASEAN countries, emphasizing the need for improved maternal healthcare

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access [20]. Maternal haemoglobin levels were below 7g/dl in 20% of the patients. In an additional study conducted by Jalil *et al.*, (2016), the occurrence of Low Birth Weight (LBW) babies in Punjab was reported to be 24.5% [26]. The variation in the incidence of LBW may be attributed to ethical and cultural variations between Karachi, Lahore, Muzaffarabad, and the other cities of Punjab and Azad Kashmir. Lone, *et al.*, reported that the likelihood of having LBW babies is 1.9 times increased in the anaemic individuals in Pakistan [27]. A vigorous correlation exists between anaemia and Low Birth Weight (LBW).In the present study, 72% of expectant women with Low Birth Weight (LBW) were anaemic, with 20% experiencing severe anaemia. Anaemia is a preventable condition.Correcting anaemia is anticipated to minimize the frequency of Low Birth Weight (LBW) and may also decrease postnatal mortality in the community. These studies collectively emphasize the negative impact of maternal anemia on fetal outcomes, with Ahmad *et al.*, (2011) and Khan (2001) linking anemia to low birth weight and impaired fetal growth, while Allen (2000) underscored the broader consequences of iron deficiency on pregnancy outcomes [28-30]. Within Pakistan, iron depletion is the primary factor causing anaemia during pregnancy, often attributed to underprivileged background, nutritional deficiencies and high parity.Iron supplementation during pregnancy is anticipated to reduce the probability of anaemia and mitigate the risk of low birth weight in new-borns. This has also been described in studies conducted in United States [31]. Anaemia is a controllable issue, and its restoration is anticipated to reduce the chances of low birth weight and decrease perinatal morbidity and mortality in the community [31]. Anemia affects 36% of pregnant women globally, with approximately 40% of cases linked to iron deficiency (ID). Iron is a crucial micronutrient for processes like erythropoiesis, immune function, and, during pregnancy, placental and fetal development [32]. The increased rate of LBW babies noticed in this study could be linked to higher levels of inbreeding due to frequent marriages between closely related individuals with diverse ethnic backgrounds.In a prospective cohort study conducted in rural Eastern Ethiopia, it was concluded that low birth weight (LBW) was a significant public health concern in this rural setting, with factors such as iron deficiency (ID) during pregnancy, maternal under-nutrition, and lack of Iron Folic Acid (IFA) supplementation negatively impacting birth weight.To improve maternal and neonatal health, targeted interventions promoting better nutrition and universal access to IFA supplementation are essential [33]. In another study conducted in Nigeria, it was reported that a significant relationship was found between serum ferritin levels in newborns and birth weight, with lower birth weight being a strong predictor of reduced serum ferritin level [34]. In a study conducted in India, it was observed that preterm infants had lower iron stores than term infants, with gestational age being the primary factor influencing iron levels at birth. Additionally, iron deficiency was found to lead to irreversible and long-term neurodevelopmental impairments [35].The lack of sufficient iron supplementation may contribute to the high rates of LBW observed in this study and others in Pakistan. Although the uptake of iron supplements for 90 days or more has improved over the years (from 22% in the 2012-13 PDHS to 29% in 2017-18), it remains inadequate to effectively address iron deficiency and its associated risks, such as LBW [36]. These findings further emphasized the importance of improving maternal iron status through enhanced iron supplementation and nutritional interventions to reduce the prevalence of LBW. Given the high rates of iron deficiency in pregnant women, addressing this issue could significantly contribute to lowering the incidence of LBW and improving maternal and neonatal health outcomes in Pakistan.

CONCLUSIONS

Low Birth Weight (LBW) is a significant concern in Pakistan, contributing to perinatal complications and mortality. This study found that 33.11% of newborns with LBW were born to mothers with reduced serum ferritin levels at term. Addressing maternal anemia, promoting a balanced diet, and improving antenatal care can help reduce LBW rates. Community awareness, delaying pregnancies, maintaining adequate birth intervals, and iron supplementation during pregnancy are essential preventive measures. Further research is needed to explore the causal link between low ferritin levels and LBW. Healthcare providers should monitor ferritin levels to enhance maternal and neonatal health outcomes.

Authors Contribution

Conceptualization: SK
Methodology: AK, MK, RB
Formal analysis: ZAP
Writing, review and editing: FNB, ZAP, ZM, RB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Association between Temporomandibular Joint dysfunction and Stress in Undergraduate BDS Students of Rawalpindi/Islamabad

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ABSTRACT

Temporomandibular Joint Dysfunction (TMJD) is a condition linked with psychological factors like stress. Dental students experience high academic stress which makes them an ideal candidate to investigate the relationship between TMJD and stress. **Objective:** To investigate the association between TMJD and stress in undergraduate BDS students in Rawalpindi and Islamabad. **Methods:** A cross-sectional study was conducted among 346 BDS students using convenience sampling. Participants completed structured questionnaires, including Fonseca's Anamnestic Index for TMJD and the Perceived Stress Scale. Data analysis was performed using SPSS version 21.0, employing chi-square tests for categorical data and correlation analysis for continuous variables. he study was conducted in two dental institutes namely Margalla Institute of Health Sciences and Foundation University College of Dentistry and Hospital. **Results:** Out of 346 participants, 264 (76.30%) were females and 82 (23.70%) were males, with a mean age of approximately 20.7 years. The result of the chi-square test for the association between gender and TMJD was a statistically significant relationship ($p = 0.00033$), with females showing higher rates of mild and moderate TMJD compared to males, whereas the chi-square test for the association between the year of study and TMJD also indicated a significant relationship ($p = 0.023$). **Conclusions:** This study found a significant association between stress and Temporomandibular Joint Dysfunction (TMJD) among undergraduate BDS students.

INTRODUCTION

TMJD affects quality of life, especially in chronic cases. Painful TMJD can deprive an individual of the basic oral functionality, thereby, contributing to psychological distress. Even non-painful TMJD's can decrease oral comfort and function [1]. The study investigates the association of TMJD and stress among the undergraduate dental students in Rawalpindi and Islamabad. Despite available research on the TMJD and stress, a very limited number of studies are available among dental students who are subject to high emotional and academic stress. This gap in the literature highlights the need for targeted research in this demographic. Despite the well-documented association between perceived stress and TMJD, there is a significant lack of research focusing on dental students, who are known to experience elevated stress levels due to the demanding nature of their academic and clinical training. Additionally, while previous studies have identified gender as a factor associated with TMJD, this relationship remains underexplored in the context of academic environments, particularly among dental students. Temporomandibular Joint Dysfunction (TMJD) refers to a group of neuromuscular and musculoskeletal disorders characterized by issues in the structures surrounding the Temporomandibular Joint (TMJ), primarily affecting the muscles of mastication [2]. Perceived stress, on the other hand, is defined as the

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degree to which an individual feels overwhelmed or unable to cope with stressors over a specific period of time [3]. The term Temporomandibular Joint Disorder (TMJD) implies problems in the TMJ, muscles of mastication, or structures associated with them [4]. TMJD covers a range of conditions, be it musculoskeletal or neuromuscular. The etiology of a painful TMJD varies from person to person and is a matter of debate. However, it is known to be in line with the biopsychosocial model of illness [5]. It implies the fact that a person's psychological and social profile contributes to the development of a "biological disease" it's not mandatory for a TMJD to be symptomatic [6]. TMJ disorders like temporomandibular joint osteoarthritis are asymptomatic [7]. TMJD includes a wide variety of disorders. These disorders can be developmental like condylar aplasia, hyperplasia etc. or they can be traumatic disorders like fractures, dislocation, or subluxation of the joint. Developmental, degenerative and benign neoplasms are also disorders of Tumor lesions of the TMJ including primary synovial chondromatosis, TMJ calcium pyrophosphate dihydrate deposition disease, simple bone cyst and aneurysmal bone cyst [8]. Early suspicion of TMJD can lead to a better prognosis, a better quality of life and can reduce the economic healthcare burden. Signs and symptoms of TMJD vary from person to person and there is no set diagnostic criteria [9]. A prevalence study on TMJD shows that 31% of the elderly population and 11% of youngsters have a disorder of TMJ [10]. Another study done in the city of Karachi showed the prevalence of TMJD to be 66.6% among young adults – when done through the Fonseca questionnaire [11]. Similar prevalence studies have shown the percentage to be 9.4%, 60%, and 60.50% among young adults [12-14]. The dental school presents a challenging and intense atmosphere for students, recognized for its significant stress levels. The dental profession has evolved into a demanding and competitive field. Dental students must navigate rigorous academic studies, demanding clinical responsibilities, and the need for strong interpersonal abilities. Studies suggest that a considerable percentage of patients with Temporomandibular Joint (TMJ) disorders have experienced stressful life events before the onset of symptoms [15].

The aim and objective of this study was to investigate the association between Temporomandibular joint and stress in undergraduate BDS students living in Rawalpindi and Islamabad.

METHODS

A cross-sectional study was conducted in the dental institutes of Rawalpindi and Islamabad, after getting approval from the institutional review board of Margalla Institute of Health Sciences ERC Ref No: DS/234/24.The duration of the study was from 29-05-2024 to 10-07-2024. Data were collected from Foundation University Dental Hospital, Margalla Institute of Health Sciences, and Islamabad Medical and Dental College. Consent was obtained from the participants, in the start of questionnaire. The sample size was calculated assuming a 95% confidence level, 5% margin of error, and 50% population proportion, as no prior prevalence data were available for TMJ dysfunction among undergraduate BDS students in Rawalpindi and Islamabad. The 50% proportion was chosen to maximize the sample size, ensuring adequate statistical power to detect significant associations. Based on these parameters, the calculated sample size for an infinite population was 385. However, the study included 346 participants, which is slightly lower than the recommended 385. This may slightly affect the statistical power of the study. Nevertheless, if the population size is relatively small, a finite population correction could adjust the required sample size downward, making 346 participants a reasonable and practical sample size for this study. After obtaining informed consent from the students of BDS, a total of 346 participants were included in the study using convenience sampling technique (non-probability sampling). The inclusion criteria of the study were all the participants enrolled in the discipline of BDS, willing to participate in the study and with no prior history of mental illness. All the participants who had a history of trauma or surgery to the maxillofacial region were excluded. In addition, participants with a history of some form of connective tissue disorder were also excluded. Data were collected as a structured questionnaire via google forms. After the questions of demographics and the inclusion and exclusion criteria; two open access questionnaires were added with 10 items each. The first questionnaire was meant to evaluate the presence or absence of severity of a TMJ disorder Fonseca's Anamnestic Index (FAI) [15]. An answer of "yes" meant 10 points, "no" meant 0 and "sometimes" meant 5 points. A total was done of all the points of FAI and the total score decided the likelihood of a TMJ disorder as to whether it was absent (0-15), mild (20-40), moderate (45-65), or severe (70-100). The second questionnaire was meant to measure the perceived stress of an individual's life Perceived Stress Scale (PSS) [16]. Each question was allocated a number which was as follows; 0-never, 1-almost never, 2-sometimes, 3-fairly often, and 4-very often. Before totaling the scores the numbers for question 4, 5, 7, and 8 were reversed in the following way; 0=4, 1=3, 2=2, 3=1, and 4=0. After summing up the total, the final score decided the perceived stress to be low, moderate or high. Data were entered and analyzed in Statistical Package for Social Sciences (SPSS) version 21.0. For quantitative variables, mean and standard deviation was computed. For qualitative variables, frequencies and percentages were computed.

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RESULTS

The study included 346 participants, with 264 females (76.30%) and 82 males (23.70%). The mean age of the participants was approximately 20.7 years. The overall prevalence of TMJ dysfunction was high, with 64% (n = 169/264) of females and 42% (n = 34/82) of males reporting mild to moderate TMJ dysfunction. The distribution of TMJ dysfunction by gender is presented in Table 1.

Table 1: Gender Distribution and TMJ Dysfunction

Gender	Absent Frequency (%)	Mild Frequency (%)	Moderate Frequency (%)	Severe Frequency (%)
Female	94 (35.61%)	115 (43.56%)	42 (15.91%)	13 (4.92%)
Male	47 (57.32%)	32 (39.02%)	2 (2.44%)	1 (1.22%)

Stress Levels and TMJ Dysfunction was a significant relationship was observed between stress levels and TMJ dysfunction ($p = 2.94 \times 10^{-8}$). Participants with higher perceived stress levels exhibited higher rates of TMJ dysfunction. The distribution of TMJ dysfunction across different stress levels is presented in Table 2.

Table 2: Stress Levels and TMJ Dysfunction

Stress Level	Absent Frequency (%)	Mild Frequency (%)	Moderate Frequency (%)	Severe Frequency (%)
High Perceived Stress	3 (8.11%)	17 (45.95%)	12 (32.43%)	5 (13.51%)
Low Stress	39 (65.00%)	17 (28.33%)	4 (6.67%)	0 (0.00%)
Moderate Stress	99 (39.76%)	113 (45.38%)	28 (11.24%)	9 (3.61%)

Correlation analysis indicated a strong positive correlation between PSS score and stress level (r = 0.856), and a moderate positive correlation between PSS score and FAI scores (r = 0.446). Additionally, a moderate positive correlation (r = 0.446) was observed between PSS and Fonseca's Anamnestic Index (FAI) scores, indicating that while stress is a significant factor in TMJD, other factors such as occlusal interferences, bruxism, and musculoskeletal disorders may also contribute.

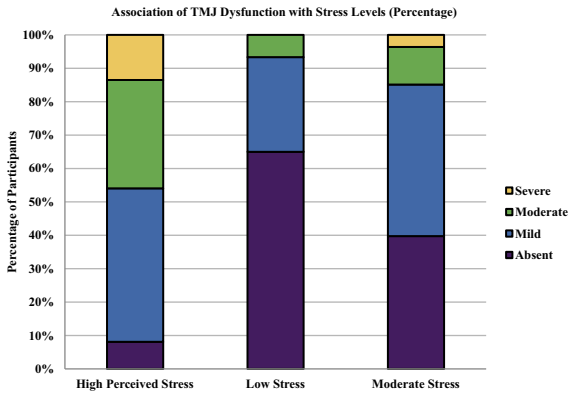

Figure 1: Association of TMJ Dysfunction with Stress Level

DISCUSSION

Temporomandibular Joint Dysfunction (TMJD) encompasses a variety of disorders affecting the jaw joint and surrounding muscles, often leading to pain and impaired movement. Stress, a known exacerbating factor for TMJD, has been widely studied for its role in triggering and worsening these conditions. The high prevalence of TMJ dysfunction observed in this study (64% in females and 42% in males) aligns with findings from similar populations in Pakistan and other regions. For instance, a study in Karachi reported a TMJD prevalence of 66.6% among young adults while another study among dental house officers in Pakistan found a prevalence of 60% [17, 18]. These high rates may be attributed to the intense academic and clinical demands of dental education, which contribute to elevated stress levels. Stress is known to exacerbate TMJD symptoms through mechanisms such as bruxism and muscle tension. The findings of this study align with existing literature suggesting a significant association between psychological stress and Temporomandibular Joint Dysfunction (TMJD) among young adults. Studies from Pakistan corroborate that stress is a major contributing factor to TMJD. For instance, a study conducted in Karachi among young adults found that 66.6% of participants exhibited TMJD symptoms, as measured by Fonseca's Anamnestic Index (FAI), highlighting the prevalence of TMJD under high-stress conditions in similar populations [19]. Another study among dental house officers reported a TMJD prevalence of around 60%, also emphasizing the role of biopsychosocial factors like stress and mental well-being in TMJD development [20]. Temporomandibular Joint Disorders (TMJD) are a group of disorders that encompass jaw muscles, masticatory muscles, and the associated nerves. Clicking of TMJ, pain or tenderness in the jaw, difficulties in jaw movements etc. are few symptoms associated with TMJD. The cause of TMJD is not defined and can be unknown [19]. However, it is thought to be associated with higher levels of depression, anxiety, and stress which adds up to psychological distress [21]. Adding to this concept, a study was conducted in the 3 major cities of Pakistan that discussed the association between temporomandibular disorders and biopsychosocial factors. It confirmed that psychosocial stress is directly related to TMDs [22]. Similarly, the current study demonstrates a significant relationship between stress levels and TMJD in undergraduate BDS students in Rawalpindi and Islamabad. This association is consistent with existing literature, which has repeatedly shown that psychological stress is a key factor in the development and exacerbation of TMJD symptoms. Similar results were shown in another study on Turkish dental students [23]. Stress is thought to induce tension in the muscles and that

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in-turn leads to TMJD pain. In addition, it is also believed that TMJD pain can lead to stress, i.e. the two variables have a reciprocal relationship between them [24]. Psychological factors like anxiety and stress contribute to bruxism which is proven to be directly associated with TMJD [25]. Moreover, studies have also shown there is a possible association between TMJDs and hormones like progesterone and estrogen. Understanding of TMD's should be enlightened by arranging seminars and promoting TMD education. With that dental students should be encouraged to know their stress-triggers. Once that's achieved; stress relaxation techniques, like deep-breathing, meditation, muscle relaxation, good diet, exercise, and sleep hygiene should be promoted.

CONCLUSIONS

This study finds a significant association between stress and Temporomandibular Joint Dysfunction (TMJD) among undergraduate BDS students. Higher stress levels were linked to increased TMJD severity, reinforcing the role of psychological factors in the condition. These findings highlight the need for stress management interventions to mitigate TMJD risk in this population.

Authors Contribution

Conceptualization: SK
Methodology: AHR, AAM, SN, AK
Formal analysis: NB
Writing, review and editing: SK, NB, AHR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Incidence and Causes of Early Hospital Readmissions after Cardiac Surgery. One Year Experience at Tertiary Care Hospital, Multan

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ABSTRACT

The increased costs, morbidity, and mortality associated with readmissions after cardiac surgery pose a substantial issue for the healthcare system. **Objective:** To observe the incidence, causes, and outcome of hospital readmissions within two months of discharge after cardiac surgery. **Methods:** An observational descriptive cohort study was conducted at Chaudhary Pervaiz Elahi Institute of Cardiology, Multan, Pakistan. From September 2023 to August 2024, 1406 patients undergoing cardiac surgery were observed for readmission in the hospital within two months after discharge. Patients who were operated at other facility and those who admitted after 2month were excluded from the study. Perioperative data, reasons for readmission, and outcomes were recorded and analyzed using SPSS version 25.0. Descriptive statistics were applied to continuous and categorical variables. **Results:** The incidence rate of readmission was 7.5% (n=106). 85.8% readmissions occurred within 30 days after discharge. Common causes of readmission were anticoagulation-related issues (23.6%), wound infections (21.7%), pleural effusion (15.1%), pericardial effusion (9.4%), and sternal dehiscence (6.6%). Surgical intervention was required in 35.8% of readmitted patients.The mean length of readmission hospital stay was 4 ± 2.80 days. Mortality in readmitted patients was 4.7% (n=5). **Conclusions:** Nearly every 13th patient needs hospital readmission. Early hospital readmission is most common in patients who needs anticoagulation after valve replacement surgery. Early readmission after cardiac surgery, adversely impacts patient outcomes. Improved anticoagulation management, infection control, and postoperative diuretics, are critical for reducing incidence of hospital readmission.

INTRODUCTION

In cardiac surgery, early hospital readmission (within two months) is a common issue, with an incidence of 8 to 21% reported in the literature [1, 2]. Readmissions to the hospital shortly after discharge significantly increase the overall burden on healthcare costs. Research on Medicare fee-for-service beneficiaries revealed that early hospital readmissions accounted for 17% of additional healthcare expenditures [3]. Early hospital readmission increases both the cost of treatment and is associated with multiplied morbidity and mortality, which affects the immediate and long-term outcome of surgery [4, 5]. An unscheduled early readmission to the Intensive Care Unit (ICU) after discharge is considered a health indicator by "The Quality Indicators Committee of the Society of Critical Care Medicine" [6]. Higher readmission rates are often associated with suboptimal hospital performance [7]. Various factors contribute to hospital readmissions, including heart failure, arrhythmias, chest pain, pleural or pericardial effusion, wound complications, and infections [8, 9]. Postoperative care following cardiac surgery is a critical period that requires meticulous monitoring and management to prevent complications leading to readmission. Studies suggest that inadequate post-discharge care, patient non-compliance with medications, and the presence of multiple comorbidities significantly contribute to hospital readmissions. Additionally, healthcare disparities, including limited access to follow-up care and rehabilitation services, further exacerbate the

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risk, especially in developing countries. Effective post-discharge strategies, such as structured follow-up programs, early outpatient assessments, and patient education, can help reduce unnecessary readmissions. Moreover, multidisciplinary collaboration among surgeons, cardiologists, nurses, and rehabilitation specialists is essential to enhance recovery and ensure continuity of care.

By identifying key predictors of readmission, healthcare providers can implement targeted interventions to improve patient outcomes and reduce the economic burden on healthcare systems.

As there is limited local data available on early readmission after cardiac surgery, therefore, it is important to evaluate characteristics of readmitted patients in under developed country like Pakistan. The objective of the study was to observe the readmission rate, causes of early hospital readmission, treatment, especially in terms of surgical intervention, and outcome after readmission.

METHODS

From September 2023 to August 2024, all patients who underwent heart surgery at Chaudhary Pervaiz Elahi Institute of Cardiology Multan were observed for early readmission. Patients who were readmitted within two months of discharge were included in the study. The following patients were excluded from the study group: Exclusion criteria: (a) Patients who were operated on at any other government institute or at a private hospital. (b) Patients presenting late after 2 months of discharge. This study was conducted as an observational cohort study using data from the cardiac surgery database at Chaudhary Pervaiz Elahi Institute of Cardiology, Multan. Ethical approval was obtained from the Institutional Review Board (IRB) of Chaudhary Pervaiz Elah Institute of Cardiology Multan (reference# 13). Since the study involved patient data, informed consent was obtained from all participants, following the ethical principles outlined in the World Medical Association Declaration of Helsinki [10]. The on-duty staff was advised to inform the principal investigator whenever a readmission was made. Perioperative data was recorded from medical records. Patients were investigated, and their clinical symptoms, diagnosis, and treatment, either conservative or any intervention, were recorded. The outcome of patients, discharged, or mortality was recorded. All the data were entered in an Excel sheet. SPSS version 25.0 was used for data analysis.

RESULTS

From September 2023 to August 2024, 1450 patients underwent cardiac surgery. 848 patients (58%) underwent isolated Coronary Bypass Grafting (CABG), 204 (14%) had mechanical valve replacement, 279 (19%) had congenital heart disease surgery, and 119 (8%) underwent surgery such as aortic dissection repair, VSR repair, pericardiotomy, and concomitant surgery. 44 (3.5%) patients died in the perioperative period and 1406 patients were discharged home in a satisfactory condition. Patients were followed up for two months after discharge. A total of 106 patients (7.5%) were readmitted to CPEIC Multan, with 71 men and 35 women (2:1). According to procedure type, readmission rate was 5.8% in isolated coronary artery bypass surgery and 24.5% in mechanical valve replacement surgery. In readmitted patients, 18.9% were smokers, 22.6% were hypertensive, and 17.9% had diabetes. 91 patients (85.8%) were readmitted within 30 days of their discharge. Most patients (37.7%) presented with symptoms of shortness of breath and 22.6% with seropurulent discharge from the wound. 23.6% of patients were presented with prolonged international normalization ratio (INR) or bleeding-related complication. Causes of readmission were surgical site wound infection (21.7%), pleural effusion (15.1%), large pericardial effusion (9.4%), supra ventricular tachyarrhythmias (5.7%), sternal dehiscence (6.6%), chest complication other than pleural effusion like pneumothorax or pneumonia (2.83%) and aortic pseudoaneurysm (1.89%) (Figure 1).

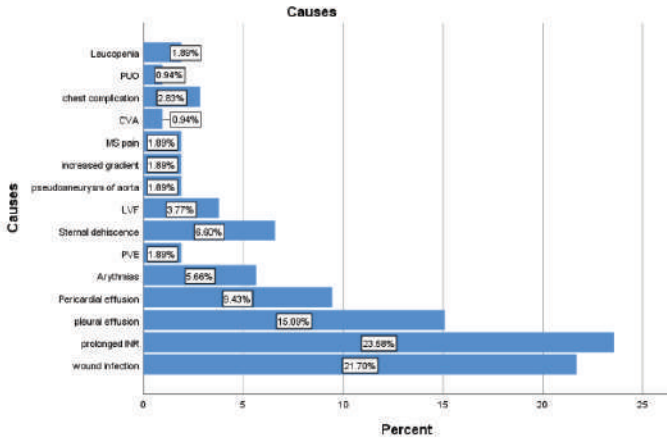

Figure 1: Causes of readmission (PUO = Pyrexia of Unknown Origin, CVA= Cerebrovascular Accident, MS pain= Musculoskeletal Pain, LVF =Left Ventricular Failure, PVE= Prosthethic Valve Endocarditis

The analysis of readmission causes across different surgical procedures highlighted several important patterns. Wound infections were predominantly seen in CABG patients, making up 82.6% of cases (19 out of 23), with a statistically significant association ($p = 0.0018$). Similarly, prolonged INR, a key factor in anticoagulation-related readmissions, was most common in valve surgeries particularly MVR (40.0%), DVR (32.0%), and AVR (12.0%) with strong statistical significance ($p = 0.001$). On the other hand, pleural effusion did not show a significant link to surgery type ($p = 0.109$), even though it was more frequently observed in CABG patients. Pleural effusion was more commonly seen in CABG patients, affecting 22.0% (11 out of 50 cases), compared to 11.1% (5 out of 45 cases) in those who underwent valvular surgeries (MVR, DVR, AVR). While

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CABG patients experienced pleural effusion at nearly twice the rate of valvular surgery patients, the statistical test (χ^2 = 2.58, p = 0.109) suggests that this difference is not significant. Pericardial effusion was more evenly distributed across valve surgeries (MVR 40.0%, DVR 40.0%, AVR 20.0%), but the association was not statistically significant (p = 0.089). Sternal dehiscence was found only in CABG patients (7 out of 7 cases), with a strong association (p = 0.004), suggesting that this complication is closely tied to CABG procedures. Arrhythmias were more common among CABG (66.7%) and DVR (33.3%) patients, but there was no strong statistical evidence (p = 0.909) to link them specifically to any surgery type. Finally, Prosthetic Valve Endocarditis (PVE), which was observed in ARR and AVR surgeries (50% each), was not significantly associated with surgery type (p = 0.011). The mean readmission day after discharge was 16.33±13.62 days. The mean hospital stay after readmission was 4±2.80 days. 38 patients (35.8%) needed some form of surgical intervention for their therapy. The duration of hospital stay following readmission varied based on the type of complication. Patients with pleural effusion had an average readmission stay of 2.94 ± 0.99 days, while those with prolonged INR stayed for 2.36 ± 0.81 days. In contrast, individuals with wound infections had a longer mean hospital stay of 4.26 ± 1.68 days, whereas patients with other complications exhibited the longest readmission duration, averaging 5.24 ± 3.76 days. The other complications category includes conditions such as sternal dehiscence, pericardial effusion, Prosthetic Valve Endocarditis (PVE), increased gradient across prosthetic valves, pseudoaneurysm of the aorta, leucopenia, chest complications, Cerebrovascular Accident (CVA), Left Ventricular Failure (LVF), Musculoskeletal (MS) pain, and Pyrexia of Unknown Origin (PUO). Among these, pseudoaneurysm of the aorta led to the longest hospital stays, increasing readmission duration by 11.17 days (p < 0.001), followed by increased gradient (+8.67 days, p < 0.001), sternal dehiscence (+4.81 days, p < 0.001), and PVE (+4.17 days, p = 0.011). A multiple linear regression analysis was conducted to examine the relationship between specific post-surgical complications and readmission hospital stay. The overall model was statistically significant (F = 8.78, p < 0.001) and explained 57.5% of the variance in readmission duration (R^2 = 0.575). The results indicated that sternal dehiscence was associated with a 4.81-day increase in hospital stay (β = +4.81, p < 0.001), while increased gradient (+8.67 days, p < 0.001) and pseudoaneurysm of the aorta (+11.17 days, p < 0.001) were the strongest predictors of prolonged hospitalization. Prosthetic Valve Endocarditis (PVE) also significantly increased hospital stay by 4.17 days (β = +4.17, p = 0.011). A large pericardial effusion (9.4%) was drained surgically in the operation theater under anesthesia by a subxiphoid incision. The pleural effusion was drained either by percutaneous aspiration (1.9%) or by inserting a small bore central venous line (10.4%) in the pleural cavity. In 3 patients a chest tube was passed in the chest cavity. Rewiring was done in 6 (5.7%) patients.3 patients needed redo on-pump surgery. 2 patients needed surgical wound debridement. A total of 5 patients (4.7%) expired following readmission. The primary complications associated with mortality were Prosthetic Valve Endocarditis (PVE) (n=2, 40%), followed by increased gradient (n=1, 20%), pericardial effusion (n=1, 20%), and leucopenia (n=1, 20%). PVE was the most frequently observed complication among deceased patients, suggesting a potential link between valve-related infections and adverse outcomes. Continuous and qualitative variables of all readmitted patients were shown in tables 1 and 2. The table 1 provided an overview of key clinical variables, including age, creatinine levels, Left Ventricle Dimensions (LVIDD and LVIDS), and Tricuspid Valve Pressure Gradient (TVPG). The length of hospital stays during the initial admission and the duration of readmission hospital stay are also included. The data show a mean age of 46.93 years, with a wide range of 15 to 72 years, indicating a diverse patient population. The mean hospital stay was approximately 5.86 days, while readmission occurred on average at 16.33 days' post-discharge.

Table 1: Patient Demographics and Clinical Variables

Variables	N	Minimum	Maximum	Mean ± SD
Age	106	15.00	72.00	46.93 ± 15.22
Creatinine	106	0.30	0.65	0.50 ±0.94
LVIDD	106	32.00	73.00	50.81 ± 8.57
LVIDS	106	22.00	58.00	33.28 ± 7.72
TVPG (mmHg)	62	0.00	140.00	43.51 ± 22.69
Hospital Stay (Days)	106	3.00	18.00	5.86 ± 2.21
Readmission Day	106	1.00	60.00	16.33 ± 13.61
Readmission Hospital Stay	106	1.00	19.00	4.00 ± 2.80

This table 2 categorized patients based on the type of cardiac surgery performed, symptoms leading to readmission, and the need for surgical intervention. The most common procedure among readmitted patients was coronary artery bypass grafting (CABG) (47.16%), followed by mitral valve replacement (MVR) (17.92%) and double valve replacement (DVR) (16.03%). The most frequently reported symptoms were shortness of breath (37.7%), wound discharge (22.6%), and prolonged INR-related complications (16%). Surgical intervention was required in 35.8% of readmitted cases, while the remaining 64.2% were managed conservatively. This data highlighted the need for improved anticoagulation management, infection control, and postoperative monitoring to reduce the risk of readmission after cardiac surgery.

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Table 2: Clinical Characteristics and Management of Readmitted Patients After Cardiac Surgery

Variables	Category	Frequency (%)
Operation	CABG	50 (47.16%)
	MVR	19 (17.92%)
	DVR	17 (16.03%)
	AVR	9 (8.49%)
	ARR	5 (4.71%)
	RSOV	2 (1.89%)
	AVR	1 (0.94%)
	ASD	1 (0.94%)
	TC	1 (0.94%)
	CABG+MVR	1 (0.94%)
Symptoms	SOB	40 (37.7%)
	Discharge From Wound	24 (22.6%)
	Prolonged INR	17 (16.0%)
	Prolonged INR Complication	6 (5.7%)
	Fever	5 (4.7%)
	Vomiting	2 (1.89%)
	Mixed	5 (4.7%)
	Chest Pain	3 (2.8%)
	Stroke	3 (2.8%)
	Palpitation	1 (0.94%)
Surgical Intervention	No	68 (64.2%)
	Yes	38 (35.8%)

DISCUSSION

The continuous increase in healthcare expenditures has shifted attention toward hospital readmission rates to enhance the quality and cost-efficiency of healthcare delivery. The literature review revealed a dearth of national research on readmissions following heart surgery in Pakistan. Despite advances in surgical technique and perioperative care, readmission following cardiac surgery still is not uncommon. The "Cardiothoracic Surgical Trials Network" investigated all-cause readmissions within 65 days following cardiac surgery in a cohort of 5,158 adults across 10 different sites. The study reported an overall readmission rate of 18.7%, with the primary causes being infections (17.1%), arrhythmias (17.1%), and volume overload (13.5%) [1]. While the present study showed readmission rate 7.5%. The decreased incidence could be because only patients readmitted at the CPE Institute of Cardiology, Multan have been recorded. The study has not included cases readmitted to another institute or private setup. Primary causes of readmission in the study were prolonged international normalization ratio (INR) or bleeding-related complication (23.6%), surgical site wound infection (21.7%), pleural effusion (15.1%), large pericardial effusion (9.4%), sternal dehiscence (6.6%) and supra ventricular tachyarrhythmia's (5.7%). The reason of different causes in readmitted patient from international literature being different disease pattern in patients undergoing cardiac surgery. The rheumatic heart disease is still common in underdeveloped countries like Pakistan [11, 12]. Patients undergo mechanical valve replacement surgery need lifelong anticoagulation. The readmission rate was highest (24.5%) in mechanical valve replacement surgery. The study revealed that complications related to over anticoagulation were seen in patients with mechanical valve replacement surgery. While pleural effusion, sternal wound infection and sternal dehiscence were observed in patients undergoing coronary artery bypass surgery. The complications of supratherapeutic INR included bleeding in various regions of the body. Patients reported skin bruises, hematomas in the calf and thigh muscles, gum bleeding, and pleural and pericardial effusions. Mortality rate was 4.7% (n=5) in readmitted patients. One patient readmitted with increased gradient across prosthetic valve, underwent redo surgery and remained in cardiac failure. One patient presented with cardiac tamponade having large pericardial effusion not revived after effusion drainage. Two patients died with prosthetic valve endocarditis. One post CABG surgery patient presented with leucopenia and expired. Therefore, mortality was high in readmitted patients with prosthetic valve surgery. Several studies have shown that many readmissions are potentially avoidable [13, 14]. Proper patient education, telemonitoring, posterior pericardiotomy in valve surgery patients, optimal sterilization, and rational use of antibiotics and diuretics may reduce the readmission rate [15]. Decreasing readmission rates is a key priority for future quality improvement initiatives [16-20]. The results of this study indicate that Prosthetic Valve Endocarditis (PVE) was the leading contributor to mortality, highlighting the importance of early detection and management of valve-related infections in post-operative care. Additionally, increased gradient and pericardial effusion were frequently observed in fatal cases, emphasizing the need for close monitoring of hemodynamic changes and timely interventions to prevent adverse outcomes. Leucopenia, another key factor in mortality, suggests that immune system suppression or hematological complications may play a role in post-surgical deaths, underscoring the need for vigilant patient monitoring. Structural and systemic complications appeared to have a significant impact on patient outcomes, reinforcing the importance of comprehensive post-operative care and continuous assessment of high-risk patients. The study has certain limitations. It was conducted at a single center and only includes readmissions to the same hospital. As a result, the observed readmission rate of 7.5% may not reflect the actual incidence of readmissions after cardiac surgery. Additionally, the study design does not account for patients who were not readmitted, making it difficult to determine associated risk factors.

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CONCLUSIONS

It was concluded that early hospital readmission is most common in patients who need anticoagulation after valve surgery. Common causes of readmission are prolonged INR and its complications, surgical site infection, pleural effusion and sternal dehiscence. Early readmission after cardiac surgery, adversely impacts patient's outcome. Improved anticoagulation management, strategies to reduce surgical site infection, and postoperative diuretics, are critical for reducing incidence of hospital readmission.

Authors Contribution

Conceptualization: MSIM
Methodology: MSIM, MHC
Formal analysis: MSIM, MHC, KH
Writing, review and editing: MSIM, MHC, KH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Breast Lump Patterns Across Different Age Groups Among Female Patients Presenting to Surgical Outpatient Department of a Tertiary Care Hospital in District Malir Karachi

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ABSTRACT

The number of patients presenting with different types of breast lumps has been on the rise in the Malir district. Many females are being diagnosed with breast cancer. **Objectives:** To determine the pattern of breast lumps in different age groups in the outpatient department of Al-Tibri Medical College hospital in District Malir, Karachi. **Methods:** It was a descriptive cross-sectional study conducted at the Department of General Surgery, Al-Tibri Medical College Hospital, Karachi, from 1st November 2022 to 31st October 2024. Patients presenting in the Surgical Outpatient Department with breast lumps were included in the study. Age at presentation, symptoms, clinical features, investigations, biopsy reports, and operation notes (if operated) were recorded and submitted for analysis. **Results:** The commonest lesions were fibro-adenoma (33.6%), inclusion cyst of the breast (19%), and breast abscess (18.5%), followed by Carcinoma breast (17.7%). 51.7 % of cases were associated with pain. Among carcinomas, 43% presented with pain. The highest peak of presenting with malignant lesions was from 39 to 43 years, and 2nd peak was from 49 to 58 years. Most benign lesions presented between 24 to 28 years. The chi-square test showed a strong association between age range and pain (p-value<0.001), age range and type of lump (p-value <0.001), and marital status and type of lump (p-value<0.001). **Conclusions:** It was concluded that fibro-adenoma is the most common breast disease. Inflammatory lesions are also present frequently in the reproductive age group. Carcinoma breast presented in middle and later age groups, predominantly in married females in our district.

INTRODUCTION

The human breast is subjected to constant physiological changes throughout life, secondary to changes in hormone levels, throughout the menstrual cycle, during pregnancy, lactation, and menopause. These changes may give rise to non-proliferative and proliferative breast lesions [1, 2]. Around 2 million patients were diagnosed with breast cancer worldwide in 2018, associated with half a million deaths [3]. It is the most common cancer in females and the second most common cause of cancer-related death. It was found to be most prevalent in developed countries as compared to developing or underdeveloped countries, but now incidence is reported to be rising in low- and middle-income countries as well [3]. Considering breast cancer, a global concern, more localized and regional data on breast cancer prevalence in low and middle-income countries is needed because the incidence and outcomes of this cancer vary greatly depending on socioeconomic, geographical, and cultural factors. In most low- and middle-income countries, due to financial and cultural constraints, disease is diagnosed at a later stage, leading to poorer outcomes. For better outcomes, it is essential to identify the disease burden correctly to ensure better

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resource allocation for the prevention, diagnosis, and treatment of breast cancer [4]. Breast cancer incidence peaks in post-menopausal women, while benign diseases primarily manifest in women of reproductive age, culminating in the second or third decade [5, 6]. The incidence of various breast lump types in women varies with age [5]. Early identification and prompt diagnosis are essential for prompt management, particularly in setups with limited resources. Understanding the patterns of breast lumps across various age groups can assist with improving diagnostic techniques, patient counselling, and treatment because age is a significant factor in determining whether a lump is benign or malignant [5]. Risk factors associated with malignant tumors include age, family history, early menarche, late menopause, age >35 at first childbirth, proliferative breast pathologies, obesity, hormonal therapy, Breast Cancer (BRCA) mutation, lobular carcinoma in situ, and radiation exposure [7]. Benign lumps can be secondary to infective conditions, inflammatory lesions, benign cysts and tumors. Histologically, they are divided into non-proliferative lesions and proliferative breast lesions with or without atypia [8]. Proliferative lesions are associated with a small increased risk of carcinoma [9]. Fibroadenoma is the most common of all the lumps and usually presents in the second and third decades of life with no risk of malignant conversion [10]. Small lesions, if confirmed via investigation, usually do not require surgery. Surgery may be associated with architectural distortion and damage to ducts [11]. Breast lumps are a common concern among females of all ages, with causes ranging from benign to malignant conditions. While there is extensive research on different aspects of breast cancer, there is still limited data available on the overall pattern of breast lumps across different age groups, especially in resource-limited setups. With age being a key determinant in breast lumps, studying their distribution will help in the better understanding of common breast lumps in different age strata. It will result in the early identification of high-risk cases and will guide healthcare professionals in prioritizing diagnostic approaches based on patient demographics.

This study aims to determine the pattern of breast lumps presenting in different age groups in the outpatient department of Al-Tibri Medical College Hospital, a tertiary care hospital situated in District Malir, Karachi. This study provided age-based trends and contributed to evidence-based decision-making for clinicians to improve patient outcomes and awareness. It also provided the basis for future data, generating insight among healthcare professionals.

METHODS

A descriptive cross-sectional study was conducted at the Department of General Surgery, Al-Tibri Medical College Hospital, Karachi, Pakistan, after obtaining approval from the Institutional Ethical Review Committee. No. ATMC/IERC/12th/02-2022/01. The study period spanned from November 2022 to October 2024. All female patients (n=271) presenting to the Surgical Outpatient Department with breast lumps during the study period were included. All patients not willing to be a part of the study, all patients previously operated on for breast lumps, as that can hinder clinical findings and patients on hormonal therapy, were excluded from the study. Informed consent was obtained from all patients. Patients from 13 to 80 years of age were included. All the patients were residents of the Malir District. All patients complained about a breast lump for any duration, with or without associated pain of any duration, with or without nipple discharge, in any quadrant of the breast, any size, shape, or consistency of lump, with or without axillary lymph nodes. The skin was examined for any redness, dimpling, or peau d'orange appearance, especially in painless lumps. Palpation findings (including characteristics of any palpable masses). An assessment of regional lymph nodes was performed. A triple assessment was used to make the diagnosis of the lump. History and clinical examination, radiology consisting of ultrasound for females aged <40 and mammogram and ultrasound for females more than 40 years of age were used. For Birad 4 and 5, trucut biopsy or excisional biopsy was undertaken, and benign and malignant lumps were separately categorized [12]. In the case of indeterminate lesions, guidelines by NCCN were followed for further imaging, repeat biopsy, or excisional biopsy [13]. Patients with fibrocystic breast disease and fibroadenomas of less than 2cm were counselled, and those with mastitis were treated conservatively with antibiotics. Breast abscesses and inclusion cysts were operated on. Malignant cases were either operated upon or went to other centers for treatment. Inoperable breast cancers were referred to a medical oncologist. The data were analyzed using SPSS version 26.0. Age parameter was further categorized to create various age ranges (Teenage=13-19, Twenties=20-29, Thirties=30-39, Forties=40-49, Fifties=50-59, Sixties=60-69, Seventies=70-79 and Eighties=80-89). Descriptive statistics were applied to determine frequencies and percentages for categorical variables. The chi-square test was applied to check the association between age range, pain, and type of lump, and between marital status and type of lump.

RESULTS

The mean age of patients was 33.9 years (S.D ± 12.66) with an age range of 13-80 years (Table 1).

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Table 1: Frequency Distribution of Demographic and Other Variables(n=271)

Baseline Characteristics	Categories	n (%)
Mean Age	33.9 ± 12.66 Years	
Marital Status	Married	203 (74.9%)
	Unmarried	67 (24.7%)
Age Distribution	Teens	21 (7.7%)
	The Twenties	97 (25.8%)
	The Thirties	75 (27.7%)
	The Forties	40 (14.8%)
	The Fifties	22 (8.1%)
	The Sixties	12 (4.4%)
	The Seventies	3 (1.1%)
	The Eighties	1 (0.4%)
Type of Lesion	Fibro-adenoma	91 (33%)
	Galactocoele	1 (0.36%)
	Abscess	50 (18%)
	Fibrocystic Disease	11 (4%)
	Sebaceous Cyst	52 (19%)
	Malignant Mass	48 (17.7%)
	Undetermined	18 (6%)
Family History of Breast Cancer	Family History of Breast Cancer Present	10 (3.7%)
	No Family History Of Breast Cancer	260 (92.3%)
Pain	Present	139 (51.2%)
	Absent	132 (48.8%)

Among the patients, 74.9% were married and 24.7% were unmarried. Most of the patients presented in their twenties and thirties. Most of the cases presented were benign lumps, 199 (73%), 48 (17.7%) were malignant, and 18 (6%) were indeterminate. The commonest benign lesion was fibro-adenoma accounting for 91 (33%) patients, 1 (.36%) had galactocele, 52(19%) sebaceous cyst, 50(18%) had breast abscess, 48(17.7%) had a malignant mass, 11(4%) had a fibrocystic disease, and 18 (6%) cases were undetermined. Only 10 (3.7%) cases had a family history of breast cancer, while 260 (92%) cases had no family history of breast cancer. In 51% of cases lump was painful, while 48.8% of lumps were painless (Figure 1).

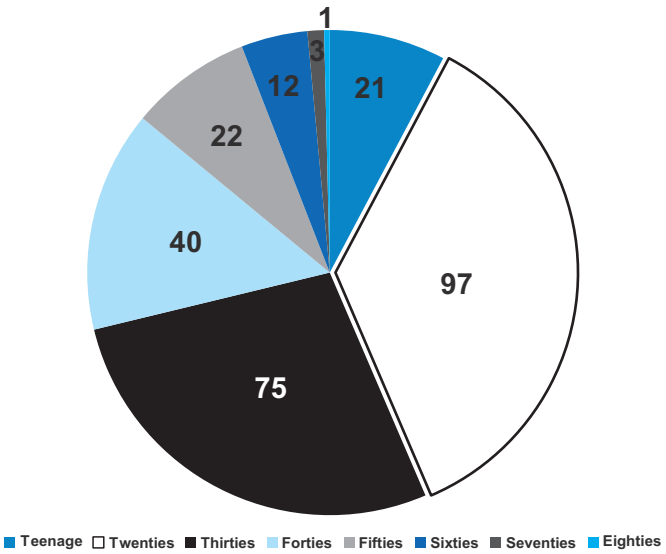

Figure 1: Frequency and Percentages of Patients in Various Age Groups

Figure 1 shows most of the patients (71.2%) presenting with breast lumps were less than 40 years of age. Only 27.8% of total patients with breast lumps were 40 years and above. A comparison of various parameters was done to check the association of different categorical parameters in different age groups (Table 2).

Table 2: Comparison of Age Range of Patients with Breast Lumps and Their Marital Status

Age Range	Marital Status			p-Value
	Married	Unmarried	Unknown	
Teenage	3	18	0	<0.001*
Twenties	59	38	0	
Thirties	66	8	1	
Forties	37	3	0	
Fifties	22	0	0	
Sixties	12	0	0	
Seventies	3	0	0	
Eighties	1	0	0	

*Level of significance was at <0.05. p-value was generated by Pearson's Chi-square test.

Comparison of the age range of patients with their marital status shows a statistically significant relationship between the two parameters (Table 3).

Table 3: Distribution of Patient Age Range and Types of Breast Lumps

Age Range	Fibro-adnoma	Galactocoele	Abscess	Fibrocystic Disease	Sebaceous Cyst	Malignant Mass	Undetermined	Chi-Square Value	p-Value
Teenage	15	0	2	1	2	0	1	159.51	<0.001*
The Twenties	52	0	25	4	13	1	2		
The Thirties	21	1	18	4	19	8	4		
The Forties	3	0	3	1	14	16	3		
The Fifties	0	0	2	0	3	13	4		
The Sixties	0	0	0	1	1	7	3		
The Seventies	0	0	0	0	0	2	1		
The Eighties	0	0	0	0	0	1	0		
Total	91 (33%)	1 (0.36%)	50 (18%)	11 (4%)	52 (19%)	48 (17.7)	18 (6%)	-	-

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*Level of Significance was at <0.05. p-value was generated by Pearson's Chi-square test.

Among benign lesions, fibro-adenoma (33%) was seen mostly in teens and twenties and was rarely present after thirties. This was followed by infective and inflammatory lesions of the breast, which are more commonly seen in the twenties and thirties. There were (18%) cases of breast abscess and mastitis, and these patients mostly belonged to the third decade of life. Fifty-two cases (19%) had infected sebaceous cysts of the breast presenting in their twenties, thirties, and forties, while 11 patients had fibrocystic disease of the breast. The rate of malignant disease was 17.7%. Malignancies were predominantly seen in the forties (16 cases) and fifties (13 cases) groups. Out of 18 indeterminate cases, 6 patients had indeterminate trucut biopsy reports and refused open biopsy, and 12 had clinically suspicious lesions with BIRAD 3 lesions on a mammogram, refusing trucut/open biopsy. Undetermined cases were spread in all age groups (Table 4).

Table 4: Association Between Patient Age Range and Presence of Pain in Breast Lumps

Age Range	Pain		Chi-Square Value	p-Value
	Present	Absent		
Teenage	5	16	26.68	<0.001*
Twenties	47	50		
Thirties	46	29		
Forties	30	10		
Fifties	7	15		
Sixties	3	9		
Seventies	2	1		
Eighties	0	1		

*Level of significance was at <0.05. p-value was generated by Pearson's Chi-square test.

Among benign lesions, most fibro-adenomas were painless, and infectious lesions were painful. Forty-eight percent of malignant lesions were painful, and the rest were painless. Most painful lumps presented in their twenties, thirties, and forties. The chi-square test also revealed that there was a statistically significant association between age group and presentation of pain and lump (p-value<0.001). Similarly, there was a strong association between marital status and the type of lump (p-value<0.001). Most cases of fibro-adenomas were diagnosed in unmarried patients. The rest of the pathologies were found in married patients with a predominance of breast abscess (49 cases), followed by malignancy (48 cases) and sebaceous cyst of the breast (40 cases) (Table 5).

Table 5: Association between Marital Status and Type of Breast Lump

Marital Status	Fibro-adnoma	Galactocoele	Abscess	Fibrocystic Disease	Sebaceous Cyst	Malignant Mass	Undetermined	Chi-Square Value	p-Value
Married	44	1	49	8	40	48	13	70.115	<0.001*
Unmarried	47	0	1	3	11	0	5		
Unknown	0	0	0	0	1	0	0		

*Level of significance was at <0.05. p-value generated by Pearson's Chi-Square Test.

DISCUSSION

The most common presenting symptom of breast disease is mastalgia, followed by a breast lump. The presence of a breast lump in females evokes anxiety. These lumps can be benign or malignant. Most lumps are benign and can be caused by infections, inflammation, trauma, or benign tumors [12]. In the current study, benign breast lumps were common in the reproductive age group, especially in the third and fourth decades of life. In the present study, the age of patients was from 13-80 years with a mean age of 33.9 years. A study by Gradishar *et al.*, shows its age range from 18 to 75 years with a mean of 37.72 years [13]. In the current study, 73% of cases were benign lesions, with most presenting in their twenties and thirties, while 17.8% were malignant and were mostly present in their forties and fifties. These results are close to the study by Al-Basha, where benign lesions were 81.5% and malignant lesions were 18.5% [14]. A recent Pakistani study by Abbasi *et al.*, also presented the same results with benign lesions at 80.35% and malignant lesions at 19.65% [15]. In another Pakistani study by Ahmed *et al.*, malignant lesions were present in 31.6% of cases of palpable breast masses of females of more than 30 years of age [16]. In another Pakistani study, the researcher mentioned the incidence of malignant breast lumps as 30% in histopathological samples [17]. The literature shows that among benign breast diseases, the most common lesion is fibro-adenoma. It usually presents in the late teens and early twenties and is rare after 40 [18, 19]. In current study also had 33% cases of fibro-adenoma mostly in teens and twenties, in contrast to a study by Fauzia *et al.*, where the incidence of fibro-adenoma was 47.1% but similar to current study presented in twenties and thirties [19] and another Pakistani study showed 42.4% incidence of fibro-adenoma [20]. Another benign lesion was breast abscess, present in 18% of the present cases, while a study conducted at a tertiary care hospital in Karachi showed an incidence of 12.8% cases of breast abscess [19]. We had a high incidence of sebaceous (epidermoid inclusion) cysts

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of 19%, and they presented in the second, third, and fourth decades, as opposed to Memon *et al.*, where it was 1.42% only [21]. Only 4% of current patients presented with fibrocystic disease of the breast, and a Pakistani study shows this incidence to be 11.6% [22], but the result coincides with the result of the study by Yadav, whose study also shows an incidence of 4% for fibrocystic disease of breast [23]. In the current study, 17.7% of cases were malignant and were mostly present in the forties and fifties, which is comparable to a study by Memon *et al.*, with an incidence of 17.9% [21]. A review of the prevalence of breast cancer in Pakistan by Nazuk *et al.*, shows an extremely high incidence of breast cancer in Pakistan, 21.5% and 34% of all female cancers, which is the highest in Asia after Israelite Jews [24]. The current study shows 6.6% cases of indeterminate lesions. The indeterminate breast lesions found on core biopsy include atypical papilloma, atypical ductal/lobular hyperplasia, and radial scar/complex lesions. As the core biopsy sample is not representative of the whole lesion, it requires a diagnostic open biopsy due to uncertain malignant potential and association with DCIS or invasive carcinoma. Tan *et al.*, present a malignancy upgrade of 0.66% in their study discussing the significant waste of resources on open biopsy for B3 lesions. They advocate the use of targeted core biopsy or stereotactic biopsy to help reduce the burden of open biopsies. Management of indeterminate lesions is still a dilemma with the need to tailor the management decisions from case to case, thus requiring more research to guide clinical management [25]. In the present study, after clinical assessment, we utilized ultrasound for imaging for patients under 40 years of age and mammogram along with ultrasound as an adjunct for patients more than 40 years of age, except for patients with epidermoid cysts, which was a clinical diagnosis. For histopathology, we used trucut biopsy for all BIRAD 4 and 5 patients, and selective BIRAD 3 patients and used excision biopsy in patients with either a benign lump (for treatment purposes) on ultrasound or an indeterminate lesion if found on trucut biopsy. Radiological evaluations, including mammography, ultrasound, and contrast-enhanced magnetic resonance imaging (MRI), are used for early detection of Breast cancer, to classify the lesion, and to predict its aggressiveness for personalized treatment [26]. Mammography has limitations in dense breasts, making ultrasound valuable for women under 40. Dynamic contrast-enhanced MRI and contrast-enhanced spectral mammography offer better results. Image-guided percutaneous biopsies are less invasive and quicker than surgical biopsies, with vacuum-assisted biopsies even potentially curative for small lesions [27]. Moreover, using AI to detect indeterminate lesions can be invaluable [28]. The current study showed a strong association between marital status and the presence of malignancy. This contrasts with previous literature citing higher breast carcinoma incidence in unmarried female [28]. This aspect needs to be further investigated in detail regarding the reason for the higher incidence of breast carcinoma in married females in Pakistan as opposed to the rest of the world. Factors such as general awareness, behavior patterns of married females towards their health, their dietary and lifestyle modifications after marriage, and hormone receptor status need to be considered that may be contributing towards the higher incidence in the present community.

CONCLUSIONS

Fibro-adenomas are the most common breast lesions in District Malir, Karachi, with inflammatory lesions the next frequently occurring lesions seen in women of reproductive age. Malignant breast lumps primarily affect women in their fifth and sixth decades. Age is a key determinant in the type of lesion a female present with. The high incidence of malignancy, particularly among married women in their forties and fifties, emphasizes the urgent need for targeted breast cancer awareness campaigns, especially in these age groups, in the region, to promote early detection and improve outcomes by initiating regular screening programs and early approaches to healthcare providers.

Authors Contribution

Conceptualization: TMG, NJ
Methodology: TMG, TM, BK, NJ
Formal analysis: TM, SUK, HWA
Writing review and editing: NJ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Diagnostic Accuracy of Optical Coherence Tomography to Detect Cystoid Macular Edema (CME) In Patients with Diabetes Mellitus (DM) Taking Fundus Fluorescein Angiography (FFA) As Gold Standard

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ABSTRACT

Macular thickening, known as Cystoid Macular Edema (CME), is brought on by fluid buildup in the inner nuclear and outer plexiform layers of the retina as a result of leaking from peri-foveal retinal capillaries. **Objective:** To determine the OCT's ability to identify cystoid macular edema in individuals with diabetes mellitus, compared to the gold standard of fundus fluorescein angiography. **Methods:** The Lahore General Hospital's Ophthalmology Outpatient Clinic served as the study's setting. From the Outpatient Department, 143 patients who met the inclusion criteria were randomly selected. Informed consent was obtained from patients before imaging. An indirect biomicroscope was used to evaluate all of the subjects. After completing fundus fluorescein angiography and optical coherence tomography, was diagnosed with cystoid macular edema according to the standardized criteria. A data collection proforma was developed. IBM SPSS version 25.0 was used to analyze the data. **Results:** In this study, 76 males (53.1%) and 67 females (46.9%) participated. The average age was 47.7 ± 10.3 years and diabetes duration was 5.4 ± 2.9 years. Optical Coherence Tomography (OCT) showed a sensitivity of 88.3%, specificity of 38.5%, PPV of 93.3%, NPV of 25.0%, and an overall accuracy of 84.6% compared to Fluorescein Angiography (FFA) in detecting cystoid macular edema. **Conclusions:** Diagnosing DME with OCT and FFA is very successful, it ensures early detection and treatment. For Diabetic Mellitus (DM) patients to avoid eyesight loss, accurate and easily accessible diagnostic strategies are essential.

INTRODUCTION

Cystoid Macular Edema (CME) is defined as disruption of the normal blood retinal barrier causes leakage from the peri-foveal retinal capillaries, causing accumulation of fluid in the retina's intracellular spaces, primarily the inner nuclear layer and outer plexiform layer, causing retinal thickening [1]. Diabetic retinopathy is a neurovascular outcome of diabetes. The most frequent cause of permanent loss of vision in patient with diabetes is diabetic macular edema, which can be develop at all stages of diabetic retinopathy [2]. Fluorescein angiography is one of the crucial diagnostic tool for diabetic retinopathy diagnosis and also crucial for the treatment process [3]. FFA is a frequently used diagnostic ophthalmology instrument in ophthalmology department [4]. FFA has been used to measure the non-perfusion zones within the retina and determines the ischemic range of micro vessels

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surrounding the area known as macula is many quadrants [5]. Furthermore, it can measure the extent/degree and position of florescence leakage, which guides the application of laser [6]. A study conducted at university of Liverpool suggested that diagnosis of both functional and structural alterations in diabetic retinopathy on time suggests that neuroretina thinning occurs before microvascular problems. Functional alterations discovered by the HRSD test in patients with early diabetic retinopathy have not been observed. Additional evidence for pre-clinical diabetic retinopathy comes from early detection of diabetic macular edema study [7]. A study conducted by Wong revealed the high false-positive rate of the existing screening technique results in disproportionate referrals, which causes patients great inconvenience and places a heavy financial burden on whole society. For DME screening, integrating universal optical coherence tomography can enhance sensitivity, cut down on false positive outcomes by eight times, and increase long lasting cost effectiveness [8]. A study conducted in India revealed proliferative diabetic retinopathy, central retinal vein occlusion, BRVO, and NPDR were the most common causes of cystoid macular edema. When compared to FFA, OCT sowed a 100 percent sensitivity and 81.38 percent diagnostic accuracy. Optical coherence tomography can therefore be suggested as the main imaging procedure for cystoid macular edema diagnosis [9]. In another study it was found that, rapid acquiring no intravenous dye requirement, and better detection of neovascular spikes and capillary drop-out are some of the benefits of optical coherence tomography angiography over FFA. It appeared promising for regular monitoring of DR. However, its usage as a stand-alone evaluation approach is hampered by its reduce field of vision, poor resolution power, difficulties recognizing microaneurysms over large regions, and incapacity to find peripheral retinal vascular sheath [10]. Once the retina has been ignited with white-blue light rays at a wavelength of 490 nano meter, an angiography can be acquired by capturing the fluorescent green light that the dye emits after being injected into the bloodstream as sodium fluorescein. In essence, this is a dye-tracing test [11]. Cystoid macular edema was diagnosed with a sensitivity of 98.7% and a specificity of 96% using FFA and OCT, respectively, in research that compared the two methods [12]. OCT had a sensitivity of 98.6% and a specificity of 100% for detecting cystoid macular edema in a study that compared it to fundus fluorescein angiography [13]. Cystoid macular edema was seen in 21.8% of cases [14]. A phakic patient with type 1 idiopathic macular telangiectasia was documented in a case report from 2013. This patient's CME responded strongly to the administration of NSAIDs but would recur if not treated [15].

This study aimed to determine the OCT's ability to identify cystoid macular edema in individuals with diabetes mellitus, compared to the gold standard of fundus fluorescein angiography.

METHODS

This Prospective Cohort study was carried out at the Ophthalmology Department of Lahore General Hospital (LGH), Lahore, over twelve months, following the approval of the study synopsis. The study was done after the final approval of the synopsis. The study duration was from April 2021 to April 2022. The IRB number was 2056-58. Data were collected after obtaining consent from patients. All the patients had OCT and FFA done. Findings of OCT were checked with FFA and tested whether OCT missed the macular edema or not taking FFA as standard reference. A non-probability purposive sampling technique was used. A sample size of 143 participants was estimated at a 95% confidence level, based on an expected sensitivity of 96% for Optical Coherence Tomography (OCT) and a specificity of 100%, with a 7% margin of error [14, 15]. The sample size calculation formula used was n = Z21-$\alpha/2$.p.q/d2.Patients of both genders, aged between 25 and 70 years, with clear ocular media and diagnosed with Diabetic Macular Edema (DME), were included in this study. Patients who have with condition of nystagmus (examined clinically), anxiety concerning the technique according to the history of the patient), allergy to fluorescein (from the history of the patient), patients with impaired renal function serum creatinine greater than 1.2 mg/dl, pregnancy, patients with significant cardiac disease and patients with moderate asthma were excluded from the study due to adverse reaction to fluorescein dye and it can also cause transient hemodynamic changes including tachycardia and hypotension, patients with uveitis, patients who had experienced IOL surgery within the last three months, as well as those who were diagnosed with CRVO, BRVO were also not included in the study. The research took place in the Lahore General Hospital Ophthalmology Department after receiving clearance from the hospital's ethics council. From the Outpatient Department, 143 patients who met the inclusion criteria were chosen at random. All patients provided consent to have their retinas photographed and examined prior to the start of the study. Snellen's acuity chart was utilized to capture far vision, while 45-degree retinal pictures were taken using close vision. All subjects in the study were evaluated using indirect biomicroscopy. Cystoid macular edema was diagnosed through two imaging techniques: FFA and OCT. Information such as names, ages, sexes, addresses, registration numbers, degrees of vision impairment, results of indirect biomicroscopic examinations, OCT, and

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FFA were collected using a standardized form. The researchers gathered all the data themselves. SPSS version 25.0 was employed for data entry and analysis. Quantitative information, such as age and duration of diabetes mellitus, was reported as Mean ± S.D., whereas qualitative information, including gender, hypertension, and smoking prevalence, was presented as frequencies and percentages. OCT was evaluated for detecting Cystoid Macular Edema (CME) in diabetic individuals against FFA as the gold standard. A Kappa correlation was calculated between FFA and OCT. The chi-square test was applied for sensitivity, specificity, and other metrics. A 2x2 contingency table compared the results with statistical significance set at p-value < 0.05.

RESULTS

The gender distribution revealed that 76 participants (53.1%) were males, while 67 participants (46.9%) were females. Therefore, male patients outnumbered female patients in this study. Table shows that 62 patients (43.4%) were in the 25-45 years age group, while 81 patients (56.6%) fell into the 46-70 years age group (Table 1).

Table 1: Demographic Characteristics

Variables	Categories	Frequency (%)
Gender	Male	76 (53.1%)
	Female	67 (46.9%)
	Total	143 (100.0%)
Age Groups	25-45 Years	62 (43.4%)
	46-70 Years	81 (56.6%)
	Total	143 (100.0%)

The table 2 presented the frequency and percentage distribution of key health-related variables among the study participants (N = 143). The prevalence of hypertension was 28.7%, while 71.3% of participants did not have hypertension. Smoking was reported by 26.6% of participants, whereas 73.4% were non-smokers. Regarding the duration of diabetes mellitus, 51.0% had the condition for ≤ 5 years, while 49.0% had it for more than 5 years.

Table 2: Distribution of Hypertension, Smoking, and Duration of Diabetes Mellitus Among Participants

Variables	Frequency (%)
Hypertension	
Yes	41 (28.7%)
No	102 (71.3%)
Total	143 (100.0%)
Smoking	
Yes	38 (26.6%)
No	105 (73.4%)
Total	143 (100.0%)
Duration of Diabetic Mellitus	
≤ 5 Years	73 (51.0%)
> 5 Years	70 (49.0%)
Total	143 (100.0%)

Table 3 illustrated that the technique of FFA was used to diagnose 130 patients (90.9 percent) with CME, based on the frequency distribution of CME (Table 3).

Table 3: Frequency Distribution of Cystoid Macular Edema Detected on FFA

Cystoid Macular Edema (CME) Detected on Fundus Fluorescein Angiography (FFA)	Frequency (%)
Yes	130 (90.9%)
No	13 (9.1%)
Total	143 (100.0%)

The table 6 showed that Cystoid Macular Edema (CME) identified by OCT revealed that 123 individuals (86.0%) were diagnosed with cystoid macular edema using this imaging technique (Table 4).

Table 4: Frequency Distribution of CME Detected on Optical Coherence Tomography (OCT)

CME Detected on Optical CoherenceTomography	Frequency (%)
Yes	123 (86.0%)
No	20 (14.0%)
Total	143 (100.0%)

The table of contingency for Optical Coherence Tomography (OCT) and FFA diagnosis of CME showed 115 true positives, 8 false positives, 5 true negatives, and 15 false -Ve. The sensitivity of OCT in the diagnosis of CME is 88.3%, showed a high ability to correctly detect positive instances, whereas the specificity is 38.5%, showed a lower ability to accurately detect negative cases. The PPV (93.3%) demonstrated OCT's reliability in confirming cystoid macular edema, whereas the NPV 925.0% showed its poor accuracy in excluding cystoid macular edema. Overall, optical coherence tomography identified CMEs with an accuracy of 84.6% (Table 5).

Table 5: CME Detected on Fundus Fluorescein Angiography versus CME on Optical Coherence Tomography

CME Detected on Optical Coherence Tomography	CME Detected on Fundus Fluorescein Angiography	True Positives (T +ve), False Positives (F -ve), True Negatives (T -ve), False Negatives (F -ve)	Total
Yes	Yes	115 (TP)	130
No	Yes	15 (FN)	
Yes	No	8 (FP)	13
No	No	5 (TN)	

Diagnostic Metrics
Sensitivity = TP/TP+FN = 115/115+15 = 88.3%
Specificity = TN/TN+FP = 5/5+8 = 38.5%
Positive Predictive Value = TP/TP+FP = 115/115+8 = 93.3%
Negative Predictive Value = TN/TN+FN = 5/5+15 = 25.0%

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Accuracy = TP+TN/Total = 115+5/143 = 84.6%

This table summarized the diagnostic performance metrics, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy. Sensitivity (88.3%) reflects the test's ability to correctly identify positive cases, while specificity (38.5%) indicates its ability to detect negatives. The PPV (93.3%) represented the likelihood that positive results are accurate, whereas the NPV (25.0%) showed the probability that negative results are correct. The overall accuracy of the test is 84.6%. The reported 95% confidence intervals provide a measure of reliability, and a significant p-value (0.001) supports the sensitivity of the test (Table 6).

Table 6: Diagnostic Performance Metrics of the Test

Metrics	Value (%)	95% Confidence Interval	p-Value
Sensitivity	88.3%	(81.7%, 93.2%)	0.001
Specificity	38.5%	(20.7%, 58.2%)	
Positive Predictive Value (PPV)	93.3%	(87.2%, 97.2%)	
Negative Predictive Value (NPV)	25.0%	(9.1%, 49.5%)	
Accuracy	84.6%	(78.2%, 89.9%)	

DISCUSSION

According to earlier research, the occurrence of DME rises with old age, with 50.6% seen in those aged 61–70 [16]. This research aimed to compare FFA and OCT as prospective diagnostic tools. By both FFA and OCT measures, the research demonstrated encouraging outcomes. Four forms of diabetic macular edema were identified by FFA: mixed, cystoid, diffuse, and focal. Patients with intraretinal edema, subretinal fluid, and mixed macular edema were all identified using Optical Coherence Tomography (OCT) [16]. In one study, it was found that in 51.6% of patients, abnormalities of the macula like an epiretinal membrane, macular exudation, full-thickness macular hole, Cystoid Macular Edema (CME), and Sub internal limiting membrane were seen. Optical coherence tomography and OCT-A detected all macular changes, whereas fundus angiography missed 18.8% and SLB and indirect ophthalmoscopy missed 50% of instances. The best corrected visual acuity was much lower in patients with macular involvement indicating fundus angiography's limits in detecting vision alterations [17]. In this study, the gender distribution revealed that 76 participants (53.1%) were male, while 67 participants (46.9%) were female, with male patients outnumbering female patients. Additionally, the average duration of diabetes mellitus in the study population was 5.4 ± 2.9 years. Research by Luxmi S *et al.*, compared the accuracy of CME diagnoses made with OCT and FFA [18]. It was demonstrated that FFA and OCT had a 98.7 and 96% sensitivity, respectively [14]. Research by Zhang HR comparing OCT with FFA found that the former has a sensitivity of 98.6% for detecting CME and a specificity of 100% [15]. CME was seen in 21.8% of patients [19]. In this study, 123 patients (86.0%) were diagnosed with CME using OCT. OCT performed well in detecting cystoid macular edema against Fluorescein Angiography (FFA), with a sensitivity of 88.5%, specificity of 78.5%, positive predictive value of 93.5%, negative predictive value of 75.0%, and an overall diagnostic accuracy of 83.9%. In a study conducted by You QS *et al.*, they found that the occlusion test confirmed the model's capacity to detect the crucial pathological regions, underscoring its clinical potential [20].The deep learning model showed strong diagnostic performance with high AUC values ranging from 0.91 to 0.994 internally, 0.970 to 0.997 externally, and excellent accuracy. Sensitivity and specificity: a slightly lower sensitivity in external validation (80.1 percent) indicates space for improvement.In another study, it was found that in diagnosing centers involved diabetic macular edema, the study showed that central macular fluid volume performed better than central subfield thickness, with a considerably higher area under the receiver operating characteristics curve (AURC) (0.907 versus 0.832) and stronger sensitivity 78.5% versus 53.8% at 95 percent specificity.

CONCLUSIONS

The study examined the diagnostic efficacy of FFA and OCT in detecting CME in Diabetic Mellitus (DM). Fundus fluorescein angiography, being the gold standard, was more accurate at diagnosing cystoid macular edema. OCT established good skills in detecting positive cases and is a useful non-invasive screening method, however, its limits in excluding cystoid macular edema emphasize its poor specificity. As a result, while optical coherence tomography is effective for preliminary evaluations, fundus fluorescein angiography is still required for confirmation and correct diagnosis.

Authors Contribution

Conceptualization: NA
Methodology: AN, MAA
Formal analysis: FKA, SS
Writing, review and editing: AN, NA, MKW

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Serum Bicarbonate Changes Among Patients on Thrice Weekly Maintenance Hemodialysis (HD): A Single-Center Study

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ABSTRACT

Metabolic acidosis in hemodialysis significantly affects morbidity and mortality. Understanding bicarbonate fluctuations is key to optimizing supplementation and dialysis protocols. **Objectives:** To determine the inter-dialytic and intra-dialytic changes in serum bicarbonate level among patients undergoing maintenance hemodialysis. **Methods:** This quasi-experimental study was conducted at the Nephrology Department, Fatima Jinnah Medical University (FJMU)/Sir Ganga Ram Hospital, Lahore, after taking synopsis approval from the CPSP from August 2024 to January 2025. After taking consent, 60 patients on maintenance haemodialysis thrice weekly who met the selection criteria were enrolled. Inter-dialytic and intra-dialytic changes in serum bicarbonate levels were determined. Data were analyzed using SPSS version 26.0. Numerical values were presented as mean ± SD, and continuous variables were analysed using frequency and percentages.Inter-dialytic and intra-dialytic changes in bicarbonate levels were compared using a paired t-test; p≤0.05 was taken as significant. **Results:** Pre-hemodialysis mean bicarbonate level was 18.65 ± 1.11 mEq/L, increased to 22.18 ± 0.85 mEq/L post-hemodialysis, and by the next hemodialysis session, the mean pre-HD bicarbonate level reduced to 18.78 ± 1.02 mEq/L. Intra-dialytic change showed a mean increase of 3.53 ± 1.19 mEq/L, p-value<0.001 and inter-dialytic change demonstrated a decrease of 3.40 ± 1.18 mEq/L, p-value<0.001. **Conclusions:** It was concluded that hemodialysis temporarily raises bicarbonate levels, but they drop before the next session, highlighting the need for optimized supplementation or dialysis adjustments to maintain stability.

INTRODUCTION

Chronic Kidney Disease (CKD) is a significant global health issue, defined by structural and functional kidney damage or an eGFR of less than 60 ml/min per 1.73 m^2, persisting for three or more months [1]. CKD can progress to end-stage renal disease (ESRD), with a global prevalence reported to be 1,500 per million populations [2]. In Pakistan, its annual incidence exceeds 100 cases per million populations [3]. Healthcare providers face numerous complications in patients undergoing maintenance HD. Among them, metabolic acidosis is a notable concern. Both high and low serum bicarbonate levels are linked to increased mortality risk [4]. Hemodialysis (HD) induces rapid correction of acidosis, leading to transient alkalemia and subsequent acid retention until the next session [5]. Post-HD metabolic alkalosis can also be detrimental, contributing to hypokalaemia, hypocalcaemia, and eventually arrhythmias. Bicarbonate levels exhibit dynamic changes during haemodialysis (HD), influenced by factors such as dialysate composition, individual buffering capacity, and residual kidney function. Rapid post-dialysis increases in serum bicarbonate can lead to transient metabolic alkalosis, while inter-dialytic declines may predispose patients to acidosis [5]. Additionally, metabolic alkalosis is associated with greater inter-dialytic weight gain and intra-dialytic hypotension, with mortality rates reaching up to 90% for pH levels exceeding 7.65 [6]. Variations in serum

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bicarbonate levels pre- and post-HD have been correlated with mortality in ESRD patients, with levels below 23 mmol/L and above 32 mmol/L increasing the hazard ratio for death to 1.23 and 1.74, respectively [7]. Bicarbonate supplementation targeting a serum level of 24 mEq/L helps preserve muscle mass [8]. A study found that serum bicarbonate levels increased by 4.9±0.3 mEq/L immediately post-HD, emphasizing significant post-dialytic shifts that impact electrolyte management in HD patients [9]. During dialysis, exposure to bicarbonate baths plays a crucial role in correcting metabolic acidosis, with clinical guidelines recommending that serum bicarbonate levels be maintained at or above 22 mEq/L [10]. Bicarbonate-based dialysate solutions are currently preferred due to their effectiveness in managing acid-base balance [11]. Despite the prevalence of metabolic acidosis in patients on maintenance haemodialysis (HD), there is a notable lack of local studies examining the fluctuations in serum bicarbonate levels during and between dialysis sessions. This gap in research is particularly important given the potential regional variations in dialysis protocols, dietary habits, and bicarbonate prescription practices in Pakistan, which may influence acid-base balance differently compared to other populations.

This study aims to evaluate the inter-dialytic and intra-dialytic changes in serum bicarbonate levels among patients undergoing maintenance HD, aiming to provide insights that could enhance patient management and improve outcomes in our local setting.

METHODS

This quasi-experimental study was conducted at the Nephrology Department, Fatima Jinnah Medical University (FJMU)/Sir Ganga Ram Hospital, Lahore, after taking synopsis approval from the CPSP from August 2024 to January 2025. Sixty patients meeting the selection criteria were enrolled in this study from the Dialysis unit. Both male and female aged 18-70 years, end-stage renal disease patients (eGFR <15ml/min/m2) on maintenance haemodialysis thrice a week via AV-fistula for more than 3 months' duration were included. Patients on maintenance hemodialysis (MHD) for less than 3 months' duration and those on oral bicarbonate replacement at the time of enrolment in the study were excluded. A sample size of 60 patients was estimated using a 95% confidence level, absolute precision (d) of 0.15, and an expected mean change in bicarbonate level of 0.21 ± 0.59 [12]. Patients were enrolled using non-probability consecutive sampling. Before enrolment, written informed consent was obtained from all patients. Data were collected using pre-designed performa. The participants' age, gender, BMI, comorbid conditions (diabetes, i.e. known diabetics or fasting BSL >126mg/dl, hypertensive (HTN) or BP >130/90mmHg, and Ischemic heart disease), hepatitis B and C status were recorded at the start of the study. Each participant underwent haemodialysis using a Fresenius machine (model 4008S, 4008B, or FX8) with RENACARB Part B (bicarbonate 35 mmol/L) and Part A. The dialysate composition included sodium 140 mmol/L, potassium 2 mmol/L, calcium 1.25 mmol/L, magnesium 0.5 mmol/L, and chloride 105 mmol/L, ensuring optimal acid-base balance. For each patient haemodialysis session lasted for 4 hours, with blood flow rate set at 250-300 mL/min and 1cc of heparin was given to all patients and ultrafiltration was done according to the patient's dry weight. Blood samples were collected at three different time points. The first sample was taken just before dialysis, from the arterial port leading to the dialyzer (Sample 1). The second sample was taken at the end of the dialysis session, after reducing the blood pump flow rate to 100 mL/min for 10-20 second period (Sample 2), and the third sample was taken 48 hours after the dialysis session, just before the next session begins (Sample 3). Serum bicarbonate levels were measured in all three samples to assess both intra-dialytic (pre-HD minus post-HD) and inter-dialytic (post-HD minus next session pre-HD) changes in bicarbonate levels. Serum bicarbonate levels were measured using a biochemical analyzer, ensuring accurate and standardized assessment of acid-base balance during and between dialysis sessions. Data were analysed using SPSS version 26.0. Quantitative variables like age, BMI, and bicarbonate levels were expressed as mean and SD, whereas qualitative variables like gender, comorbidities were presented as frequency and percentages. Change in bicarbonate levels (both inter and intra HD session) was compared using a paired t-test, $p \leq 0.05$ was taken as significant.

RESULTS

The study population (n=60) had a mean age of 49.80 ± 12.08 years; among them, 55% were male (n=33), and 45% were female (n=27). The mean BMI noted was 24.30 ± 1.72 kg/m^2. Regarding comorbidities, 42% had DM, 60% had HTN, 32% had IHD, 12% tested positive for Hepatitis B, and 10% tested positive for Hepatitis C. Pre-haemodialysis bicarbonate was 18.65 ± 1.11 mEq/L, rising to 22.18 ± 0.85 mEq/L post-dialysis but declining to 18.78 ± 1.02 mEq/L by the next session, showing a cyclical pattern (Table 1).

Table 1: Summary of Qualitative and Quantitative Variables of Study Population (n=60)

Variables		n (%), (Mean ± SD)
Age (Years)		49.80 ± 12.08
BMI (Kg/m^2)		24.30 1.72
Gender	Male	33 (55%)
	Female	27 (45%)

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DM	Yes	25 (42%)
	No	35 (58%)
HTN	Yes	36 (60%)
	No	24 (40%)
IHD	Yes	19 (32%)
	No	41 (68%)
Hepatitis B Positive	Yes	7 (12%)
	No	53 (88%)
Hepatitis C Positive	Yes	6 (10%)
	No	54 (90%)
Pre HD Bicarbonate mEq/L		18.65 ± 1.11
Post HD Bicarbonate mEq/L		22.18 ± 0.85
Next Session Pre-HD Bicarbonate mEq/L		18.78 ± 1.02

Results present the changes in serum bicarbonate levels; intra-dialytic change, showed mean increase of 3.53 ± 1.19 mEq/L, with 95% confidence interval ranging from 3.22 to 3.84, which was statistically significant (p-value=0.000). The inter-dialytic change, demonstrated decrease of 3.40 ± 1.18 mEq/L, also reaching statistical significance (p-value=0.000)(Table 2).

Table 2: Mean Change in Bicarbonate Level

Change in Bicarbonate Level	Mean ± SD (mEq/L)	95% (CI) (Lower-Upper)	p-Value
Intra Dialytic Change (Post HD-Pre HD)	3.53 ± 1.19	3.22-3.84	<0.001
Inter Dialytic Change (Post HD-Next Session Pre HD)	3.40 ± 1.18	3.09-3.70	<0.001

When the data were stratified for age, gender, BMI, DM, and HTN, both intra-dialytic and inter-dialytic bicarbonate levels showed a significant increase in post-HD and a decrease in next session pre-HD bicarbonate levels, p<0.001(Table 3).

Table 3: Data Stratification

Stratified Groups		Inter and Intra Dialytic Change in Bicarbonate Level	Mean ± SD (mEq/L)	p-Value
Gender	Male (n=35)	Inter	3.48 ± 1.22	<0.001
		Intra	3.57 ± 1.29	<0.001
	Female (n=27)	Inter	3.29 ± 1.13	<0.001
		Intra	3.48 ± 1.08	<0.001
DM	Yes (n=25)	Inter	3.52 ± 1.26	<0.001
		Intra	3.56 ± 1.32	<0.001
	No (n=35)	Inter	3.31 ± 1.13	<0.001
		Intra	3.51 ± 1.12	<0.001
HTN	Yes (n=36)	Inter	3.47 ± 1.18	<0.001
		Intra	3.55 ± 1.25	<0.001
	No (n=24)	Inter	3.29 ± 1.19	<0.001
		Intra	3.50 ± 1.14	<0.001
Age	<50 Years (n=29)	Inter	3.40 ± 1.45	<0.001
		Intra	3.60 ± 1.45	<0.001
	≥50 Years (29)	Inter	3.40 ± 0.85	<0.001
		Intra	3.46 ± 0.89	<0.001

DISCUSSION

Proper management of acid-base balance, specifically metabolic acidosis in ESRD patients undergoing HD, is essential, as persistent acidosis can lead to adverse outcomes such as cardiovascular complications, bone disease, and muscle wasting, underscoring the importance of effective bicarbonate regulation in this population.This study has examined serum bicarbonate fluctuations in patients undergoing thrice-weekly maintenance hemodialysis. Recent guidelines emphasize individualized bicarbonate prescriptions based on baseline acid-base status, dietary acid load, and comorbidities to prevent complications such as post-dialysis alkalosis, intradialytic hypotension, and increased mortality risk. Maintaining pre-dialysis serum bicarbonate levels around 22–24 mmol/L is recommended to optimize clinical outcomes and muscle mass preservation [10]. Current study demographics showed a mean age of 49.80 ± 12.08 years among ESRD patients, with a higher proportion of male (55%) compared to female (45%). In this study, 42% of ESRD patients on HD had DM, 60% had HTN, 32% had IHD, 12% tested positive for Hepatitis B, and 10% for Hepatitis C. Local studies from Lahore and Karachi reported mean ages of ESRD patients at 43.13 and 51.68 years, respectively [13, 14]. In a study by Ejaz *et al.*, hypertension was present in 69.5% and diabetes in 64.8% of ESRD patients, higher than current observations, though gender distribution was similar (male 58.1%, female 41.9%) [15]. A 2022 study in Pakistan found slightly lower rates of Hepatitis B and C (8% and 4%, respectively) in ESRD patients on HD [16].In the current study, pre-HD mean bicarbonate levels were 18.65 ± 1.11 mEq/L, rising to 22.18 ± 0.85 mEq/L post-HD, but dropping to 18.78 ± 1.02 mEq/L by the next session.Similarly, Abd *et al.*, reported mean bicarbonate levels increasing from 18.0 ± 1.8 to 23.4 ± 2.1 mmol/L, effectively correcting intradialytic acidosis [17]. Kourtellidou *et al.*, also observed pre-dialysis bicarbonate levels rising from 18.15 ± 1.35 to 20.27 ± 1.88 mmol/L [18].A mathematical model suggests that individualized bicarbonate dialysate prescriptions can maintain pre-dialytic bicarbonate levels within the target range, improving patient outcomes, as maintaining levels above 22 mmol/L is crucial due to the associated lower mortality risk [19]. Some studies, however, indicate that rapid changes in bicarbonate levels during dialysis may not be necessary, as levels often return to baseline within 44 to 68 hours' post-dialysis, aligning with the current findings [20].The literature underscores that while increasing dialysate bicarbonate can alleviate pre-dialysis acidemia, it often results in post-dialysis alkalemia and does not sufficiently maintain acid-base balance during the inter-dialytic period. Oral bicarbonate supplementation provides a more effective solution by stabilizing acid-base status without causing significant post-dialysis alkalemia,

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suggesting that individualized bicarbonate management could improve patient outcomes by maintaining a more consistent acid-base balance throughout the dialysis cycle [21]. Bicarbonate fluctuations in haemodialysis patients are influenced by multiple factors, including dialysate bicarbonate concentration, diffusion gradients, and the body's compensatory mechanisms. During dialysis, bicarbonate is transferred from the dialysate into blood via diffusion, rapidly correcting metabolic acidosis. However, post-dialysis, a phenomenon known as "bicarbonate rebound" occurs due to the redistribution of bicarbonate from the extracellular to the intracellular compartment and ongoing metabolic acid production. Inter-dialytic fluctuations arise from dietary acid intake, residual kidney function, and the body's inability to maintain acid-base homeostasis between sessions [5].

CONCLUSIONS

It was concluded that hemodialysis temporarily raises bicarbonate levels, but they drop before the next session, highlighting the need for optimized supplementation or dialysis adjustments to maintain stability.

Authors Contribution

Conceptualization: HJ
Methodology: HJ, SA[1], MSY, SA[2], SAR, SR
Formal analysis: HJ
Writing review and editing: MSY, Sa[2]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Polycystic Ovary Syndrome (PCOS): A Biochemical and Physiological Perspective on a Common Gynaecological Disorder in a Local Hospital of Peshawar

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting reproductive and metabolic health. It is characterized by hormonal imbalances, insulin resistance, dyslipidemia, and chronic inflammation, increasing long-term health risks. **Objective:** To compare biochemical, metabolic, and ultrasound markers in women with and without PCOS. **Methods:** A comparative cross-sectional study was conducted at Health Net Hospital, Peshawar, over six months. In total, 110 participants were recruited and divided equally into 2 groups, with each group considered as PCOS (n=55) and Non-PCOS (n=55). PCOS was diagnosed using the Rotterdam Criteria. Hormonal, metabolic, and inflammatory markers, including luteinizing hormone, Follicle-Stimulating Hormone, testosterone, Dehydroepiandrosterone Sulphate, Anti-Müllerian Hormone, fasting glucose, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), lipid profile, C-reactive protein, Malondialdehyde, and Total Antioxidant Capacity (TAC), were analyzed. Ultrasound findings assessed ovarian morphology, endometrial thickness, and stromal resistance index. Data were analyzed using SPSS. **Results:** PCOS patients had significantly higher BMI, insulin resistance, and androgen levels. Luteinizing hormone/Follicle-Stimulating Hormone ratio and Anti-Müllerian Hormone were elevated, while Follicle-Stimulating Hormone was lower. Metabolic markers showed increased fasting glucose, HOMA-IR, and dyslipidaemia, with higher LDL and triglycerides and lower HDL. Inflammatory and oxidative stress markers (C-reactive protein, Malondialdehyde) were significantly elevated, while TAC was reduced. Ultrasound findings showed increased endometrial thickness and ovarian stromal resistance in PCOS. **Conclusions:** It was concluded that PCOS is associated with significant hormonal, metabolic, and inflammatory disturbances. Elevated androgens, insulin resistance, and oxidative stress highlight the need for early screening and a multidisciplinary approach for Effective Management.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) affects 6% to 21% of reproductive-age women, involving hormonal, metabolic, and ovarian abnormalities [1, 2]. The Rotterdam Criteria, the most used diagnostic tool, requires two of the following: oligo/anovulation, hyperandrogenism, or polycystic ovaries [3, 4]. Beyond reproduction, PCOS poses lifelong metabolic risks, including insulin resistance and cardiovascular disease. PCOS disrupts hormonal and metabolic balance. Androgen excess causes hirsutism, acne, and alopecia due to elevated testosterone and Dehydroepiandrosterone Sulphate (DHEA-S). An altered luteinizing hormone (LH)/Follicle-Stimulating Hormone (FSH) ratio contributes to ovarian dysfunction. High Anti-Müllerian Hormone (AMH) reflects increased ovarian follicles. Insulin resistance worsens hormonal dysregulation, raising risks for type 2 diabetes and

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cardiovascular disease [5]. Beyond hormonal imbalances, metabolic dysfunction is a major concern in PCOS. Insulin resistance and hyperinsulinemia occur even in normal-weight women [6]. These metabolic shifts increase dyslipidaemia risk, characterized by high cholesterol and LDL with low HDL, elevating cardiovascular disease risk. Oxidative stress and chronic low-grade inflammation, marked by elevated C-reactive protein (CRP) and Malondialdehyde (MDA), further exacerbate metabolic and reproductive complications [7, 8]. Ultrasound is a key diagnostic tool for PCOS, revealing increased ovarian volume, multiple small follicles, and altered ovarian stromal vascularity [9]. However, not all women with PCOS exhibit polycystic ovarian morphology, and some without PCOS may present similar findings. This highlights the complexity of PCOS and the need for a multidimensional approach combining biochemical, metabolic, and imaging assessments for accurate diagnosis and management [10]. Despite extensive research, gaps remain in understanding the biochemical, metabolic, and inflammatory profile of PCOS across different populations. Most studies focus on either reproductive or metabolic aspects, with few taking an integrated approach. The link between insulin resistance, inflammation, and oxidative stress in PCOS warrants further investigation to enhance comprehensive disease management. Another key research gap is the role of systemic inflammation and oxidative stress in PCOS. While CRP and MDA are linked to insulin resistance and cardiovascular risk, their exact contribution to PCOS pathophysiology remains unclear. Additionally, transvaginal ultrasound findings, particularly ovarian stromal resistance index (RI), require further correlation with biochemical markers. Most studies focus on Western populations, emphasizing the need to examine these variations in the Pakistani population, particularly in Peshawar, where genetic predisposition, diet, and lifestyle may influence PCOS presentation and progression.

This study aims to comprehensively compare PCOS and non-PCOS women by evaluating hormonal, metabolic, inflammatory, and ultrasound parameters. Addressing these gaps enhances understanding of PCOS pathophysiology, supporting improved diagnosis and management strategies.

METHODS

A comparative cross-sectional analysis was conducted at Health Net Hospital, Peshawar. The study adhered to ethical guidelines outlined in the Declaration of Helsinki. Ethical approval was granted by the Ethics Review Committee of Health Net Hospital (Ref No: 3002/HNH/HR). All participants were provided written informed consent before data collection, and confidentiality of personal and medical information was strictly maintained. The study was carried out over six months, from January 2024 to June 2024. The sample size was initially calculated using Cochran's formula, considering a 95% confidence interval, an expected PCOS prevalence of 10%, and a 5% margin of error, which suggested a requirement of 138 participants [11]. However, due to practical constraints, a final sample of 110 participants was selected. To ensure adequate statistical power, a post-hoc power analysis was conducted, confirming that the sample size retained sufficient power for detecting significant differences between the groups. Additionally, a finite population correction was applied to improve the accuracy of estimates given the restricted hospital-based population. A non-probability consecutive sampling technique was used to recruit participants meeting the eligibility criteria. Participants were divided into two groups: COS Group (n=55): Women diagnosed with PCOS based on the Rotterdam criteria, requiring at least two of the following: oligo/anovulation, hyperandrogenism (clinical/biochemical), or polycystic ovarian morphology, Non-PCOS Group (n=55): Age-matched women with regular menstrual cycles, no signs of hyperandrogenism, and normal ovarian function. Exclusion criteria included pregnancy, lactation, use of hormonal medications within the past three months, diabetes, thyroid disorders, adrenal disorders, and other metabolic or endocrine conditions that could influence study variables. Data collection included demographic and clinical characteristics, such as age, height and weight were measured to calculate BMI (kg/m2, Marital status, education level, employment status, physical activity, dietary habits, smoking status, and history of infertility were recorded through a structured questionnaire. Blood samples were collected after overnight fasting following standard phlebotomy protocol and analysed using a fully automated chemistry analyzer (Abbott Architect c4000, Abbott Diagnostics, USA) following laboratory quality control standards and manufacturer's guidelines. Hormonal and biochemical markers were analyzed using Chemiluminescent Immunoassay kits (Innovative Research) following the manufacturer's instructions and guidelines. Hormonal and biochemical markers were analysed using Chemiluminiscent Immunoassay kits (Innovative Research) following the manufacturer's instructions and guidelines. Luteinizing Hormone (LH) was measured using the Human Luteinizing Hormone Chemiluminescent Immunoassay Kit from Innovative Research (Cat#03045838). Follicle-Stimulating Hormone (FSH) was assessed with the Human Follicle-Stimulating Hormone Chemiluminescent Immunoassay Kit from Innovative Research (Cat# IRAPKT-FSH-HU). Total Testosterone was determined using the Human Total Testosterone

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Chemiluminescent Immunoassay Kit from Innovative Research (Cat# IRAPKT-TTESTO-HU). Free Testosterone was evaluated with the Human Free Testosterone Chemiluminescent Immunoassay Kit from Innovative Research (Cat# IRAPKT-FTESTO-HU). Dehydroepiandrosterone Sulphate (DHEA-S) was measured using the Human DHEA-S Chemiluminescent Immunoassay Kit from Innovative Research (Cat# IRAPKT-DHEAS-HU). Anti-Müllerian Hormone (AMH) was assessed with the Human AMH Chemiluminescent Immunoassay Kit from Innovative Research (Cat# IRAPKT-AMH-HU). Prolactin was determined using the Human Prolactin Chemiluminescent Immunoassay Kit from Innovative Research (Cat# IRAPKT-PRL-HU). Fasting Glucose was measured with the Glucose Assay Kit from Sigma-Aldrich (Cat# MAK181). Haemoglobin A1c (HbA1c) was assessed using the HbA1c Assay Kit from Sigma-Aldrich (Cat# MAK018). Total Cholesterol, LDL, HDL, and Triglycerides were evaluated using the Lipid Panel Assay Kit from Sigma-Aldrich (Cat# MAK045). C-Reactive Protein (CRP) was measured with the Human CRP Chemiluminescent Immunoassay Kit from Innovative Research (Cat# IRAPKT-CRP-HU). Malondialdehyde (MDA) was assessed using the MDA Assay Kit from Sigma-Aldrich (Cat# MAK085). Total Antioxidant Capacity (TAC) was determined using the TAC Assay Kit from Sigma-Aldrich (Cat# ab65329). Ultrasound parameters assessed included endometrial thickness, ovarian stromal resistance index (RI), polycystic ovarian morphology, and ovarian volume. All scans were performed by certified radiologists using a high-resolution ultrasound machine, following standardized protocols. However, individual ultrasound images were not archived for study documentation. Instead, key findings have been summarized based on standardized measurement criteria. All scans were performed by certified radiologists using a high-resolution ultrasound machine, following standardized protocols. The cut-off for an elevated ovarian stromal RI was set at ≥0.55 based on established literature [12]. Insulin resistance was assessed using HOMA-IR, calculated as (fasting insulin × fasting glucose) / 405. The oral glucose tolerance test (OGTT) was not performed in this study. To ensure validity, data collection followed standardized protocols, and biochemical analyses were conducted in a blinded manner. Reliability was maintained through duplicate testing of biochemical markers and inter-observer agreement for ultrasound evaluations, with scans reviewed independently by two radiologists. Statistical analysis was conducted using SPSS version 25. Normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed variables, independent t-tests were used to compare means between PCOS and non-PCOS groups. These included age, LH, FSH, prolactin, fasting blood glucose, HOMA-IR, total cholesterol, LDL, HDL, triglycerides, CRP, MDA, TAC, endometrial thickness, and ovarian stromal resistance index. Non-normally distributed variables, including BMI, LH/FSH ratio, total testosterone, free testosterone, DHEA-S, AMH, and HbA1c, were analyzed using the Mann-Whitney U test. Categorical variables, marital status, education level, employment status, physical activity level, dietary habits, smoking status, parity, history of infertility, polycystic ovarian morphology, and increased ovarian volume, were analyzed using the Chi-square test. Post-hoc Bonferroni corrections were applied to employment status and education level due to their significant Chi-square results. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The study population showed significant differences between women with PCOS and those without. Women with PCOS were younger and had a higher BMI, reinforcing the link between PCOS and obesity. Employment status also varied, with fewer employed women and more students in the PCOS group. Other demographic factors did not show significant differences (Table 1).

Table 1: Demographic and Clinical Characteristics of the Study Population

Variables	Category	PCOS Group (Mean ± SD) / Frequency (%)	Non-PCOS Group (Mean ± SD) / Frequency (%)	p-Value
Age (years)	-	25.43 ± 2.75	27.97 ± 2.65	<0.001** (t-test)
BMI (kg/m^2)	-	30.08 ± 4.04	24.55 ± 2.94	<0.001 (Mann-Whitney U=410.000, Z= -6.591)
Marital Status	Married	37 (67.3%)	31 (56.4%)	0.239 (Chi-square)
	Single	18 (32.7%)	24 (43.6%)	
Education Level	Higher	21 (38.2%)	14 (25.5%)	0.201 (Chi-square, No significant post-hoc results)
	No Education	1 (1.8%)	4 (7.3%)	
	Primary	12 (21.8%)	9 (16.4%)	
	Secondary	21 (38.2%)	28 (50.9%)	
Employment Status	Employed	14 (25.5%)	30 (54.5%)	0.004 (PCOS < Non-PCOS)
	Unemployed	22 (40.0%)	17 (30.9%)	Not significant
	Student	19 (34.5%)	8 (14.5%)	PCOS >Non-PCOS

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Physical Activity	Sedentary	35 (63.6%)	27 (49.1%)	0.054 (Chi-square)
	Moderate	16 (29.1%)	15 (27.3%)	
	Active	4 (7.3%)	13 (23.6%)	
Dietary Habits	Healthy	14 (25.5%)	12 (21.8%)	0.654 (Chi-square)
	Unhealthy	41 (74.5%)	43 (78.2%)	
Smoking Status	Smoker	9 (16.4%)	6 (10.9%)	0.405 (Chi-square)
	Non-Smoker	46 (83.6%)	49 (89.1%)	
Parity	0	24 (43.6%)	19 (34.5%)	0.418 (Chi-square, No Significant post-hoc Results)
	1-2	26 (47.3%)	27 (49.1%)	
	3+	5 (9.1%)	9 (16.4%)	
History of Infertility	Yes	18 (32.7%)	17 (30.9%)	0.838 (Chi-square)
	No	37 (67.3%)	38 (69.1%)	

Hormonal analysis revealed higher luteinizing hormone (LH) and lower follicle-stimulating hormone (FSH) in PCOS, leading to an increased LH/FSH ratio. Elevated total and free testosterone, dehydroepiandrosterone sulphate (DHEA-S), and anti-Müllerian hormone (AMH) indicated androgen excess and greater ovarian reserve. Prolactin was slightly higher in the PCOS group, but the difference was minor. These findings align with typical hormonal imbalances in PCOS (Table 2).

Table 2: Hormonal Profile of PCOS and Non-PCOS Groups

Variables	PCOS Group (Mean ± SD)	Non-PCOS Group (Mean ± SD)	p-Value
LH (mIU/mL)	11.15 ± 1.93	7.14 ± 1.44	<0.001** (t-test)
FSH (mIU/mL)	5.59 ± 1.06	6.44 ± 0.98	<0.001** (t-test)
LH/FSH Ratio	2.09 ± 0.65	1.13 ± 0.29	<0.001** (Mann-Whitney U=169.000, Z= -8.032)
Total Testosterone (ng/dL)	65.99 ± 11.48	34.57 ± 7.39	<0.001** (Mann-Whitney U=29.000, Z= -8.869)
Free Testosterone (pg/mL)	5.03 ± 1.03	2.02 ± 0.43	<0.001** (Mann-Whitney U=2.000, Z= -9.030)
DHEA-S (µg/dL)	178.25 ± 33.25	124.95 ± 18.68	<0.001** (Mann-Whitney U=242.000, Z = -7.595)
AMH (ng/mL)	7.32 ± 1.57	2.99 ± 1.05	<0.001** (Mann-Whitney U=20.000, Z= -8.922)
Prolactin (ng/mL)	14.63 ± 3.31	13.48 ± 2.36	0.038* (t-test)

Metabolic markers showed elevated fasting blood glucose, insulin resistance (HOMA-IR), and haemoglobin A1c (HbA1c) in PCOS, highlighting glucose metabolism disturbances. Lipid profile abnormalities included higher total cholesterol, low-density lipoprotein (LDL), and triglycerides, with lower high-density lipoprotein (HDL). Inflammatory and oxidative stress markers, such as C-reactive protein (CRP) and malondialdehyde (MDA), were elevated, while total antioxidant capacity (TAC) was reduced, indicating increased oxidative stress (Table 3).

Table 3: Metabolic and Oxidative Stress Profile of PCOS and Non-PCOS Groups

Variables	PCOS Group (Mean ± SD)	Non-PCOS Group (Mean ± SD)	p-Value
Fasting Blood Glucose (mg/dL)	98.96 ± 5.09	89.39 ± 5.15	<0.001** (t-test)
HOMA-IR	3.38 ± 0.65	2.10 ± 0.47	<0.001** (t-test)
HbA1c (%)	5.81 ± 0.32	5.33 ± 0.20	<0.001** (Mann-Whitney U=278.000, Z= -7.380)
Total Cholesterol (mg/dL)	206.26 ± 20.31	189.85 ± 13.68	<0.001** (t-test)
LDL (mg/dL)	129.77 ± 14.41	110.30 ± 12.02	<0.001** (t-test)
HDL (mg/dL)	42.64 ± 5.16	51.04 ± 3.82	<0.001** (t-test)
Triglycerides (mg/dL)	157.02 ± 22.77	119.46 ± 19.04	<0.001** (t-test)
CRP (mg/L)	3.55 ± 1.24	2.25 ± 0.92	<0.001** (t-test)
MDA (nmol/L)	4.58 ± 0.87	2.94 ± 0.61	<0.001** (t-test)
TAC (mmol/L)	0.92 ± 0.20	1.33 ± 0.28	<0.001** (t-test)

Gynaecological and ultrasound findings further supported PCOS diagnosis. Endometrial thickness was significantly greater, likely due to prolonged estrogen exposure. The ovarian stromal resistance index (RI) was also higher, indicating altered ovarian blood flow. However, polycystic ovarian morphology and ovarian volume did not significantly differ, reflecting variability in ultrasound features among individuals with PCOS (Table 4).

Table 4: Gynaecological and Ultrasound Features of PCOS and Non-PCOS Groups

Variables	Category	PCOS Group (Mean ± SD) / Frequency (%)	Non-PCOS Group (Mean ± SD) / Frequency (%)	p-Value
Endometrial Thickness (mm)	-	9.66 ± 1.72	7.19 ± 1.62	<0.001**
Ovarian Stromal RI	-	0.60 ± 0.11	0.40 ± 0.07	<0.001**
Polycystic Ovarian Morphology	Yes/No	44 (80.0%) / 11 (20.0%)	43 (78.2%) / 12 (21.8%)	0.815
Increased Ovarian Volume	Yes/No	39 (70.9%) / 16 (29.1%)	43 (78.2%) / 12 (21.8%)	0.381

DISCUSSION

This research sheds light on the biochemical, physiological, and metabolic changes related to polycystic ovary syndrome (PCOS). Our results also corroborate the

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hormonal and metabolic imbalances described in the existing literature on PCOS, which play a crucial role in its pathophysiology. Women with PCOS showed elevated levels of luteinizing hormone (LH) and a remarkably increased LH/FSH ratio compared to those without PCOS. These findings were supported by other research that found an increased LH/FSH ratio as a defining feature of PCOS and a factor of ovarian pathology [13-15]. The increased levels of total and free testosterone, as well as DHEA-S, support the indication of hyperandrogenism, which was a prominent feature of PCOS. These results aligned with earlier studies, which suggested that elevated androgen levels are associated with the clinical features of hirsutism, acne, and alopecia [16-18]. Women with PCOS face a higher risk of insulin resistance and cardiovascular disease. Elevated fasting blood glucose and HOMA-IR levels confirm prevalent insulin resistance, which contributes to hyperandrogenism and ovarian dysfunction [19, 20]. Dyslipidaemia, marked by high cholesterol, LDL, and triglycerides, with low HDL, further exacerbates metabolic risks in PCOS. Markers of inflammation and oxidative stress suggest systemic inflammation in PCOS. Increased CRP and MDA levels indicate heightened inflammatory and oxidative stress, common in metabolic dysfunction. Reduced total antioxidant capacity (TAC) suggests impaired oxidative defence. These findings align with studies linking chronic inflammation and oxidative stress to insulin resistance and cardiovascular risk in PCOS [21-23]. Ultrasound findings support the diagnosis of PCOS, revealing ovarian abnormalities. Increased endometrial thickness results from excess estrogenic secretion due to anovulation. Elevated ovarian stromal RI suggests androgen hypersecretion and follicular arrest. However, polycystic ovarian morphology and ovarian volume did not differ significantly between groups, indicating that while common in PCOS, these features are not definitive diagnostic markers. The study findings align with existing literature, reinforcing the distinct hormonal, metabolic, and inflammatory disruptions in PCOS [24-26]. Early metabolic screening in women with PCOS is essential to prevent long-term complications such as Type 2 Diabetes and cardiovascular diseases. This study supports existing literature by validating the hormonal, metabolic, and inflammatory disruptions characteristic of PCOS [24-26]. Early metabolic screening is crucial in preventing long-term complications such as Type 2 Diabetes and cardiovascular diseases. However, further research should be conducted to focus on targeted interventions addressing both metabolic and reproductive aspects of PCOS to enhance patient outcomes.

CONCLUSIONS

It was concluded that this study highlights the hormonal, metabolic and inflammatory abnormalities of PCOS. An elevated LH/FSH ratio, hyperandrogenism, and insulin resistance denote the endocrine disorder. The metabolic complications of dyslipidaemia, along with increased oxidative stress, are risk factors for cardiovascular diseases. Ultrasound findings confirm ovarian dysfunction; though polycystic morphology alone may not be a definitive diagnostic marker. Such complex findings illustrate the importance of early metabolic assessment and comprehensive intervention for the sustainability of women.

Authors Contribution

Conceptualization: SA
Methodology: SA, SN, SJS, ET
Formal analysis: SN, SJS, MR, SS
Writing review and editing: ET, MR, SS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

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The Role of 8% Branched Amino Acids (BCAA) in Patients with Hepatic Encephalopathy

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ABSTRACT

Hepatic Encephalopathy (HE) is a neuropsychiatric disorder caused by liver dysfunction, commonly seen in cirrhosis or acute liver failure. **Objective:** To address the safety and efficacy of branched-chain amino acids (BCAA) solution in patients with HE. **Methods:** This retrospective study was performed at the Sheikh Khalifa Bin Zayed Al Nahyan Hospital, CMH Rawalakot, Azad Kashmir, Pakistan. Data from patients fulfilling the eligibility criteria during the study span from February 2022 to August 2024 were analyzed. The inclusion criteria were adults aged 18-70 years, diagnosed cases of cirrhosis of the liver, and admitted with HE. The BCCA group was given 8% BCCA solution administered through intravenous (IV) transfusion. Patients receiving any other treatments were categorized as conventional treatment. Psychometric hepatic encephalopathy score (PHES), serum ammonia levels, duration of hospitalization, treatment-related adverse events, and mortality were documented. **Results:** 467 patients were analyzed, the median age was 54.00 (48.00-63.00) years, and 280 (60.0%) were male. 315 (67.5%) received IV BCAA, while the remaining 152 (32.5%) received conventional therapy. Patients in the BCAA group showed a significant improvement in PHES scores, (-2.1 ± 1.9 vs.-4.6 ± 2.2, p=<0.001), reduction in serum ammonia levels (45.3 ± 8.1 vs. 56.2 ± 10.8 µmol/L, p<0.001), mean duration of hospitalization (8.9 ± 3.7 vs. 10.1 ± 4.5 days, p=0.002), and mortality (3.8% vs. 9.2%, p<0.001). In the BCAA group, 8 (2.2%) patients experienced mild gastrointestinal discomfort, and 4 (1.3%) patients reported transient dizziness. **Conclusions:** Intravenous 8% BCAA solution effectively enhances cognitive function, lowers serum ammonia, shortens hospitalization, and reduces mortality in hepatic encephalopathy patients.

INTRODUCTION

Hepatic Encephalopathy (HE) is a complex neuropsychiatric disorder that arises as a result of liver dysfunction, most frequently observed in patients with cirrhosis or acute liver failure. HE is characterized by the accumulation of toxic substances, primarily ammonia, in the bloodstream [1]. Normally, the liver detoxifies ammonia; however, in the presence of liver dysfunction, ammonia levels rise and accumulate in the brain, leading to cognitive impairments ranging from mild confusion to deep coma [2]. The pathophysiology of HE is explained by the direct toxicity of ammonia and alterations in neurotransmission, neuroinflammation, and oxidative stress [3]. HE is estimated to affect as many as 40% of cirrhotic patients with varying degrees of severity depending upon the extent of disease [4]. Data reports 30-40% of hospitalized cirrhotic patients developing overt HE, while the presence of HE is expected to worsen the overall progress of cirrhosis of the liver [5,6]. Standard treatments for HE typically focus on reducing ammonia levels in the bloodstream. The most common interventions include dietary protein restriction, the use of lactulose, and the administration of rifaximin [7]. While these therapies are

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widely used and can be effective. Recent research has suggested that branched-chain amino acids (BCAAs) may offer a novel approach to managing HE by modulating ammonia metabolism and neurotransmitter function [8]. BCAAs, which include leucine, isoleucine, and valine, are essential amino acids involved in protein synthesis and energy metabolism [9]. Emerging evidence suggests that BCAAs may also improve cognitive function in HE patients by serving as an alternative substrate for ammonia detoxification. BCAAs have been shown to influence neurotransmitter synthesis, particularly by modulating the balance between excitatory and inhibitory neurotransmitters in the brain [10]. Utilization of BCAAs in HE is gaining attention due to their potential role in reducing ammonia levels and restoring the neurochemical balance in the brain. BCAAs compete with aromatic amino acids for transport into the brain, thereby reducing the influx of ammonia and improving neurotransmitter balance [11]. Given the significant morbidity and mortality associated with HE, the need for alternative, more effective treatments is pressing. While global research on BCAAs in HE is abundant, local data in Pakistan is scarce. This gap in local evidence underscores the need for further investigation into the efficacy of BCAAs in HE.

This study aimed to address the safety and efficacy of BCAA solution in patients with HE. By assessing clinical outcomes such as cognitive function and ammonia levels, the findings of this study may help in determining whether BCAA can serve as a valuable option to current HE therapies.

METHODS

This retrospective study was performed at the Sheikh Khalifa Bin Zayed Al Nahyan Hospital, CMH Rawalakot, Azad Kashmir, Pakistan. Data of all patients fulfilling the eligibility criteria during the study span from February 2022 to August 2024 were analyzed. Exemption from Institutional Ethical Committee was obtained for conducting this research (PMC/RKT/15/2024). The inclusion criteria were adults aged 18-70 years, diagnosed cases of cirrhosis of the liver, and admitted with hepatic encephalopathy (HE) based on clinical features and confirmed by ammonia levels and neuropsychiatric testing. Data of patients with end-stage liver disease requiring liver transplantation, pregnancy, or lactation were excluded. Patients with other neurological disorders, including stroke, dementia, or epilepsy, chronic renal failure, or heart failure, were also excluded. HE was defined based on clinical symptoms and elevated serum ammonia levels (greater than 50 µmol/L) by the attending consultant gastroenterologist at the time of diagnosis. Demographic characteristics like gender, age, and area of residence were noted from hospital records. Clinical information, like etiology of cirrhosis, Child-Pugh class, presence of comorbidities, and psychometric hepatic encephalopathy score, was also documented from the hospital record. Patients were either categorized as BCCA treated or conventional treatment based on the treatment they received. Patients who had received 8% BCCA solution administered through intravenous (IV) transfusion (Aminoleban by Otsuka Pakistan Ltd) were labeled as the BCCA-treated group. Patients receiving any other treatments like lactulose, rifaximin, or other supportive care like electrolyte management, diuretics, or nutritional support were categorized as conventional treatment. The BCAA solution was administered as 500 ml twice a day over 4 to 6 hours, for 5-7 days, with the dosage adjusted according to clinical response and ammonia levels [12]. If any adverse events were observed or if significant improvements in cognitive function and ammonia levels occurred, the dosage was reduced. Regular monitoring of ammonia levels, as well as renal and liver function, was made to ensure safety and guide appropriate dose adjustments. All patients received standard care for liver disease, including management of underlying cirrhosis, based on their clinical needs. The treatment was provided by the medical team under the supervision of attending physicians and a consultant gastroenterologist managing HE cases. The BCAA solution was administered by trained healthcare staff, including nurses, under the supervision of the treating physicians. The primary outcome included evaluation of cognitive function improvement through analysis of psychometric hepatic encephalopathy score (PHES). The PHES evaluation was conducted by a team of trained healthcare professionals, including a consultant neurologist, hepatologists, and a specialized medical staff, as part of the routine assessment for patients with HE. PHES involves various psychometric tasks, including timed reaction tests, digit-symbol substitution, and other cognitive assessments that have been validated for detecting HE. Secondary outcomes were recorded from the hospital records, in the form of serum ammonia levels (pre-treatment and after 1 week), duration of hospitalization, treatment-related adverse events, and mortality. Data analysis was performed using IBM-SPSS Statistics, version 26.0. Continuous variables were summarized using mean and standard deviation (SD) or median and interquartile range, and categorical variables were shown using frequencies and percentages. The characteristics and outcomes in patients were compared using an independent sample t-test (for normal distribution) or the Mann-Whitney U test (for skewed data), or the chi-square test. Kaplan-Meier curves were estimated to conduct survival analysis, applying the log-rank test. A $p<0.05$ was considered statistically significant.

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RESULTS

Data from 520 patients were initially screened for eligibility. After excluding 53 patients due to conditions such as end-stage liver disease (n=18), pregnancy (n=5), lactation (n=1), neurological disorders (n=8), chronic renal failure (n=11), and heart failure (n=10), 467 patients were considered for this study (Figure 1).

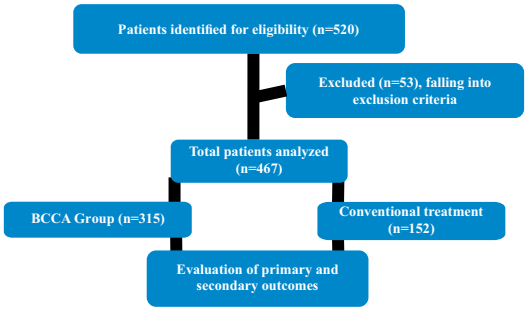

Figure 1: Study Flow Diagram

In 467 patients analyzed, the median age was 54.00 (48.00-63.00) years, and 280 (60.0%) were male. The residential status of 288 (61.7%) patients was rural. There were 228 (48.8%) who were having Child-Paugh Class-B. Hypertension was the common comorbidity, noted in 197 (42.2%) patients. Baseline serum ammonia level was 75.4 ± 21.7 umol/L. Baseline mean PHES was 6.4 ± 2.2. Of the total 467 patients, 315 (67.5%) received BCAA, while the remaining 152 (32.5%) received conventional therapy. Concerning treatment given, there was no significant differences regarding age (p=0.204), gender (p=0.819), residence (p=0.958), etiology of liver disease (p=0.389), Child-Paugh Class (p=0.939), diabetes mellitus (p=0.416), hypertension (p=0.533), renal dysfunction (p=0.401), serum ammonia level (p=0.401), and PHES (p=0.651), and the details are shown in Table 1.

Table 1: Characteristics of patients with hepatic encephalopathy (n=467)

Variables	Category	Total Range/ Frequency (%)	BCAA-Treated Group Range/ Frequency (%) (n=315)	Conventional Treatment (n=152)	p-Value
Age	Median (Interquartile Range) Years	54.00 (48.00-63.00)	56.00 (48.00-63.00)	54.00 (48.00-59.75)	0.380
Gender	Male	280 (60.0%)	190 (60.3%)	90 (59.2%)	0.819
	Female	187 (40.0%)	125 (39.7%)	62 (40.8%)	
Residence	Rural	288 (61.7%)	194 (61.6%)	94 (61.8%)	0.958
	Urban	179 (38.3%)	121 (38.4%)	58 (38.2%)	
Child-Paugh Class	A	176 (37.7%)	120 (38.1%)	56 (36.8%)	0.939
	B	228 (48.8%)	152 (48.2%)	76 (50.0%)	
	C	63 (13.5%)	43 (13.7%)	20 (13.2%)	
Comorbidities	Diabetes mellitus	148 (31.7%)	96 (30.5%)	52 (34.2%)	0.416
	Hypertension	197 (42.2%)	136 (43.2%)	61 (40.1%)	0.533
	Baseline renal dysfunction (serum creatinine > 1.5 mg/dl)	55 (11.8%)	39 (12.4%)	16 (10.5%)	0.560
Baseline serum ammonia (µmol/L)		75.4 ± 21.7	76.6 ± 21.3	74.8 ± 22.5	0.401
Psychometric Hepatic Encephalopathy Score		-6.4 ± 2.2	-6.4 ± 2.3	-6.5 ± 2.1	0.651

Patients in the BCAA group showed a significant improvement in PHES scores, with a mean change from -6.4 ± 2.2 at baseline to -2.1 ± 1.9 after treatment, in contrast to conventional treatment with a baseline of -6.4 ± 2.3 to -4.6 ± 2.2 (p <0.001). Patients in the BCAA group demonstrated a significant reduction in serum ammonia levels, with a mean decrease from 75.4 ± 21.7 umol/L at baseline to 45.3 ± 8.1 µmol/L after treatment, in comparison to baseline levels of 76.6 ± 21.3 µmol/L to 56.2 ± 10.8 µmol/L with conventional treatment (p<0.001). The mean duration of hospitalization was significantly shorter in the BCAA group (8.9 ± 3.7 vs. 10.1 ± 4.5 days, p=0.002). In the BCAA group, 8 (2.2%) patients experienced mild gastrointestinal discomfort, and 4 (1.3%) patients reported transient dizziness. Mortality was significantly less among patients who were given BCCA (3.8% vs. 9.2%, p<0.001). In Child-Pugh Class A, mortality was noted in 2 patients in the BCAA-treated group versus 3 in the conventional treatment group. In Child-Pugh Class B, 5 patients died in the BCCA patients, versus 4 in the conventional treatment group. In Child-Pugh class C, 5 patients died in the BCAA treatment group versus 7 in conventional treatment. There was no significant difference in mortality and various Child-pugh classifications (p=0.781). The comparison of primary and secondary outcome details between BCCA and conventional treatment is shown in Table 2.

Table 2: Comparison of primary and secondary outcomes in patients with hepatic encephalopathy (n=467)

Outcomes	BCAA-Treated Group (n=315)	Conventional Treatment (n=152)	p-Value
Psychometric Hepatic Encephalopathy Score	-2.1 ± 1.9	-4.6 ± 2.2	<0.001
Serum ammonia (umol/L)	45.3 ± 8.1	56.2 ± 10.8	<0.001
Duration of hospitalization	8.9 ± 3.7	10.1 ± 4.5	0.002

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Adverse Events	Gastrointestinal discomfort	8 (2.2%)	-	0.047
	Transient dizziness	4 (1.3%)	-	0.163
	Nausea	-	5 (3.3%)	0.001
Mortality		12 (3.8%)	14 (9.2%)	0.017

Survival analysis showed statistically significant differences between both study groups (p=0.035), and the details are depicted in Figure 2.

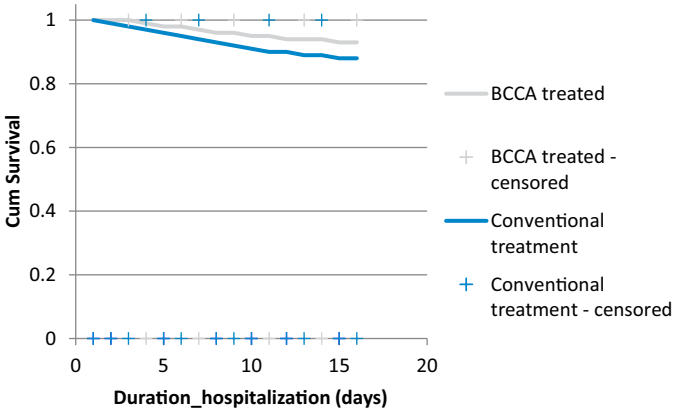

Figure 2: Kaplan-Meier survival analysis between study groups

DISCUSSION

The findings of this study indicate that BCAA supplementation is effective in improving cognitive function, reducing ammonia levels, and decreasing the length of hospitalization in patients with HE. These results provide compelling evidence for the therapeutic potential of BCAA supplementation in patients with HE. A Cochrane systematic review by Gluud *et al.*, which included 16 randomized clinical trials with 827 participants, found that BCAA supplementation significantly improved HE (RR 0.73, 95% CI 0.61 to 0.88) [13]. They also found no significant effect of BCAA on mortality, but reported improvements in HE symptoms. The present study reported significantly better survival among patients using BCAA, which contradicts the findings of Gludd *et al.,* [13]. Dam *et al.,* found beneficial effects of BCAA on HE and emphasized the ammonia-lowering effects of BCAAs, which is consistent with the present findings [14]. The reduction in ammonia levels in the BCAA group in this study (from 76.6 to 45.3 µmol/L) further supports the hypothesis that BCAAs may help lower ammonia levels through muscle metabolism, as suggested by Dam *et al.*, and Holeček [14, 15]. These findings are important because elevated ammonia is a key neurotoxic mediator in HE, and its reduction could be a mechanism through which BCAAs exert their cognitive benefits [16]. Marrone *et al.*, highlighted that the BCAA-induced balance of amino acids could be associated with improved HE symptoms [17]. Afridi *et al.*, in a local study, observed that BCAA supplementation was more effective than conventional therapy in improving clinical outcomes in patients with HE due to cirrhosis [12]. Afridi *et al.*, adopted a similar methodology with a randomized controlled trial design and showed significant clinical improvement in the BCAA group, which mirrors the current results in terms of PHES and ammonia levels [12]. While there is a wealth of studies supporting the benefits of BCAAs, particularly on cognitive outcomes and ammonia reduction, the differences in results across studies can often be attributed to factors such as the administration route (oral vs intravenous), the duration of supplementation, and variations in patient populations. The IV BCAA administration may provide more immediate therapeutic effects, as observed in this study, compared to oral supplementation, which may take longer to achieve clinical improvements [18]. The clinical implications of the present study are significant.HE is a common and debilitating complication of liver cirrhosis and other liver diseases, associated with significant morbidity, mortality, and healthcare costs [19, 20]. Current treatments, such as lactulose or rifaximin, are effective in reducing ammonia levels; their role in addressing the underlying neurochemical disturbances in the brain remains questionable [21].The introduction of BCAA supplementation could provide an additional avenue for improving cognitive function, reducing ammonia levels, and shortening hospitalization times in patients with HE. This study demonstrated a significant reduction in the length of hospitalization in the BCAA group, which is particularly important in a clinical setting where reducing hospital stays can help alleviate the burden on healthcare systems and reduce associated costs. The low incidence of adverse events (e.g., gastrointestinal discomfort, transient dizziness) in the BCAA group further underscores the safety of this therapy [22, 23]. Given that HE is a progressive condition and patients often experience repeated episodes, BCAA supplementation could also play a role in improving long-term outcomes, such as reducing the risk of recurrent HE episodes and improving overall quality of life. Several limitations of this research should be noted. The study design was retrospective, which limits the ability to draw definitive conclusions about causality. Although the results are compelling, further randomized controlled trials are needed to confirm the efficacy of BCAA supplementation in larger and more diverse patient populations. While this study observed significant improvements in cognitive function and serum ammonia levels, the long-term benefits of BCAA supplementation in patients with HE remain unclear.Longer-term studies

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would provide valuable insights into the sustainability of these improvements and the potential impact on liver disease progression and survival.Future studies should include a broader range of liver disease etiologies to determine whether BCAA supplementation is equally effective in these groups.

CONCLUSIONS

This study demonstrates that the intravenous administration of 8% BCAA solution is effective in improving cognitive function, lowering serum ammonia levels, reducing the duration of hospitalization, and decreasing mortality in patients with hepatic encephalopathy. These findings support the use of BCAA supplementation in the management of HE. BCAA supplementation could be considered an important addition to the therapeutic armamentarium for HE.

Authors Contribution

Conceptualization: AS
Methodology: RS, HM, MAQ, AS
Formal analysis: MAQ, RM, RS, HM
Writing review and editing: AS, MAQ, AM, RS, HM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Association of Personality Traits and Future Specialty Preference among MBBS Students

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ABSTRACT

Different personality traits may have a significant impact on medical students' choices on future selection of their future specialty selection. **Objectives:** To determine the most common personality traits among medical students. Also, to establish if there is any association between traits and future specialty preference. **Methods:** An analytical cross-sectional study was conducted from June 2024 to December 2024. A validated questionnaire was used and distributed through social media platforms, and quota non-purposive sampling was done. The Big Five Inventory (BFI) was used for personality traits assessment. For demographics and specialty choice, frequencies and percentages were calculated. The chi-square test was used to assess the association between gender and choice of specialty. Analysis of variance (ANOVA) was employed to assess the mean comparisons of personality traits with specialty preferences. Post hoc, a Tukey HSD test was done to determine the statistical significance of the association between specialty selection and personality traits. p-value≤0.05 was taken as significant. **Results:** Between gender and specialty selection, a significant association was seen (p=0.033). The personality profiles of medical students showed a higher Mean + SD in the agreeableness profile (3.77 + 0.52). Significant associations with agreeableness and openness traits (p=0.05) were seen with the specialty chosen. **Conclusions:** The findings offered important perspectives on the relationship between personality traits and specialty selection among medical students. Future studies should build on these ideas, looking into various dynamic influences that affect specialty choice and the significance of personality traits in this regard.

INTRODUCTION

It is the most important decision for medical students as to which medical specialty to choose; it has great relevance not only for their future careers but also for the total health service workforce. Choosing a medical specialty is guided by quite a variety of factors, such as personal interests, career ambitions, lifestyle choices, and societal demand. However, today personality traits have started to be one factor contributing to the determination of this choice [1]. Personality traits are the stable patterns of thought, feeling, and behavior that each human demonstrates, meaning that personality traits are part of the choose the option that one prefers and is inclined towards professional choices. Between personality traits and specialty preference, the association has academic interest but also practical use in career counseling, medical education, and workforce planning [2]. Deciding on the medical specialty to choose is the most critical decision for medical students; it not only determines their future careers but also that of the entire health service workforce. Some determinants for specialty choice include personal interests, career ambitions, lifestyle preferences, and societal demand. Lately, personality traits have become one such factor that has begun attracting more attention. Personality traits are stable patterns of thought, feeling, and behavior shown by almost all human beings; therefore, personality traits are part of the options that one prefers and will determine professional choices as well. The relationship between personality traits and specialty

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preference holds academic interest but equally serves as valuable information for career counseling, medical education, and workforce planning. The Big Five Inventory (BFI-44) is the non-irrefutable instrument for the evaluation of personality traits. It encompasses five major divisions termed Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. Each of these traits contains aspects related to one's personality, and a composite of these traits will provide a more holistic picture of one's behavioral tendencies and preferences in the profession [3]. High levels of conscientiousness have been associated with preferences for structured and detail-oriented specialties, while extraversion may predispose individuals to specialties requiring high levels of interpersonal interaction. Similarly, openness to experience might drive interest in research-oriented or innovative fields, whereas neuroticism could influence preferences based on perceived stress levels in different specialties [4]. The BFI traits serve as a well-established theoretical basis for this research. Openness to Experience, which includes curiosity, creativity, and a tendency towards new experiences, may encourage students to opt for fields that provide avenues for innovation, research, and ongoing learning. Conscientiousness, which reflects traits like organization, diligence, and dependability, is often associated with preferences for fields that demand precision and meticulousness, such as surgery or internal medicine [5]. Extraversion, which encompasses sociability, assertiveness, and a preference for dynamic interactions, might steer students towards specialties that involve patient interaction, such as pediatrics, family medicine, or psychiatry [6]. Agreeableness, characterized by empathy, cooperation, and a selfless attitude, may correlate with fields that prioritize patient care and teamwork, like obstetrics and gynecology [7]. Lastly, Neuroticism, which suggests emotional instability and sensitivity to stress, could sway specialty preferences based on how different fields are perceived in terms of work-life balance and stress levels [8]. This research utilizes the BFI-44 inventory to evaluate the personality traits of MBBS students and explores how these traits relate to their chosen specialties. Employing the BFI-44 guarantees a trustworthy and valid evaluation of personality aspects, enabling thorough analysis and understanding. Furthermore, comprehending the link between personality traits and specialty preference has broader implications beyond individual career decisions. It can assist in tackling larger issues within healthcare delivery, including the uneven distribution of specialists, physician burnout, and the alignment of healthcare professionals with the needs of varied patient demographics. For example, recognizing personality traits tied to underrepresented specialties, such as family medicine or public health, could lead to targeted strategies to motivate students with compatible traits to enter these areas [9]. Similarly, understanding the influence of neuroticism on specialty choice could facilitate initiatives aimed at helping students manage stress and achieve a better work-life balance, thus improving their overall health and job satisfaction. The importance of this study is heightened by the challenges confronting Pakistan's healthcare system. With a burgeoning population and an escalating burden from both communicable and non-communicable diseases, the demand for a well-distributed and suitably trained healthcare workforce has become increasingly urgent. Even though personality traits are being accepted increasingly as important variables in affecting medical specialty choice, most research on the subject has been conducted within countries that can be classified as high-income. Health systems, structures of medical education, and motivations for careers in such countries may differ greatly from those in developing nations. Be that as it may, the appropriateness of the data obtained from such surveys about medical students in Pakistan remains debatable, as culture, economics, and society may differ in the impact they have on a person's specialty preference. Not much has been researched on how personality traits are aligned with the orientation of specialists in Pakistan's health care system, where a lopsided workforce remains a critical issue.

This study aimed to fill this existing gap by studying the relationship between personality traits and specialty preferences among MBBS students in Faisalabad and thus using the BFI-44 personality inventory, hoping to give region-specific insights on how personality affects careers in a developing country context. This will also contribute to medical education planning, career counseling, and workforce distribution strategies in the health sector of Pakistan.

METHODS

The analytical cross-sectional study was conducted among medical students of a private medical college in Faisalabad city, Pakistan. Before conducting the study, ethical approval was taken from the institutional ethical committee with reference number IEC/310-24. The duration of the study was 7 months, i.e. June 2024 to December 2024. All medical students of the MBBS classes were invited to participate in the study. A validated questionnaire was used for this study after taking consent from the respective author [10]. It was made on Google Forms and distributed through social media platforms. Sample size determination was based on feasibility and statistical merit. The target population comprised all MBBS students from a private medical college; hence, quota

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sampling methodology was applied for equal representation of students from all academic years (1st to 5th year), also given gender balance. Three hundred fifty participants were finally selected. A formal power analysis was not conducted, given that a sample size of 350 would normally be fairly high for ANOVA and Chi-square tests, requiring, on average, a sample size of 50 per group to pick up an effect of interest. Only those students were taken who filled out the questionnaire completely first in their respective classes, and the rest were excluded. The questionnaire has 3 components: 1st section has informed consent, in the 2nd section there were questions regarding demographics and speciality options and 3rd section has questions regarding personality traits to identify five different personality dimensions i.e. Big Five Inventory (BFI) having 44 questions on a Likert scale ranging from strongly disagree=0 to strongly agree=5. After data collection, the data were imported into an Excel sheet and then into SPSS version 25.0 for analysis. For demographics and specialty choice, frequencies and percentages were calculated. The mean ± SD were taken for personality traits. The Chi-square test was used to answer the questions posed by the categorical variables-gender and specialty preference. ANOVA tests were found suitable for checking the differences between means of personality trait scores (continuous variable) against multiple specialty choices (categorical variable). After a significant ANOVA result, Tukey's Honest Significant Difference (HSD) test was performed under the assumption of equal variances, which had also been tested using Levene's test. p-value<0.05 was taken as significant.

RESULTS

Out of 350, 175(50%) were male, and an equal percentage of female were included. An equal percentage of students were taken from each MBBS class, i.e. 70 (20%), having equal representation of male and female (50%) in each class. The mean + SD of participants' age was 21.4 + 1.64. In terms of specialty choices, most of them chose surgery (139, 39.7%); followed by medicine (95, 27.1%), about one-fourth of them (76, 21.7%) were unsure at the moment for their career choices, while 40 (11.4%) chose career in basic sciences. Between gender and specialty selection, a significant association was seen by using the chi-square test, as shown in Table 1.

Table 1: Future Career Selection and Gender Association

Variable		Future Career Selection				p-Value
		Medicine	Surgery	Not Decided	Basic Sciences	
Gender	Male	50	63	34	28	0.033
	Female	45	76	42	12	

The chi-square test result suggests that gender significantly influences specialty choice, with more female favoring surgery, more male opting for basic sciences, and a higher proportion of female remaining undecided. The significant association between gender and specialty selection may stem from a combination of intrinsic preferences, societal norms, mentorship availability, work-life balance concerns, and confidence levels. These factors collectively shape how male and female students approach their future career paths in medicine. The personality profiles of medical students showed higher Mean + SD in the agreeableness profile, followed by openness and conscientiousness, as shown in Table 2.

Table 2: Dominant Personality Traits of Medical Students

Sr. No	Personality Traits	Mean ± SD
1	Agreeableness	3.77 ± 0.52
2	Openness	3.53 ± 0.45
3	Conscientiousness	3.43 ± 0.51
4	Neuroticism	3.27 ± 0.58
5	Extraversion	3.19 ± 0.49

Findings show the relationship between participants' personality profiles and specialty selected by using ANOVA. As per specialty chosen by medical students, their personality profiles were stratified, which showed significant associations with agreeableness and openness traits, with openness having the highest means, while no significant associations were seen with extraversion, conscientiousness and neuroticism. Extraversion showing borderline significance in specialty selection, also in Surgery, often assumed to attract extraverts, had a mean extraversion score similar to other specialties, signifying that skill and technical precision might play a greater role in specialty selection than extraversion alone. Conscientiousness (diligence, organization) is generally linked to highly structured fields like internal medicine or surgery, but since conscientiousness scores were similar across all groups, it may not have been a deciding factor in specialty selection. Neuroticism usually goes with a concern for sensitivity to stress and work-life balance. Probably, if some students were too high in neuroticism, they might avoid stressful types of specialties, but since there is diverse tolerance to stress by different people, this factor may not have led to clear specialty-based differentiation, as shown in Table 3.

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Table 3: Association of Personality Traits Means with Specialty Preference

Personality Traits	Specialty				p-Value
	Medicine	Surgery	Not Decided	Basic Sciences	
Extraversion	25.79 ± 3.81	26.06 ± 4.12	25.15 ± 3.71	24.61 ± 3.74	0.06
Agreeableness	33.97 ± 4.65	34.17 ± 4.38	32.03 ± 5.23	34.43 ± 4.86	0.05
Conscientiousness	30.84 ± 4.34	31.06 ± 4.89	31.53 ± 3.78	30.17 ± 4.85	0.43
Neuroticism	27.15 ± 4.51	25.68 ± 4.48	25.65 ± 5.07	26.34 ± 4.82	0.09
Openness	35.41 ± 4.45	36.02 ± 4.18	34.30 ± 5.02	34.57 ± 4.54	0.05

To determine the statistical significance between agreeableness and openness with specialty selection, post hoc Tukey HSD was applied. Findings show an association between specialty and personality trait 'Agreeableness'. Evidence appears borderline different across specialty groups, where not yet decided tend to score significantly less as compared to those who chose basic sciences. This finding may prove worthwhile in investigating the reason for some specialties in students being less agreeable. Agreeableness tends to go with cooperation, empathy, and social harmony. The lower agreeableness scores in undecided students suggest that reduced social cooperation, skepticism in decision-making, and difficulty in teamwork may contribute to their career uncertainty. Addressing these factors through mentorship, career counseling, and exposure to different specialties could help guide these students toward a fulfilling career path. Although openness was significantly associated with specialty selection, the differences between individual specialty groups were not strong or distinct enough to reach significance in post hoc comparisons. This could be due to small sample sizes, overlapping openness scores, and the general influence of openness across multiple specialties rather than a strong preference for any single specialty. Extraversion, conscientiousness, and neuroticism may not have shown significant associations because they are either broadly applicable across all specialties (extraversion, conscientiousness) or more related to career satisfaction rather than selection (neuroticism). In contrast, agreeableness and openness play a direct role in decision-making, teamwork, and adaptability, making them more relevant in specialty selection, as shown in Table 4.

Table 4: Association Between Specialty and Personality Trait 'Agreeableness'

Specialty (I)	Specialty (J)	Mean Difference (I-J)	SD Error	Sig	95% Confidence Interval	
					Lower Bound	Upper Bound
Medicine	Surgery	-0.197	0.620	0.989	-1.80	1.40
	Not Decided	1.943	0.886	0.128	-0.35	4.23
	Basic Sciences	-0.466	0.717	0.916	-2.32	1.39
Surgery	Medicine	0.197	0.620	0.989	-1.40	1.80
	Not Decided	2.140	0.845	0.057	-0.04	4.32
	Basic Sciences	-0.269	0.665	0.978	-1.99	1.45
Not Decided	Medicine	-1.943	0.886	0.128	-4.23	0.35
	Surgery	-2.140	0.845	0.057	-4.32	0.04
	Basic Sciences	-2.409*	0.918	0.045	-4.78	-0.04
Basic Sciences	Medicine	0.466	0.717	0.916	-1.39	2.32
	Surgery	0.269	0.665	0.978	-1.45	1.99
	Not Decided	2.409*	0.918	0.045	0.04	4.78

Results show the association between specialty and personality trait 'Openness'. No specialty group was significantly different from the other. Hence, this trait seems to be stable for any chosen specialty. The trait openness to experience (curiosity, creativity, willingness to try new things) is beneficial across multiple specialties rather than being confined to one. For example, both basic sciences and surgery may attract open individuals, one due to its research focus and the other due to innovation in surgical techniques. The mean openness scores are relatively close across specialties, meaning no single specialty group had a distinctly high or low openness score; see Table 5.

Table 5: Association Between Specialty and Personality Trait 'Agreeableness'

Specialty (I)	Specialty (J)	Mean Difference (I-J)	SD Error	Sig	95% Confidence Interval	
					Lower Bound	Upper Bound
Medicine	Surgery	-0.611	0.591	0.729	-2.14	0.91
	Not Decided	1.111	0.836	0.546	-1.05	3.27
	Basic Sciences	0.845	0.683	0.604	-0.92	2.61
Surgery	Medicine	0.611	0.591	0.729	-0.91	2.14
	Not Decided	1.722	0.796	0.136	-0.33	3.78

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	Basic Sciences	1.456	0.633	0.100	-0.18	3.09
Not Decided	Medicine	-1.111	0.836	0.546	-3.27	1.05
	Surgery	-1.722	0.796	0.136	-3.78	0.33
	Basic Sciences	-0.266	0.867	0.990	-2.50	1.97
Basic Sciences	Medicine	-0.845	0.683	0.604	-2.61	0.92
	Surgery	-1.456	0.633	0.100	-3.09	0.18
	Not Decided	0.266	0.867	0.990	-1.97	2.50

DISCUSSION

This study sought to explore the relationship between personality traits and career specialty choices among medical students, utilizing a sample of 350 participants with an equal gender distribution. The findings revealed a preference for surgical specialties among participants, with a significant association between gender and specialty choice. Furthermore, personality profiling demonstrated that agreeableness and openness were the most dominant traits among the students, which may influence their career aspirations. A study done by Borracci *et al.*, showed that only neuroticism was significantly associated with specialty choice, but in our study, it was not significantly associated [1]. The difference may be due to the sample size characteristics, as they included only students of two classes, while in our study, students from all classes were included. A research done by Coenen *et al.*, also showed that specialty preference was significantly associated with openness and agreeableness traits, similar to our study, but different in terms of extraversion, in which there was no significant association in our study [11]. A study conducted by Vedel, showed that students scored higher on extraversion and agreeableness traits, while in our study, there were agreeableness and openness [12]. The difference may be because she included participants from different fields of study rather than the medical field only. A study done by Turska *et al.*, showed that conscientiousness and agreeableness were the significant predictors in choosing a specialty, which was similar in agreeableness but different in openness trait, as in our study [13]. A study done by Fino *et al.*, showed that openness was significantly associated with specialty selection, similar to our study [14]. A study done by Khamees *et al.*, showed similar results to our study, i.e. most common specialty chosen was surgery, followed by medicine and then yet to decide, and the least chosen was basic sciences. Also significant association was seen with gender, with female choosing surgery more than male [15]. In contrast, the study done by Kuteesa *et al.*, showed that female was less likely to opt for surgery fields than male [16].This could be the kind of divergence that can be attributed to differences in context within the area of education and local health needs, around which students were exposed to these specialties during training. It thereby lends credence to the argument for exploring aspects of individual educational context when viewing specialty choice data as a result of external factors influencing the decision-making process significantly. A study done by Levaillant *et al.*, showed that surgery and medicine were the most commonly opted specialties, with gender having a significant effect on this selection, as in our study [17]. A study done by Al-Zubi *et al.*, showed that medicine was the most preferred specialty among medical students, with male choosing it more than female, which was similar in terms of gender selection but different in choice of field [18]. A study done by Mahfouz *et al.*, showed that family medicine was the most common specialty, which was different from our study. It may be due to the smaller sample size and different sample demographics from our study [19]. Research conducted by Asiri *et al.*, showed that although gender had a significant role in specialty selection, as in our study but female chose pediatrics and male chose medicine as the dominant specialty, which was different from our study results. The difference may be attributed to the larger sample size and different population dynamics in that study [20]. The borderline differences noted in specialty groups concerning agreeableness warrant further investigation. As shown in our post hoc analyses, students yet to decide on a specialty tended to demonstrate lower agreeableness scores when compared to those inclined towards basic sciences. This could suggest a potential underlying apprehension towards commitment to a specialty, raising important questions about the psychological factors at play in decision-making.

CONCLUSIONS

It was concluded that a significant correlation between specialty choice and personality traits is found only in the case of agreeableness and openness. Although extraversion, conscientiousness, and neuroticism are unrelated, students who do not choose their specialties have significantly lower agreeableness scores than students taking basic sciences. Such data collates with certain trends in literature already available, but also indicates the need for a more profound investigation into the real reasons behind preferences for certain areas in varying educational cultures. Future studies should follow this research by focusing on other possible influencers such as mentorship, career aspirations, and institutional

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factors to render the personality traits comprehension in specialty choice even better.

Authors Contribution

Conceptualization: AR
Methodology: MUD, HA, MA, MJ, IN, S
Formal analysis: MUD
Writing review and editing: MUD, HA, AR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Evaluating the Incidence of Co-Existing Injuries in Anterior Talofibular Ligament Injuries a Magnetic Resonance Imaging Study

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ABSTRACT

Ankle lateral ligament injuries are common in everyday life as well as in athletic activities. Ankle injuries most commonly affect the anterior talofibular ligament (ATFL). Due to ATFL's susceptibility, achieving intelligent localization and injury evaluation is extremely important from a clinical standpoint. **Objectives:** To evaluate the incidence and patterns of co-existing injuries in ATFL damage using Magnetic Resonance Imaging (MRI). **Methods:** In this cross-sectional study, fifty-five patients undergoing surgical management for ATFL injuries were included. Preoperative MRIs of affected ankles were analyzed to document ATFL integrity and associated injuries. Descriptive statistics were used to summarize findings, with categorical variables reported as frequencies and percentages and continuous variables as means ± SD. **Results:** The mean age of the patients was 36.8 ± 12.4 years, with 61.8% male and 38.2% female. Associated injuries were observed in 72.7% of patients. ATFL injuries included 30.9% low-grade incomplete, 21.8% high-grade incomplete, and 14.5% complete tears. calcaneofibular ligament (CFL) injuries were common, with 36.4% showing partial tears, and 3.6% complete tears.The deep deltoid ligament was intact in 56.4%, while 43.6% had injuries.The superficial deltoid ligament was intact in 70.9%. The peroneal tendon was intact in 83.6%, with 5.5% having injuries and 10.9% showing tendinosis. Osteochondral Defects (OCDs) were present in 21.8% of cases. **Conclusions:** It was concluded that ATFL injuries frequently occur with damage to other structures, particularly the CFL and deltoid ligaments. MRI facilitates accurate diagnosis, emphasizing the need for comprehensive assessment and concurrent management of associated injuries during ATFL repair.

INTRODUCTION

In sports, Ankle sprains are among the most common injuries, comprising up to 40% of all athletic injuries [1]. Despite their frequency, the patterns of associated structural damage, optimal diagnostic approaches, and their clinical significance continue to be areas of clinical interest. The ankle joint, which is formed by the tibia, fibula, and talus bones, is a hinged synovial joint. This joint is supported by the medial and lateral ligament complexes as well as the syndesmotic ligaments. Among these, the lateral ligament complex is most vulnerable to injury, particularly during inversion movements. These movements account for the majority of ankle sprains. This ligament complex includes the ATFL, the calcaneofibular ligament (CFL), and the posterior talofibular ligament (PTFL). The ATFL is the most frequently injured structure due to its primary role in stabilizing the ankle during plantarflexion and resisting anterolateral talar translation. Studies suggest that the ATFL is damaged in as many as 90% of significant ankle injuries, compared to 50–75% for the CFL and only 10% for the PTFL [2, 3]. Lateral ankle

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sprains typically occur when excessive abduction and internal rotation of the rear foot are combined with external rotation of the lower leg. Such movements place undue tension on the lateral ligaments, particularly during plantarflexion, increasing the risk of ligamentous injury. Damage occurs when the tensile forces acting on these ligaments exceed their physiological strength [4, 5]. While the primary injury involves the ATFL, co-existing injuries to adjacent structures such as the CFL, deltoid ligaments, peroneal tendons, and osteochondral surfaces are frequently observed. These injuries can influence treatment decisions and long-term outcomes, making their accurate detection clinically significant. The initial clinical evaluation of an ankle sprain focuses on identifying dislocations or asymmetries. It also focuses on palpating for tenderness over the medial and lateral ankle ligaments, and assessing the fibula. To rule out more severe injuries, observations for edema, ecchymosis, muscle strength deficits, and range of motion restrictions are crucial, along with neurovascular examinations [6, 7]. Advanced imaging modalities, such as ultrasonography (US), MRI, arthrography, and stress radiography, play a key role in diagnosing ligament injuries, especially in chronic cases [8]. Although stress radiography is particularly useful in ruling out fractures, which occur in less than 15% of cases, US and MRI are more sensitive in detecting ligamentous injuries [9]. US is a valuable bedside tool, with a reported 91% accuracy in identifying ATFL injuries, while MRI demonstrates 97% accuracy, particularly for detecting associated injuries such as bone marrow edema, tendon abnormalities, and osteochondral defects [10]. However, the diagnostic sensitivity of MRI for acute ATFL injuries varies widely, ranging from 40% to 95%, with specificity reported between 70% and 97% [11, 12]. MRI findings for ATFL injuries may include ligament discontinuity, irregular contours, thickening or thinning, the bright rim sign [13], or bone avulsions [14, 15]. Despite these advantages, MRI is often underutilized in the acute setting due to its variable sensitivity, cost, and limited availability. Additionally, most existing literature focuses on chronic instability rather than the early detection of concurrent injuries in acute ATFL tears [16]. Persistent symptoms such as instability, stiffness, edema, pain, and muscle weakness are reported in 10%-30% of patients following initial treatment, underscoring the need for careful long-term management [12, 15]. While physical therapy is effective for most cases, surgical intervention may be required in patients with unresolved symptoms or chronic instability. A key limitation in the current understanding of ATFL injuries is the lack of studies assessing the prevalence and patterns of associated injuries using MRI in the acute phase. Identifying these injuries early can help tailor rehabilitation strategies and prevent long-term complications.

This study aims to systematically evaluate the prevalence and patterns of associated injuries in patients with ATFL tears using MRI. By identifying the structures most commonly affected alongside the ATFL, this research seeks to bridge a critical knowledge gap and improve both diagnostic accuracy and patient management strategies.

METHODS

A cross-sectional study was conducted over six months commencing from March, 2024, up till August, 2024. This study was conducted at Pak International Medical College, Hayatabad, Peshawar, Pakistan. A total of 55 patients were selected for the study, who experienced surgical procedures for ATFL injuries. Written informed consent was obtained from all participants. The Institutional Review Board (IRB) of Pak International Medical College has been permitted to carry out this study with reference number PIMC/DMR/2. The sample size of 55 was calculated using G*Power software, based on an estimated effect size of 0.5, a power of 80%, and a significance level (α) of 0.05. The effect size was determined from prior studies assessing associated injuries in ATFL tears. To minimize potential biases due to loss of follow-up, all participants were assessed at a single time point using MRI before surgery, ensuring a standardized evaluation of associated injuries. The sample was selected through purposive sampling. The sample focused on patients who fulfilled the defined inclusion and exclusion criteria. The participants undergoing a preoperative MRI scan of the affected ankle, with reports specifically addressing the integrity of the ATFL, deltoid ligaments, peroneal tendons, CFL, and the presence of an OCD were included. Patients with systemic diseases or fracturing the same ankle were excluded. Additionally, individuals who did not undergo a preoperative MRI scan with the surgery for ATFL injuries were also excluded from the study. To standardize the classification of structural integrity all MRI scans were analyzed by three investigators using predefined terminology. These investigators included two musculoskeletal radiologists with over five years of experience in MRI interpretation and one orthopaedic surgeon with expertise in foot and ankle injuries. To minimize variability in reporting, terms such as "scarred" or "scarring" were interpreted as "sprain" for the determinations of the study. In cases of disagreement regarding the interpretation of MRI findings, the investigators convened to reach a consensus. Data were examined by incorporating SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the findings. Continuous variables are reported as means and standard deviations (SD), which include such as age and body mass index (BMI). On the other hand, categorical variables are presented as frequencies and

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percentages, comprising gender distribution, injury types, and ligament integrity.

RESULTS

The mean age of the patients was 36.8 ± 12.4 years, with 61.8% male and 38.2% female. The mean BMI was 28.43 ± 6.7 kg/m^2. The right ankle was affected in 54.5% of cases, while the left was affected in 45.5% (Table 1).

Table 1: Patient Demographics (n=55)

Measurements		n (%)
Age in Years	19-64 Years	36.8 ± 12.4
Gender	Male	34 (61.8%)
	Female	21 (38.2%)
Body Mass Index (kg/m^2)	19.2-38.9 Kg/M^2	28.43 ± 6.7
Operated Side	Right	30 (54.5%)
	Left	25 (45.5%)

The majority of cases (29.1%) exhibited low-grade incomplete injuries, followed by high-grade incomplete injuries (23.6%) and complete injuries (14.5%). A smaller proportion of participants had an undamaged ATFL (7.3%), while 25.5% had some form of injury without further classification (Table 2).

Table 2: Extent of Anterior Talofibular Ligament (ATFL) Injury

ATFL Injury Type	n (%)
Undamaged	4 (7.3%)
Injured	14 (25.5%)
Low-Grade Incomplete Injury	16 (29.1%)
High-Grade Incomplete Injury	13 (23.6%)
Complete Injury	8 (14.5%)

A total of 72.7% of patients had associated injuries, while 27.3% presented isolated ATFL injuries. 32.7% of patients had an undamaged ATFL, while 52.7% had some degree of incomplete injury (30.9% low-grade, 21.8% high-grade). Complete ATFL tears were observed in 14.5% of cases. Associated injuries predominantly involved the CFL and deltoid ligaments, highlighting their frequent co-involvement in ATFL damage (Table 3).

Table 3: Extent and Nature of Injuries to the ATFL

Measurement	n (%)
Degree of Injury	
Single Injury	15 (27.3%)
Related Injuries	40 (72.7%)
ATFL Integrity	
Undamaged	18 (32.7%)
Injured	29 (52.7%)
Low-Grade Incomplete Injury	17 (30.9%)
High-Grade Incomplete Injury	12 (21.8%)
Whole Tear	8 (14.5%)

The CFL was intact in 60% of patients. Partial tears (low- and high-grade combined) accounted for 36.4% (20% low-grade, 16.4% high-grade), while complete tears were uncommon, seen in 3.6% of patients. The deep deltoid ligament was intact in 56.4% of patients, while 43.6% had some degree of injury (29.1% low-grade, 14.5% high-grade). The superficial deltoid ligament was intact in 70.9% of cases, with 29.1% showing some level of injury (14.5% low-grade, 14.5% high-grade). The peroneal tendon was intact in 83.6% of patients, while 5.5% had injuries, and 10.9% had tendinosis. OCD was associated with 21.8% of cases (Table 4).

Table 4: Associated Injuries

Measurement	n (%)
Calcaneofibular ligament (CFL)	
Undamaged	33 (60%)
Injured	22 (40%)
Low-Grade Incomplete Injury	11 (20%)
High-Grade Incomplete Injury	9 (16.4%)
Complete Injury	2 (3.6%)
Deep Deltoid Ligament	
Undamaged	31 (56.4%)
Injured	24 (43.6%)
Low-Grade Incomplete Injury	16 (29.1%)
High-Grade Incomplete Injury	8 (14.5%)
Superficial Deltoid Ligament	
Undamaged	39 (70.9%)
Injured	16 (29.1%)
Low-Grade Incomplete Injury	8 (14.5%)
High-Grade Incomplete Injury	8 (14.5%)
Peroneal tendon	
Undamaged	46 (83.6%)
Injured	3 (5.5%)
Tendinosis	6 (10.9%)
Osteochondral Defect (OCD)	
Associated OCD	12 (21.8%)
No Associated OCD	43 (78.2%)

DISCUSSION

Ankle sprains, particularly those involving the lateral ligament complex, remain one of the most common injuries in both athletic and general populations. Among these, the most frequently injured is the ATFL often in combination with other anatomical structures such as the deltoid ligament complex, CFL, osteochondral surfaces and peroneal tendons. Accurate diagnosis and understanding of co-existing injuries are crucial for effective management. It is also important to prevent long-term complications like instability or osteoarthritis. MRI plays a vital role in evaluating such injuries by offering detailed insights into both acute and chronic damage. This study investigates the spectrum and prevalence of co-existing injuries associated with ATFL damage. Hence, providing valuable data to inform clinical decision-making [17]. The most frequently injured structure associated with ATFL injuries was the CFL, with 41.8% involvement. This high prevalence underscores the importance of understanding

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the biomechanical relationship between the ATFL and CFL. The CFL plays a pivotal part in maintaining lateral stabilization and resisting inversion forces [18]. Given the shared mechanism of injury in lateral ankle sprains, concurrent CFL damage is common. Despite this, MRI sensitivity for detecting CFL injuries varies significantly, with accuracies reported between 66% for partial tears and 88% for complete tears [19]. This diagnostic challenge necessitates a combination of imaging and clinical tests, such as the medial talar tilt stress test, to enhance diagnostic accuracy when MRI findings are inconclusive [20, 21]. Similarly, the deltoid ligament complex was frequently involved despite its primary role in stabilizing the medial ankle. This is likely due to compensatory stresses placed on the medial structures when the lateral stabilizers fail. Up to 15% of inversion injuries have been reported to involve the deltoid ligament, a finding consistent with our study [22]. Interestingly, while deltoid ligament injuries are classically linked to eversion mechanisms, up to 15% of inversion injuries may also involve this complex [23]. In this study, the deep deltoid ligament was intact in 56.4% of patients, with partial tears (low- and high-grade) and sprains observed in the remaining cases. Similarly, the superficial deltoid ligament was intact in 70.9% of cases, with a smaller proportion showing sprains or partial tears. Failure to recognize deltoid ligament injuries may contribute to residual instability despite surgical correction of ATFL tears, highlighting the need for a comprehensive medial and lateral ligament evaluation. The peroneal tendons are key stabilizers in lateral ankle movements. These were intact in the majority of patients. However, tendinosis was noted in 10.9% of cases, while tears were observed in 5.5%. These conclusions are consistent with earlier studies that emphasize the role of the peroneus longus tendon in stabilizing the lateral ankle during inversion injuries [24]. Despite their critical role, peroneal tendon injuries are frequently overlooked during routine evaluations [25]. Given their contribution to ankle stability, clinicians should assess peroneal tendon integrity in all cases of ATFL injury. Moreover, surgical management of ATFL injuries should address any co-existing peroneal tendon damage to optimize outcomes and prevent recurrent instability [26]. Osteochondral defects (OCDs), often resulting from direct trauma or repetitive micro-trauma, were observed in 21.8% of cases. These defects commonly occur during ankle sprains when forced talar rotation generates compression and shear forces on the talar cartilage [27]. Cadaveric studies have corroborated this mechanism, demonstrating similar cartilage injuries under experimental inversion stress [28]. Additionally, chronic lateral instability due to ATFL injury has been linked to the development of OCDs, where repetitive micro-trauma and altered joint biomechanics exacerbate cartilage damage [29, 30]. The prevalence of OCDs in this study underscores the importance of evaluating talar cartilage integrity during the assessment of ATFL injuries, as timely intervention can mitigate long-term consequences like post-traumatic arthritis.

CONCLUSIONS

It was concluded that this study highlights a high prevalence of associated injuries in ATFL tears, particularly in the CFL (41.8%) and deltoid ligament complexes, reinforcing the interconnected nature of lateral and medial ankle stability. Additionally, osteochondral defects were present in 21.8% of cases, underscoring the long-term impact of ATFL injuries on joint health. Despite this, surgical treatment often focuses on ATFL repair alone, potentially overlooking concurrent injuries that contribute to persistent instability. The findings emphasize the need for a comprehensive assessment of ligamentous, tendinous, and osteochondral structures in ATFL injuries.

Authors Contribution

Conceptualization: FQ
Methodology: FQ, MA, FB
Formal analysis: OS, WIA
Writing review and editing: MM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Increased First Trimester Serum Uric Acid as A Predictor of Gestational Diabetes Mellitus

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ABSTRACT

The gestational period of diabetes type 2 (GDM) is a serious condition that can harm both mothers and newborns throughout pregnancy. **Objective:** To determine if elevated first-trimester serum uric acid levels lead to gestational diabetes mellitus onset during pregnancy. **Methods:** A comparative cross-sectional study was conducted between November 2023 and April 2024 at Niazi Medical and Dental College in Sargodha. The study sample consisted of 139 pregnant women separated into two groups: those exhibiting and those absent diabetes in women. The researchers employed independent t-test and Chi-square statistical methods to evaluate age and BMI data, as well as diabetes familial histories and delivery history. **Results:** Gestational diabetes mellitus patients had higher serum uric acid levels compared to pregnant women without Gestational diabetes mellitus ($p<0.001$). This study found that uric acid levels above 4.5 mg/dL increased the likelihood of abnormal fasting glucose values by 74.5% ($p<0.001$). Women with high uric acid levels had a 40% higher risk of developing Gestational diabetes mellitus (OR: 1.40; 95% CI: 1.10-1.80; $p=0.02$). **Conclusions:** It was concluded that women who have gestational diabetes mellitus display increased serum uric acid concentrations during their first trimester. Monitoring serum uric acid levels presents an opportunity to detect susceptible pregnant women with gestational diabetes in the early stages, allowing for quick implementation of preventive measures that promote maternal and fetal health.

INTRODUCTION

During pregnancy, women can develop Gestational Diabetes Mellitus (GDM), which causes different glucose intolerance levels to appear in mothers. Both mother and baby face severe health dangers from Gestational Diabetes Mellitus because it increases the occurrence of cesarean sections alongside shoulder dystocia, along with fetal growth problems and birth defects. Medical authorities identify this condition as a worldwide health threat while media publicity enhances its impact, which leads to additional deaths of mothers and newborns [1]. The most recent investigations have concentrated on the association between blood uric acid and premature births, finding signs of gestational diabetes and the effects of metabolic diseases on serum uric acid concentrations. The usual physiologic levels of serum uric acid vary from 2 to 6.5 mg/dl. Pregnancy-demanding modifications to the glomerular filtration rate frequently result in decreased levels of fetal uric acid. Scientific research demonstrates that elevated serum uric acid shows strong links to insulin resistance and likely serves as an essential factor that leads to diabetes mellitus development, according to studies [2, 3]. Xanthine oxidase activates because of

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cytoimmunologic factors and placental hypoxia to produce greater levels of oxidative stress and uric acid during purine metabolism. Elevated levels of uric acid in the blood in pregnant women are linked to developing insulin resistance and metabolic syndrome, implying that it may operate as a GDM risk factor alongside preeclampsia [4, 5]. The buildup of uric acid in pregnant women damages insulin-producing β-cells and causes insulin signaling impairment as well as endothelial dysfunction, which leads to worse vascular health while simultaneously impairing glucose metabolism [6, 7]. Complete prevention of type 2 diabetes requires early clinical interventions for women who have GDM since these women face elevated future type 2 diabetes risks [8-10]. Pregnancy-related gestational diabetes mellitus is more likely to occur in women with elevated blood uric acid levels in the first trimester.

This study aims to determine whether higher levels of blood uric acid in the first trimester were linked to the onset of gestational diabetes mellitus later in pregnancy.

METHODS

A comparative cross-sectional study was conducted in the Department of Gynecology and Biochemistry at Niazi Medical and Dental College in Sargodha for a six-month study from November 2023 to April 2024. Convenience sampling was employed to recruit pregnant women who matched the inclusion criteria. Inclusion criteria were any pregnant woman who was not diabetic and was less than 12 weeks pregnant in her first trimester. Renal illness, hypertension, liver disease, gout, smoking, and alcohol use are all exclusion factors. A cross-sectional study's sample size was typically calculated by estimating a proportion (such as GDM prevalence) with a predetermined degree of precision. The formula in this case was n= Z2. P. (1-P)/E2, where n is the sample size, Z is the confidence level (1.96 or 95%), P is the estimated proportion (0.20 or 20%), and E is the margin of error (0.05 or 5%). The required sample size was n=139, divided into two groups: GDM (69) and Non-GDM (70). Venous blood samples were taken from pregnant ladies whose gestational age was less than 12 weeks. A colorimetric approach with a detection limit of 0.2–20 mg/Dl and an automated biochemical analyzer (Cobas C 501 analyzers) were used by the laboratory technician of the institution to assess the serum uric acid levels following centrifugation. Between weeks 24 and 28 of pregnancy, these women had to have an oral glucose tolerance test (OGTT). Following an overnight fast of 8–10 hours, fasting blood sugar levels were assessed. Then, 75 grams of oral glucose dissolved in either plain or lime water were given to the patient to improve compliance. According to ADA guidelines, the venous sample is measured and evaluated for GDM after a fast of one or two hours. The Institutional Review Board (IRB) approved this study with IRB numbers (IRB/NM&DC/61). The objectives, methodology, possible hazards, and advantages of the study were explained to each participant, who also gave written informed consent. SPSS version 21.0 was used for data processing. Using the independent t-test and Chi-square, categorical and continuous factors like age, BMI, family history of diabetes, and parity were represented. The chi-square test was used to measure blood uric acid levels in the first trimester for both the GDM and non-GDM groups. Using logistic regression, the odds ratio of GDM in blood uric acid levels is displayed. An indication of a significant value was p<0.005.

RESULTS

Women diagnosed with GDM maintained an average age of 30.2 ± 6.1 years, different from the non-GDM patients who averaged 27.8 ± 5.2 years (p<0.04). The individuals in the GDM group maintained higher BMI compared to other patients (28.1 ± 3.9 kg/m^2 vs. 24.5 ± 3.6 kg/m^2); (p<0.01). Diabetes existed in 45.8% of women with GDM but only affected 12.8% without the condition (p<0.001). A statistical link (p=0.03) existed between multiple pregnancies and GDM since GDM group members faced stronger prevalence rates (58.3% compared to 31.4%) (Table 1).

Table 1: Comparing Demographic Variable Mean Between Two Groups (GDM vs. Non-GDM)

Variables	GDM Group (n=69)	Non-GDM Group (n=70)	p-Value
Age (Years)	30.2 ± 6.1	27.8 ± 5.2	0.04*
BMI (kg/m^2)	28.1 ± 3.9	24.5 ± 3.6	<0.01**
Family History of Diabetes	22 (45.8%)	13 (12.8%)	<0.001***
Parity (Multiparous)	28 (58.3%)	32 (31.4%)	0.03*

The percentage of GDM individuals who had levels of uric acid in their blood <3.5 mg/dL was 17.4%, while it reached 42.9% among women without GDM. At uric acid levels between 3.5 and 4.5 mg/dL, the risk of GDM was evenly distributed between the two groups (36.2% and 35.7%, respectively). A statistically significant correlation (p<0.001) exists between elevated uric acid levels (>4.5 mg/dL) and GDM because GDM women (46.4%) experienced this condition much more often than non-GDM women (21.4%). Research shows that women with higher than 4.5 mg/dL uric acid levels face a higher possibility of developing GDM (Table 2).

Table 2: Evaluation of Serum Uric Acid Category

Serum Uric Acid Category (mg/dL)	GDM (n=69)	Non-GDM (n=70)	Total (n=139)	p-Value
<3.5 mg/dL	12 (17.4%)	30 (42.9%)	42 (30.2%)	<0.0001***
3.5-4.5 mg/dL	25 (36.2%)	25 (35.7%)	50 (36.0%)	<0.0001***
>4.5 mg/dL	32 (46.4%)	15 (21.4%)	47 (33.8%)	<0.0001***

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For every year of age, the independent analysis found that the risk of Gestational Diabetes Mellitus increases by 5% per year (p=0.03; odds ratio (OR)=1.05). A higher BMI is a significant risk factor for GDM since it increases the risk of GDM by 20% for every unit rise (OR 1.20, p<0.001). GDM is substantially more likely to develop in those with a family history of diabetes (OR=3.50, p<0.001). During the first trimester, the chance of having GDM increases when uric acid levels rise above normal (OR=1.40, p=0.02)(Table 3).

Table 3: Serum Uric Acid as a Predictor of GDM

Variables	Odds Ratio (OR)	95% CI	p-Value
Age (Years)	1.05	1.01-1.10	0.03*
BMI (kg/m^2)	1.20	1.10-1.35	<0.001**
Family History of Diabetes	3.50	1.90-6.45	<0.001***
Serum Uric Acid (mg/dL)	1.40	1.10-1.80	0.02*

The GDM group exhibited elevated glucose levels compared to non-GDM participants according to results from the two-sample t-test in fasting states and hours one and two (p<0.001). All GDM patients failed the glucose tolerance test (GTT) according to a Chi-square analysis, which was strongly linked to GDM diagnosis (p<0.001)(Table 4).

Table 4: Evaluating Differences in Glucose Tolerance Test Results

GTT Time Point	GDM Group (n=69)	Non-GDM Group (n=70)	p-Value
Fasting Glucose (mg/dL)	96.5 ± 12.3	84.2 ± 10.5	<0.001**
1-Hour Glucose (mg/dL)	182.4 ± 24.8	142.7 ± 19.4	<0.001**
2-Hour Glucose (mg/dL)	158.6 ± 22.1	115.3 ± 18.8	<0.001**
GTT Pass (n, %)	0 (0%)	65 (92.9%)	<0.001**
GTT Fail (n, %)	59 (100%)	5 (7.1%)	0.001

Women with serum uric acid levels below 3.5 mg/dL showed abnormal fasting glucose results among 23.8% of participants. Similarly, 76.2% had normal glucose levels, 50% with intermediate uric acid values presented abnormal glucose results, and 74.5% showed high levels of abnormal glucose results. The data showed that of all the examined women, 74.5% presented abnormal fasting glucose measurements with levels greater than 4.5 mg/dL. This correlation reached statistical significance with an Extremely Low p-value of 0.001. The analysis showed 11.9% women exhibited abnormal glucose levels (<3.5 mg/dL) but 40% and 68.1% showed abnormal readings between 3.5–4.5 mg/dL and >4.5 mg/dL respectively during 1-hour GTT interventions and these results had a statistically significant correlation (p=0.003). Of the studied women, 63.8% presented with abnormal glucose values at 4.5 mg/dL or higher at the 2-hour measurement period, while uric acid levels were closely associated with this outcome (p=0.001)(Table 5).

Table 5: Serum Uric Acid and Its Association with Abnormal GTT Results in Pregnant Women

Serum Uric Acid Category (mg/dL)	Abnormal Fasting GTT	Normal Fasting GTT	p-Value	Abnormal 1-Hour GTT	Normal 1-Hour GTT	p-value	Abnormal 2-hour GTT	Normal 2-Hour GTT	p-value
				n (%)					
<3.5 mg/dL	10 (23.8%)	32 (76.2%)	<0.001**	5 (11.9%)	37 (88.1%)	0.003 **	4 (9.5%)	38 (90.5%)	0.001**
3.5-4.5 mg/dL	25 (50%)	25 (50%)	0.001**	20 (40%)	30 (60%)		18 (36%)	32 (64%)	0.001**
>4.5 mg/dL	35 (74.5%)	12 (25.5%)	0.001**	32 (68.1%)	15 (31.9%)		30 (63.8%)	17 (36.2%)	0.001**
Total (n=139)	70 (50.4%)	69 (49.6%)	0.001**	57 (41%)	82 (59%)		52 (37.4%)	87 (62.6%)	0.001**

DISCUSSION

In order to determine the main factors determining the prevalence and risk of gestational diabetes mellitus (GDM), the study uses demographic analysis, which reveals notable differences between those with and without GDM. The mean age of the women in the GDM group was 27.8 ± 5.2 years, which is in line with earlier studies showing that older mothers are more likely to develop GDM because their insulin resistance deteriorates with age [11, 12]. The healthcare practice demands attention to maternal age when providing prenatal care programs because older pregnant women should receive early screening tests [13]. BMI levels directly affected insulin resistance through obesity, which serves as a main factor for GDM development. Weight management, along with dietary counselling, should become a necessity to prevent GDM risk [14]. The presence of diabetes in family members functioned as a significant risk factor during pregnancy, so healthcare providers should recognize its importance by initiating screenings followed by lifestyle interventions to reduce GDM risk [15]. The case for additional monitoring of these patient groups is supported by the fact that women with higher parity have a higher risk of gestational diabetes due to alterations in their metabolism between pregnancies [16]. This study discovered that out of all participants, high serum uric acid levels were present in 46.4% of cases, yet only 21.4% did not have diabetes, which makes uric acid a potential tool to identify early signs of GDM along with enabling timely preventive measures [17]. The findings are also in line with past research that indicates age, body mass index, family history, and elevated blood uric acid levels are the main indicators of risk for diabetes during pregnancy.The odds of having GDM

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increase by 5% for each year that a mother's age increases. This finding is in line with research that indicates impaired glucose metabolism and insulin resistance are closely linked to older maternal ages. The substantial correlation between obesity and diabetes during pregnancy was further highlighted by the discovery that BMI greatly increased the likelihood of developing GDM, with probabilities rising by 20% for every unit increase in BMI [18]. Women with relatives with a diagnosis of diabetes were three times more likely to get gestational diabetes than those without a family background ($p<0.001$). This strong link emphasizes the importance of family history in identifying high-risk individuals and offering early intervention [19]. Additionally, the uric acid odds ratio revealed that for every unit rise in blood uric acid levels, the risk of developing GDM increased by 40% ($p=0.02$). Because of this connection, high uric acid could be a good sign of gestational diabetes [20]. Oxidative stress and systemic inflammation, which are key factors in the development of insulin resistance and diabetes mellitus during pregnancy, have been connected to elevated uric acid levels. Serum uric acid can be used as a biomarker in standard prenatal care, which shows promise for identifying women at risk of GDM early and providing opportunities for preventive treatments. It is also evident that additional research is required to examine the associations between uric acid and the development of diabetes mellitus. Uric acid is a significant prognostic marker for diabetes, as evidenced by the correlation between blood uric acid levels and postprandial glucose tolerance test (GTT) results. Women with serum uric acid levels greater than 4.5 mg/dL exhibited significantly higher rates of abnormal GTT results, with 74.5% showing abnormal fasting GTT results, 68.1% exhibiting abnormal 1-hour GTT results, and 63.8% having abnormal 2-hour GTT results ($p<0.001$). These findings suggest that hyperuricemia contributes to impaired glucose metabolism during pregnancy, likely through mechanisms such as insulin resistance and increased oxidative stress [21].

CONCLUSIONS

It was concluded that elevated blood uric acid significantly predicts GDM, at higher levels corresponding to a greater likelihood of abnormal GTT results.

Authors Contribution

Conceptualization: MFJ
Methodology: A, SJ, FS
Formal analysis: A, NN
Writing review and editing: MFJ, SJ, FS, TM, NN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Frequency of Urinary Incontinence and Its Risk Factors in Patients Attending Gynae Outpatient Department (OPD) of Lady Reading Hospital (LRH) Peshawar, Pakistan

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ABSTRACT

Urinary incontinence (UI) is an important health issue acknowledged by the World Health Organization (WHO) that adversely affects the quality of life. **Objectives:** To find out the occurrence of UI in female presenting to the Gynaecology Out-Patient Department of Lady Reading Hospital and also to find out the frequencies of its risk factors for urinary incontinence in women presenting with UI. **Methods:** A descriptive cross-sectional design was used to conduct this study. The sample consisted of 163 women who presented to the Gynaecology Out-Patient Department of Lady Reading Hospital for any complaints were included in the study. **Results:** UI was observed in 15.3% of patients. Moreover, Stress UI was 48%, followed by overflow UI 24%, urge UI 20%, and mixed UI 8%. The leading factors for UI consisted of 3.75% more than three normal vaginal deliveries, 24% chronic cough, 12% history of gynaecological operation, 80% Illiterate, and 56% lower urinary tract infection (LUTI). **Conclusions:** It was concluded that based on the findings of the current study, UI is 15.3% prevalent in Pakistan which is comparable to that of other Asian nations. Furthermore, normal vaginal delivery more than three times and UTI may develop the key risk issues for the development of UI. The magnitude of UI problems may impact on daily lives and habits of the patients.

INTRODUCTION

The International Incontinence Society defines urinary incontinence (UI) as a social and hygienic issue where involuntary urine leakage is objectively observable [1]. After giving birth, over 29.6% of women reported having urine incontinence [2]. Its prevalence in the Turkish population has been estimated to reach 50% [3]. According to Oman research, 28.25% of the women were between the ages of 50 and 59 years. Among Omani women aged 20 to 60, the point prevalence (per 1000) of UI was 44%. Stress UI (41.6%) is found in the majority of the women. Furthermore, 15.2% of women with UI had mild UI, 50.3% had moderate UI, 33.1% had severe UI, and just 1.3% had extremely intense UI [4]. Similarly, a research study in Indonesia estimated the prevalence of urinary incontinence at 13.0% overall [5]. Moreover, a study in India analysed that 27.7% of women have urinary incontinence in which urge UI (16.3%) followed by mixed UI (32.7%) and stress UI (51.0%) [6]. Furthermore, a similar study in India showed that the overall prevalence of urinary incontinence in patients presenting to the hospital was about 12% [7]. According to research done in Turkey, 37.2% of these women experienced urine incontinence, however, only 29.3% of them sought medical attention for the issue. Stress-type incontinence was considered the most observable type in 160 women with urine incontinence findings (33.7%), followed by other types (overflow,

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continuous urinary incontinence) (13.7%), urge type (20.6%) and mixed type (31.8%) [8]. Forty-one (10.30%) of the women were diagnosed with stress urine incontinence. Tuberculosis and other lung conditions were found to be the most prevalent co-morbidities. Only 4% of the women in the trial developed a UTI that tested positive for culture [9]. Research has shown that more than three normal vaginal births, chronic cough, history of gynaecological procedures, and illiteracy have all been identified as the key risk factors for UI [10]. UI has been shown to have negative effects on sexual relationships, work/school performance, and family life [11]. Among women over 40, UI was described to be significantly higher (69.7%). Out of 198 participants, 179 (90.4%) were from the poor socioeconomic group, followed by 17 participants from the middle class, and 2 (1%) were from the higher socioeconomic group. Increasing parity was linked to incontinence, particularly stress incontinence since 81 patients (40.9%) had grand multipara, which is a substantial risk factor for urine incontinence. Additional risk factors were a history of prolapse (34.8%), constipation (51%), elevated BMI > 25 per kg/m2 (47%), vaginal birth (85.4%), and chronic respiratory illness (10%) [12]. Numerous pregnancies, UI in the mother and sister, prior UI during pregnancy, the postpartum period, and body mass index were found to be linked to an increased risk of incontinence. Just 40 out of 92 women (43.5%) have sought medical assistance, whereas 92 out of 288 women (31.9%) said that UI negatively affects their quality of life. The kind of UI, the frequency of UI episodes, and the degree of leakage were all associated with a worse quality of life [13]. Age, vaginal birth, and body mass index (BMI) all contributed to an increase in the prevalence of urine incontinence. Stress urinary incontinence (45.2%), urgency urinary incontinence (22.0%), and mixed urinary incontinence (32.8%) were reported by participants with undiagnosed UI. Urinary incontinence was shown to be significantly correlated with constipation and a high body mass index [14]. In women with Stress Urinary Incontinence (SUI), Mid Urethral Sling (MUS) surgery and Pelvic Floor Muscle Training (FPMT) dramatically enhance quality of life. In the surgical intervention arm, we saw 100% symptomatic alleviation, a high rate of Quality of Life (QoL) improvement, and few easily manageable sequelae. Despite improving quality of life, PFMT needs ongoing encouragement because 22% of participants stopped using it. In the absence of medication, SUI patients' quality of life was rather constant [15].

This study aims to find out the occurrence of UI in female presenting to the Gynaecology Out-Patient Department of Lady Reading Hospital and also to find out the frequencies of its risk factors for urinary incontinence in women presenting with UI.

METHODS

A descriptive cross-sectional approach was applied to conduct this study in the Obstetrics and Gynecology unit of Lady Reading Hospital (LRH), Peshawar. Using Openepi software, an anticipated population Proportion (P) of urinary incontinence in patients presenting to the hospital was about 12% [7], confidence interval of 95% and a 5% margin of error, the calculated sample size was 163 women through non-probability consecutive sampling technique. This study was completed in six months starting from July 1st to December 31st, 2020. The written approval of the ethical committee of the hospital was granted before the conduct of this study. Along with this, study participants signed written informed consent at the start of the data collection. The quantitative data was collected through a structured questionnaire Performa. The inclusion criteria include all those women who presented to Gynae OPD of LRH for any complaint, having aged between 25 to 65 years, gravidity and parity both greater than one and willing to take part in this research. Similarly, all those women having known carcinoma of the genital tract, pregnancy, obstetric problems, and present for any type of prolapse like uterine prolapse and vaginal prolapse were excluded. SPSS version 23.00 software was used for data analysis. Mean and standard deviation were calculated in descriptive statistics for continuous variables like participants' age, gravidity and BMI. Percentage and frequency were calculated for categorical variables like urinary incontinence, different types of UI and for each risk factor. The inferential statistics include a Chi-square test for an association between the dependent variable (Urinary Incontinence) and independent variables (Selected Demographics). All the results were statistically significant when the p-value was < 0.5 at a 95% confidence interval.

RESULTS

The mean age of the participants in this study was 42.65 ± 7.37 years; moreover, the mean gravida was 4.25 ± 1.04 and the mean BMI was 27.64 ± 2.21 Kg/m2. 15.3% of the sample population in the current study have UI; followed by 84.7% of participants who have no UI. Similarly, 48% of the participants have stress UI, followed by 24% overflow UI, 20% Urge UI, and 08% have Mixed UI in the current study (Table 1).

Table 1: Urinary Incontinence and Its Sub-Types (n=163)

Sr. no	Variables	Frequency	Percentage
Urinary Incontinence			
1.	Yes	25	15.3%
2.	No	138	84.7%
Urinary Incontinence Sub-Types (n=25)			
1.	Stress UI	12	48%
2.	Overflow UI	06	24%

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3.	Urge UI	05	20%
4.	Mixed UI	02	08%

More than three normal vaginal deliveries accounted for 30.64% of UI, followed by 09.67% chronic cough, 04.83% history of gynaecological operations, 32.25% educational status of the participants, and 22.58% lower urinary tract infection respectively. Whereas the percentage of individual risk factors shows that 76% of UI patients have more than three normal deliveries and 24% of UI patients have less than three normal vaginal deliveries. Furthermore, 24% of UI patients have chronic cough and 76% of UI patients have no chronic cough. 12% of UI patients have a history of gynaecological operations and 88% of UI patients have no history of gynaecological operations. 80% of UI patients were illiterate and 20% of UI patients were literate. Similarly, 56% of UI patients have lower urinary tract infections and 44% of UI patients were negative for lower urinary tract infections (Table 2).

Table 2: Risk Factor of Urinary Incontinence (n=25)

Sr. no	Risk factors	Frequency (%)	Commuted %
Normal Vaginal Deliveries > 3			
1.	Yes	19 (76%)	30.64%
2.	No	06 (24%)	09.52%
Chronic Cough			
1.	Yes	06 (24%)	09.67%
2.	No	19 (76%)	30.15%
History of Gynecological Operations			
1.	Yes	03 (12%)	04.83%
2.	No	22 (88%)	34.92%
Educational Status			
1.	Illiterate	20 (80%)	32.25%
2.	Educated	05 (20%)	07.93%
Lower Urinary Tract Infection			
1.	Yes	14 (56%)	22.58%
2.	No	11 (44%)	19.04%

UI and selected demographics in the current study were checked for an association through the Chi-square test. It was evident that there was no association between UI and age categories as the p-value (0.626>0.05) at a 95% confidence interval. Furthermore, UI and gravidity were not associated with each other as the p-value (0.930>0.05) at a 95% confidence interval. However, there was an association between UI and BMI in the current study as the p-value (0.013<0.05) at a 95% confidence interval (Table 3).

Table 3: Chi-Square test between Urinary Incontinence and Selected Variables

Sr. no	Variables	Urinary Incontinence		p-Value
		Yes	No	
1.	**Age Categories**			
	25 – 40 Years	12 (16.9%)	58 (83.1%)	0.626
	41 – 65 years	13 (14.1%)	79 (85.9%)	
2.	**Gravida**			
	1 – 3	06 (15.8%)	32 (84.2%)	0.930
	>3	19 (15.2%)	106 (84.8%)	
3.	**BMI (Kg/m^2)**			
	≤25	00 (0%)	28 (100%)	0.013*
	>25	25 (15.3%)	138 (81.5%)	

*p<0.05 Significance Level and at 95% Confidence Interval

DISCUSSION

This research reported a 15.3% prevalence of urine incontinence, which was lower than the 25–45% noted in European studies [9]. Garg *et al.*, revealed that 21.8% of Indian women had UI [16]. Because UI is frequently seen as a demeaning disease in Pakistani and other Asian cultures, the decreased incidence in this study may be because patients did not report their experiences with UI. Nonetheless, it is predicted that the number of UI patients will increase more in Asia (22%) than in the United States (18%) and Europe (5%) [17]. It suggests that the iceberg phenomenon and the scope of UI issues in Asian locations are comparable. In the female population of this study, the most prevalent UI was the stress type UI. The stress-type UI was the most common among the study's female participants. Garg *et al.*, and Rashidi *et al.*, also find similar results. There are several potential risk factors for stress UI in women, including decreased estrogen levels during the menopausal period, pelvic floor muscle, nerve, and connective tissue injury that occurs throughout pregnancy to delivery, and a history of gynaecological surgery [16, 18]. These many causes can result in urethral hypermobility, problems in the intrinsic structure of the urethral sphincter, and damage to the urethral supporting tissue (the levator ani, the anterior vaginal wall, and the extrinsic structure of the urethra), all of which can be signs of stress UI [19].Multiparity and urodynamic parameters are the primary risk factors for the development of UI in Lower Urinary Tract infections (LUTI), according to retrospective research conducted on Japanese female patients.The characteristics of LUTI in urodynamics, maximum free flow rate, maximal urethral closure pressure, and functional profile length, are linked to a higher incidence of UI in female patients [14].Urinary incontinence risk factors include metabolic syndrome, spontaneous birth, inadequate sanitation, advanced age, and urinary tract infections, according to a different study conducted on Chinese women [20]. In the present study, stress urinary

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incontinence was 48%, Overflow urinary incontinence 24%, Urge urinary incontinence 20% and mixed urinary incontinence 8%. Factors leading to urinary incontinence were normal vaginal delivery>3 76%, chronic cough 24%, history of gynaecological operation 12%, Illiterate 80% and lower urinary tract infection 56%. UI impairs social life components, physical activity, sexual relationships, and religious responsibilities. Furthermore, Age, UI intensity, UI kind, frequency of episodes, body weight, psychological variables, and medical treatment patterns are the elements that impact UI patients' quality of life.

CONCLUSIONS

It was concluded that UI is 15.3% prevalent in Pakistan, comparable to other Asian nations. Furthermore, low educational status (Illiterate) accounted for 32.25% of UI followed by 30.64% normal vaginal delivery >3, 22.58% Lower urinary tract infection, 09.67% Chronic cough, and 04.83% history of gynaecological operations. UTI may become the main risk factor in the development of UI. In addition, normal vaginal delivery more than three times and UTI may develop the key risk issues for the development of UI. The magnitude of UI problems may have an impact on the daily lives and habits of the patients.

Authors Contribution

Conceptualization: AJ
Methodology: AJ, AF
Formal analysis: SB, AF
Writing review and editing: SB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Clinical and Biochemical Parameters among Hemodialysis Patients before and during the month of Ramadan

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ABSTRACT

Ramadan fasting among hemodialysis patients is a complex issue in the Muslim world, with varying opinions and outcomes. **Objectives:** To evaluate clinical and biochemical parameters in hemodialysis patients before and after Ramadan. **Methods:** This quasi-experimental study was conducted in a private tertiary care hospital in Karachi from March to April 2024.Patients undergoing hemodialysis for more than three months were included, except those who did not consent.Participants were categorized into three groups: complete fasting, intermittent fasting, and non-fasting. Clinical and biochemical parameters were measured before and after Ramadan, including ultra-filtrate, dry weight, potassium, phosphorus, and albumin. Data were analyzed using SPSS version 27.0, with paired t-tests and significance set at $p<0.05$. **Results:** 132 patients participated (56.1% male, 43.9% female). Most (90.9%) did not fast, while 5.3% fasted continuously and 8.3% intermittently. Hypertension was the most common comorbidity (47.7%). Ultra-filtrate levels significantly increased in both male and female. Potassium levels rose significantly in female and in patients on thrice-weekly dialysis. Albumin levels declined across all groups. No significant changes were observed in dry weight or phosphorus levels. **Conclusions:** It was concluded that increased ultra-filtrate and potassium levels post-Ramadan, with albumin declining in most groups. However, the fasting group showed no significant changes, highlighting the need for group-specific monitoring in hemodialysis patients during Ramadan.

INTRODUCTION

Ramadan fasting brings certain clinical, hemodynamically, and biochemical changes among healthy individuals, specifically and generally for chronic kidney diseases (CKD) and diabetic patients [1].However, these changes are not without side effects in certain high-risk groups of patients, and there are still no established guidelines to follow for Ramadan fasting [2].Ramadan fasting among hemodialysis patients has been a challenging problem and area of discussion in the Muslim world due to different opinions and outcomes [3].Studies on clinical or biochemical changes have not been conducted in a large number of studies recently. Previous studies were summarized in a literature review by Habas *et al.*, revealing hyperkalemia, hyperphosphatemia, and higher mortality in one study published in 2015, which might be related to other comorbidities [2].A recent study by Adanan *et al.*, depicts the opposite picture with improvement in phosphorus, serum creatinine levels, and weight reduction with the demography of younger patients [4]. A prospective cohort study conducted in Palestine on clinical and biochemical parameters shows that all dialysis patients, whether doing complete or partial fasting, developed intradialytic weight gains and high potassium levels.This study also concludes with the remark that hemodialysis patients should be aware of the potential risk of hyperkalemia and fluid gain [5]. A study from the dialysis unit of an Egyptian hospital on

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hemodialysis patients fasting during Ramadan concluded that complete or partial fasting may be tolerated without any significant complications, that are intradialytic hypotension (IDH) and muscle cramps.Moreover, an interesting finding was that significant weight reduction was observed in the fasting group as compared to the non-fasting group [6].No recent study or data are available to see the changes regarding biochemical parameters or clinical symptoms in hemodialysis patients with fasting in the population living in South Asia.In a center in Karachi, fasting and non-fasting hemodialysis patients were compared with a focus on pre-dialysis weight, electrolytes reflecting the dietary pattern at the beginning and during the last week of Ramadan.This study shows a decrease in phosphorus and an increase in albumin in the non-fasting group as compared to an increase only in phosphorus level in the fasting group [7].However, this study contradicts the dietary pattern of our population as dietary habits of mostly Pakistani families during Ramadan consists of food rich in carbohydrates and fat which is further augmented with phosphorus containing items and fluids intake at Iftar time [8] which might also reflect certain biochemical changes during the month of Ramadan in high-risk patients of hemodialysis [9].Despite all the above-mentioned literature, this question still arises and remains unanswered that is whether hemodialysis patients should fast during Ramadan or not, and whether this month's (Ramadan) dietary habits of hemodialysis patients reflect in their clinical symptoms or alteration in biochemical parameters, or not in both fasting and non-fasting.

This study aims to assess and compare the biochemical parameters among hemodialysis patients before and during the month of Ramadan.

METHODS

This quasi-experimental study was conducted among patients on hemodialysis in the dialysis unit of a private tertiary care unit in Karachi from the month of Ramadan from March 2024 to April 2024 using a purposive sampling technique after taking IRB approval from Memon Medical Institute Hospital (IRB/MMH/2023/14). Patients undergoing regular hemodialysis sessions (twice or thrice weekly, with each session lasting approximately 3 to 4 hours) for more than three months were selected for the study. Patients with a history of recent hospitalization within the past month, acute bacterial or viral infections, active malignancy, decompensated liver disease, or any unstable medical condition were excluded. Ramadan fasting was defined as abstaining from eating any food and drinks from dawn to sunset during Ramadan [10]. Informed consent was taken from the patients. They were assured that their information would be kept confidential and used only for research. All patients on maintenance hemodialysis were divided into three groups based on their fasting status during Ramadan. Complete fasting group (those who fast for the whole month), intermittent fasting group (those who fast on non-dialysis days), and non-fasting group (who didn't fast for the whole month). Demographic data, including age, gender, co-morbidities, and cause of end-stage renal disease (ESRD), were collected. All biochemical parameters (serum potassium, serum phosphorus, and serum albumin) before and during the month of Ramadan were measured at an interval of 30 days. Hyperphosphatemia is a serum phosphate concentration >4.5 mg/dL [11]. The serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL as per KDOQI guidelines 2003, however 2017 KDOQI guidelines suggest keeping the Phosphorus level towards normal value. For hyperphosphatemia >5.5 mg/dl was used as a cut-off value to label as hyperphosphatemia [12]. Hyperkalemia was taken as a serum potassium concentration greater than approximately 5.5 mEq/L in adults [13]. The normal range of serum albumin was taken as 3.5 to 5.5 g/dL [14]. Similarly, clinical parameters like average ultrafiltration (in liters) during dialysis and average dry weight (in kilograms) were measured before and during the month of Ramadan. Ultrafiltration was defined as the removal of fluid (in liters) from a patient and is one of the functions of the kidneys that dialysis treatment replaces. Ultrafiltration occurs when fluid passes across a semipermeable membrane (a membrane that allows some substances to pass through but not others) due to a driving pressure [15]. Dry weight was defined as the optimum post-dialysis weight (in kilograms) at which all or most excess body fluids have been removed [16]. Any visit to ER, admission to hospital, or extra need for dialysis was notified, including any sign or symptom (like shortness of breath, nausea, fluid overload, deranged laboratory parameters). During the month of Ramadan. Data analysis was done by using SPSS software version 27.0. Age was mentioned as mean ± standard deviation. Gender, co-morbidities, and cause of ESRD were mentioned as percentages and frequencies. Continuous variables like serum phosphorus, potassium, albumin, ultrafiltration, and dry weight before and during Ramadan were compared for complete fasting, intermittent fasting, and non-fasting groups and were presented as mean ± standard deviation. The difference in numerical data pre and post was assessed by a Paired T test. Association between categorical variables was assessed using the chi-square. A p-value less than 0.05 was taken as significant.

RESULTS

A total of 132 patients were included in the study, with 74 (56.1%) male and 58 (43.9%) female. Among them, 61 (46.2%) underwent dialysis twice weekly, while 71 (53.8%)

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were on thrice-weekly dialysis. Hypertension was the most common comorbidity, affecting 67 (47.7%) participants. The fasting group comprised 7 (5.3%) participants, the intermittent fasting group included 11 (8.3%) participants, and the non-fasting group accounted for 120 (90.9%) participants. The results indicate significant shifts in certain parameters, particularly ultrafiltrate, potassium, and albumin levels. Ultra-filtrate levels showed a significant increase after Ramadan, rising from a pre-Ramadan mean of 2.44 ± 0.91 L to 2.69 ± 0.96 L (p=0.000). This suggests an increased fluid removal requirement post-Ramadan, potentially due to changes in dietary habits and fluid intake during fasting. Dry weight remained relatively stable, with a slight increase from 60.12 ± 14.25 kg to 60.23 ± 14.31 kg. However, this change was not statistically significant (p=0.231), indicating that fasting did not have a notable impact on overall body weight. Potassium levels increased significantly from 4.89 ± 0.76 mEq/L pre-Ramadan to 5.18 ± 0.80 mEq/L post-Ramadan (p=0.000). This suggests a higher risk of hyperkalemia, possibly due to dietary changes or alterations in dialysis sessions during Ramadan. Phosphorus levels showed a minor increase from 5.21 ± 1.61 mg/dL to 5.36 ± 1.56 mg/dL, but the difference was not statistically significant (p=0.229). This indicates that fasting had little effect on phosphorus balance in this patient population. Albumin levels significantly declined from 4.07 ± 0.50 g/dL to 4.22 ± 0.49 g/dL (p=0.000), suggesting potential nutritional concerns during Ramadan. This decrease may reflect inadequate protein intake or changes in metabolic processes due to fasting (Table 1).

Table 1: Pre and Post-Ramadan Changes Among All Participants

Parameter	n	Pre-Ramadan Mean ± SD	Post-Ramadan Mean ± SD	Mean Difference	t	p-value
Ultrafiltrate (L)	132	2.44 ± 0.91	2.69 ± 0.96	-0.253	-5.89	0.000
Dry Weight (kg)	132	60.12 ± 14.25	60.23 ± 14.31	0.111	1.20	0.231
Potassium (mEq/L)	132	4.89 ± 0.76	5.18 ± 0.80	-0.294	-4.21	0.000
Phosphorus (mg/dL)	132	5.21 ± 1.61	5.36 ± 1.56	-0.152	-1.20	0.229
Albumin (g/dL)	132	4.07 ± 0.50	4.22 ± 0.49	0.153	5.45	0.000

The results indicate significant changes in ultra-filtrate, potassium, and albumin levels, while dry weight and phosphorus levels remained relatively stable. Ultra-filtrate levels significantly increased from a pre-Ramadan mean of 2.46 ± 0.92 L to 2.70 ± 0.97 L (p=0.000), indicating a higher fluid removal requirement despite the patients not fasting. This could be attributed to dietary variations or fluid intake adjustments during Ramadan. Dry weight showed a minor increase from 60.24 ± 14.51 kg to 60.34 ± 14.55 kg, but this change was not statistically significant (p=0.306). This suggests that the non-fasting group maintained relatively stable body weight throughout the period. Potassium levels significantly increased from 4.90 ± 0.77 mEq/L to 5.17 ± 0.81 mEq/L (p=0.000), indicating a notable rise in potassium levels post-Ramadan. This may suggest dietary influences or altered dialysis efficiency, even among those who did not fast. Phosphorus levels showed a slight increase from 5.22 ± 1.63 mg/dL to 5.34 ± 1.57 mg/dL, but the difference was not statistically significant (p=0.368), implying minimal impact of Ramadan on phosphorus balance in the non-fasting group. Albumin levels significantly increased from 4.08 ± 0.50 g/dL to 4.23 ± 0.49 g/dL (p=0.000). This suggests improved nutritional status or protein intake in the non-fasting group, potentially due to regular meal consumption. The result presents the pre- and post-Ramadan changes in clinical and biochemical parameters among the non-fasting group of hemodialysis patients (n=120) (Table 2).

Table 2: Pre and Post-Ramadan Changes in Non-Fasting Group

Parameter	n	Pre-Ramadan Mean ± SD	Post-Ramadan Mean ± SD	Mean Difference	t	p-value
Ultrafiltrate (L)	120	2.46 ± 0.92	2.70 ± 0.97	-0.239	-5.20	0.000
Dry Weight (kg)	120	60.24 ± 14.51	60.34 ± 14.55	0.101	1.02	0.306
Potassium (mEq/L)	120	4.90 ± 0.77	5.17 ± 0.81	-0.269	-3.64	0.000
Phosphorus (mg/dL)	120	5.22 ± 1.63	5.34 ± 1.57	-0.121	-0.903	0.368
Albumin (g/dL)	120	4.08 ± 0.50	4.23 ± 0.49	0.151	5.09	0.000

Despite the small sample size, notable differences were observed in ultrafiltrate and potassium levels, while other parameters showed minimal changes. Ultrafiltrate levels significantly increased from 2.38 ± 0.89 L to 2.74 ± 0.91 L (p=0.010), indicating a greater need for fluid removal post-Ramadan. This suggests possible fluctuations in fluid intake or retention due to intermittent fasting patterns. Dry weight remained almost unchanged, with a slight increase from 58.92 ± 12.34 kg to 58.96 ± 12.36 kg (p=0.844), confirming that intermittent fasting did not lead to significant weight variations in this group. Potassium levels showed a significant increase from 4.91 ± 0.74 mEq/L to 5.50 ± 0.79 mEq/L (p=0.021). This notable rise suggests a potential risk of hyperkalemia, possibly due to dietary changes, reduced dialysis frequency, or altered potassium excretion during fasting. Phosphorus levels increased from 5.24 ± 1.59 mg/dL to 5.83 ± 1.62 mg/dL, but this change was not statistically

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significant (p=0.148).This indicates that intermittent fasting had a limited impact on phosphorus regulation.Albumin levels showed a slight increase from 4.07 ± 0.52 g/dL to 4.22 ± 0.53 g/dL, but the difference was not statistically significant (p=0.155), suggesting stable nutritional status despite intermittent fasting. The result presents the pre- and post-Ramadan changes in clinical and biochemical parameters among the intermittent fasting group (n=11)(Table 3).

Table 3: Pre and Post-Ramadan Changes in Intermittent Fasting Group

Parameter	n	Pre-Ramadan Mean ± SD	Post-Ramadan Mean ± SD	Mean Difference	t	p-value
Ultrafiltrate (L)	11	2.38 ± 0.89	2.74 ± 0.91	-0.363	-3.19	0.010
Dry Weight (kg)	11	58.92 ± 12.34	58.96 ± 12.36	0.036	0.201	0.844
Potassium (mEq/L)	11	4.91 ± 0.74	5.50 ± 0.79	-0.590	-2.72	0.021
Phosphorus (mg/dL)	11	5.24 ± 1.59	5.83 ± 1.62	-0.590	-1.56	0.148
Albumin (g/dL)	11	4.07 ± 0.52	4.22 ± 0.53)	0.154	1.53	0.155

Due to the small sample size, no statistically significant changes were observed in any parameter. Ultra-filtrate levels increased from 2.40 ± 0.93 L to 2.79 ± 1.02 L, but this change was not significant (p=0.142), suggesting a potential but inconclusive increase in fluid removal needs post-Ramadan. Dry weight showed a slight decrease from 57.46 ± 13.12 kg to 57.32 ± 13.18 kg (p=0.766), indicating minimal weight fluctuations among fasting patients. Potassium levels remained almost unchanged, increasing marginally from 4.87 ± 0.75 mEq/L to 4.88 ± 0.78 mEq/L (p=0.962), suggesting no significant impact of fasting on potassium balance. Phosphorus levels increased from 5.30 ± 1.68 mg/dL to 6.18 ± 1.74 mg/dL, but this change was not statistically significant (p=0.193), indicating a potential trend toward higher phosphorus levels without conclusive evidence. Albumin levels slightly increased from 4.05 ± 0.51 g/dL to 4.14 ± 0.52 g/dL (p=0.578), suggesting stable nutritional status during fasting. The result presents the pre- and post-Ramadan changes in clinical and biochemical parameters among the fasting group (n=7)(Table 4).

Table 4: Pre and Post-Ramadan Changes in Fasting Group

Parameter	n	Pre-Ramadan Mean ± SD	Post-Ramadan Mean ± SD	Mean Difference	t	p-value
Ultrafiltrate (L)	7	2.40 ± 0.93	2.79 ± 1.02	-0.389	-1.68	0.142
Dry Weight (kg)	7	57.46 ± 13.12	57.32 ± 13.18	-0.142	-0.311	0.766
Potassium (mEq/L)	7	4.87 ± 0.75	4.88 ± 0.78	-0.014	-0.05	0.962
Phosphorus (mg/dL)	7	5.30 ± 1.68	6.18 ± 1.74	-0.877	-1.46	0.193
Albumin (g/dL)	7	4.05 ± 0.51	4.14 ± 0.52	0.088	0.588	0.578

DISCUSSION

The current study indicates that hyperkalemia and increased ultra-filtrate removal were observed among the non-fasting and intermittent fasting groups, suggesting that dietary habits during Ramadan may contribute to these changes. Despite not fasting, these patients may have consumed potassium-rich diets and increased fluid intake while eating with their families. This finding contrasts with a study from Saudi Arabia, where non-fasting dialysis patients showed no significant changes in potassium levels or intradialytic weight gain [17]. Likely, reflecting dietary variations between populations. Regarding weight changes, our study found a decrease in dry weight in the non-fasting and intermittent fasting groups, while the fasting group experienced weight gain. This contrasts with a study from Egypt, where both complete and partial fasting groups showed significant weight loss without adverse effects [6]. While an Indonesian study reported significant pre-dialysis weight loss in fasting patients [18]. Since intradialytic weight gain is associated with high mortality and poor survival rates [19]. Understanding these variations is crucial. Some of the observed biochemical and clinical changes, such as the statistically significant decrease in albumin and ultra-filtrate removal, may have important clinical implications. Hypoalbuminemia is a known risk factor for poor nutritional status and increased mortality in dialysis patients [20]. And its decline across all groups suggests potential nutritional deficiencies, emphasizing the need for closer monitoring and dietary guidance during dialysis prescriptions to prevent complications like volume overload or dehydration. Similarly, significant changes in ultra-filtrate removal may reflect altered fluid balance, necessitating adjustments. Also, show that phosphorus levels increased post-Ramadan, while albumin levels declined across all groups, consistent with findings from a Malaysian study, which reported significant hyperphosphatemia and a decline in serum albumin after prolonged fasting [4]. Hyperphosphatemia is strongly associated with cardiovascular mortality in dialysis patients [20]. Emphasizing the need for dietary phosphate control, while low albumin levels are linked to higher first-year mortality rates [21]. Reinforcing the importance of nutritional interventions during Ramadan. In the Malaysian cohort, prolonged fasting and poor dietary intake contributed to hypoalbuminemia [4], and in the current study, the decline

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in albumin levels may indicate insufficient dietary protein intake, which should be addressed through targeted nutritional counseling. Despite these biochemical changes, most patients remained asymptomatic, with only a few experiencing acute shortness of breath, regardless of fasting status. No studies have reported worse outcomes in dialysis patients due to Ramadan fasting; however, a multicenter study from Egypt found higher mortality in the non-fasting group, potentially because fasting patients were younger [22]. This study is unique in assessing the impact of Ramadan fasting on dialysis patients in Karachi, Pakistan, where the climate is moderate during March and April, and it highlights dietary pattern changes during Ramadan, regardless of fasting status.

CONCLUSIONS

It was concluded that ultra-filtrate and potassium levels significantly increased post-Ramadan in the overall population, with similar trends observed in the non-fasting and intermittent fasting groups. Albumin levels significantly declined in the overall and non-fasting groups but remained stable in the intermittent fasting group. However, in the fasting group, no significant changes were observed in ultra-filtrate, potassium, phosphorus, or dry weight, while albumin showed a slight, non-significant increase. These findings emphasize the need for group-specific monitoring of hemodialysis patients during Ramadan.

Authors Contribution

Conceptualization: ARQ
Methodology: ARQ, SF
Formal analysis: FA, SHD,
Writing review and editing: ARQ, FA, SHD

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Can Early Orthotic Support and Physical Therapy Improve the Functional Level in Pediatric Burn Patients?

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ABSTRACT

Physiotherapy prevents contractures and aids mobility in pediatric burn patients. **Objective:** To evaluate the potential benefits of implementing early orthotic interventions and physiotherapy programs in pediatric patients with burn injuries. **Methods:** This quasi experimental study was conducted on 27 children at Department of Physical Medicine and Rehabilitation (PM and R), The Children Hospital and University of Child Health Sciences, Lahore between August 2022 and August 2023. The sample size included 27 pediatric burn patients. Convenient sampling technique was used to collect data. Children under age of 16 years with burn were included in the study. ROM (measured via a goniometer), muscle tone (assessed using the Ashworth scale), and muscle strength (evaluated via the Oxford scale MMT) was systematically assessed. Related pre-treatment questionnaire was filled first, they were undergoing the burn rehabilitation protocol (anti-contracture positioning, ROM, casting, splinting, stretching) followed by verbal questionnaire filling after 3months. Wilcoxon Signed Rank Test was used to measure difference before and after the intervention. **Results:** Muscle tone of majority of patients was tested which was possible against gravity was possible now against some resistance. Result suggest that Physical activities like carrying an object and other ADLs which were severe difficult after burn were improved. ROM which was limited before orthotic intervention and physiotherapy protocol was now partially limited. **Conclusions:** In conclusion, the amalgamation of physiotherapy and orthosis represented a pivotal cornerstone in the comprehensive care paradigm for burn patients, yielding a myriad of positive effects that significantly enhance their rehabilitation journey.

INTRODUCTION

Burns are a common reason of admission to hospital in developing countries [1]. In this injury necrosis of tissues of body occurs and it may be limited to skin superficially or deep to the extent that it involves muscles, joints, blood vessels and vital organs [2]. Boiling liquids, Heat, electrical energy and corroding agents such as acids are common causes of burn injuries [3]. The WHO estimates that 11 million burn injuries of all types occur annually worldwide, 180,000 of which are fatal [4]. Superficial burns heal rapidly from dermis present beneath and usually does not require any surgical procedure while deep burns are complicated. Deep burns require time to heal properly as dermis is also damaged in deep burn injuries. So there are chance of contracture development and scarring usually decreased by plastic surgery [5]. Scar with contractures develop and expand to underlying connective tissues resulting in decreased range of motion and poor quality of life [6]. It may need dressings and repetitive surgical treatment [7]. Unfortunately, burns are very common in pediatric age groups with serious complications and high rate of morbidity and mortality [8]. These patients are encountered with a widespread somatic and psycho-social drawback, disturbing all aspects of their life [9]. In these conditions, early and intensive rehabilitation likely matters

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to an individual's physiological profile and functional recovery [10]. Physical therapy plays important role in management of burn [11]. It helps to improve functional capacity of damaged part with quality of life. Basically burn management is a multi-disciplinary approach which includes physicians, rehabilitation therapists, occupational therapist, and psychologists to deal with the pathology, ADL, social and psychological issues [6]. Proper Physical Therapy program and use of orthoses with moisturizing and massage after burn injuries is essential [12]. It helps in prevention of contracture, edema, improving Range of Motion (ROM), prevents growth of keloids or hypertrophic scars, regain the muscle strength and better cosmetic outcomes [13, 14]. Orthoses keep the damaged limb in best possible position. Burn orthoses are used to sustain a constant, mild stretching to the injured area, help to adapt scar tissue such as it maintains anatomical curves [15]. Moreover, caregiver's attitude also plays an important role in recovery [16]. Burn patient leads towards complications from positioning in spot of comfort. It may be adducted or flexed at chief joints [17]. Orthoses keep the position of affected body section in an anti-contracture position [18]. A chain of points should be planned for every joint because fixed positioning is usually not properly tolerated [19]. Major goal of this plan is to gain functional independence and resumption of activities like pre-burn times. Regardless of the large amount of international literature on pediatric burn rehabilitation by using physical therapy and orthoses, there is limited knowledge regarding their management with help of physical therapy and orthoses in pediatric population in Pakistan.

Therefore, this study aimed to evaluate the potential benefits of implementing early orthotic interventions and physiotherapy programs in pediatric patients who have sustained burn injuries

METHODS

This quasi experimental study was conducted on 27 children at Department of Physical Medicine and Rehabilitation (PM and R), The Children Hospital and University of Child Health Sciences, Lahore between August 2022 and August 2023. The sample size included 27 pediatric burn patients calculated by formula:

$$n = \frac{(Z_{\alpha/2} + Z\beta)2 \times 2 \times \sigma^2}{\delta^2}$$

Convenient sampling technique was used to collect data. Children under age of 16 years with first, second and third degree burn were included in the study. All children were conscious and oriented. While children with inability to comprehend instructions such as those who are on mechanical ventilators etc., any comorbidity and trauma or fracture of bone were excluded from the study. ROM (measured via a goniometer), muscle tone (assessed using the Ashworth scale), and muscle strength (evaluated via the Oxford scale MMT) was systematically assessed. Consent was taken from the parents of pediatric patients and they were informed about the protocols of the study. Related pretreatment questionnaire was filled first, they were undergoing the burn rehabilitation protocol (anti contracture positioning, ROM, casting, splinting, stretching) 3 times a week for a total duration of 3 months. They were asked to perform 3 sets of PROM and AROMs protocol daily and post treatment questionnaire was filled verbally again to have the feedback inquiring about the effectiveness of physical therapy in preventing contractures after burn. The data were entered and analyzed using software IBM SPSS version 23.0. The continuous variables were expressed as mean ± SD, whereas the categorical variables were in the form of percentage. Wilcoxon Signed Rank Test was employed to test the difference before and after the intervention. A p value < 0.05 was considered as statistically significant. Ethical clearance was obtained from the ethical committee of the School of Allied Health Sciences CH and UCHS Lahore (No.1183/SAHS).

RESULTS

Demographic features of the subjects are described in table 1.27 pediatric patients of burn injury who met the inclusion criteria participated in order to collect data. Majority of patients were male. Mean age of the patients was 9.07± 3.83. Majority of the patients belonged to middle class. Most of the patients was from urban areas. The most common cause of burn was electricity covering a percentage of 51.9. The area of body in burn injury involved shoulder, arm, hand, leg and foot. Arm was the most common part of body in burn injury with a percentage of 37.0.

Table 1: Socio-Demographic Characteristics of Subjects

Variables	Category	Frequency (%)
Gender	Male	20 (74.1%)
	Female	7 (25.9%)
Socio-economic Status	Upper	2 (7.4%)
	Middle	20 (74.1%)
	Lower	5 (18.5%)
Place of Residence	Urban	17 (63%)
	Rural	10 (37%)

Table 2 presented the effect of the intervention on muscle tone using the MAS. Post-intervention, there was a significant decrease in higher MAS grades (Grades 2–4), indicated decreased muscle tone, while lower grades (Grades 0–1+) showed an increase, suggesting improved control. The p-values (<0.05) confirm statistically

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significant changes, representing the intervention's effectiveness in reducing spasticity.

Table 2: Effect on Muscle Tone before and After Intervention (Modified Ashworth Scale)

Muscle Tone Measurement (MAS Grade)	Pre-Intervention Frequency (%)	Post-Intervention Frequency (%)	p-Value
Grade 0 (No increase in tone)	0 (0%)	5 (18.5%)	0.002
Grade 1 (Slight increase in tone)	2 (7.4%)	8 (29.6%)	0.001
Grade 1+ (Minimal resistance)	5 (18.5%)	7 (25.9%)	0.003
Grade 2 (More marked increase in tone)	10 (37.0%)	5 (18.5%)	0.004
Grade 3 (Considerable increase, passive movement difficult)	7 (25.9%)	2 (7.4%)	0.005
Grade 4 (Rigid in flexion/extension)	3 (11.1%)	0 (0%)	0.006

Table 3 illustrated the effect of the intervention on muscle strength using the Oxford Scale MMT. Post-intervention, there was a significant drop in lower strength grades (Grades 0–3), indicating improvement in muscle activation and movement. Higher strength grades (Grades 4 and 5) increased, replicating enhanced functional strength. The statistically significant p-values (<0.05) confirm the intervention's efficiency in improving muscle strength.

Table 3: Effect on Muscle Strength before and After Intervention (Oxford Scale of MMT)

Muscle Strength (Oxford Scale of MMT Grade)	Category	Pre-Intervention Frequency (%)	Post-Intervention Frequency (%)	p-value
Grade 0	No Contraction	3 (11.1%)	0 (0%)	0.005*
Grade 1	Flicker Contraction, No Movement	5 (18.5%)	2 (7.4%)	0.004*
Grade 2	Movement with Gravity Eliminated	7 (25.9%)	4 (14.8%)	0.003*
Grade 3	Movement Against Gravity Only	8 (29.6%)	6 (22.2%)	0.002*
Grade 4	Movement Against Resistance, Reduced Strength	4 (14.8%)	10 (37.0%)	0.001*
Grade 5	Normal Muscle Strength	0 (0%)	5 (18.5%)	0.006*

*p-Values indicate statistical significance ($p < 0.05$)

Table 4 demonstrated the effect of the intervention on the ROM of the affected joints. Post-intervention, there was a significant increase in ROM across all measured movements, with shoulder flexion, elbow extension, hip flexion, and knee extension showing marked improvements. The statistically significant p-values (<0.05) approves that the joint mobility was enhanced.

Table 4: Effect on Range of Motion (ROM) of Joint Involved before and after Intervention

ROM Measurement	Pre-Intervention (Mean ± SD)	Post-Intervention (Mean ± SD)	p-Value
Shoulder Flexion	80° ± 10°	130° ± 15°	0.001*
Elbow Extension	40° ± 5°	90° ± 10°	0.002*
Hip Flexion	50° ± 8°	100° ± 12°	0.003*
Knee Extension	30° ± 6°	80° ± 9°	0.005*

*p-values indicate statistical significance ($p < 0.05$)

Table 5 presented the effect of the intervention on physical status using the DASH scale. Post-intervention, there was a significant shift towards improved functional ability, with an increase in participants experiencing no or mild difficulty and a reduction in those with moderate to severe difficulty. Notably, no participants remained in the "Unable to Perform" category. The statistically significant p-values (<0.05) confirm the intervention's effectiveness in enhancing physical function.

Table 5: Effect on Physical Status before and After Intervention (DASH Scale)

DASH Score	Category	Pre-Intervention Frequency (%)	Post-Intervention Frequency (%)	p-value
No Difficulty	0-20 DASH Score	2 (7.4%)	10 (37.0%)	0.002*
Mild Difficulty	21-40	5 (18.5%)	8 (29.6%)	0.003*
Moderate Difficulty	41-60	10 (37.0%)	6 (22.2%)	0.001*
Severe Difficulty	61-80	7 (25.9%)	3 (11.1%)	0.004*
Unable to Perform	81-100	3 (11.1%)	0 (0%)	0.005*

*p-values indicate statistical significance ($p < 0.05$)

DISCUSSION

This study was carried out to determine the prevention of joint contracture by physical therapy interventions in burn injury.27 pediatric patients participated to collect data. Burn injuries usually result in muscle atrophy and reduced joint movement due to prolonged stasis during recovery [20]. The best approach is to introduce physiotherapy program and for execution of physical exercises are proper education to patients or their care givers and to supervise effective presentation of movements [21]. The manual muscle tone testing results were significant after therapy. Current study showed that the muscle that show contraction against some resistance have full muscle power after physiotherapy. Mohammed HE *et al.*, studied

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the effect of physiotherapy protocol on post burn injury [6]. His study showed that there is gradual increase in muscles force in post physiotherapy protocol application (22.2%, 59.3% respectively) with high statistical significance difference. Early range of motion and splinting of upper limbs were effective methods to increase muscle force, reducing burn scar and pain which influence positively on restoring upper extremity function post burn. The results of this study revealed a highly statistically compelling difference in improving quality of life.There is high statistical significance (p-value<0.05).Above study support these results that there was improvement after implementation of physiotherapy protocols. In conclusion, physiotherapy protocols emerge as highly effective in positively influencing manual muscle tone in burn children. The physical activities like carry an object, functional activities and recreational activities which require little after burn showed significant change after application of physiotherapy exercises. After orthotic support and proper physiotherapy protocol significant improvement was observed. Patient now could carry the objects with moderate difficulty now.Mohammed HE *et al.*, study showed the gradual improvement of the physical status of upper limbs post burn protocol among study sample [6]. Activities of daily living, play, and sports are integrated into the rehabilitation process, allowing children to regain confidence and autonomy in their physical capabilities. So, physiotherapy exercises play a crucial role in restoring physical activities in burn children.Current study concluded that there is significant increase in range of motion of joint involved from (25% to 77%).This shows improvement in affected joint and prevention of contractures.ROM was markedly restricted in majority of patients. Which was after regimen of physiotherapy program improved from fully limited to partially limited ranges. M. Asadullah *et al.*, studied early range of motion exercises in burn patients [2].His results showed that the early passive range of motion exercises with anti-contractures positioning can reduce the formation of scar formation, prevent contractures and increase the quality of physical therapy management in sub-acute stage of burn patients. So their study supports these results. This study showed that orthosis and physiotherapy could be an effective approach in managing burns in paeds patients [22].

CONCLUSIONS

In conclusion, the amalgamation of physiotherapy and orthosis represented a pivotal cornerstone in the comprehensive care paradigm for burn patients, yielding a myriad of positive effects that significantly enhance their rehabilitation journey. Through meticulous rehabilitation strategies tailored to individual needs, physiotherapy empowers patients to regain functional independence, improve mobility, and alleviate pain, thereby fostering a holistic recovery trajectory. Thus, the integration of physiotherapy and orthosis stands in the multidisciplinary care continuum for burn patients, epitomizing the transformative potential of comprehensive rehabilitation in restoring both physical and psychological equilibrium.

Authors Contribution

Conceptualization: MS[1]
Methodology: MS[1], SRAH, BA, MSM
Formal analysis: MS[2]
Writing, review and editing: SA, TM, SF, MSM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Role of Diagnostic and Prognostic Immunohistochemical Markers in Hepatocellular Carcinoma

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ABSTRACT

As the primary cause of cancer-related death globally, Hepatocellular Carcinoma requires accurate diagnostic and prognostic markers.Immunohistochemical indicators have been identified as promising instruments to improve the precision of hepatocellular Carcinoma diagnosis and forecast patient outcomes. **Objectives:** To evaluate the relationships between clinicopathological characteristics associated with hepatocellular carcinoma, such as tumor grade, vascular invasion, and patient characteristics, and the expression of immunohistochemical markers. **Methods:** A cross-sectional study was conducted for six months from Feb 2024 to Jul 2024 in the Department of Pathology at a tertiary care hospital. There were 323 patients with Hepatocellular Carcinoma diagnoses in all. Immunohistochemical was used to examine specimens of tissue for the markers Ki-67, CK19, Glypican-3, alpha-fetoprotein (AFP), HepPar-1, and CD34. Kaplan-Meier survival analysis, t-tests, and chi-square tests were used to evaluate correlation with clinicopathological characteristics and survival results. **Results:** High percentages of positive expression were seen for CD34 (88.2%), Glypican-3 (75.9%), and HepPar-1 (82.7%). There were noteworthy associations discovered between tumor size, vascular invasion, and serum AFP levels and IHC markers. Notably, HepPar-1 positive predicted a better prognosis (HR 0.72, p=0.032), but Glypican-3 (HR 1.58, p=0.001) and Ki-67 (HR 2.10, p=0.002) were linked to poor overall survival. **Conclusions:** It was concluded that the significant associations between specific immunohistochemical markers (e.g., HepPar-1, Glypican-3, and Ki-67) and clinicopathological characteristics, as well as their impact on prognosis in Hepatocellular Carcinoma patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide and one of the most common types of liver cancer. Alcohol misuse, metabolic problems, and chronic liver diseases, in particular, cirrhosis carried on by viral hepatitis (HCV and HBV), are commonly associated with it. Clinical management and treatment of HCC are significantly challenged because of the disease's sneaky development and sometimes delayed diagnosis. To improve patient outcomes and customize treatment plans, early identification and precise prognostication are essential [1, 2]. In countries like China and some regions of Southeast Asia where the hepatitis B virus (HBV) is endemic, HCC is particularly widespread, making up a substantial percentage of morbidity and death due to cancer. Nevertheless, in Western nations, where hepatitis C, NAFLD, and virus (HCV) infection pose serious risk variables, the prevalence of HCC has been increasing steadily within the past few decades [3, 4]. Since HCC frequently manifests as asymptomatic or with nebulous symptoms that are easily confused with other illnesses, many patients receive their diagnosis of the disease at an advanced stage. The disease may have advanced to the point that curative measures, including surgical excision or

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transplantation, are no longer a possibility by the time a diagnosis is made. Because HCC develops slowly, routine screening is crucial but often neglected, particularly in high-risk populations [5, 6]. Treatment outcomes could be greatly improved by early detection achieved by routine imaging and biomarker investigations. Treatment choices become considerably limited for people with advanced HCC. Options for treatment could also be made more complex by parameters like the functioning of the liver, treatment obstructions, and complexity of the tumor [7, 8]. A useful method for evaluating the histopathology of HCC is immunohistochemical (IHC) staining. HepPar-1, Glypican-3, alpha-fetoprotein (AFP), CK19, CD34, and Ki-67 are examples of IHC markers that can be used to determine the biological behavior, differentiation state, and possible metastasis of a tumor. The diagnostic and treatment choices can be guided by these markers, which can help differentiate HCC from other liver diseases [9]. The primary risk factors for HCC include chronic viral infections, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV), along with alcohol abuse, metabolic disorders, and non-alcoholic fatty liver disease (NAFLD). These risk factors often lead to liver cirrhosis, which is a major predisposing condition for the development of HCC.

This study aims to evaluate the relationships between clinicopathological characteristics associated with hepatocellular carcinoma, such as tumor grade, vascular invasion, and patient characteristics, and the expression of immunohistochemical markers.

METHODS

A cross-sectional study was conducted for six months from Feb 2024 to Jul 2024 in the Department of Pathology at a tertiary care hospital. The study was approved by the Institutional Review Board (KMC/RERC78) of the hospital, and informed consent was obtained from all participants before their inclusion in the study. Inclusion criteria were participants diagnosed with HCC were confirmed by histological findings, demographic information, laboratory results, imaging findings, and treatment history, and follow-up data were carefully extracted. Exclusion criteria were patients with metastatic liver cancer, incomplete clinical data, inadequate biopsy samples. The sample size for a cross-sectional study, such as evaluating immunohistochemical markers in hepatocellular carcinoma, was determined by the frequency of an outcome in particular (e.g., the expression of certain markers, such as HepPar-1, Glypican-3, etc.). The following formula was used to determine the sample size in cross-sectional studies: $n = (Z^2 * p * (1-p)) / d^2$, where Z was the 95% confidence level, p=estimated the prevalence (0.07), and d was the margin of error (5%). The sample size of 323 participants was calculated using the G*Power tool for correlation analysis. The calculation was based on prior studies assessing GP73 levels to fibrosis staging. The gold standard study/reference was used for justification [10]. Liver tissue specimens (FFPE) from 323 participants with histopathologically confirmed hepatocellular carcinoma (HCC) were used. Following tissue collection by biopsy or surgical resection, the tissues were dehydrated, cleaned in xylene, and embedded in paraffin before being fixed in 10% neutral buffered formalin for 24 to 48 hours. Glass slides were prepared with sections that were 4-5 microns thick. Using citrate or EDTA buffer, antigen retrieval was carried out following deparaffinization and rehydration. Using 3% hydrogen peroxide, endogenous peroxidase activity was inhibited. A panel of commercially available antibodies targeting specific markers associated with HCC, including alpha-fetoprotein (AFP), glypican-3 (GPC3), heat shock protein 70 (HSP70), and cytokeratin 19 (CK19), was selected based on their relevance and established utility in HCC diagnosis and characterization. Before staining, optimization of IHC protocols was conducted to ensure optimal antigen retrieval, antibody specificity, and signal detection. For the HCC IHC panel, the primary antibodies include HepPar-1 (OCH1E5, mouse, Dako, M7158), Glypican-3 (GPC3) (1G12, mouse, Abcam, ab66596), AFP (Merc Millipore Cat. No. MABX5512-10KC), CK19 (Zeta corporation-Catalogue Number Z2134ML.), CD34 (QBEnd/10, mouse, Dako, M7165), and Ki-67 (MIB-1, mouse, Dako, M7240) and goat anti-mouse IgGfor secondary antibodies. For DAB staining, HRP-conjugated anti-mouse IgG (Abcam, ab6789) was used. For immunofluorescence, Alexa Fluor 488-conjugated anti-mouse IgG (Invitrogen, A11001) was used following the manufacturer's instructions. The ABC technique with DAB chromogen was used for visualization. Slides were mounted and counterstained with hematoxylin so that a pathologist could examine them. There were positive and negative controls for every antibody in the quality control system. The clinical information was assessed by the immunohistochemically stained slides [11]. HepPar-1, Glypican-3, AFP, and CK19 were among the markers whose staining intensity and distribution were evaluated. Staining intensity (0: negative, 1+: mild, 2+: moderate, 3+: strong) and the percentage of positively stained samples are included in a semi-quantitative scoring system that was used to standardize the tumour cells' interpretation of the findings of staining. The study utilized electronic medical records and pathology reports to collect and record clinicopathological information, patient demographics, tumor characteristics (size, number, and grade), laboratory parameters (AFP levels), imaging findings, therapeutic approaches, and clinical results. Patient demographics and clinicopathological features were summarized using descriptive statistics.

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The relationships between the expression levels of immunohistochemical markers and several clinicopathological variables were examined statistically. Chi-square and t-tests were used to evaluate the significance of these relationships and find independent predictors of clinical outcomes. The IHC marker's predictive significance in predicting patient survival outcomes was assessed using the Kaplan-Meier technique and log-rank analysis.

RESULTS

The majority of HCC patients (68.4%) were aged 50 or older. Males were predominantly affected (76.1%), aligning with global trends. Tumors larger than 5 cm were found in 58.2% of cases, while 41.8% had smaller tumors. A single tumor was present in 66.6% of patients, suggesting a potentially better prognosis. Vascular invasion was observed in 28.5% of cases. Cirrhosis was present in 60.1% of patients. AFP levels ≥400 ng/mL were seen in 54.2% of cases. HBV was detected in 48.3% of patients, while HCV was found in 37.8% (Table 1).

Table 1: Demographic Characteristics of HCC Patients

Characteristics	(n=323)
Age (Years)	
<50	102 (31.6%)
≥50	221 (68.4%)
Gender	
Male	246 (76.1%)
Female	77 (23.9%)
Tumor Size (cm)	
≤5	135 (41.8%)
>5	188 (58.2%)
Number of Tumors	
Single	215 (66.6%)
Multiple	108 (33.4%)
Vascular Invasion	
Present	92 (28.5%)
Absent	231 (71.5%)
Cirrhosis Status	
Cirrhosis Present	194 (60.1%)
No Cirrhosis	129 (39.9%)
Serum AFP Levels (ng/mL)	
<400	148 (45.8%)
≥400	175 (54.2%)
Virus	
Hepatitis B Virus (HBV) Positive	156 (48.3%)
Hepatitis C Virus (HCV) Positive	122 (37.8%)

For IHC expression, robust positive expression of HepPar-1 in 82.7% (267 patients) and the negative expression of 17.3% (56 patients) was observed in HCC. 75.9% of HCC patients overexpressed Glypican-3 with a negative expression in 78 cases (24.1%). For AFP, 61.3% positive expression of AFP, and (38.7%) of negative expression was observed in patients. Although only 30% of patients have CK19 positivity, those who do have the protein have a more aggressive form of HCC with cholangiocarcinoma-like characteristics (biliary differentiation), and 70.0% of them express CK19 negatively. The abundant vascularity of HCC tumors is reflected by the high expression of CD34, an angiogenesis marker (88.2%) in HCC tissues. The cell proliferation marker Ki-67 was used. In around 35% of patients, the proliferation index was less than 10%. The tumor growth may be comparatively slower in the remaining 65% of cases with a lower proliferation index (<10%)(Table 2).

Table 2: Expression of IHC Markers HepPar-1. Glypican-3, AFP, CK19, CD34 and Ki-67 in HCC Tissues

IHC Markers	Positive Expression n (%)	Negative Expression n (%)
HepPar-1	267 (82.7%)	56 (17.3%)
Glypican-3 (GPC3)	245 (75.9%)	78 (24.1%)
AFP	198 (61.3%)	125 (38.7%)
CK19	97 (30.0%)	226 (70.0%)
CD34 (Angiogenesis)	285 (88.2%)	38 (11.8%)
Ki-67 (Proliferation Index)		
<10%	210 (65.0%)	–
≥10%	113 (35.0%)	-

HCC patients show significant correlations between IHC markers and clinicopathological features (Table 3). AFP (p=0.022*) and Ki-67 ≥10% (p=0.029*) are higher in patients aged ≥50 years. Larger tumors (>5 cm) express AFP, CD34, HepPar-1, Glypican-3, and Ki-67 ≥10% at significantly higher levels (p<0.05). Vascular invasion is linked with increased expression of HepPar-1, Glypican-3, AFP, CK19, CD34, and Ki-67 ≥10% (p<0.05). Cirrhosis correlates with AFP, CK19, and Ki-67 ≥10% (p<0.01). Higher AFP levels (≥400 ng/mL) are associated with elevated expression of HepPar-1, Glypican-3, CK19, CD34, and Ki-67 ≥10%, suggesting more aggressive tumor behavior (Table 3).

Table 3: Correlation between Clinic-Pathological Parameters and IHC Marker Expression in HCC

Parameter	HepPar-1 (p-value)	Glypican-3 (p-value)	AFP (p-value)	Ck19 (p-value)	Cd34 (p-value)	Ki-67 ≥10% (p-value)
Age (<50 vs ≥50)	0.141	0.342	0.022*	0.518	0.113	0.029*
Tumor Size (≤5 vs >5 cm)	0.002*	0.015*	0.001*	0.061	0.039*	0.001*

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Vascular Invasion	0.031*	0.018*	0.003*	0.014*	0.042*	0.002*
Cirrhosis	0.277	0.125	0.009*	0.002*	0.111	0.008*
AFP Levels (<400 vs ≥400 ng/mL)	0.001*	0.002*	-	0.016*	0.033*	0.005*

HepPar-1 was expressed in 82.7% of HCC cases and correlated with better prognosis (HR=0.72, p=0.032*), reducing mortality risk by 28%, with a median survival of 32 months. GPC3 was expressed in 75.9% of cases and linked to worse outcomes (HR=1.58, p=0.001*), increasing mortality risk by 58%, with a median survival of 28 months. AFP was positive in 61.3% of cases, associated with a 42% higher mortality risk (HR=1.42, p=0.005*), and a median survival of 26 months. CK19, expressed in 30% of cases, showed the worst prognosis (HR=1.85, p=0.001*), with an 85% increased mortality risk and a median survival of 22 months (Table 4).

Table 4: IHC Markers in HCC Correlating with Survival in HCC Patients

Marker	No. of Patients (n=323)	Median OS (Months)	1-Year Survival Rate (%)	3-Year Survival Rate (%)	Hazard Ratio (HR) [95% CI]	p-value (Log-Rank)
HepPar-1	Positive: 267 (82.7%)	32	80%	40%	0.72 [0.56-0.90]	0.032*
Glypican-3 (GPC3)	Positive: 245 (75.9%)	28	78%	35%	1.58 [1.25-2.00]	0.001*
AFP	Positive: 198 (61.3%)	26	75%	30%	1.42 [1.12-1.80]	0.005*
CK19	Positive: 97 (30.0%)	22	70%	25%	1.85 [1.40-2.45]	0.001*
CD34 (Angiogenesis)	Positive: 285 (88.2%)	30	77%	38%	0.83 [0.65-1.05]	0.015*
Ki-67 (Proliferation Index)	Positive: 113 (35.0%)	20	65%	20%	2.10 [1.65-2.65]	0.002*

Immunohistochemistry Expression of HepPar-1 is shown (Figure 1).

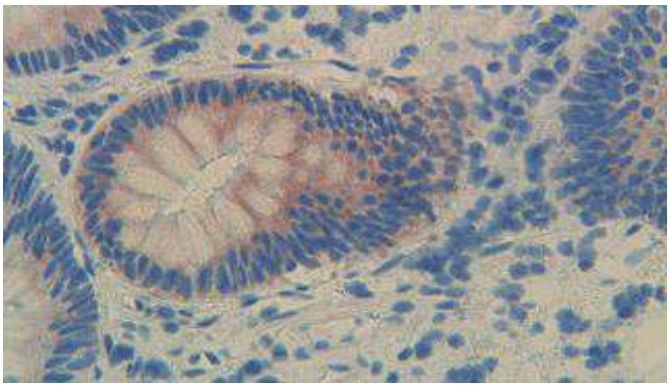

Figure 1: Immunohistochemistry Expression of HepPar-1

Immunohistochemistry expression of Glypican is shown (Figure 2).

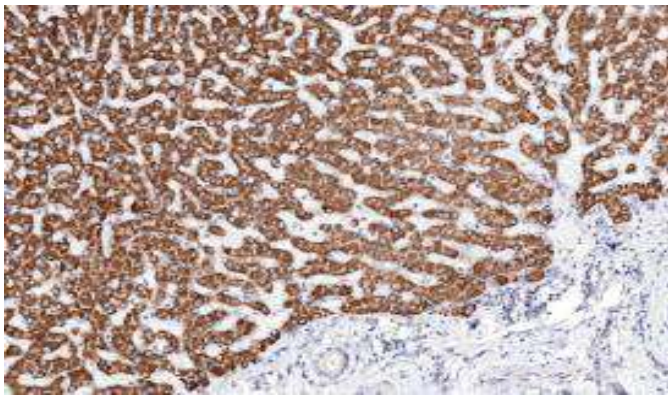

Figure 2: Immunohistochemistry Expression of Glypican

Immunohistochemistry expression of CK19 is shown (Figure 3).

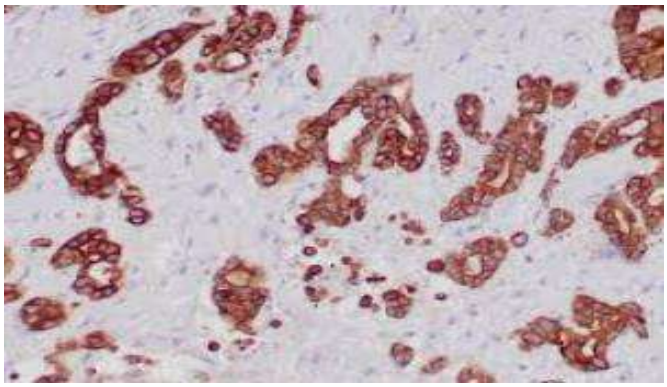

Figure 3: Immunohistochemistry Expression of CK19

Immunohistochemistry expression of Ki-67 is shown (Figure 4).

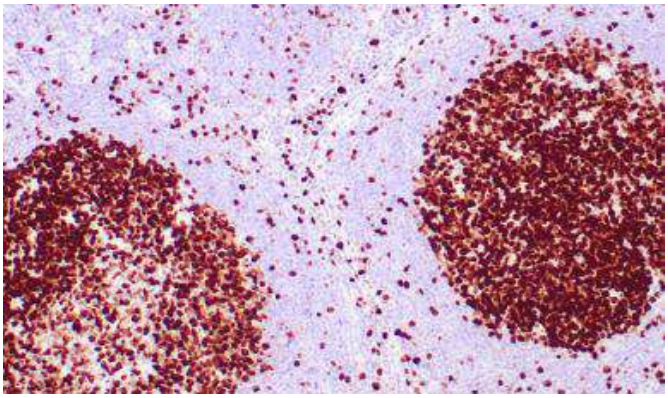

Figure 4: Immunohistochemistry Expression of Ki-67

Immunohistochemistry expression of AFP is shown (Figure 5).

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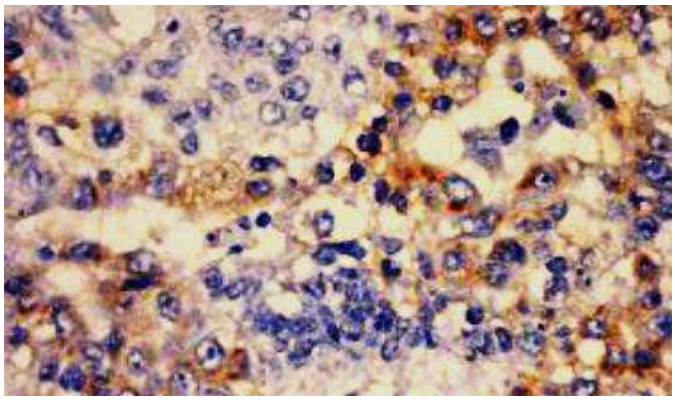

Figure 5: Immunohistochemistry Expression of AFP

Immunohistochemistry expression of CD 34 in HCC is shown, magnification used 40X (Figure 6).

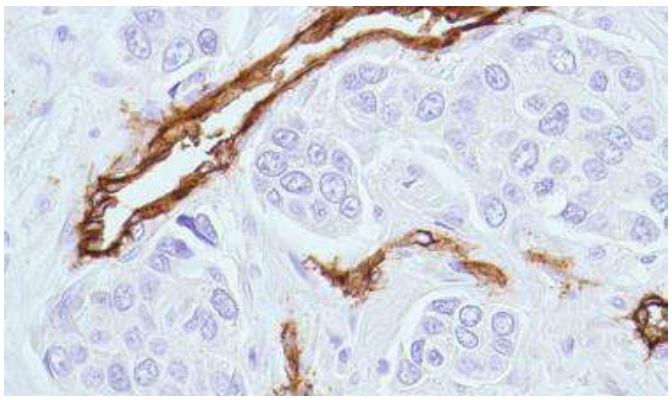

Figure 6: Immunohistochemistry Expression of CD 34 in HCC, Magnification Used 40X

DISCUSSION

Histological and molecular features of hepatocellular carcinoma (HCC) vary, and it poses a substantial worldwide health burden. The present investigation examined the expression of multiple important immunohistochemistry (IHC) markers in hepatocellular carcinoma (HCC) tissues, and assessed the associations between these markers and clinicopathological characteristics as well as overall survival (OS). In order to help with patient care and stratification, the results emphasize the significance of these indicators in predicting the clinical course of HCC [12]. HepPar-1 is a hepatocyte-specific marker that is widely used to confirm hepatocellular differentiation. The high positive expression rate of HepPar-1 (82.7%) observed in this study underscores its role as a reliable diagnostic marker for HCC. HepPar-1 positivity has been linked to well-differentiated HCC tumors, suggesting that its expression reflects a tumor's ability to retain hepatocellular features, which may be associated with less aggressive behavior. Our findings revealed high positive expression rates for several IHC markers, most notably Glypican-3 (75.9%), and CD34 (88.2%). These markers are crucial in the biological characterization and diagnosis of hepatocellular carcinoma (HCC) [13]. We were agreed from the previous research has repeatedly shown, HepPar-1 and Glypican-3 expression is highly expressed in HCC cases making it an essential marker for differentiating HCC from metastatic liver cancers. This highlights the necessity of having a panel of markers in instances when there is no HepPar-1 expression, especially in more aggressive tumor subtypes [14]. As previous study, by interacting with growth factors such as Wnt and Hedgehog, GPC3 has been demonstrated to stimulate cell proliferation and block apoptosis, hence contributing to the malignant transformation of hepatocytes. GPC3 expression was found to be highly expressed in our investigation. GPC3 expression is clinically correlated with worse outcomes; patients who tested positive for GPC3 had a significantly lower median overall survival (28 months). This correlation implies that GPC3 may be a viable target for therapy in addition to acting as a diagnostic marker. GPC3-specific immunotherapies and other GPC3-targeted medicines are the subject of ongoing clinical trials and may offer new therapy options for individuals with high GPC3 expression in their HCC [15]. In 88.2% of HCC cases, neovascularization is crucial in HCC to sustain the growing tumor mass, especially in more advanced tumors. We were observed previous study similar results as our study that, high CD34 positive rate indicates that angiogenesis is a characteristic that is present in most HCC cases, which means that it should be taken into account when making decisions about therapy and prognosis. Patients who are positive for CD34 may be more likely to benefit from anti-angiogenic treatments, such as sorafenib, which are currently being used to treat advanced HCC. Monitoring the response to anti-angiogenic therapy can be facilitated by the function of CD34 in determining the vascularity of tumors [16, 17]. The comparison of correlations between IHC markers and pathological variables such as age, tumor size, vascular invasion, cirrhosis, and AFP levels reveals important relationships that may assist in determining the development, outcomes, and severity of HCC. The strong correlation found between younger age groups and higher AFP levels could suggest that AFP-positive tumors in this age group are more aggressive and physiologically active, which could lead to an earlier beginning and possibly faster development of the disease [18, 19]. This emphasizes the necessity for younger patients with increased AFP to get more careful monitoring and care. Proliferative index is higher in younger patients, as indicated by the association between Ki-67, a well-established marker of proliferation. Consequently, surveillance programs and early detection tests are critical for the timely diagnosis and treatment of HCC. Screening efforts primarily target populations with multiple risk factors, such as known carriers of the hepatitis virus, individuals with cirrhosis, or those with a

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family history of HCC [20]. One important indicator of prognosis in HCC is the size of the tumor, with larger tumors typically denoting more aggressive illness. Since HepPar-1 tends to disappear in later-stage and less distinct cancers, the highly significant correlation between larger tumor size and minimized HepPar-1 expression may be attributed to this occurrence. Alternatively, GPC3 may be linked to more aggressive, quickly growing tumors, consistent with its function in activating oncogenic signaling pathways, as indicated by the positive connection between Glypican-3 and larger tumors [20, 21]. Increased angiogenesis, as shown by CD34 expression (p=0.039), and higher AFP levels (p=0.001) were also associated with stronger tumor sizes. This supports the function of AFP as a gauge of tumor aggressiveness and burden, and the correlation with CD34 emphasizes the role angiogenesis plays in promoting tumor growth in larger tumors. Since larger tumors have higher proliferative activity, which is a sign of more aggressive illness and cause worse outcomes [22]. HepPar-1 expression has decreased in vascular invasion instances (p=0.031), which indicates that an even more invasive tumor has been related to a decline of differentiated as shown by lower HepPar-1. Glypican-3 and AFP have significant associations with vascular invasion, which confirms both of their roles as markers for vigorous tumor dissemination and invasion through their contribution in Wnt/β-catenin signaling. AFP-positive and CK19-positive tumors are more likely to develop in the context of cirrhotic liver tissue, according to the strong association between AFP and CK19 and cirrhosis. The proliferative index (Ki-67 ≥10%) is higher in cirrhotic patients, suggesting a larger potential for tumor growth and aggressive character. This emphasizes the necessity of closely monitoring cirrhotic individuals with elevated Ki-67 expression and maybe more severe treatment [23]. The strong inverse relationship between high levels of AFP and HepPar-1 expression implies that when tumors grow more aggressive and poorly differentiated, they lose HepPar-1 expression and increase their production of AFP. These markers, Glypican-3, CK19, and CD34, are significantly correlated with increased levels of AFP, suggesting that they are frequently expressed in more aggressive tumors that produce AFP. The greater AFP production is associated with more aggressive proliferation rates in tumors, which indicates a worse prognosis and faster disease progression. This is shown in the link between greater AFP levels and increased Ki-67 expression [24]. IHC markers have a significant prognostic impact in HCC; HepPar-1 and CD34 may be predictive of improved outcomes, but GPC3, AFP, CK19, and Ki-67 are associated with a poor prognosis [25, 26]. Comprehending these correlations facilitates better patient matching, customized therapy regimens, and knowledgeable medical judgment, consequently augmenting HCC patients' management approaches. This study's sample size, while adequate, may not fully represent the broader HCC population, and larger multicenter studies are necessary for validation. The retrospective design introduces potential selection bias, and there is a lack of prospective validation. Variability in IHC staining techniques across laboratories could also affect reproducibility. Additionally, without molecular and genetic profiling of the tumors, the study may have missed other contributing factors in HCC progression. Future research should focus on larger, multicenter, prospective studies to validate these IHC markers. Incorporating molecular and genetic profiling of tumors would provide a deeper understanding of their role in HCC. Clinical trials exploring targeted therapies and immunotherapies, particularly focusing on GPC3, are also recommended to improve personalized treatment options for HCC patients.

CONCLUSIONS

It was concluded that significant clinicopathological factors are correlated with the elevated expression rates of immunohistochemistry (IHC) markers in HCC tissues, including HepPar-1 and Glypican-3. The connection between them highlights its potential importance in selecting of diagnosis and duration of treatments.

Authors Contribution

Conceptualization: AQM
Methodology: SA, AA, AHP
Formal analysis: SA, RKR
Writing review and editing: AA, AHP, SAP, RKR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Screening Student Behavior: Exploring the Impact of Daily Screen Time on Sleep Quality, Mental Distress, and Academic Performance in Students

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ABSTRACT

The pervasive influence of technology, particularly screen usage, on daily routines and its implications for sleep quality, mental health, academic performance, and physical activity has become an increasing area of concern. **Objective:** To evaluate the daily screen time of students from different fields of study and to assess its association with demographic variables, sleep quality, psychological symptoms, physical activity, and academic performance. **Methods:** This study was performed at Isra University, Hyderabad from February 2024 to August 2024, with 152 participants. Data on demographics, sleep quality (PSQI), mental distress (DASS-42), academic performance, and screen time were collected after informed consent. Statistical analysis, conducted using SPSS version 25.0, determined correlations between daily screen time, PSQI, and DAS scores. **Results:** The participants had a mean age of 20.59 ± 2.16 years, with most residing in urban areas (87.5%) and being day scholars (74.34%). Average daily screen time was 5.85 ± 1.14 hours, significantly higher among those with GPAs below 2.5 and low physical activity levels ($p<0.05$). Mean scores for depression, anxiety, stress, and PSQI were 13.34 ± 12.01, 11.17 ± 9.41, 15.32 ± 11.09, and 6.45 ± 3.48, respectively. Screen time positively correlated with depression ($r = 0.81$, $p<0.01$), anxiety ($r = 0.78$, $p<0.01$), stress ($r = 0.83$, $p<0.01$), and PSQI ($r = 0.75$, $p<0.01$). **Conclusion:** Increased screen time was linked to poorer sleep quality, elevated mental distress, and reduced academic performance, particularly in urban populations and individuals using screens for recreation.

INTRODUCTION

With the rise of online connectivity, mobile devices, and social media platforms, technology has become an integral part of daily life, serving both recreational and professional purposes. This shift has led to a significant increase in the number of individuals using computers and electronic devices, thereby contributing to higher screen time[1, 2]. Prolonged exposure to screens emitting blue light disrupts the body's circadian rhythm, leading to sleep disturbances such as insomnia and irregular sleep patterns, which hinder sleep initiation and overall sleep quality [3]. Previous studies have shown that students with higher smartphone usage, particularly at night, experience poorer sleep quality and heightened anxiety levels [4,5]. Sleep plays a critical role in physical health, cognitive function, and academic performance. Inadequate sleep has been associated with cardiometabolic disorders such as obesity, diabetes, and hypertension, as well as psychological issues like stress, depression, and anxiety [6]. Sleep deprivation impairs attention, mental processing speed, logical reasoning, and productivity, ultimately leading to declining academic performance [6]. Like poor sleep, depression is more prevalent among younger individuals with prolonged digital content consumption, particularly on computers [1]. Research suggests that excessive screen use, combined with social media-driven validation pressures, increases vulnerability to depression. This reliance on virtual interactions reduces face-to-face socialization, often leading to social withdrawal and

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hormonal imbalances in dopamine, serotonin, and endorphins—neurotransmitters critical for emotional well-being [7].While digital technology has revolutionized education, communication, and information accessibility, prolonged screen exposure is associated with negative health consequences, including sleep deprivation, social behavior disruptions, and academic decline [8]. The global prevalence of mobile internet device usage has increased exponentially, with a thousand-fold rise in the past decade [9]. Studies indicate that daily screen time exceeding two hours is now common and may adversely impact both physical and psychological health [10]. Excessive screen time has been strongly linked to declining academic performance, largely due to its effects on cognitive function, concentration, and sleep patterns. Research suggests that late-night screen exposure disrupts sleep cycles and reduces memory consolidation, impairing focus, learning efficiency, and information retention [11]. Additionally, screen-based activities, particularly social media and entertainment content, contribute to academic procrastination, reducing the time available for studying and completing assignments [12]. Studies have also found a direct relationship between increased screen time and lower GPA, with students reporting difficulty concentrating, increased fatigue, and reduced classroom engagement [13]. Given these concerns, understanding the role of screen time in academic success is essential for developing strategies to balance digital engagement with educational achievement. Although many studies have explored the effects of screen time on sleep and mental health, research focusing on university students remains limited, particularly in developing countries, where digital habits and academic pressures may differ. Furthermore, prior research often examines mental health and sleep disturbances separately, without considering how these factors collectively impact academic performance. This study aims to bridge these gaps by providing a comprehensive analysis of the relationship between screen time, sleep quality, mental distress, and academic performance among university students.

This study's objective was to evaluate the daily screen time of students across various fields of study and to assess its association with demographic variables, sleep quality, mental health symptoms, and academic achievement.

METHODS

This cross-sectional research was performed from February 2024 to August 2024, conducted at Isra University, Hyderabad after being approved by the Isra University Ethical Review Board (ERB letter # IU/RR-10-IRC-24/N/2024/108). The sample size was estimated using the OpenEpi calculator, with a 95% confidence level (α = 0.05) and 80% statistical power (β = 0.20). An anticipated moderate correlation ($r \approx 0.3$) between screen time and mental health outcomes was used, based on previous studies that reported similar effect sizes[14]. To mitigate the impact of dropouts and non-responses, the initial estimate of 85 participants was adjusted upward by 20%, yielding a final target of 102 participants. However, a total of 152 students from various academic disciplines were recruited using purposive sampling, ensuring sufficient power for subgroup analyses and correlation studies. The sample included students from medical and allied health sciences (MBBS: 30, BDS: 20, DPT: 15, Pharmacy: 12) and non-medical fields (Engineering: 25, MBA: 25, BBA: 25), to capture a broad spectrum of screen time habits and their impacts. Informed consent was obtained after explaining the study objectives. The inclusion criteria were students who consented to participate, while those with pre-existing mental health conditions, undergoing psychological treatment, or unwilling to participate were excluded. This study controlled for certain confounding variables through eligibility criteria and participant selection. Students with pre-existing mental health conditions or those undergoing psychological treatment were excluded to minimize health-related confounders. Additionally, socioeconomic status was considered in the questionnaire, ensuring that only participants from similar educational and financial backgrounds were included, thereby reducing potential disparities. While other lifestyle factors were not explicitly controlled, the homogeneity of the sample helped minimize their impact. Demographic data included age, gender, residence, and campus accommodation. Academic performance data were self-reported by participants, providing their GPA as an indicator of their scholastic achievements. Participants provided consent for accessing their most recent GPA, which was verified through official academic records maintained by the institution. Physical activity levels were evaluated by asking participants about their frequency of exercise, categorized as frequent (≥3 times/week) or rare/none. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a standardized self-reported questionnaire that evaluates sleep disturbances over the past month. It consists of seven components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The total PSQI score ranges from 0 to 21, with higher scores indicating poorer sleep quality. The PSQI has demonstrated high internal consistency (Cronbach's α = 0.68) and strong validity in measuring sleep disturbances [15]. Mental distress, including depression, anxiety, and stress, was assessed using the Depression, Anxiety, and Stress Scale (DASS-42), a widely validated self-reported instrument. It consists of

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42 items divided into three subscales, each measuring symptoms of depression, anxiety, and stress over the past week. Each item is rated on a 4-point Likert scale (0 = Did not apply to me at all, 3 = Applied to me very much or most of the time), with higher scores indicating greater psychological distress. The total score is obtained by summing the responses for each subscale, with established cutoff points to categorize symptom severity. The DASS-42 has demonstrated excellent reliability, with Cronbach's α = 0.96 [16]. Daily screen time data were self-reported, measured in hours per day, and categorized into <5 and ≥5 hours. Pearson's correlation coefficient was used to assess the linear relationship between the quantitative variables: daily screen time, PSQI, and DASS scores. The Chi-square test was applied to evaluate associations between the qualitative variables: screen time, demographic factors (gender, residence, accommodation type), GPA categories, and physical activity levels. Data were analyzed by SPSS version 25.0.

RESULTS

The mean age of the participants was 20.59±2.16 years. The majority of the participants i.e. 50% belonged to the 18-20 years' age group while only 4.6% of participants belonged to the <18-year age group. A vast majority of the participants belonged to urban areas (87.5%) and were day scholars (74.34%). Table 1 provides the demographic details of the study participants.

Table 1: Demographic variables of the study population (n=152)

Category	Frequency (%)
Age Group (Years)	
<18	07 (4.60%)
18 - 20	76 (50.00%)
21 - 22	47 (30.92%)
>22	22 (14.47%)
Gender	
Male	73 (48.02)
Female	79 (51.97)
Residence	
Urban	133 (87.5)
Rural	19 (12.5)
Accommodation	
Day Scholar	113 (74.34)
Hostelite	39 (25.65)
Field of Study	
Medical	77 (50.65)
Non-medical	75 (49.34)

The study participant's mean daily screen time was identified as 5.85±1.14 hours. A statistically significant association was observed between daily screen time and participants from the urban population ($p<0.05$), as shown in Table 2. Additionally, screen usage purpose was significantly associated with daily screen time, with participants engaging in recreational screen time being more prone to report higher usage compared to those using screens mainly for academic purposes ($p<0.05$). GPA also showed a significant relationship, where students with a GPA below 2.5 exhibited significantly higher screen time compared to their peers with a GPA above 2.5 ($p<0.05$). Similarly, exercise frequency was associated with screen time, as students who engaged in regular physical activity (≥3 times/week) reported lower screen time than those with rare or no physical activity ($p<0.05$). However, no significant association was noted between daily screen time and gender or campus accommodation ($p>0.05$).

Table 2: Association of Demographic Variables With Daily Screen Time

Variables	Category	Daily Screen time in hours		X^2	p-Value
		<5	≥5		
Gender	Male	19	54	0.21	0.64
	Female	18	61		
Residence	Urban	28	105	6.25	0.01*
	Rural	9	10		
Accommodation	Day Scholar	29	84	0.41	0.51
	Hostelite	8	31		
GPA	>2.5	31	14	68.87	0.001*
	< 2.5	6	101		
Screen Usage Purpose	Academic	26	18	40.60	0.001*
	Recreational	11	97		
Exercise Frequency	≥3 times/ week	33	25	53.96	0.001*
	Rare/None	4	90		

The average PSQI score among participants was 6.45±3.48. A significant positive correlation ($r = 0.75$, $p<0.01$) indicated that increased daily screen time was linked to poorer sleep quality.

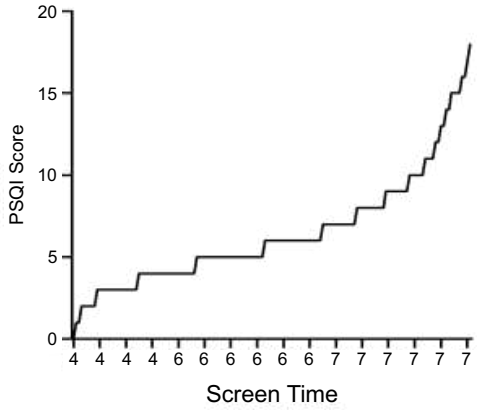

Figure 1: Correlation of Daily Screen Time with Sleep Quality (PSQI Score)

The mean scored of depression, anxiety, and stress were found to be 13.34±12.01, 11.17±9.41, and 15.32±11.09 respectively. Figure 2 shows the correlation of these mental health variables with daily screen time. There was a

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statistically significant positive relationship observed between screen time and depression (r = 0.81, p<0.01), anxiety (r = 0.78, p<0.01), and stress (r = 0.83, p<0.01).

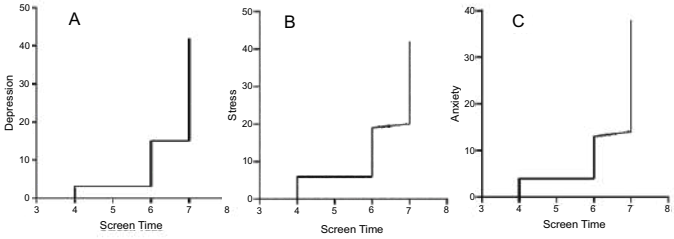

Figure 2: Correlation of Daily Screen Time with A) Depression B) Stress C) Anxiety

DISCUSSION

This study's objective was to evaluate the daily screen time of students across various fields of study and to assess its association with demographic variables, sleep quality, mental health symptoms, and academic achievement. These findings revealed a statistically significant association between daily screen time and urban residency. This is consistent with the explanation provided by Nedjar-Guerre *et al.*, who noted that urban families generally own more screen devices compared to their rural counterparts, contributing to higher screen time in urban populations[17]. However, this contrasts with Varadarajan *et al.*, and Wang *et al.*, who found no association between screen time and residential settings [18, 19]. These discrepancies may stem from differences in study populations, as this research focused on university students, whereas previous studies included younger age groups or mixed demographics. Additionally, variations in internet accessibility, urban infrastructure, and cultural screen use habits across different regions may contribute to these conflicting findings.This study found no significant correlation between daily screen time and gender.However, research by Whiting *et al.*, reported higher screen time among boys compared to girls [20]. These differences could be influenced by cultural and social norms, where in some regions, males may engage more in gaming or entertainment-based screen use, whereas in others, screen exposure may be more evenly distributed due to educational demands or technological accessibility among both genders.The study identified a significant positive correlation between screen time and PSQI scores, implying that greater screen time correlates with lower sleep quality. This aligns with Maurya *et al.*, who demonstrated that excessive screen time among young adults raised the likelihood of sleep problems [21]. Similarly, Adamczewska-Chmiel *et al.*, found that individuals with problematic smartphone usage experienced shorter sleep durations and more frequent sleep deprivation due to decreased serum melatonin levels caused by smartphone-induced magnetic fields [22]. Moreover, prolonged screen exposure, especially before bedtime, delays sleep onset due to blue light exposure and impairs body regeneration processes [23, 24]. Guerrero *et al.*, suggested that excessive screen behaviors replace essential activities such as sleep, further emphasizing the importance of balanced screen time [23].This research found a significant positive association between screen time and mental health parameters, including depression, anxiety, and stress, aligning with findings by Li *et al.*, and Adamczewska-Chmiel *et al.*, who reported that high screen time correlates with heightened anxiety and depressive symptoms [5, 22].These effects can be explained by several neurophysiological mechanisms, including dopamine dysregulation, cortisol elevation, and melatonin suppression [7, 9, 25].Digital media, particularly social media and gaming, overstimulates the dopaminergic reward system, leading to reduced dopamine receptor sensitivity, which contributes to mood instability, impulsivity, and depressive symptoms [26].Additionally, prolonged screen exposure triggers chronic low-grade stress responses, causing sustained cortisol elevation, which is linked to increased anxiety, emotional dysregulation, and cognitive impairments [7]. Furthermore, blue light from screens suppresses melatonin production, disrupting circadian rhythms, reducing deep sleep, and increasing emotional reactivity, further compounding mental health challenges [27]. Boers *et al.*, demonstrated that each additional hour spent on online platforms significantly increases depressive symptoms among youth [28], while Ma *et al.*, highlighted the role of social media and television exposure in exacerbating depressive tendencies [29].The present study highlighted that students who used screens primarily for recreational purposes were more likely to exhibit higher screen times, poorer sleep quality, and elevated mental distress compared to those who used screens for academic purposes.Furthermore, a significant relationship was observed between lower GPA scores and increased screen time, suggesting that excessive screen exposure detracts from academic performance. This aligns with the results of Sapci *et al.*, who reported that higher screen time significantly reduces GPA [30]. Similarly, an association was noted between higher screen time and lower physical activity, suggesting a more sedentary lifestyle, which contrasts with the findings of Hadianfard *et al.*, who found that recreational screen activities (≥2 hours/day) were linked to increased physical activity [31].The relationship between screen time and physical activity varies across studies due to differences in screen type, usage purpose, and study context. Television and gaming are linked to prolonged sedentary behavior, whereas smartphones may allow mobility (e.g., listening to music while exercising). Additionally, academic screen use

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may reduce activity, while fitness apps and social media challenges encourage it.These variations suggest that screen time's impact on physical activity is not universal and depends on multiple contextual factors.In light of these findings, it is evident that excessive screen time poses considerable risks to physical, mental, and academic well-being. Future research should further explore these contextual factors to better understand the complexities of screen exposure and its effects. Although the study contributes to the field, its limitations must be acknowledged, particularly the small sample size, which may restrict the extent to which the findings can be generalized. Future investigations should aim to bridge these gaps to offer an in-depth understanding of the complex relationships between screen time, health, and academic performance.

CONCLUSIONS

The study concluded that increased screen time is strongly correlated with diminished sleep quality, amplified mental distress manifested as raised levels of depression, anxiety, and stress and lower academic performance.These effects were particularly pronounced among urban populations and students using screens predominantly for recreational purposes. These observations stress the significance of balancing screen usage to safeguard both physical and mental health while supporting academic success.

Authors Contribution

Conceptualization: KAM, MT, AK, HF, UM, M
Methodology: MT, AK, HF, UM, M
Formal analysis: KAM
Writing, review and editing: KAM, MT, AK, HF, UM, M

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Femoral Condyle Measurements in Anterior Cruciate Ligament Injury: 1 Tesla Magnetic Resonance Imaging Analysis

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ABSTRACT

Orthopedic injury of Anterior Cruciate Ligament (ACL) remains an increasingly frequent issue that primarily affects athletes with permanent complications as a result. The modern Magnetic Resonance Imaging (MRI) technology enables better accuracy when measuring femoral condyles. **Objective:** To investigate the dimension analysis of the femoral condyles regarding ACL injuries alongside their implications for both surgical procedures and preventive management. **Methods:** Descriptive cross-sectional study from September 2023 to August 2024 in the Orthopedic department. The study enrolled 385 participants between 18 to 60 years old. All subjects completed scanning with a 1 Tesla MRI and the researchers recorded femoral condyle dimensions. Data analysis occurred with SPSS version 26.0. while linear regression and ANOVA. **Results:** The research analysis involved 385 participants whose mean age equaled 34.7 ± 6.95 years. The majority were male (70.6%). Mean measurement of Lateral Condyle AP was 6.28 ± 0.43 cm while Medial Condyle AP recorded 6.11 ± 0.46 cm, and Trans-epicondylar Axis reached 7.96 ± 0.53 cm. ANOVA analysis found significant measurement distinctions in knee joints that occurred between different age groups ($p<0.001$). The results from independent t-tests showed knee measurement discrepancies between men and women signify statistical significance at $p<0.001$. **Conclusions:** This research demonstrated that the dimensions of femoral condyles act as major factors that determine risk for ACL injuries. Preventive strategies alongside treatment plans for ACL injuries need to adopt age- and sex-specific considerations according to the research results.

INTRODUCTION

The knee joint depends on the anterior cruciate ligament (ACL) as its primary stabilizing structure, ensuring joint stability and mobility during movement [1]. ACL tears are one of the most common orthopedic injuries, affecting both athletes and non-athletes. In the United States alone, over 200,000 ACL injuries occur annually, with a rising trend observed in recent years [2]. These injuries are particularly frequent in sports requiring rapid movements, jumping, and pivoting, such as basketball, soccer, and skiing [3]. ACL injuries can lead to chronic complications, including persistent knee instability, meniscal damage, and an increased risk of osteoarthritis [4]. Knee biomechanics rely heavily on the femoral condyles, which play a key role in load distribution and joint stability through articulation with the tibia [5]. Studies suggest that femoral condyle morphology such as condyle size and intercondylar notch width directly affects knee joint mechanics and ACL injury vulnerability [6]. High-impact activities may further amplify this risk by altering joint loading patterns associated with different condyle dimensions [7]. Traditional imaging techniques, such as X-rays, fail to provide a comprehensive view of knee soft tissue structures [8]. Magnetic resonance imaging (MRI) is the preferred technique because it captures detailed images

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of both hard and soft tissues, including the femoral condyles, menisci, cartilage, and ACL [9]. While higher-field MRIs (e.g., 3 Tesla) provide higher resolution, 1 Tesla MRI remains widely used in clinical settings due to its accessibility, affordability, and ability to produce reliable femoral condyle measurements [10]. MRI-based femoral condyle assessments have critical implications in ACL injury management. Accurate measurements help surgeons select the most appropriate grafts and optimize surgical techniques, improving ACL reconstruction outcomes [11]. Additionally, evaluating femoral condyle morphology allows for early identification of individuals at higher risk of ACL injuries, which is particularly beneficial for athletes in high-risk sports [12]. While gender-based differences in ACL injury susceptibility have been observed, the relationship between femoral condyle dimensions and these differences remains an area of ongoing research [13]. The MRI findings of the studied group revealed a high prevalence of joint effusion (80%), followed by ACL injuries (63.3%) and PHMM injuries (56.7%). In contrast, LCL injuries were relatively rare, occurring in only 3.3% of the study group [14].

The aim of this study was to explore the relationship between femoral condyle dimensions and ACL injury risk by analyzing differences across age and gender.

METHODS

The study took place from September 2023 to August 2024 at Peshawar General Hospital and Peshawar Medical College Orthopedics department (Reference No. 1010). A total of 385 patients were included in the study based, just above the calculated need of 381 based on a population of 2,481,000 and an anticipated frequency of 55% with a 5% margin of error at a 95% confidence level [15, 16]. Choosing this slightly larger sample size helps ensure that the findings are more robust and reliable. The study was approved by the hospital's ethics committee, and informed consent was obtained from each participant before data collection. Inclusion criteria comprised of patients aged 18 to 60 years, patients with no prior knee joint surgery, patients who provided informed consent for participation and patients with clinical indications for knee MRI. While patients with a history of knee joint surgery, contraindications for MRI, incomplete MRI data and who declined to participate or did not provide informed consent were excluded from the study. All patients underwent MRI using a Shimadzu SMT-50A MR imaging system (Shimadzu CO Ltd, Kyoto, Japan) with a field strength of 1 tesla. T1-weighted MR imaging was performed following a standardized protocol. To minimize movement artifacts, subjects were restrained, and special footwear was used to stabilize the foot and maintain posture. The imaging process did not involve the use of contrast media. All the individuals were scanned with knee joint protocols. Knee joint sagittal and transverse images were obtained with a time to echo (TE) of 35ms and a repetition time (TR) of 650ms. Measurements were conducted on sagittal plane slices through the most anterior regions of both femoral condyles. The articular surface of each femoral condyle was segmented into distal and posterior sections. Data were collected from radiographic images in various planes to ensure comprehensive assessment. Data confidentiality was thoroughly maintained. Collected data was analyzed by SPSS version 26. All the Categorical variables such as age groups, gender of participants and side of knee were expressed in frequencies and percentages. Mean and SD were calculated for continuous variables such as Lateral and Medial condylar-AP, Notch width and Height etc. Linear regression analysis was performed to assess the association of age with the width and height of the notch. ANOVA was performed to assess the difference between various age groups and continuous variables. A p-value of <0.05 considered statistically significant.

RESULTS

This study enrolled 385 participants, the ages of the participants range from 19 to 52 years, with mean age of 34.7 ± 6.95 Years. The age was categorized into distinct groups in which the largest proportion of participants were in the 26-30 years age group (n=116), accounting for 30.1% of the participants. This was followed by the 31-35 years age group (n=102), which represented 26.5% of the participants. Regarding gender of the participants, the majority of participants were male about 70.6%(n=272), while females constituted 29.4% (n=113). This indicates a substantial male predominance in the study population, as illustrated in Figure 1.

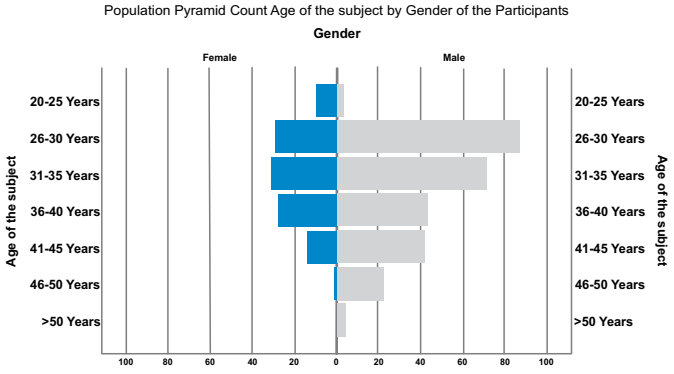

Figure 1 : Gender Wise Distribution of the Age of the Participants

The Lateral Condyle AP measurements ranged from 5.57 to 7.19 cm, with a mean of 6.28 cm and a standard deviation of 0.43 cm, indicated that most measurements were closely clustered around the average.The Medial Condyle AP measurements exhibited a similar pattern, with values

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ranging from 5.33 cm to 7.12 cm, a mean of 6.11 cm, and a standard deviation of 0.46 cm. The Trans-epicondylar Axis showed a wider range, from 6.78 cm to 8.83 cm, with a mean of 7.96 cm and a standard deviation of 0.53 cm, reflecting slightly greater variability. The Width of the Notch varied between 1.75 cm and 3.01 cm, with a mean of 2.29 cm and a standard deviation of 0.35 cm (Table 1).

Table 1: Descriptive Statistics of Knee Joint Measurements

Knee Joint Measurements	Number	Minimum	Maximum	Mean ± SD
Lateral condyle AP	385	5.57	7.19	6.284 ± 0.430
Medial condyle AP		5.33	7.12	6.113 ± 0.455
Trans-epicondylar axis		6.78	8.83	7.960 ± 0.525
Dimension of lateral femoral condyle		2.28	3.54	3.011 ± 0.316
Dimension of medial femoral condyle		2.29	3.62	3.008 ± 0.319
Width of notch		1.75	3.01	2.293 ± 0.346
Height of notch		1.95	3.39	2.625 ± 0.360

The distribution of knee joints by side in the 385 participants, 55.1% had measurements from the right knee (n=212), while 44.9% had measurements from the left knee (n=173). This distribution shows a slight predominance of right knee measurements in the sample (Figure 2).

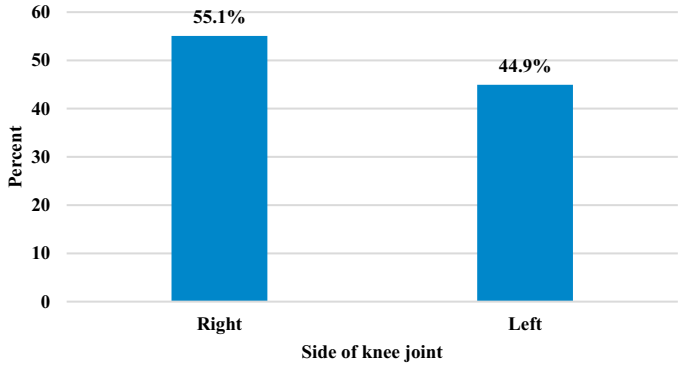

Figure 2: Participants Experienced Knee Joint Involvement On One Side Of Their Knees

ANOVA tests produce vital differences between groups in Lateral Condyle AP measurements where the F-value reached 10.590 and the p-value equaled <0.001. ANOVA analysis revealed significant differences in Trans-epicondylar Axis measurements across age groups ($F = 14.644$, $p < 0.001$). The ANOVA analysis of Width of Notch reveals a substantial F-value of 4.903 together with a p-value of less than 0.001. The measurements of Height of Notch demonstrate statistically important differences because both F-value and p-value fall below 0.001. ANOVA analysis of Dimension of the Medial Femoral Condyle determined an 8.010 F-value together with a p-value under 0.001. The data demonstrates the Dimension of the Medial Femoral Condyle exhibits notable differences between various age groups as indicated by the p-value of <0.001 (Table 2).

Table 2: Correlation of Age of Participants with Knee joint measurements

ANOVA (Age of the Participants)	Sum of Squares	Mean Square	F	Significance
Lateral condyle AP	10.222	1.704	10.590	0.000
Medial condyle AP	13.020	2.170	12.337	0.000
Trans-epicondylar axis	19.985	3.331	14.644	0.000
Width of notch	3.330	0.555	4.903	0.000
Height of notch	9.155	1.526	14.154	0.000
Dimension of lateral femoral condyle	10.877	1.813	24.850	0.000
Dimension of medial femoral condyle	4.411	0.735	8.010	0.000

For the Lateral Condyle AP, males (mean = 6.3758, SD = 0.43378) have significantly larger measurements than females (mean = 6.0654, SD = 0.33209). The t-test shows a mean difference of 0.31037 with a p-value of .000, indicating a statistically significant difference. Levene's test for equality of variances was significant ($F = 5.407$, $p = .021$), but results are consistent under both equal and unequal variance assumptions, illustrated by boxplot in Figure 3.

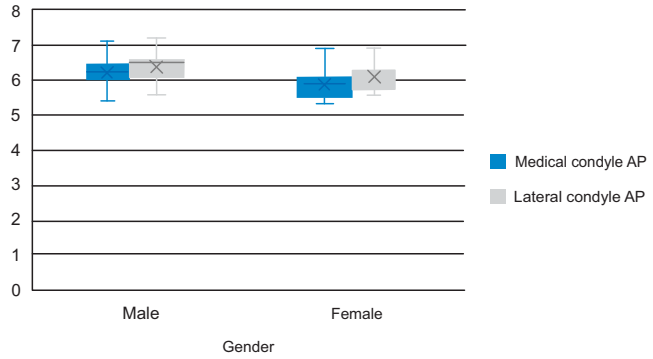

Figure 3: Analysis of Lateral and Medical Condylar Anterior Posterior by gender of the participants

The findings of analysis indicated a notable difference in knee joint dimensions between genders, with males generally showing larger measurements, as shown in Table 3.

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Table 3: Association of Gender of participants with Knee Joint Measurements

Knee Joint Measurements	F	Significance	Significance (2-tailed)	Mean Difference	Standard Error Difference
Lateral condyle AP	5.407	0.021	0.000	0.31037	0.04552
Medial condyle AP	4.461	0.035	0.000	0.33657	0.04801
Width of notch	50.692	0.000	0.000	0.17962	0.03774
Height of notch	32.959	0.000	0.005	0.11214	0.03999
Trans-epicondylar axis	2.167	0.142	0.000	0.64218	0.04887

The t-test results show a mean difference of -0.07360 with a p-value of .095, indicating no significant difference between the right and left knees. Levene's test for equality of variances ($F = 0.045$, $p = .833$) supports that variances are equal. For the Width of Notch, the right knee has a mean of 2.2677 ($SD = 0.33693$) and the left knee has a mean of 2.3246 ($SD = 0.35651$). The mean difference is -0.05694 with a p-value of .109, which is not significant. The Levene's test ($F = 2.492$, $p = .115$) shows that the variance is similar across the sides. In the Height of Notch, the mean for the right knee is 2.6238 ($SD = 0.36048$) and for the left knee is 2.6270 ($SD = 0.36157$). The mean difference is -0.00317 with a p-value of .932, indicating no significant difference. Levene's test ($F = 0.112$, $p = .739$) confirms equal variances (Table 4).

Table 4: Correlation of Side of knee joint with the Knee Joint Measurements

Side of the Knee Joint	F	Significance	Significance (2-tailed)	Mean Difference	Standard Error Difference
Lateral condyle AP	0.045	0.833	0.095	-0.07360	0.04396
Medial condyle AP	0.126	0.723	0.085	-0.08024	0.04650
Width of notch	2.492	0.115	0.109	-0.05694	0.03544
Height of notch	0.112	0.739	0.932	-0.00317	0.03698
Trans-epicondylar axis	0.006	0.939	0.236	-0.06386	0.05379

For the Width of Notch, there was 7.3% of the variance for age and gender as predictors. Age has a positive and significant impact ($\beta = 0.130$, $p = 0.009$), indicating that as age increases, the Width of Notch also increases. Gender also significantly affects this measurement with a negative coefficient ($\beta = -0.221$, $p = 0.000$), suggesting differences between genders. In terms of the Height of Notch, the analysis revealed 8.8% of the variance.

DISCUSSION

Previous research at the orthopedic departments of Peshawar General Hospital and Peshawar Medical College in Peshawar, Pakistan, has utilized MRI analysis to measure knee joints for ACL injury prediction. Researchers can use these findings to expand knowledge of ACL injury risk factors by comparing them with similar investigations within the existing literature [17].The study results demonstrate significant knee joint dimension variations based on age groups and gender differences, aligning with findings from other studies.The measurements of lateral and medial condyles in the AP direction, along with the trans-epicondylar axis and notch dimensions, exhibit age-dependent changes. These results align with those of Are M *et al.*, who documented femoral condyle morphological changes due to variations in cartilage thickness and bone structure [18]. These structural changes may contribute to ACL injury risk, as they occur naturally with aging.This research confirmed that males have larger knee joint dimensions than females, particularly in the lateral condyle AP measurement and notch width. The article by Şenişik *et al.*, supported this finding, reporting that females typically have smaller femoral condyles and narrower intercondylar notches than males [19]. Researchers suggest that these anatomical differences contribute to the higher risk of ACL tears in female athletes [20].The study identified a correlation between femoral condyle morphology and ACL injury risk, notably in the role of notch height and width as susceptibility factors. These findings support Souryal *et al.*, who reported that individuals with smaller notch widths face higher ACL injury risk due to restricted ACL movement during knee motion [21]. Similarly, Wang *et al.*, emphasized the importance of femoral notch morphology in ACL injury risk assessment [22].A study on young athletes demonstrated that femoral notch width and angle are key predictors of ACL injury vulnerability.Furthermore, these findings suggest that anatomical differences in notch width among females may contribute to their increased ACL injury risk.MRI enables precise femoral condyle measurements, aiding in both diagnosis and preoperative planning [23].The findings of Park *et al.*, demonstrate that MRI plays a vital role in ACL assessment, allowing surgeons to measure femoral condyle dimensions for improved surgical planning [23].Accurate MRI-based measurements help in selecting the appropriate graft material and optimizing graft placement for ACL reconstruction. A study by Gultekin *et al.*, supports the research, highlighting substantial variations in knee joint dimensions across different populations [24]. Understanding these variations can help develop patient-specific treatment strategies, as seen in previous research advocating for individualized prevention and rehabilitation programs [25].These

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findings on knee joint dimension variability are consistent with global data, as reported by Irarrázaval, Mensch and Amstutz [26, 27]. A limitation of this study is its geographical scope, as it was conducted only in one district (Peshawar, KPK, Pakistan). Future research should include participants from other regions to provide broader insights.Additionally, further studies should assess additional femoral condyle parameters to refine risk assessment models. Based on these findings, clinicians should incorporate MRI-based femoral condyle assessments, particularly focusing on notch morphology, to identify individuals at higher ACL injury risk. High-resolution MRI offers both diagnostic and preoperative benefits, allowing for precise knee anatomy evaluation and improved surgical planning. Developing gender-specific prevention and rehabilitation programs tailored to anatomical differences may help reduce ACL injury risk. Raising awareness among athletes and healthcare providers about these risk factors could enhance injury prevention and management strategies.

CONCLUSIONS

The research established significant distinctions in knee joint measurements based on age and sex groups where $p < 0.05$ values appear ($p<0.05$) and delivers vital understanding about ACL injuries and femoral condyle dimensions. Research findings from previous studies demonstrate that ACL injury risk depends on condyle morphology together with femoral notch width, as important anatomical variables. Preventing and treating ACL injuries demands sex-specific preventative techniques and person-specific evaluation methods according to the results generated by this study and other research studies.

Authors Contribution

Conceptualization: MUK
Methodology: MUK, HU, ZA, MJI
Formal analysis: HU, SA, ZA, MJI
Writing, review and editing: SA, JK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Comparison of Analgesic Effectiveness of Tapentadol and Tramadol in Relieving Postoperative Pain in Patients Undergoing Laparoscopic Cholecystectomy Under General Anesthesia

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ABSTRACT

Various pharmacological interventions have aimed to address postoperative pain, however the search for optimal preemptive analgesic continues. In this assessment, it was sought to evaluate tapentadol and tramadol as preemptive analgesic, in order to identify the more effective option for managing postoperative pain. **Objective:** To compare the analgesic effectiveness of tapentadol and tramadol in relieving postoperative pain in patients undergoing laparoscopic cholecystectomy under general anesthesia. **Methods:** This quasi experimental study was conducted at Anesthesia Department of Mayo Hospital, Lahore from 30-11-2022 to 30-05-2023 after taking ethical approval from IRB. 60 individuals were enrolled after taking written informed consent, who were planned for laparoscopic cholecystectomy under general anesthesia. Patients were assigned to either group A (tramadol) or group B (tapentadol). Analgesic effectiveness was assessed in terms of time to first rescue analgesia, total rescue analgesic consumption in 24 hours, and VAS score at different interval postoperatively. **Results:** Mean time to 1st analgesia requirement calculated was 1.667±0.365 hours for group A and 4.46±1.45 hours for group B; p <0.0001. Mean total rescue analgesic (injection nalbuphine) consumption in group A and group B was 17.06±5.16mg and 8.4 ± 2.59mg, respectively (p <0.001). Mean of VAS score at different intervals noted was less in group B as compared to group A postoperatively, p <0.001. **Conclusions:** The findings of this study demonstrate that tapentadol 75 mg is more effective than tramadol 50 mg as preemptive analgesia in patients undergoing laparoscopic cholecystectomy.

INTRODUCTION

Postoperative pain following laparoscopic cholecystectomy is a common complaint, leading to prolonged hospital stay. Typically, pain is maximum within few hours after the surgery and then gradually subsides over a period of 2-3 days [1, 2]. Preemptive analgesia is strategy for preventing central neuro-sensitization by administering prophylactic anti-nociceptive measures prior to the start of surgical pain, it helps in minimizing postoperative pain and reduces the hyperactivity of spinal neurons, leading to decreased postoperative pain intensity [3]. Numerous pharmacological approaches have been explored to achieve the aforementioned goals. However, the quest for an "ideal preemptive analgesic" persists [4]. One challenge while managing postoperative pain, revolves around the reliance on opioids as powerful pain reliever and need for careful dosage control to mitigate their potential side effects [5].Tapentadol exhibits strong analgesic efficacy and is well tolerated for different intensities of pain

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following different types of surgeries [6] It functions as an agonist of μ-opioid receptor and acts as a norepinephrine reuptake inhibitor [7, 8]. Tramadol is a centrally acting analgesic and has dual mechanism of action by inhibiting the reuptake of norepinephrine and serotonin, as well as exerting a weak agonist effect on opioid receptors [9]. Tapentadol and tramadol were compared for their analgesic efficacy in multiple studies. One study found that tapentadol had better analgesic effect than tramadol after surgical removal of mandibular third molar, P <0.05 [10]. The efficacy of Tapentadol in mitigating pain has been substantiated through numerous trials conducted in both acute and chronic pain scenarios. Prior investigations have delved into the analgesic effectiveness of Tapentadol within a dosage range of 50 to 200 mg. However, its potential as a preemptive pain reliever remains unexplored. Consequently, the primary focus of the study is to assess the preemptive capabilities of tapentadol in comparison to tramadol, for. Notably, there is a lack of previous studies within the local population on this particular subject.

So, we are conducted this study to compare the analgesic effectiveness of tapentadol and tramadol in relieving postoperative pain in patients undergoing laparoscopic cholecystectomy under general anesthesia.

METHODS

This quasi experimental study was conducted at anesthesia department, KEMU, Mayo Hospital Lahore after taking ethical approval from IRB [111/PEC/RC/KEMU]. This study was done over a period of 6 months from 30-11-2022 to 30-05-2023. Sample size of 60 patients was calculated using significance level of 5%, power of test 80%. Expected mean value of total rescue analgesic consumption for intervention group is estimated to be 13.3 ± 22.5mg, while for control group, it is estimated to be 33.3±33 mg.[10] Sample size was calculated using formula; $n= Z\ \sigma^2(Ƶ1 - \alpha + Ƶ1 - \beta)^2 / (\mu_1 - \mu_2)^2$; where: n = required sample size per group=30, Z1–α= standard normal variate corresponding to the significance level (5%), Z1–β = standard normal variate corresponding to the power (80%), σ1,σ2 = standard deviations of the intervention and control groups, respectively and μ1, μ2 = expected mean values of total rescue analgesic consumption for the intervention and control groups. Patients selection was done using non-probability consecutive sampling. Total 60 patients aged 20 to 60 years of both genders with ASA status I & II, who were planned to undergo laparoscopic cholecystectomy under general anesthesia were included. Patients with uncontrolled diabetes (BSL > 200mg/dl), uncontrolled hypertension (BP >140/90mmHg), impaired liver function test (ALT/AST > 40IU/L), renal insufficiency (serum creatinine >1.5mg/dl), psychiatric illness, chronic pain or patients on analgesic medications, having allergy to opioids, alcoholics, and pregnant or lactating ladies were excluded. Written informed consent was taken from all patients and performing surgeons. During the pre-anesthetic assessment, the patients were provided with information regarding the Visual Analogue Scale for pain. Patients were divided into 2 equal groups; odd number assigned to group A (tramadol) and even numbers to group B (tapentdol). Tapentdol 75mg or tramadol 50mg based on the allocation in respective groups were administered to the patients 2 hours before the surgery. In the operating room, standard monitoring equipment was used to continuously measure ECG, heart rate, SpO2, non-invasive blood pressure, and EtCO2 levels. Routine general anaesthesia protocols were followed utilizing endotracheal tube intubation. Continuous monitoring of ECG, heart rate, NIBP, SpO2, and EtCO2 was performed throughout the surgery. Approximately 15 minutes before surgery completion, patients were given IV ondansetron (8mg) to prevent postoperative nausea and vomiting. In PACU, continuous monitoring of vital signs was performed. The starting point for the postoperative observation was marked when the patient regained consciousness and was able to respond to verbal commands. Injection paracetamol 1g IV TDS was given to all patients. However, rescue analgesia was given in the form of injection Nalbuphine at a dose of 0.1mg/kg (maximum 10mg) IV bolus whenever the patient reported VAS of greater than 3 for pain and time to first analgesia requirement was noted. The total amount of analgesic consumption within first 24 hours after surgery was recorded. Postoperative pain evaluations were conducted at specific time intervals by a blinded observer at 0, 2, 4, 6, 12, and 24 hours after completion of surgery. At 24-hour period end, total amount of analgesics consumed by each patient was recorded. All information recorded on preformed proforma. The data were enlisted into SPSS 26.0 for statistical analysis. Quantitative variables such as age, BMI, surgical time, and anesthesia time were showed as mean and SD. On the other hand, qualitative variables like gender, DM, and HTN, were presented as frequencies and percentages. Comparison among pain score using VAS scale at different intervals of both groups using independent sample t test, p-value was taken as ≤ 0.05 statistically significant.

RESULTS

Mean age in Group A and B calculated was 35.26 ± 5.65 years and 36.33 ± 6.12 years, respectively. In Group A 8 (26.7%) patients were male and 22 (73.3%) were female and in Group B 6 (20%) were male and 24 (80%) were female. Mean BMI of patients in Group A and B calculated was 25.6 ± 4kg/m2 and 26.9 ± 3.2kg/m2, respectively. Mean duration of anesthesia in Group A and B noted was 107.30 ± 18.9

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minutes and 106.3 ± 21.73 minutes. 67% patients in Group A and 70% in Group B belonged to ASA status I, while 33% and 30% belongs to ASA status II. Mean weight in group A and B calculated was 66.55 ± 5.43 and 65.23 ± 6.01, respectively.

Table 1: Demographic and Clinical Characteristics of Patients in Group A (Tramadol) and Group B (Tapentadol) (n=60)

Variables	Group A (Tramadol) Frequency (%)/ Mean ± SD	Group B (Tapentadol) Frequency (%)/ Mean ± SD		p-Value
Age (Years)	35.26 ± 5.65	36.33 ± 6.12		0.484
Gender	Male	8 (26.7%)	6 (20%)	0.541
	Female	22 (73.3%)	24 (80%)	
BMI (kg/m2)	25.6 ± 4.0	26.9 ± 3.2		0.168
ASA Status	I	20 (67%)	21 (70%)	0.781
	II	10 (33%)	9 (30%)	
Duration of anaesthesia (Minutes)	107.30 ± 18.9	106.3 ± 21.73		0.849
Weight (Kg)	66.55 ± 5.43	65.23 ± 6.01		0.375

As shown in table 2, mean time to first analgesia requirement noted was prolonged in group B as compared to group A (Group A: 1.67 ± 0.36 hours' vs Group B: 4.46 ± 1.45 hours; p<0.001 i.e. statistically significant). Mean total injection nalbuphine (mg) consumption in group A was more as compared to group B (17.06 ± 5.16mg and 8.40 ± 2.59mg, respectively; p <0.001 i.e. statistically significant).

Table 2: Comparison of Time to 1st Rescue Analgesia and Total Rescue Analgesic Consumption Among Groups (n=60)

Variables	Group A (Tramadol) Mean ± SD	Group B (Tapentadol) Mean ± SD	p-Value	95% CI
24-Hour Total Rescue Analgesic (nalbuphine) Requirement (mg)	17.06 ± 5.16	8.40±2.59	<0.001	6.550-10.770
Time to 1st Analgesia (Hours)	1.67 ± 0.36	4.46±1.45	<0.001	2.246-3.339

Mean of VAS score at different interval noted was higher in group A as compared to group B, and this difference was statistically significant p <0.0001 at 0hr, 2hr, 4hr, 6hr, 12hr and 24hr.

Table 3: Comparison of Vas Score at Different Interval Post-Operatively (n=60)

VAS Score at Different Intervals	Group A (Tramadol) Mean ± SD)	Group B (Tapentadol) Mean ± SD	p-Value
VAS Score at 0 Hour	4.60±1.06	0.86±0.50	<0.001
VAS Score at 2 Hours	3.70±0.74	3.10±0.60	<0.001
VAS Score at 4 Hours	3.76±1.38	2.13±0.89	<0.001
VAS Score at 6 Hours	2.20±0.40	2.73±1.22	<0.001
VAS Score at 12 Hours	3.76±1.38	1.20±0.96	<0.001
VAS Score at 24 Hours	2.20±0.40	0.43±1.00	<0.001

DISCUSSION

Effective pain management after laparoscopic cholecystectomy is crucial for enhancing recovery, reducing opioid consumption, and improving patient satisfaction [11]. Despite being minimally invasive procedure, LC can cause significant postoperative pain due to peritoneal distension, diaphragmatic irritation from residual CO_2, and port-site trauma [12]. Optimizing postoperative pain control not only facilitates early mobilization and discharge but also minimizes complications [13]. In current study, time taken for first analgesic administration in Post-Anesthesia Care Unit was significantly longer in tapentdol groups as compared to tramadol group 1.67 ± 0.36 hours vs 4.46 ± 1.45 hours (P < 0.001). Additionally, the total dose of injection Nalbuphine needed was significantly reduced in tapentdol group 8.40 ± 2.59mg vs tramadol group 17.06 ± 5.16mg. Studies have also highlighted the potential of tapentdol as effective analgesic option for postoperative pain relief in different surgical procedures [14].The use of tapentadol as preemptive analgesic in laparoscopic cholecystectomy has also shown promising results in reducing postoperative pain and need for rescue analgesics. A study by Yadav *et al.*, reported that a single preoperative dose of tapentadol significantly lowered perioperative analgesic requirements and improved pain scores in the immediate postoperative period.Specifically, their study found that total rescue analgesic consumption was 13.3 ± 22.5 mg in the intervention group compared to 33.3 ± 33 mg in control group, highlighting tapentadol's efficacy in managing acute pain with minimal side effects [10].The opioid-sparing effect of tapentadol makes it promising option for managing postoperative pain, potentially leading to quicker recovery and reduced hospital stays [15]. Tapentadol is not considered as first-line opioid, it represents a valuable option for patients who may benefit from its specific pharmacological profile, especially when considering individual patient factors and potential drug interactions [16]. Apart from LC, tapentadol has also gain favor in other laparoscopic procedures. It was found by Comelon *et al.*, that tapentadol found to have similar analgesic efficacy to oxycodone during the first 24 h after laparascopic hysterectomy [17].Premedication with analgesics in laparoscopic cholecystectomy is crucial for effective pain management and improved postoperative outcomes.Furthermore, employing multimodal analgesia approach, can further optimize pain relief while decreasing reliance on opioids [18]. This strategy not only improves patient comfort but also contributes to faster recovery and shorter hospital stays, making it valuable consideration in anesthetic regimen for laparoscopic cholecystectomy [19]. Furthermore, Putta *et al.*, found preemptive analgesics more effective as compared to postoperative

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pain management, in patients after LC [20].This study primarily focused on evaluating the effectiveness of tapentdol 75 mg compared to tramadol 50 mg as preemptive analgesia in patients undergoing laparoscopic cholecystectomy. However, the safety profile of both medications was not assessed, which limited the comprehensive understanding of their overall clinical utility.Additionally, long-term outcomes, potential side effects, and patient-reported satisfaction beyond the immediate postoperative period were not studied, leaving gaps in evaluating the broader implications of these analgesic strategies.

Future studies should address these aspects to provide a more holistic evaluation of tapentdol and tramadol in similar clinical settings.

CONCLUSIONS

The findings of this study demonstrate that tapentdol 75 mg is more effective than tramadol 50 mg as preemptive analgesia in patients undergoing laparoscopic cholecystectomy. Tapentdol not only reduced the need for postoperative rescue analgesia but also significantly prolonged the time to the first analgesic requirement, highlighting its superior efficacy in managing postoperative pain.

Authors Contribution

Conceptualization: AM, MHZ, AI
Methodology: AM, MHZ, AA, ZAC, AY
Formal analysis: SK
Writing, review and editing: AA, ZAC, AI, SK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Association of Partial Edentulism with Signs and Symptoms of Temporomandibular Disorders

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ABSTRACT

Temporomandibular Joint (TMJ) is a complex joint and occlusal disharmony affects the joint health and result into temporomandibular joint dysfunction syndrome. **Objective:** To assess the signs and symptoms of temporomandibular joint disorders in partially edentulous patients and find out the association between TMD's and edentulous span, tooth loss quadrant and occlusal support. **Methods:** 200 partially edentulous patients selected by non-probability purposive sampling and TMJ were examined for maximum mouth opening, joint deviation, tenderness of muscles of mastication and joint pain with clicking.The sample was grouped into 3 characteristics i.e.; number of partially lost teeth, number of dental quadrants with posterior teeth loss and the numbers of Occlusal Support Zones (OSZ) based on Eichner Classification system. **Results:** TMJ muscle pain existed in 8.0% and joint pain was 23.0%. Many patients had missing teeth in 2 quadrants 30.0% and had 5-8 numbers of missing teeth 42.5%. A3 support zone was frequently found 29.5%. Significant association of gender was found for TMJ pain, and maximum mouth opening. The tooth loss quadrant, number of partially lost teeth and occlusal support zones had significant association with muscle pain, TMJ pain with clicking and maximum mouth opening. **Conclusions:** It can be concluded that the partially edentulous patients frequently develop one or more signs and symptoms of TMJ disorders and number of teeth lost, number of quadrants with missing teeth and loss of occlusal support disturb the joint function and associated stomatognathic system.

INTRODUCTION

The Temporomandibular Joint (TMJ) is a synovial joint that has rotating and gliding movements in the joint cavity assisted by ligaments [1]. There is harmony in the joint and the associated stomatognathic system. The joint has a complex anatomy of 3-point articulating surfaces where condyle fossa being 2 points of contact and the occluding teeth surfaces are the third point. If any of the components of these points altered; the effect will disturb the whole joint structure [2]. The term Temporomandibular Joint Disorder (TMDs) depicts such problems that affect TMJ and associated muscles. There are contrasting results documented in the dental literature regarding the association of tooth loss, their numbers and support mechanism with the development of TMJ disorders and the matter remained controversial [3]. Other studies documented that temporomandibular joint disorders are greatly associated with the occlusion [4, 5]. A change in the normal occlusion due to loss of a single tooth results in occlusal interferences and risk of developing TMJ problems. Many patients manage to adjust the occlusion and position of their condyle in a not so ideal position and adaptive mechanism helps but if the adaptive capacity

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exceeds the patients started to develop symptoms of degenerative joint disease [6]. Loss of posterior teeth results in overloading of joint and associated muscles more than the loss of anterior teeth because of transferring heavy occlusal forces of chewing and mastication over the remaining occlusal table [7]. The TMJ problems most commonly present as pain related diseases of muscle and joint pain, structural disorders mainly articular disc displacements and degenerative changes [6, 7]. In The development of TMJ disorders in partially edentulous patients with lost posterior teeth support results joint and muscles pain, crepitus, limited or reduced mouth opening and mandible jaw movement deviation. This will lead to pain in masticatory muscles, myofascial pain disorders, joint derangements and locking [8]. The difficulty in chewing and mastication, limited mouth opening, joint sounds and deviation of mandibular movements will further affect the life quality and wellbeing of the individual [7, 8]. The disorder is progressive and problems become complex if not timely diagnosed and treated. Early diagnosis and management can efficiently reverse the harmful effects and cure the disease. [9, 10]. In this region especially the poor patients seek prosthodontic help very late due to financial constrains until irreversible damage has occurred. The percentage of patients seeing the subjective manifestations of the TMD is high as compare to the ones who look for the treatment. Furthermore, many patients with tooth loss can have one or more signs of the joint problems that go unnoticed until later that transformed into recognizable dysfunction [11]. To this knowledge the studies on investigating TMJ problems in partially edentulous patients is scars in region. The results of the study will help in knowing the frequency of partially edentulous patients with undergoing TMJ problems so that strategies could be made in teaching hospital for timely diagnosis and treatment of developing disorders.

The objective of the current study was to assess the signs and symptoms of temporomandibular joint disorders in partially edentulous patients and find out the association between TMD's and edentulous span, tooth loss quadrant and occlusal support.

METHODS

The cross-sectional observational study was carried out in the Out Patient Department of Prosthodontic, Lahore Medical and Dental College, Lahore. The study was conducted in a span of 3 months i.e.; October 1st 2024 till January 1st 2025.A total of 200 partially edentulous patients presenting to the department for the provision of partial dentures were recruited for the study. Patients of both genders within the age ranged from 30 to 70 years were selected. Non probability purposive sampling technique was used to select the sample. The sample size was estimated via computer aided software RAO Soft Epi Calculator against 11.6% prevalence of TMD in adults with in age ranged from 31 to 65 years of age; keeping margin of error 5% at 95% confidence interval [12]. Inclusion criteria was set to include all the healthy patients with partial tooth loss for at least 6 months and patients with a history of trauma, previous surgeries, genetic and developmental defects were excluded. Verbal informed consent from each patient was taken. The ethical clearance was obtained from the Ethical Review Board of the Dental College, Ref No. FD/5309/24. Patients after comfortably seated in the dental chair were assessed by two experienced prosthodontists. Temporomandibular Joints (TMJ) of every patient were clinically examined using TMD diagnostic criteria. Maximum mouth opening distance was measured in mm by asking patients to widely open their mouth and distance from the maxillary incisal edges to mandibular incisors edges was measured with graduated scale; mouth opening >40mm was considered normal and <35mm was considered as restricted, presence or absence of joint deviation (right or left) upon mouth opening was assessed by asking patients to open their mouth and any deviation from midline and its direction was checked, presence or absence of tenderness in muscles of mastication (temporalis, masseter, lateral and medial pterygoids) was checked by bimanual palpation method. Pain was assessed as being present or absent and severity of pain was not checked. The joint pain with clicking during mandibular movements was assessed in preauricular area via digital palpation as present or absent; and clicking and popping sounds were checked during mandibular movements via stethoscope as present or absent [9, 11]. The sample was grouped into 3 characteristics i.e.; number of partially lost teeth (1-4, 5-8, >8), number of dental quadrants with loss of posterior teeth (1, 2, 3, 4) and the numbers of Occlusal Support Zones (OSZ) based on Eichner Classification system [13]. The index classifies teeth into 3 categories A =OSZ are 4, B where OSZ are 3 and C= zero support zone. Category A (A2= has 4 OSZ with missing teeth in one arch only), (A3=has 4 OSZ and missing teeth in both arches). Category B (B1 = 3 OSZ), B2= (2 OSZ), (B3=1 OSZ), (B4= zero OSZ with no opposing molar contact). Category C (C1=zero OSZ; teeth in both arches but not in contact), (C2=zero OSZ teeth in only one arch). Data were entered and analyzed by computer software SPSS Version 26.0. Frequency distribution (n, %) was found for the qualitative variables like gender, number of partially lost teeth, tooth loss quadrant and number of occlusal support zones. Descriptive statistics for quantitative variables like age (mean and SD) was calculated. Association of TMD with edentulous span, tooth loss quadrant and occlusal support was found using Chi square. Statistical significance $p<0.05$ was set.

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RESULTS

The current study was carried out on 200 partially edentulous patients and their TMJs were examined to find out the signs and symptoms of the disorders of the joints. Both genders i.e.; males 82(41.0%) and females 118 (59.0%) were included in the study. The age ranged from 30 to 70 years with the mean age 56.15 ± 9.937. Patients with maximum mouth opening i.e.; >40 mm were 171 (85.5%), frequency of mandibular deviation was 53 (26.5%), TMJ muscle pain was present in 16 (8.0%) and frequency of joint pain with clicking was 46 (23.0%), Table 1.

Table 1: Frequency distribution of TMJ signs and symptoms (n=200)

Variables	Frequency (%)
Maximum Mouth Opening	
>40mm	171 (85.5%)
35-39mm	19 (9.5%)
<35mm	10 (5.5%)
Mandibular Deviation	
Yes	53 (26.5%)
No	147 (73.5%)
Muscle Pain	
Yes	16 (8.0%)
No	184 (92.0%)
Joint Pain with Clicking	
Yes	46 (23.0%)
No	154 (77.0%)

Maximum patients had missing teeth in 2 quadrants 60 (30.0%), maximum patients presented with in range of 5-8 numbers of missing teeth 85 (42.5%) and A3 i.e.; support zone 4 with missing teeth in both arches was frequently reported 59 (29.5%), Table 2.

Table 2: Frequency distribution of number of partially missing teeth, tooth loss quadrant and number of occlusal support zone; n=200

Variables	Frequency (%)
Number of Partially Missing Teeth	
1-4	39 (19.5%)
5-8	85(42.5%)
>8	76 (38.0%)
Tooth Loss Quadrant	
1	23 (11.5%)
2	87 (43.5%)
3	60 (30.0%)
4	30 (15.0%)
Number of Occlusal Support Zone	
A1	0 (0.00%)
A2	27 (13.5%)
A3	59 (29.5%)
B1	44 (22.0%)
B2	31 (15.5%)
B3	10 (5.0%)
B4	6 (3.0%)
C1	5 (2.5%)
C2	18 (9.0%)

The TMJ pain with clicking in males was 32.9% and in females it was 16.1%. Muscle pain was 8.5% and 7.6% in males and females respectively. Deviation of mouth opening existed in males 23.2%and females 28.8%. Restricted mouth opening i.e.; was present in 6.1% males and 4.2% females. The association of gender with signs and symptoms of TMJ was significantly found for TMJ pain; p0.05, and measurement of maximum mouth opening; p-value 0.02. Tooth loss number >8 had TMJ pain 17.1%, muscle pain 40.8%, deviation of jaw 32.9% and 11.8% restricted mouth opening i.e.;<35 mm. The Chi Square test significance of number of partially lost teeth with muscle pain; p-value 0.00, TMJ pain; p 0.00 and maximum mouth opening was significant; p-value 0.00. Deviation of jaw up on mouth opening had insignificant association with gender; p-value 0.37 and number of tooth loss; p-value 0.10, (Table 3).

Table 3: Association of Gender and Number of Partial Tooth Loss with Signs and Symptoms of TMJ (n=200)

Variables	TMJ Pain with Clicking Frequency (%)		Muscle Pain Frequency (%)		Deviation of Jaw Frequency (%)		Maximum Mouth Opening Frequency (%)		
Gender	Yes	No	Yes	No	Yes	No	>40mm	35-40mm	<35mm
Male	27 (32.9%)	55 (67.1%)	7 (8.5%)	75 (91.5%)	19 (23.2%)	63 (76.8%)	64 (78.0%)	13 (15.9%)	5(6.1%)
Female	19 (16.1%)	99 (83.9%)	9 (7.6%)	109 (92.4%)	34 (28.8%)	84 (71.2%)	107 (90.7%)	6 (5.1%)	5(4.2%)
p-Value	0.05		0.81		0.37		0.02		
Number of Tooth Loss									
1-4	0 (0.00%)	39 (100.0%)	2 (5.1%)	37 (94.9%)	12 (30.8%)	27 (69.2%)	38 (97.4%)	1 (2.6%)	0 (0.00%)
5-8	3 (3.5%)	82 (96.5%)	13 (15.3%)	72 (84.7%)	16 (18.8%)	69 (81.2%)	81 (95.3%)	3 (3.5%)	1 (1.2%)
>8	13 (17.1%)	31 (40.0%)	31 (40.8%)	45 (59.2%)	25 (32.9%)	51 (67.1%)	52 (68.4%)	15 (19.7%)	9 (11.8%)
p-Value	0.00		0.00		0.10		0.00		

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Significance value; p<0.05

The TMJ pain with clicking was 4.3% in quadrant 1, 2.3 % in tooth loss quadrant 2, 10.0% in quadrant 3 and 23.3% in quadrant 4. The muscle pain was 21.7%, 14.9%, 23.3% and 46.7% in quadrants 1, 2, 3 and 4 respectively. Deviation of mouth opening was 26.1%, 28.7%, 20.0% and 33.3% in quadrants 1, 2, 3 and tooth loss quadrant 4. Restricted mouth opening i.e.; <35 mm was found in quadrants 1, 2, 3, and 4 as 0.00%1.1%, 6.7% and 16.7% respectively. The association of tooth loss quadrant with muscle pain, TMJ pain with clicking and maximum mouth opening was significant however insignificant association with deviation of jaw was found p 0.52. The maximum TMJ pain with clicking, muscle pain and deviation of jaw were found in C2 occlusal support zone; 72.2%, 55.6%, 50.0% however maximum rescripted mouth opening was found in C1.40.0%. Significant association of number of occlusal support zones with all signs and symptoms of TMJ was found, (Table 4).

Table 4: Association of tooth loss quadrant and number of occlusal support zone with signs and symptoms of TMJ (n=200)

Variables	TMJ Pain with Clicking Frequency (%)		Muscle Pain Frequency (%)		Deviation of Jaw Frequency (%)		Maximum Mouth Opening Frequency (%)		
Tooth Loss Quadrant	Yes	No	Yes	No	Yes	No	>40mm	35-40mm	<35mm
1	1 (4.3%)	22 (95.7%)	5 (21.7%)	18 (78.3%)	6(26.1%)	17 (73.9%)	21 (91.3%)	2 (8.7%)	0 (0.00%)
2	2 (2.3%)	85 (97.7%)	13 (14.9%)	74 (85.1%)	25 (28.7%)	62 (71.3%)	80 (92.0%)	6 (6.9%)	1 (1.1%)
3	6 (10.0%)	54 (90.0%)	14 (23.3%)	46 (76.7%)	12 (20.0%)	48 (80.0%)	49 (81.7%)	7 (11.7%)	4 (6.7%)
4	7 (23.3%)	23 (76.7%)	14 (46.7%)	16 (53.3%)	10 (33.3%)	20 (66.7%)	21 (70.0%)	4 (13.3%)	5 (16.7%)
p-Value	0.03		0.00		0.52		0.02		
Number of Occlusal Support Zone									
A2	0 (0.00%)	27 (100.0%)	0 (0.00%)	27 (100.0%)	6 (22.2%)	21 (77.8%)	26 (96.3%)	1 (3.7%)	0 (0.00%)
A3	13 (22.2%)	46 (78.0%)	1 (1.7%)	46 (78.8%)	16 (27.1%)	43 (72.9%)	58 (98.3%)	1 (1.7%)	0 (0.00%)
B1	6 (13.6%)	38 (86.4%)	2 (4.5%)	38 (86.4%)	9 (20.5%)	35 (79.5%)	42 (95.5%)	2 (4.5%)	0 (0.00%)
B2	7 (22.6%)	24 (77.4%)	1 (3.2%)	24 (77.4%)	4 (12.9%)	27 (87.1%)	31 (100.0) %	0 (0.00%)	0 (0.00%)
B3	1 (10.0%)	9 (90.0%)	1 (10.0%)	9 (90.0%)	2 (20.0%)	8 (80.0%)	6 (60.0%)	3 (30.0%)	1 (10.0%)
B4	3 (50.0%)	3 (50.0%)	0 (0.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	0 (0.00%)
C1	3 (60.0%)	3 (40.0%)	1 (20.0%)	3 (40.0%)	4 (80.0%)	1 (20.0%)	1 (20.0%)	2 (40.0%)	2 (40.0%)
C2	13 (72.2%)	5 (27.8%)	10 (55.6%)	5 (27.8%)	9 (50.0%)	10 (55.6%)	4 (22.2%)	7 (38.9%)	7 (38.9%)
p-Value	0.00		0.01		0.00		0.00		

Significance value; p<0.05

DISCUSSION

The current study was conducted on 200 partially edentulous patients reporting to the prosthodontics department for tooth replacements. Patients' TMJs were clinically assessed for the signs and symptoms of TMJ disorders. The signs and symptoms were found in partially edentulous patients where 23.0% TMJ joint pain, 8.0% muscle pain, 26.5% mandibular deviation and 5.5% with restricted mouth opening was seen. Lekaviciute and Kriauciunas, demonstrated low prevalence of joint disorder in partially edentulous patients. p=0.06 [14]. In contrast, Zielinski *et al.*, and Rawat *et al.*, in their respective studies reported the development of at least one or more joint disorders symptoms in partially and completely edentulous patients [15, 16]. In contrast Zakir and coworkers found no correlation of developing TMJ problems in their patients with edentulism [11].TMJ pain and clicking results from overloading of joint articular surfaces due to tooth loss and masticatory load.The mandibular movements cease or reduced due to pain and over period become very limited [10]. Maximum number of females were reported with tooth loss 59.0% however the signs and symptoms of TMJ dysfunction were significantly more in males 32.9% than in females 16.1%. In the present study the male patients 6.1% had restricted mouth opening i.e.; <35mm whereas only 4.2% females had reduced opening. Muscle pain was more in females 7.6% as compare to males but the finding was insignificant. In accordance with the results of current study more male patients were reported in the studies carried out by Mundt *et al.*, stating

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the fact that women did not show a significant relationship with tooth loss and developing TMJ problems [17].In contrast to the results of current study more female patients with TMJ problems were reported in the studies done by Shet *et al.*, and Zakir and coworkers [18, 19]. Likewise, Amin and coworkers found more female patients with signs and symptoms of joint disorders [20]. Quin and coworkers however found no difference in pain intensity with in gender [21]. Similarly, Zakir and coworkers reported no correlation of developing TMJ disorder with respect to gender [11]. The variation in the results could be explained on the fact that social and cultural differences in different parts of the world could make impact and the reason of diversity in the results [21].Tooth loss in a partially edentulous patient may affect the occlusal integrity and condylar posture of the joint. Shifting of the remaining opposite or adjacent teeth to fill in the gap results in premature contacts disturbing to the joint anatomy [16]. In the current study association of number of tooth loss and signs and symptoms of TMJ disorders was significantly found. Frequently missing number of teeth was from 5- 8 teeth i.e.; 42.5%. Signs of TMJ dysfunction were more prevalent in patient with >8 teeth loss. 17.1% TMJ pain and clicking, 40.8% muscle pain, 32.9% mandibular deviation and 11.8% restricted mouth opening i.e.;<35mm was reported in patient with more than 8 teeth lost. Rawat *et al.*, and Lekaviciute and Kriauciunas, in their respective study concluded that the chances of developing TMJ disorder is directly related to the number of missing teeth [14, 16]. Increase. In contrast Chairunnisa and Sihombing, reported no association of number of missing teeth and joint problems [22]. In the present study frequently found tooth loss was seen in 2 quadrants 43.5%, and association of tooth loss in number of quadrants was significant with signs and symptoms of TMJ disorders. Muscle pain and restricted mouth opening was frequently found in teeth missing in all 4 quadrants i.e.; 46.7% and 16.7% and the association was significant whereas deviation of mouth opening was seen in tooth loss in 2nd quadrant 71.3% but the insignificant association was found. Similarly, Wang and fellows reported that loss of tooth support in different quadrants is more detrimental to the joint health than loss of tooth support in one [23]. Likewise, Chairunnisa and Sihombing, found significant association of missing posterior teeth quadrants with signs of developing TMDs [22]. Similarly, a study concluded that the loss of posterior teeth and resultant loss of support greatly affects the health of the joint even more than the loss of anterior teeth [15]. A3 occlusal support zone 29.5% was frequently existed in the patients. Significant association of number of occlusal support zones and signs and symptoms of TMJ disfunction was found $p<0.05$. C2 and C3 zones had maximum TMJ symptoms i.e.; 72.2% TMJ pain and clicking, 38.9% restricted mouth opening and 55.6%muscle pain. In contrast Chairunnisa and Sihombing, and Hiltunen found no correlation between occlusal support and joint problems claiming that number of teeth cannot describe the masticatory system functionality [22, 24]. Bertram and coworkers documented that bilateral loss of posterior teeth has more pronounced effect on the joint health as it results in condyle displacement and erosion [25]. Amin and coworkers in their study stated the multifactorial etiology of TMJ disorder in partially and completely edentulous patients and stressed that not only occlusal support loss damages the stomatognathic system but occlusal disharmony, masticatory pattern and parafunction influences the joint health [20]. Ammanna and coworkers claimed it is still debatable that loss of posterior support and position of the condyle that very little is about the negative impact on the condylar position of the joint and the missing anterior teeth [26]. There is always an undergoing damage to TMJ due to loss of teeth that may go unnoticed as the detrimental effects not always end up in pain so recording other symptoms like restricted mouth opening, deviated mandibular movements and clicking in partially edentulous patients should also be recorded for accurate diagnosis. The limitation of the study was its small sample size and the cross- section study design. The study lac the follow up and studies recommended on larger group and long term follow ups for more precise outcomes. This will help in early identifying of TMJ problems and timely cure would be beneficial to the society.

CONCLUSIONS

It can be concluded that the partially edentulous patients frequently develop one or more signs and symptoms of TMJ disorders and number of teeth lost, number of quadrants with missing teeth and loss of occlusal support disturb the joint function and associated stomatognathic system.

Authors Contribution

Conceptualization: MIAM
Methodology: S, SN, KQ
Formal analysis: MIAM
Writing, review and editing: MM, MHR, KY, TH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Vaginal Birth after C-Section and Factors Associated with Successful Trial of Vaginal Birth after C-Section

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ABSTRACT

A repeat cesarean section is often a more favorable and comfortable option for women who have previously undergone a cesarean section. **Objective:** To determine the prevalence and the maternal and obstetric factors influencing the likelihood of a successful vaginal birth after cesarean (VBAC) among women attempting a trial of labor. **Methods:** This descriptive case series was conducted at the Gynecology Unit 3 of Sir Ganga Ram Hospital, Lahore, from August 2023 to February 2024. A total of 158 women with a history of one prior lower-segment cesarean section were enrolled through a non-probability sampling technique. Labor progression was monitored using the WHO labor guide, which guided the decision for either a repeat cesarean section or a vaginal birth. Data on factors associated with a successful VBAC were collected and analyzed by comparing their frequency between successful and unsuccessful cases. **Results:** Among the women undergoing a trial of labor, 115 (72.78%) achieved a successful vaginal delivery. When comparing maternal and obstetric factors between successful and unsuccessful groups, the following differences were observed: maternal age below 30 years (55.65% vs. 39.53%), gestational age under 40 weeks (59.13% vs. 48.84%), BMI less than 25 kg/m^2 (57.39% vs. 30.23%), and an inter-delivery interval exceeding two years (80.0% vs. 60.47%). **Conclusions:** This study found that the success rate of vaginal delivery in women with a prior cesarean section undergoing a trial of labor was 72.78%. Several maternal and obstetric factors were associated with an increased likelihood of successful VBAC.

INTRODUCTION

The incidence of caesarean-section is different in the different region of the world. In most of the states, it is above the WHO recommended rate.World Health Organization suggests the caesarean-section rate of 15% or less. In order to decrease the surge in caesarean-section rates, one has to undergo the vaginal birth after cesarean-section technique [1]. During past, it was believed that the patients who have once undergone cesarean-section will always have cesarean-section in future deliveries. This previous old concept is totally changed now due to highly expert staff and advance facilities that a patient can have successful vaginal birth after her first cesarean after fulfilling selected criteria [2]. Many studies conducted in past years to show the success of (VBAC) vaginal birth after cesarean section.The vaginal delivery after caesarean-section was 84% and independent association of gestational age, estimated birth weight, previous vaginal birth, body mass index, cervix bishop score etc. with vaginal birth after cesarean section. [3]. According to WHO experts, there is 10-15% surge in caesarean- section cases

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in many countries of the world. The main factor of increase in caesarean section is pointed out to be repeat caesarean-section in a patient [4, 5]. Cervical dilatation, fetal head station, and premature rupture of membrane, are factors leading to successful vaginal birth after C-section (VBAC) [6]. 72.13% women were successful for trial of labor (vaginal delivery) after caesarean-section [7]. In addition to above mentioned life threats, the repeated caesarean-section further cause various extremely dangerous health hazards like infection, bladder injury and placenta accrete [8]. When vaginal delivery is compared with caesarean section, there is 5-10 times increase in health issues of patients in later case [9]. Vaginal birth after caesarean section is the only option to avoid health hazards associated with repeated caesarean section [10]. Complications of (VBAC)vaginal birth after cesarean section include ruptured uterus, postpartum hemorrhage, and neonatal and maternal morbidity and mortality [11]. Health care experts should know the merits and demerits of (VBAC) vaginal birth after caesarean section.so that they are able to guide patients properly and manage them accordingly to achieve successful vaginal birth after caesarean section [12]. In order for medical professionals to better assist patients in having a successful vaginal birth following a caesarean section, my study aims to determine the prevalence and related factors (obstetric and maternal) that contribute to successful vaginal birth with prior one caesarean section undergoing trial off labor in the local population.

Health care professionals should be aware of the benefits and drawbacks of vaginal delivery following cesarean section in order to effectively guide and manage patients in order to have a successful vaginal birth following cesarean procedure.

METHODS

This study was a descriptive case series, conducted in Gynaecology Unit 3, Sir Ganga Ram hospital, I Lahore from August 02, 2023 till Feb 01,2024 by non-probability consecutive technique. The study received ethical clearance from the ethical review board of the college (Ref No: CPSP/REU/OBG-2020-059-10155). After taking written informed consent, details about age, co-morbidities, gestational age were taken from the patient. A total of 158 females were estimated using the expected proportion of vagina delivery after Cesarian section is equal to 72.1% with 95% confidence level and 7% margin of error was used. Pregnant patients with a singleton pregnancy at 37 weeks of gestation with vertex presentation, an acceptable pelvis with cervical dilatation, and an interest to go through a scar trial were included in the study, as were women who had one lower segment cesarean section for a non-recurrent reason, while females with history of medical disorders, with previous classical cesarian section , previous myomectomy , intrauterine growth , fetal distress and estimated fetal rate >3.5 kg were excluded from study. Information regarding BMI and inter-delivery interval was taken from antenatal cards. Information regarding previous caesarean section indication and scar was taken from previous caesarean section notes. Clinical examination was performed and cervical dilatation, fetal head station, and premature rupture of membrane, were assessed and noted. Fetal weight, fetal lie, and fetal presentation were assessed during ultrasound. A decision regarding an additional a cesarean or a vaginal delivery following a C-section was made based on the patient's observation during labor utilizing the WHO labor guide. The information on the elements that led to a successful VBAC was then collected, and the frequency of these elements in the successful and unsuccessful groups was compared. To reduce bias, the researcher gathered all of the data herself, and the inclusion/exclusion criteria were closely adhered to. SPSS version 26.0 was utilized for statistical analysis of the data. Mean and standard deviation (±SD) was calculated for numerical variables i.e., age, BMI, gestational age, inter-delivery interval, fetal weight, total duration of active stage of labour. Frequency and percentage were calculated for categorical variables i.e., successful vaginal delivery, cervical dilatation ≥4cm, fetal head station at or below -2, BMI <25 kg/m^2, GA <40 weeks, interdelivery interval >2 years, fetal weight 3-3.5 kg, labour 6-7 hours and premature rupture of membranes on admission. Chi-square test was used to compare the factors between the groups (vaginal delivery vs c-section).

RESULTS

The age range in this study was 18 to 40 years old, with a mean age of 28.54 ± 4.52 years.The majority of the cases, 81 (71.27%), involved people under 30.A mean of 39.42 ± 1.74 weeks was the gestational age.A mean BMI of 24.77 ± 4.76 kg/m^2 was recorded.The average time between deliveries was 3.14 ± 1.23 years.At admission, the average cervical dilatation was 5.21 ± 1.89 cm. Fetal weight was 3.19 ± 0.87 kg on average.The average labor lasted 6.22 ± 1.78 hours.Table I displays the average number of patients incorporating extra factors that contribute to confusion.

Table 1: Demographic and Clinical Profile of Subjects (n=158)

Variables		Category	Frequency (%)
Age	28.54 ± 4.52 Years	≤30 years	81 (51.27)
		>30 years	77 (48.73)
Gestational Age (Weeks)		<40 weeks	89 (56.33)
		≥40 weeks	69 (43.67)
BMI (Kg/m^2)		<25 kg/m^2	79 (50.0)
		≥25 kg/m^2	79 (50.0)
Inter-Delivery Interval		≤2 years	40 (25.32)
		>2 years	118 (74.68)
Cervical Dilation On Admission		≤4 cm	49 (31.01)

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	>4 cm	109 (68.99)
Fetal Head Station on Presentation	≤-2 station	30 (18.99)
	>-2 station	128 (81.01)
PROM	Yes	71 (44.94)
	No	87 (55.06)
Fetal Weight (Kg)	<3 kg	128 (81.01)
	3.0-3.5 kg	30 (18.99)
Duration of Labour (Hours)	≤7 hours	110 (69.62)
	>7 hours	48 (30.38)

In my study, frequency of successful vaginal delivery among women with a previous caesarean section undergoing trial of labour was found in 115 (72.78%) patients as shown in Figure 1.

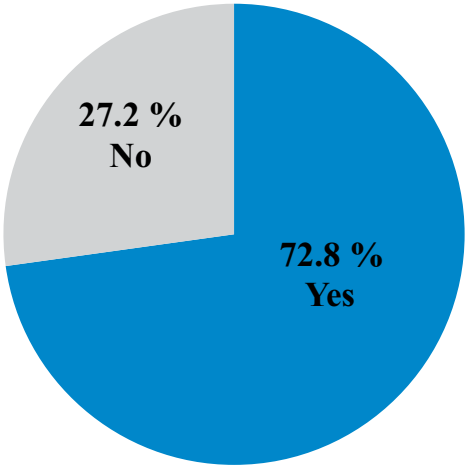

Figure 1: Frequency of successful vaginal delivery among women with a previous caesarean section undergoing trial of labour (n=158)

Comparison of the frequency of maternal and obstetric parameters linked with the better vaginal delivery among successful and unsuccessful groups were as follows; age <30 years in 55.65% vs 39.53%, gestational age <40 weeks in 59.13% vs 48.84%, BMI <25 kg/m^2 in 57.39% vs 30.23%, inter-delivery interval >2 years in 80.0% vs 60.47%, cervical dilatation ≥4 cm in 72.17% vs 60.47%, fetal head station ≤-2 in 15.65% vs 27.91%, PROM in 38.26% vs 62.79%, Fetal weight 3-3.5 kg in 90.43% vs 55.81% and duration of labour ≤7 hours in 70.43% vs 67.44% respectively (Table 2).

Table 2: Comparison of the prevalence of obstetric and maternal traits correlated with positive and negative vaginal deliveries

Variables	Category	Successful Frequency (%)	Unsuccessful Frequency (%)	p-Value
Age <30 Years	Yes	64 (55.65%)	17 (39.53%)	0.071
	No	51 (44.35%)	26 (60.47%)	
Gestational Age <40 Weeks	Yes	68 (59.13%)	21 (48.84%)	0.246
	No	47 (40.87%)	22 (51.16%)	
BMI <25 Kg/m^2	Yes	66 (57.39%)	13 (30.23%)	0.002
	No	49 (42.61%)	30 (69.77%)	
Inter-delivery interval >2 Years	Yes	92 (80.0%)	26 (60.47%)	0.012
	No	23 (20.0%)	17 (39.53%)	
Cervical Dilation ≥4 cm	Yes	83 (72.17%)	26 (60.47%)	0.157
	No	32 (27.83%)	17 (39.53%)	
Fetal Head station ≤ -2	Yes	18 (15.65%)	12 (27.91%)	0.081
	No	97 (84.35%)	31 (72.09%)	
PROM	Yes	44 (38.26%)	27 (62.79%)	0.006
	No	71 (61.74%)	16 (37.21%)	
Fetal Weight 3.0-3.5 Kg	Yes	11 (9.57%)	19 (44.19%)	0.0001
	No	104 (90.43%)	24 (55.81%)	
Duration of Labor >7 Hours	Yes	34 (29.57%)	14 (32.56%)	0.716
	No	81 (70.43%)	29 (67.44%)	
	Total	115 (72.8%)	43 (27.2%)	-

DISCUSSION

The most frequent and main reason for a repeat vaginal delivery is a prior one. Reduction in cesarean section rate can be obtained by giving trial of labour in such patients [13]. For this purpose, we have to follow certain practical guidelines made by local national medical associations, but there is disparity among different countries.Keeping in mind, VBAC is considered relatively successful and safe as compared to repeat cesarean section.But in recent era, reduction in TOLAC rates have been observed throughout world [14, 15].Trial of labour when given to a patient with previous cesarean section, provides a last opportunity to go through normal vaginal labour process [16].However, repeat cesarean section has less complications, but if VBAC is failed, it will end up with increased chances of maternal and perinatal morbidity. If we want to enhance the success of VBAC, then we have to carefully and accurately select the patients opting for choice of trial of labour. [17]. In addition to it, if we discuss and communicate with patient regarding success of VBAC and get their opinions, it will help us. In this study, 115 (72.78%) of the women who had previously undergone a caesarean section and were undertaking a trial of labor had a successful delivery via the vaginal canal. Comparison of the frequency of maternal and obstetric characteristics related with success of vaginal delivery among successful and unsuccessful groups were as follows; age <30 years in 55.65% vs 39.53%, gestational age <40 weeks in 59.13% vs 48.84%, BMI <35 kg/m^2 in 57.39% vs 30.23%, inter-delivery interval >2 years in 80.0% vs 60.47%, cervical dilatation ≥4 cm in 72.17% vs 60.47%, fetal head station ≤-2 in 15.65% vs 27.91%, PROM in 38.26% vs 62.79%, Fetal weight 3-3.5 kg in 90.43% vs 55.81% and duration of labour ≤7 hours in 70.43% vs 67.44% respectively. In a study conducted by Tesfahun *et al.*, 2023, the vaginal delivery after caesarean-section was 84% [18]. According to WHO experts, there is 10-15% surge in caesarean-section cases in many countries of the world. The main factor of increase in the caesarean section has been pointed out to be a repeat caesarean-section in a patient.[19].As well as maternal wish for caesarean-section is known to be another leading factor of increase in caesarean-section rate. A study conducted by Zhang *et al.*,

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2021, 122 women were entered in study, out of which 72.13% (88) women were successful for trial of labour (vaginal delivery) after caesarean-section [20].They discovered that characteristics linked to a successful trial of vaginal delivery following caesarean section included mother age 26.8 ± 4.28, body mass index ≤ 25 kg, trimester age ≤ forty weeks of pregnancy, and inter-delivery duration < 2 years (P<0.000). A study by Majzoobi MM *et al.*, 2014, reported trial of labour in 65% patients but successful vaginal birth in 35% women and Memon S *et al.*, 2023, associates in 83.5% of cases. Brattele and associates reported success in 65.6% [21, 22]. Another study reported by Soh *et al.*, 2020, observed the percentage of (VBAC) that how many pregnant women delivered vaginally who have previously delivered baby by Caesarean section.74% of pregnant women delivered through vaginal route successfully who delivered baby previously by cesarean section, and no significant maternal and mortality identified in these cases. Most patients who have had a Caesarean delivery in the past can safely and successfully give birth through the vagina.There are certain factors which are related with success of VBAC. If patients have previous vaginal delivery before cesarean section, normal range body mass index before pregnancy, young maternal age, non-recurring indication or cesarean section, chances of success are more [23].There are certain parameters which are important during labor, like spontaneous onset of labor, favorable bishop score, amniotic membrane and cervical status, station of fetal head and weight of baby, much play crucial role in success of vaginal birth after cesarean section [24].Limitations of the study includes single center study and its applicability. If we conduct it on a larger scale, it will definitely help the healthcare professionals in seeking best decision for their patients.

CONCLUSIONS

This study found that the following common factors are associated with effective vaginal delivery of babies after cesarean section: age <30 years, BMI <25 kg/m^2, inter-delivery interval >2 years, cervical dilatation ≥4 cm, PROM, and fetal weight 3-3.5 kg. The frequency of a positive the genital tract delivery among women with a previous caesarean section undergoing trial of labor was 72.78%. So, we recommend that all these factors should be taken into consideration before any women undergoing TOLAC for a better future outcome in every aspect to reduce adverse maternal outcome.For this purpose, we have to follow certain practical guidelines made by local national medical associations.If we want to enhance the success of VBAC, then we have to carefully and accurately select the patients opting for choice of trial of labour.

Authors Contribution

Conceptualization: MJ, FJ
Methodology: QM, IZ
Formal analysis: SZS, AZ
Writing, review and editing: SZS, AZ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Syndrome of Inappropriate Antidiuretic Hormone in Patients with Guillain-Barré Syndrome Presenting at Tertiary Care Hospital, Karachi

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ABSTRACT

Guillain-Barré Syndrome (GBS) is a condition that causes inflammation in the nerves and can sometimes lead to a problem called SIADH. SIADH happens when the body makes too much of a hormone that controls water balance, leading to low sodium levels in the blood. **Objective:** To determine the frequency of SIADH inpatients with GBS presenting at Tertiary Care Hospital, Karachi. **Methods:** This Cross-sectional study was conducted at Department of Neurology, Civil Hospital, Karachi, from 12-07-19 till 12-01-20. Total 119 GBS patients who met the inclusion criteria were included. A brief history was recorded, and demographic details were noted in the form. Numerical data were summarized using simple descriptive statistics.Categorical data were shown as numbers and percentages. **Results:** 71 (59.7%) were male and 48 (40.3%) were female. Mean age in the study was 46.78 ± 2.81 years. Whereas, Mean age, duration of symptoms, serum sodium and GC Sinour study was 46.78 ± 2.81 years, 25 ± 10.78 hours, 128.65 ± 7.52 mmol/L and 11.21 ± 3.14 % respectively. Out of 119 GBS patients, 21% had SIADH. **Conclusions:** This study showed that SIADH is present in significant proportion of patients with GBS. Thus, it is essential to focus on a comprehensive way of management of GBS and its comorbidities rather than primarily treating the neurological symptoms.

INTRODUCTION

Guillain-Barré Syndrome (GBS) is the most common cause of sudden muscle weakness in developed countries [1]. GBS has different types, including AIDP (affects nerve coating), AMAN (affects motor nerves), AMSAN (affects both motor and sensory nerves), and Miller Fisher Syndrome (affects coordination and reflexes) [2]. GBS can cause a range of problems, including sudden weakness that affects both sides of the body, usually starting in the legs and moving upwards. It also leads to the loss of reflexes, changes in sensation, and issues with the autonomic nervous system, which controls functions like blood pressure and heart rate [3]. The condition occurs worldwide and can affect people of all ages and genders. Research suggests that GBS happens when the immune system mistakenly attacks parts of the peripheral nerves. Scientists have found that immune cells (T-lymphocytes) and antibodies target proteins in nerve coverings, such as myelin antigens (P0, P2), glycoproteins, and glycolipids [4]. Other general inflammatory processes also contribute to nerve damage [4]. The exact cause of GBS is still unclear.

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However, it is believed to be triggered by an infection, as about two-thirds of patients experience an infection before developing symptoms [5]. Sodium is the main electrolyte found outside the cells and plays a key role in maintaining the body's fluid balance. Disorders related to sodium levels can lead to serious health complications and even death [6]. Because sodium imbalances are common and can cause neurological problems, it is important to determine the exact cause before starting treatment [7]. Electrolyte imbalances in patients with neurological diseases occur at similar rates as in other medical conditions and are mainly influenced by underlying health problems [8]. The exact cause of SIADH in GBS is not fully understood. One possible explanation is that damage to certain brain cells (in the hypothalamus) causes the inappropriate release of antidiuretic hormone (ADH) into the bloodstream [9, 10]. Another theory suggests that the body's osmoreceptors, which regulate water balance, become misregulated [11]. Recent studies have linked interleukin-6 (IL-6), an inflammatory molecule, to SIADH in GBS. IL-6 can trigger the release of vasopressin (ADH) by stimulating specific brain regions that control thirst and fluid balance [12, 13]. Research has also shown that IL-6-producing immune cells increase early in the acute phase of GBS, further supporting its role in the condition. Elevated IL-6 in acute GBS may trigger inappropriate ADH secretion via the hypothalamic-pituitary axis, contributing to hyponatremia and electrolyte imbalance [14]. Saifudheen et al., found the prevalence of SIADH to be 48 % in patients presenting with GBS [15]. Scarcity of the locally available literature on the frequency of SIADH in patients with GBS is important to determine in order to establish the local perspective. The results of this study will serves as a cornerstone for various healthcare institutions and guidelines for early detection in case of finding positive association in the study. Thus, the patients with GBS can be referred and managed in specialized units. Data from this study would potentially offer new information to clinician that can influence clinical practice of GBS, quality of life, and patient outcomes in the population in light of variable demographic, socioeconomic and co-morbid conditions. Hence the study was designed to aimed in determining the frequency of SIADH in patients with GBS presenting at Tertiary Care Hospital, Karachi.

METHODS

A cross-sectional study was conducted in the Neurology Department of Civil Hospital, Karachi, from July, 2019, to January, 2020, using non-probability consecutive sampling. The study included newly diagnosed GBS patients aged 20-65 years of either gender who presented within 24 hours of symptom onset. Patients who did not consent or had a history of psychiatric disorders such as mania, bipolar disorder, or PTSD, as well as those with lung cancer, thyroid disorders, addison's disease, tuberculosis, asthma, kidney disease, heart conditions (heart failure or myocardial infarction), chronic liver disease, chronic obstructive pulmonary disease (COPD), or central nervous system diseases like head trauma or multiple sclerosis, were excluded from the study. The study was approved by CPSP vide letter no. CPSP/REU/NEU-2017-183-420; dated: July 12, 2019. The required sample size was determined to be 119 patients, based on an estimated SIADH frequency of 48%, [15] a 9% margin of error, and a 95% confidence level, calculated using WHO software. A brief medical history, including illness duration and demographic details, was collected at admission. If the patient had difficulty speaking (aphasia) or a low Glasgow Coma Scale (GCS) score, the information was gathered from their attendants. GBS was diagnosed using Brighton's criteria. within 24 hours followed by a plateau phase, and no other identifiable cause for the weakness [16].SIADH in GBS patients was diagnosed if plasmasodiumconcentration<135mmol/L, plasmaosmolality<280mOsmol/kg, urineosmolality >100m Osmol/kg, urinarysodiumconcentration>30mmol/L, and clinically normal fluid balance (euvolemia) indicated by a supine heartrate≤100bpm and systolic blood pressure ≥100 mmHg.Additionally, patients had to show no signs of adrenal dysfunction (ACTH: 10–60 pg/mL) or thyroid dysfunction and must not have used diuretics in the past three months [17].SPSS version 21.0 was used for data analysis.Chi square was applied to check for the association between SIADH and other categorical variables. P value <0.05 was set as statistically-significant.

RESULTS

Among 19 GBS patients, the mean age of participant was reported to be 46.78 ± 2.81 years with most of the participants belonging to the > 50 years of age group. 71 (59.7%) participants were male and 48 (40.3%) were female. The presence of comorbidities of diabetes mellitus type II was 22.7% (n=27), hypertension was 30.3% (n=36) prevalent and 16.8% (n=20) population were smokers, (Table 1).

Table 1: Sample Description (N=119)

Variables	Value Frequency (%)
Age	
Mean Age of Participants	46.78 ± 2.81
20 - 30 Years	4 (3.36%)
31 - 40 Years	37 (31.09%)
41 - 50 Years	20 (16.81%)
51 - 60 Years	58 (48.74%)
Duration Of Symptoms (Hours)	
Mean Duration of Symptoms	25 ± 10.78
< 48 Hours	56 (47.06%)
> 48 Hours	63 (52.94%)

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Gender	
Male	48 (40.34%)
Female	71 (59.66%)
Diabetes Mellitus	
Present	27 (2.69%)
Absent	92 (771.31%)
Hypertension	
Present	36 (30.25%)
Absent	83 (69.75%)
Smoking Status	
Smoker	20 (16.81%)
Non Smoker	99 (83.19%)

Out of 119 GBS patients, 25 (21%) had and did not have SIADH, as shown in Figure 1.

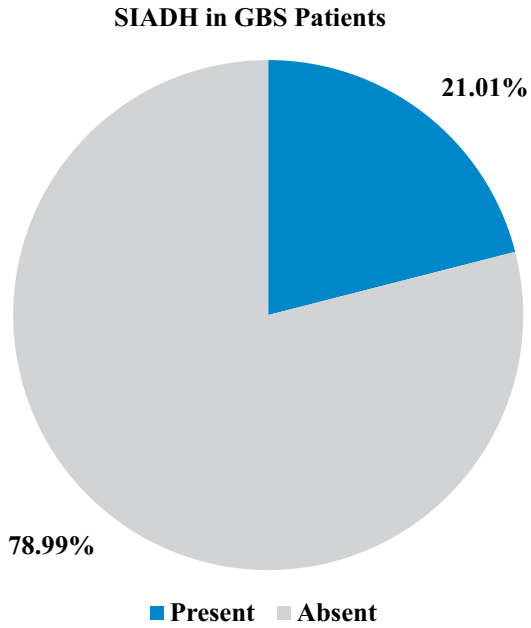

Figure 1: Percentage of Syndrome of Inappropriate Antidiuretic Hormone Secretion among patients of Guillain-Barré Syndrome

The relation between age, gender and duration of symptoms with that of presence of SIADH is showed in Table 2. Age group between 31 to 40 and 51 to 60 has the highest prevalence of SIADH.While 52% (13) of SIADH patients were male.The SIADH was more prevalent in patients who had the duration of symptoms of > 48-hours which was statistically significant (p=0.014).

Table 2: SIADH According To Age, Gender And Duration Of Symptoms Status (N=119)

Groups	Frequency (%)	SIADH		p-Value
		Present Frequency (%)	Absent Frequency (%)	
Age (Years)				
20-30 Years	04 (3.4%)	01 (4%)	03 (3.2%)	0.34
31-40 Years	37 (31.1%)	11 (44%)	26 (27.7%)	
41-50 Years	20 (16.8%)	02 (8%)	18 (19.1%)	
51-60 Years	58 (48.7%)	11 (44%)	47 (50%)	
Gender				
Male	71 (59.7%)	13 (52%)	58 (61.7%)	0.25
Female	48 (40.3%)	12 (48%)	36 (38.3%)	
Duration Of Symptoms				
< 48 Hours	56 (47.1%)	15 (60%)	41 (43.6%)	0.014*
> 48 Hours	63 (52.9%)	10 (40%)	53 (56.4%)	

**Statistically-significant(Chi-square)*

A small portion of patients had the diabetes mellitus along with the SIADH (p=0.28). One-fourth (24%; n=6) patients with SIADH were having comorbidity of hypertension (0.17). A very small portion i.e. 03 (12%) of people with SIADH were smokers. (p=0.09). None of the association was found to be statistically significant (Table 3).

Table 3: SIADH According To Comorbidities (N=119)

Groups	Frequency (%)	SIADH		p-Value
		Present Frequency (%)	Absent Frequency (%)	
Diabetes Mellitus				
Present	27 (22.7%)	07 (28%)	20 (21.3%)	0.28
Negative	92 (77.3%)	18 (72%)	74 (78.7%)	
Hypertension				
Present	36 (30.3%)	06 (24%)	30 (31.9%)	0.17
Negative	83 (69.7%)	19 (76%)	64 (68.1%)	
Smoking Status				
Smokers	20 (16.8%)	03 (12%)	17 (18.1%)	0.09
Non-Smokers	99 (83.2%)	22 (88%)	77 (81.9%)	

DISCUSSION

The results of these study revealed that 21% of the 119 GBS patients had SIADH, consistent with previous literature that indicates SIADH as a recognized but underreported complication of GBS.SIADH is characterized by hyponatremia resulting from excessive antidiuretic hormone (ADH) secretion, leading to impaired water excretion and dilutional hyponatremia. In the present study, the mean serum sodium level among participants was 128.65 ± 7.52 mmol/L, which falls below the normal reference range (135-145 mmol/L), supporting the diagnosis of SIADH in a subset of patients. This finding is comparable to a study conducted by Santoro *et al.*, where hyponatremia was observed in 18.4% of GBS patients, with a mean sodium level of 127.8 ± 6.4 mmol/L [18].The prevalence of SIADH in GBS varies across populations and study designs.For instance, a study conducted in the United Kingdom by James and Jose, reported a SIADH frequency of 25%, slightly higher than these findings [19]. Similarly, a cohort study by Shah PM *et al.*, found that 22% of GBS patients developed SIADH, reinforcing that the frequency observed in this study aligns with global trends [20].These variations can be attributed to differences in patient demographics, severity of GBS, and diagnostic criteria for SIADH across studies.Demographically, this study found that SIADH predominantly affected middle-

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aged and older adults, with most participants being in the 51–60-year age group (48.74%).This is consistent with international studies that indicate older age as a risk factor for SIADH due to decreased renal water excretion and increased sensitivity to ADH [19, 20].The duration of symptoms also appeared to influence the occurrence of SIADH, as more than half of the participants (52.94%) had symptoms lasting longer than 48 hours before presentation.Prolonged illness duration has been associated with increased autonomic dysfunction, which may further contribute to SIADH development [21].The highest prevalence of SIADH was observed in the 31–40 and 51–60 age groups, consistent with international studies that suggest middle-aged and older adults are more susceptible to SIADH due to decreased renal sodium regulation and increased ADH sensitivity [18].A study by James *et al.*, similarly found that SIADH was more frequent in patients above 40 years of age, reinforcing the notion that autonomic dysfunction, a hallmark of GBS, is more pronounced in older populations [19].Gender-wise, this study found that 52% of SIADH patients were male, though the association was not statistically significant.This contrasts with a study by Shah PM *et al.*, which reported a higher prevalence of SIADH in female GBS patients, suggesting potential regional or genetic variations [20]. The non-significant p-value (0.25) in this study indicated that gender alone may not be a decisive factor in SIADH development among GBS patients.A key finding was that SIADH was significantly more prevalent in patients with a symptom duration of more than 48 hours (p=0.014). This aligns with existing literature, as prolonged disease duration is linked to worsening autonomic dysfunction, which may enhance inappropriate ADH secretion [21]. The study also analyzed comorbidities such as diabetes mellitus, hypertension, and smoking. None of these factors showed a significant association with SIADH, consistent with previous research suggesting that autonomic dysfunction rather than metabolic or cardiovascular conditions primarily drives SIADH in GBS [19, 21].

CONCLUSIONS

The study showed that SIADH is present in significant proportion of patients with GBS and is prevalence is associated with longer duration of symptoms (>48-hours). Strategies aimed at preventing hyponatremia in high-risk populations need to be optimized.

Authors Contribution

Conceptualization: MK
Methodology: MK, IA
Formal analysis: MS
Writing, review and editing: MK, SGA, FH, TD, MS, IA

All authors have read and agreed to the published version of the manuscript

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The Efficacy and Difficulties of Implementing a Multifaceted of Strategies to Improve Retainer Compliance

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ABSTRACT

Orthodontic therapy with both permanent and removable appliances is known to be impacted by poor compliance. **Objective:** To investigate the barriers affecting orthodontic retainer compliance and to explore the effectiveness of a multifaceted approach in enhancing adherence to retainer wear. **Methods:** In this mixed-methods study, 100 patients were recruited from Jinnah Medical and Dental College, and treatments improved these patients' retainer compliance. Two groups were made control and intervention in which the control group received orthodontic treatment, and the other group received education, digital tools, and behavioral techniques. For statistical analysis descriptive statistics, logistic regression, and chi-square tests were used, and for qualitative data thematic analysis. **Results:** The self-reported adherence rates of the control group were higher (78%) as compared to the control group (52%; $p < 0.05$). The intervention group had higher retention wear adherence than the control group (78% vs. 52%, $p < 0.05$) which was further confirmed by smart monitoring (6.5 vs. 4.2 nights/week, $p = 0.03$) and orthodontists (76% vs. 50%, $p < 0.05$). The impact of digital interventions and behavioral strategies in improving retainer compliance was demonstrated by the compliance-improving techniques that ranked mobile health reminders (82%) as the most effective. **Conclusions:** A multifaceted approach, such as behavioral approaches, digital technologies, and education, considerably increased retainer compliance. Hence, orthodontic retention regimens that incorporate behavioral techniques and technology may produce improved long-term treatment results.

INTRODUCTION

After active orthodontic treatment, orthodontic retention is an essential phase that ensures the long-term stability of the improved oral alignment and occlusion. To prevent relapse, the natural tendency of teeth to return to their pre-treatment positions due to varying biological and behavioral forces retainers is crucial [1]. However, patient adherence to retainer wear is crucial for long-term stability [2]. One of the main reasons for orthodontic relapse and, consequently, the need for additional corrective treatment is non-compliance with retainers. To identify the success rate of orthodontic treatment it is essential to understand the compliance of retainers [3]. Earlier the success rate of Orthodontic treatment was evaluated based on improved aesthetics and occlusion along with minimum changes done after treatment [4]. Nowadays the treatment comprises of patient-centered, interdisciplinary perspective as it helps to determine the quality of life of an individual. With time the criteria to evaluate the efficiency of orthodontic treatment is no longer clinical success, other factors such as self-esteem and confidence are of more importance nowadays [5]. Although great advancements have been made in the field even though both patients and doctors need to work hard to achieve optimal compliance with retainer. Several factors are associated with poor retainer adherence such as patient-related issues [6]. Hence daily routines, lifestyle choices,

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and patient attitudes toward orthodontic treatment are also essential for long-term compliance. Inadequate follow-up visits, a lack of reinforcing mechanisms, and poor patient education are components of low adherence [7]. All the patient's needs can be addressed by specific strategies and proper planning. Maintaining orthodontic treatment results requires increasing patient adherence to wearing retainers. Implementing remote monitoring systems, applying behavioral reinforcement strategies, and offering thorough patient education are all components of a comprehensive strategy. Including parents or peers for support, tailoring retainer kinds to the patient's preferences, and making sure follow-up sessions are scheduled regularly are all important ways to improve compliance. Furthermore, innovations like smart retainers with compliance sensors provide unbiased wear-time tracking. Together, these diverse approaches tackle the different aspects that affect retainer adherence, which supports treatment stability over the long run [8]. Those patients who are non-compliant in wearing retainers usually suffer from more orthodontic relapse, consisting of the efficacy of the early treatment, and require more corrective measures. Hence, researchers and clinicians have investigated several methods to improve adherence because of the challenges faced by patients in retainer compliance. A multifaceted approach consists of several approaches related to education, behavior, and technology to meet the needs of patients [9, 10]. The main fundamentals to achieve sustained retainer compliance include Clinician-patient communication and follow-up care [11]. One of the emerging approaches of today's time is remote monitoring and virtual check-ins, which help in providing timely interventions whenever there is a compliance issue [12]. Orthodontic retention poses a significant challenge, particularly in the context of Pakistan, where socio-cultural and economic factors greatly influence patient compliance. Although there is a growing demand for orthodontic services, local research on retainer adherence is scarce, with the majority of studies concentrating on short-term results rather than long-term stability [5]. Research conducted internationally has shown that interventions related to behavior change, digital tools, and educating patients can effectively enhance compliance; however, these approaches need to be researched within the Pakistani context [13].

The study was conducted to fill the gaps by investigating the barriers affecting orthodontic retainer compliance and to explore the effectiveness of a multifaceted approach in enhancing adherence to retainer wear.

METHODS

In Karachi, Pakistan, Jinnah Medical and Dental College conducted a mixed-methods quasi-experimental non-randomized controlled study from April to September 2024. The ERB/JMDC/Approval# #:00006/24 was used to obtain ethical approval. A total 100 orthodontic patients were recruited in the study. The Open-Epi (Version 3.01) sample size calculator for comparing two proportions was used to determine the sample size for this quasi-experimental investigation. A 95% confidence level, 80% power, and a 1:1 allocation ratio between the control and intervention groups were among the assumptions made for the computation. The control group was projected to have a 50% adherence rate, whereas the intervention group was intended to reach an 80% adherence rate. 0.05 was used as the two-sided significance threshold. Group 1(Control) had 50% adherence, Group 2 (Intervention) had 80% adherence, $\alpha = 0.05$, power = 80%, and a ratio of 1 were the values entered using Open-Epi's "Sample Size for Two Proportions" tool. This resulted in a minimal sample size of 90 participants, or 45 participants each group. The ultimate sample size was 100 participants, with 50 in each group, after a 10% buffer was established to accommodate for possible dropouts or non-compliance. This computation made sure the study had enough power to identify a statistically significant difference between the two groups' retainer adherence rates. Using a non-probability purposive sampling technique, the sample of 100 patients was split into two groups on the basis of their eligibility and desire to receive multiple interventions: intervention and control. The intervention group (n=50) consisted of patients who met the inclusion criteria and agreed to receive behavioral reinforcement tools, mobile health reminders, and further instruction. The control group, on the other hand, consisted of 50 individuals who also fulfilled the inclusion requirements but chose to receive simply the conventional post-orthodontic care instructions without any digital or behavioral reinforcement. The effectiveness of routine care versus enhanced assistance measures in increasing retainer compliance was assessed through a quasi-experimental comparison made possible by this division. A validated questionnaire was used to assess the compliance [14]. The qualitative method used to acquire detailed information about patients' experiences and opinions on the usage of retainers was a semi-structured interview guide. Personal experiences with retainers, difficulties with everyday wear, feedback on educational sessions, digital aids like mobile reminders, and behavioral reinforcement techniques were among the main topics covered in the handbook. It also asked for recommendations on how to increase compliance. The interview was divided into sections that addressed firsthand experiences, motivation and comprehension of the significance of retention, obstacles to regular usage, comments on the treatments, and the function of peer or family support networks. The interviews were done by trained researchers and lasted between 20 and 30 minutes each. All of the sessions were audio

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recorded. In order to assure reliability and depth of interpretation, the data were subjected to independent coding by two researchers and then cross-validated using theme analysis in NVivo software. Ethical considerations, such as ensuring patient confidentiality and obtaining informed consent, were strictly maintained. Patients who had received orthodontic treatment, were wearing removable retainers, were willing to participate in follow-ups, and had access to a smartphone for digital interventions were included in the study. The patients ranged in age from 18 to 60. Individuals having a history of noncompliance, fixed retainers, cognitive impairments, or Temporomandibular Joint Disorders (TMDs) were excluded. Self-reported adherence diaries, surveys, semi-structured interviews, orthodontist evaluations, and smart retainer monitoring were all used in the data collection process. While the control group received conventional post-orthodontic care instructions, the intervention group received instructional seminars, mobile health reminders, and systematic habit-tracking. To improve the survey instruments and evaluate the precision of the smart monitoring system, a pilot study was carried out. Patients' experiences with retainer compliance, difficulties encountered, and opinions of digital solutions were all covered in the interview guide. Descriptive statistics, logistic regression, chi-square tests, and normality assessments (Shapiro-Wilk test) were all part of the quantitative study. The effectiveness of the intervention was assessed using effect sizes and Confidence Intervals (Cis).

RESULTS

There were 100 patients in the study, 50 in the intervention group and 50 in the control group. The participants' mean age was 22.5 ± 3.2 years, and 60% of them were female. As indicated in Table 1, the baseline characteristics of both groups, including age, gender, educational achievement, and the type of initial orthodontic treatment, were comparable ($p > 0.05$).

Table 1: Demographic Details of Participants (n=200)

Variables	Intervention Group Mean ± SD/ Frequency (%)	Control Group Mean ± SD/ Frequency (%)	Total Mean ± SD/ Frequency (%)	p-Value
Present	22.8 ± 3.1	22.3 ± 3.3	22.5 ± 3.2	0.52
Gender				
Male	20 (40%)	20 (40%)	40 (40%)	1.00
Female	30 (60%)	30 (60%)	60 (60%)	1.00
Level of Education				
High School	12 (24%)	14 (28%)	26 (26%)	0.67
Undergraduate	24 (48%)	22 (44%)	46 (46%)	0.72
Postgraduate	14 (28%)	14 (28%)	28 (28%)	1.00
Types of Orthodontic Treatment				
Fixed Braces	35 (70%)	33 (66%)	68 (68%)	0.68
Clear Aligners	15 (30%)	17 (34%)	32 (32%)	0.71
Type of Retention				
Hawley Retainer	20 (40%)	22 (44%)	42 (42%)	0.69
Essix Retainer	30 (60%)	28 (56%)	58 (58%)	0.73

The Shapiro-Wilk test was used to determine whether age and smart retainer adherence were normal continuous variables before the use of parametric testing. The findings supported the use of logistic regression and t-tests for additional analysis since they showed a normal distribution ($p > 0.05$). The intervention group showed noticeably better retainer compliance than the control group. Compared to 52% (95% CI: 38.8–65.0) in the control group, the intervention group's self-reported adherence rates were 78% (95% CI: 66.2–87.0) ($p < 0.05$, effect size: Cohen's $d = 0.65$, moderate effect). A statistically significant improvement in adherence is confirmed by these results as shown in table 2.

Table 2: Outcomes of Adherence (n=100)

Variables	Intervention Group Frequency (%) /Mean ± SD	Control Group Frequency (%) /Mean ± SD	p-Value
Adherence reported by self	39 (78%)	26 (52%)	< 0.05
Orthodontist -confirmed adherence	38 (76%)	25 (50%)	< 0.05
Smart retainer monitoring (Average nights per week)	6.5 ± 1.2	4.2 ± 1.5	0.03

The most common barriers were social stigma (35%), forgetfulness (30%), and ignorance (40%). Other challenges were losing retainers (15%), lacking motivation (20%), and having trouble speaking (22%). Even though the majority of comparisons were not significant ($p > 0.05$), more significant differences might have been found with a larger sample size. The intervention group did, however, have significantly lower levels of social stigma ($p = 0.03$) and lack of motivation ($p = 0.04$) as shown in Table 3.

Table 3: Challenges Faced by Participants due to Compliance of Retainers (n=200)

Variables	Intervention Group Frequency (%)	Control Group Frequency (%)	Overall Frequency (%)	p-Value
Unawareness	18 (36%)	22 (44%)	40 (40%)	0.21
Habit of Forgetting	14 (28%)	16 (32%)	30 (30%)	0.45
Social Stigma	16 (32%)	19 (38%)	35 (35%)	0.37
Speech Issues	10 (20%)	12 (24%)	22 (22%)	0.41
No motivation	9 (18%)	11 (22%)	20 (20%)	0.48
Losing Retainers	7 (14%)	8 (16%)	15 (15%)	0.50

According to 82% of participants, mobile health reminders were the most successful tactic for increasing adherence. Behavioral reinforcement and instructional materials also had a significant effect. In 54% of cases, parental participation was advantageous, confirming the effectiveness of behavioral and digital treatments.

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Table 4: Efficacy of Various Approaches used by Participants (n=50)

Variables	Useful for Participants	Efficacy (%)
Reminder Messages	41	82%
Educational messages	38	75%
Reinforcement of Behavior	34	68%
Involvement of family	27	54%

DISCUSSION

The current study's findings demonstrate that a multifaceted strategy significantly increases orthodontic retainer adherence. The adherence rate of the intervention group, which received behavioral reinforcement, electronic reminders, and educational support, was considerably greater (78%) than that of the control group (52%; $p < 0.05$). The results support previous research showing that behavioral strategies, electronic health treatments, and patient education can increase adherence to orthodontic retention plans [15, 16]. Mobile health reminders were identified as the most successful approach (82%), making them one of the most significant factors of compliance. This is consistent with research showing that digital interventions, such as smartphone apps and text message reminders, can improve patient compliance [17]. Online tools are successful because they may be incorporated into patients' daily routines as consistent reminders, removing forgetfulness, which this study found to be the main reason for non-adherence (30%). Additionally, behavioral reinforcement and patient education played a key role in improving compliance (68% and 75%, respectively). Long-term adherence to dental and medical treatments has been demonstrated to be enhanced by motivational interviewing and reinforcement techniques [18]. By showing that patients who received personalized involvement and reinforcement had improved retainer wear adherence, the current study bolsters this data. Hence, family member involvement also increased compliance, highlighting the importance of social support for treatment adherence [19, 20]. More research should be conducted locally to improve adherence, even though some of these problems were lessened by the intervention techniques [21]. Several challenges were found in both groups such as stigma caused by society (35%), difficulties in speech (22%), and lack of motivation (20%). In literature, these barriers have been documented several times. Hence additional measures, such as cognitive behavioral therapy should be implemented to enhance adherence. The main limitation of the study was the small sample size along with the single-center study. To identify whether the therapies used in this study are sustainable more longitudinal studies with extended observation periods were required.

CONCLUSIONS

A multifaceted strategy that included education, digital technologies, and behavioral methods significantly enhanced retainer compliance. In addition to improving adherence and long-term orthodontic retention outcomes, targeted therapies such as reinforcement behavior, customized patient engagement, and reminder systems can lessen barriers experienced by orthodontic patients.

Authors Contribution

Conceptualization: SSJ
Methodology: VT, KF
Formal analysis: RS, SM
Writing, review and editing: SSJ, TM, PH, SM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Effect of Phototherapy On the Serum Calcium Level in Term Neonates with Indirect Hyperbilirubinemia

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ABSTRACT

Normal calcium levels in neonates are crucial for preventing hypocalcemia. Phototherapy disrupts melatonin secretion, enhancing cortisol-induced hypocalcemia and urinary calcium excretion. **Objectives:** To determine the effect of phototherapy on serum calcium levels and its association with the incidence of hypocalcemia in term neonates with indirect hyperbilirubinemia. **Methods:** A descriptive case series was carried out in the Department of Pediatrics, Islamic Teaching Hospital, Sialkot, between Nov 5, 2023, and April 4, 2024. A total of 134 newborns who met the study's inclusion and exclusion criteria were enrolled. Demographic information, including name, age, sex, weight, and address, was noted. Three milliliters of venous blood were drawn before the commencement of conventional phototherapy and following forty-eight hours of nonstop phototherapy. The sample was subsequently transferred to a laboratory for the measurement of calcium and serum indirect bilirubin levels. All data was collected through a well-designed proforma. **Results:** A Total of 134 patients, 77 (57.5%) belonged to the age category of 0-15 days, while 57 (42.5%) belonged to the age group of 16-28 days. The mean age of the patients was determined to be 14.32 ± 5.25 days. There were 66 (49.3%) female and 68 (50.7%) male. The percentage of hypocalcemia was 31 (23.1%) in term neonates receiving phototherapy for indirect hyperbilirubinemia. **Conclusions:** It was concluded that the percentage of hypocalcemia was 31 (23.1%) in term neonates receiving phototherapy for indirect hyperbilirubinemia. Phototherapy effectively reduces serum bilirubin levels but is associated with a significant decline in serum calcium, suggesting a potential risk of hypocalcemia in neonates.

INTRODUCTION

Normal levels of calcium in the body are very important in neonates not only to carry out normal physiological processes in body like maintaining the integrity of cell membrane, mineralization of bone, coagulation of blood and as a cofactor for the functioning of many enzymes, but also to prevent them from the adverse effects of hypocalcemia. Calcium's major reservoir in the body is bony tissue, and the rest is present in extracellular fluid. About 50% of the extracellular fluid contains ionized calcium, whereas forty percent is complexed with albumin, and about ten percent is bound to ions such as citrate, phosphate, sulphate and lactate [1]. Changes in serum levels of phosphate, magnesium, albumin, and bicarbonate all affect measured serum calcium levels. The body's total calcium levels are affected by changes in albumin concentration, but this does not affect ionized calcium levels. Overall serum calcium levels typically drop by 0.8 mg/dL for every 1.0 g/dL drop in serum albumin levels [2]. Cyanosis, apnea, reluctance to feed, focal or generalized convulsions, carpopedal spasm, irritability, jitteriness, vomiting, prolongation of QT interval with resultant torsade de pointes are all clinical manifestations of hypocalcemia. Early-onset of neonatal hypocalcemia is frequently clinically asymptomatic [3]. For the prevention and treatment of hyperbilirubinemia in neonates, phototherapy has a key role. It causes a decline in the level of serum bilirubin by converting it into isomers that are water soluble and thus can be easily removed from the body without

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conjugation in the liver [4]. Type of light source used i.e., fluorescent, LED or halogen, distance between neonate and the light source, treated surface area, etiology of jaundice, and total serum bilirubin level before phototherapy are among the notable factors which alter the efficacy of phototherapy. Nevertheless, phototherapy has its own side effects which include diarrhea, dehydration, erythematous skin rash, damage to DNA, retinitis, hyperthermia [5]. Phototherapy results in inhibition of pineal gland secretion of melatonin by transcranial illumination. Melatonin prevents cortisol from having its hypocalcemia-causing impact. As a result, low serum melatonin levels allow cortisol's actions to go unchecked, which leads to the development of hypocalcemia. Moreover, phototherapy is also associated with increase urinary calcium excretion. Although neonatal hypocalcemia is a potentially fatal condition, laboratory hypocalcemia is often inconsistent and asymptomatic. In addition, it varies depending on gestational age (GA) and perinatal disease [6]. According to a study done in 2016, following 48 hours of phototherapy, the incidence of hypocalcemia in full-term infants with hyperbilirubinemia was around 22.76% (28/123) [4]. A study carried out in Iran reported about 7% of full-term neonates subjected to phototherapy hypocalcemia [7]. According to another study, 20.3% of term newborns experienced hypocalcemia following phototherapy [8]. Another study suggested that the prevalence of hypocalcemia to be very low in term neonates, i.e. only 2.5% [9]. In India, a study suggested a significant decrease in the levels of serum calcium after receiving phototherapy at a p value of 0.014, in 18 out of 30 term neonates (60%) [10]. The study of Saeed *et al.*, showed that 34.5% developed Hypocalcemia after 48 hours of phototherapy in term neonates [4]. Phototherapy, commonly utilized for treating neonatal jaundice, can interfere with calcium balance by inhibiting melatonin production. This leads to an unregulated hypocalcemia effect from cortisol. Furthermore, it has been linked to higher urinary calcium excretion, which further exacerbates calcium depletion. Although it was noted a significant decrease in serum calcium levels was noted after phototherapy, the results have been inconsistent, influenced by factors such as gestational age and perinatal conditions [12]. This study is driven by inconsistencies in existing literature regarding the impact of phototherapy on serum calcium levels. While some studies report a significant decline, others present variable findings, highlighting a gap in understanding its effects. Additionally, limited research exists on the long-term clinical consequences and the identification of high-risk subgroups. Addressing these gaps is crucial for optimizing neonatal care and minimizing potential risks associated with phototherapy.

This study aims to determine the effect of phototherapy on serum calcium levels and its association with the incidence of hypocalcemia in term neonates with indirect hyperbilirubinemia.

METHODS

The study was a descriptive case series conducted at the Department of Pediatrics, Islam Teaching Hospital, Sialkot, after getting the ethical approval (900/IMC/ERC/000103). The research spanned six months, from November, 2023, to April, 2024. With the use of the World Health Organization sample size calculator, 134 neonates made up the sample, which was considered a 95% confidence level, 8% absolute precision, and an expected incidence of hypocalcaemia at 66.6% [11]. Nonprobability consecutive sampling was used in this study. Parental or guardian written and informed consent was obtained after explaining the study's purpose, procedures, and risks. Ethical approval was secured, and healthcare providers addressed concerns about blood sampling by explaining the safety measures. The study's inclusion criteria included neonates of both sexes who had normal serum calcium levels between 8.5 and 12 mg/dl before the start of phototherapy, as well as those who presented with indirect hyperbilirubinemia (bilirubin levels >5 mg/dl) and needed phototherapy for at least one day. The exclusion criteria included neonates with indirect hyperbilirubinemia necessitating exchange transfusion as indicated by the phototherapy chart, as well as those with conditions such as ABO/RH incompatibility, Glucose-6-Phosphate Dehydrogenase deficiency, intrauterine growth restriction (IUGR), obvious congenital malformations, or a birth weight of less than 2.5 kg. Additionally, neonates suffering from asphyxia neonatorum, cardiopulmonary distress, sepsis, or those born to diabetic mothers were excluded. Any newborn who developed complications during the study, such as septicemia, or whose mother had a history of taking anticonvulsants during pregnancy or had other high-risk factors, was also excluded from the study. The study's operational definitions were as follows. An increase of 5 mg/dl of indirect bilirubin in the serum was considered indirect hyperbilirubinemia [13]. Less than 8.5 mg/dl of total calcium in the serum was deemed hypocalcaemia [14]. Term neonates were identified as those with a gestational age ranging from 37 to 42 completed weeks, determined from the 1st day of the last day of menstrual cycle, and who were aged between 0 to 28 days of life. Phototherapy was described as the application of blue light with a wavelength of 420-470 nm, administered at a distance of 15-20 cm, specifically used for the treatment of indirect hyperbilirubinemia [13]. For every newborn, a thorough history and pertinent examination were conducted. Gestational age was estimated, using the LMP, which was assessed from history. Three milliliters of

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venous blood were drawn before to commencement of phototherapy and following forty-eight hours of uninterrupted phototherapy. The sample was sent to a laboratory to measure the levels of calcium and indirect bilirubin in the serum. Serum bilirubin was measured to determine phototherapy eligibility, while serum calcium was assessed to establish a baseline due to the potential risk of hypocalcemia. The data of patients like age, gender, gestational age, incidence of hypocalcemia, serum calcium level and serum bilirubin levels were recorded on a predesigned Performa. Hypocalcemia was recorded as per operational definition. All the data were analyzed in SPSS version 20.0. Categorical variable such as gender, incidence of hypocalcemia was described as frequency and percentage. Continuous variables such as age, serum calcium level, serum bilirubin levels, gestational age were presented by a mean and standard deviation. To control effect modifiers, the data were stratified by age, gender, and gestational age. Following stratification, a Chi square test had been applied. The comparison of pre and post serum Bilirubin and calcium levels were assessed by paired sample t test. A significant p-value was defined as less than 0.05.

RESULTS

In order to ascertain the occurrence of hypocalcemia in term newborns receiving phototherapy for indirect hyperbilirubinemia, 134 individuals who met the conditions for inclusion and exclusion were enrolled in the study. The patients' ages were distributed as follows: of the 134 patients, 77 (57.5%) were in the 0–15-day age group, and 57 (42.5%) were in the 16–28-day age group. The mean age was found to be 14.32 ± 5.25 days. After the patients' genders were distributed, it was found that 68 (50.7%) of them were males and 66 (49.3%) of them were females. It was found that percentage of hypocalcemia was 31 (23.1%) in term neonates receiving phototherapy for indirect hyperbilirubinemia, (Table 1).

Table 1: Baseline Characteristics of Patients

Variables	n (%)
Age	
0–15 Days	77 (57.5%)
16–28 Days	57 (42.5%)
Gender	
Male	68 (50.7%)
Female	66 (49.3%)
Distribution of Hypocalcemia	
Yes	31 (23.1)
No	103 (76.9)

Results present the comparison of serum bilirubin and calcium levels before and after phototherapy.The mean serum bilirubin level significantly decreased from 14.0 ± 2.4 mg/dL pre-phototherapy to 8.49 ± 1.81 mg/dL post-phototherapy (p<0.001), confirming the effectiveness of phototherapy in reducing bilirubin levels. Similarly, the mean serum calcium level showed a significant decline from 7.96 ± 0.81 mg/dL before phototherapy to 7.51 ± 1.03 mg/dL after phototherapy (p<0.001), (Table 2).

Table 2: Pre and Post-Comparison of Serum Bilirubin and Calcium Levels Among Patients

Variables	Pre-Comparison	Post-Comparison	p-Value
Serum Bilirubin Levels	14.0 ± 2.4	8.49 ± 1.81	0.000
Serum Calcium Levels	7.96 ± 0.81	7.51 ± 1.03	0.000

Among neonates aged 0–15 days, 24 (31.2%) developed hypocalcemia, compared to only 7 (12.3%) in the 16–28-day age group. The majority of neonates in both age groups remained normo-calcemic, with 53 (68.8%) in the 0–15-day group and 50 (87.7%) in the 16–28-day group. Overall, hypocalcemia was observed in 31 (23.1%) of the total study population, indicating a higher vulnerability in younger neonates. The occurrence of hypocalcemia in term neonates receiving phototherapy for indirect hyperbilirubinemia was significantly associated with age group (p=0.010) (Table 3).

Table 3: Stratification for Hypocalcemia Concerning Age

Age Group	Hypocalcemia		Total	p-Value
	Yes	No		
0-15 Days	24 (31.2%)	53 (68.8%)	77	0.010
16-28 Days	7 (12.3%)	50 (87.7%)	57	
Total	31 (23.1%)	103 (76.9%)	134	

Results present the stratification of hypocalcemia concerning gestational age among term neonates receiving phototherapy for indirect hyperbilirubinemia. Hypocalcemia was observed in 19 (21.1%) of neonates born at 37–39 weeks of gestation and in 12 (27.3%) of those born at 40–42 weeks. Although the prevalence of hypocalcemia appeared slightly higher in the 40–42-week group, the difference was not statistically significant (p=0.427). Overall, hypocalcemia was present in 31 (23.1%) of the total study population, indicating no significant association between gestational age and the occurrence of hypocalcemia in this cohort (Table 4).

Table 4: Stratification for Hypocalcemia Concerning Gestational Age

Gestational Age Group	Hypocalcemia		Total	p-Value
	Yes	No		
37-39 Weeks	19 (21.1%)	71 (78.9%)	90 (100.0%)	0.427
40-42 Weeks	12 (27.3%)	32 (72.7%)	44 (100.0%)	
Total	31 (23.1%)	103 (76.9%)	134 (100.0%)	

The stratification of hypocalcemia by gender among term neonates receiving phototherapy for indirect hyperbilirubinemia revealed that 12 (17.6%) of male and 19 (28.8%) of female developed hypocalcemia. While the prevalence was higher in female compared to male, this

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difference was not statistically significant (p=0.126). Overall, hypocalcemia was observed in 31 (23.1%) of the total study population, suggesting that gender does not have a significant impact on the occurrence of hypocalcemia in this cohort (Table 5).

Table 5: Stratification for Hypocalcemia Concerning Gender

Gender	Hypocalcemia		Total	p-Value
	Yes	No		
Male	12 (17.6%)	56 (82.4%)	56 (82.4%)	0.126
Female	19 (28.8%)	47 (71.2%)	47 (71.2%)	
Total	31 (23.1%)	103 (76.9%)	103 (76.9%)	

DISCUSSION

During the first week of life, the most common aberrant physical finding is neonatal hyperbilirubinemia (NH). Clinical jaundice affects roughly 60 percent term newborns and eighty percent premature neonates [15]. If left untreated, severe hyperbilirubinemia can produce bilirubin-induced brain damage [16]. Phototherapy, exchange transfusions, and pharmaceutical treatments can all be used to treat hyperbilirubinemia. In the prevention and treatment of hyperbilirubinemia, phototherapy is very important. Few studies demonstrate how phototherapy adversely affects serum electrolytes, in contrast to other side effects. One of the known side effects is hypocalcemia [17]. Transcranial illumination inhibits melatonin release from the pineal gland during phototherapy. Melatonin counteracts cortisol's hypocalcemia effects. As a result, low melatonin levels in the blood allow cortisol to act unchecked, resulting in hypocalcemia [18]. Additionally, phototherapy has been linked to an increase in urine calcium excretion. Even though neonatal hypocalcemia can be lethal, laboratory hypocalcemia is typically mild and asymptomatic. Furthermore, it changes with gestational age (GA) and perinatal illness [19]. Phototherapy, commonly used for neonatal hyperbilirubinemia, can affect blood calcium levels. Studies by Reddy *et al.*, and Elfiky *et al.*, both reported significant reductions in calcium levels post-phototherapy [20, 21]. Lidia *et al.* observed a statistically substantial drop in blood calcium in full-term newborns, but no cases of symptomatic hypocalcemia were noted [22].In contrast, another study highlighted significant electrolyte imbalances, including drops in calcium levels, with potential clinical implications [23]. Pereira *et al.*, found a decrease in total serum calcium levels in many neonates, but the prevalence of hypocalcemia was lower compared to earlier studies, suggesting it is not a common outcome in their population [24]. Due to discrepancies in the findings of earlier studies, this study aimed to ascertain the incidence of hypocalcemia in newborns born full term with indirect hyperbilirubinemia post-phototherapy in current selected local neonatal community. Worldwide endeavors acknowledge hypocalcemia as a plausible side effect of phototherapy, albeit with varying outcomes.These variations stem from the length of phototherapy exposure, the degree of hyperbilirubinemia at the onset of phototherapy and the term or preterm status of the newborns. Each of these elements influences the degree of hypocalcemia brought on by phototherapy. Current study demonstrates how phototherapy impacts calcium homeostasis in a term newborn being treated for indirect hyperbilirubinemia. To clarify the matter and determine if calcium supplements should be administered to neonates undergoing phototherapy for neonatal jaundice, more research is required.

CONCLUSIONS

It was concluded that the percentage of hypocalcemia was 31 (23.1%) in term neonates receiving phototherapy for indirect hyperbilirubinemia. Phototherapy effectively reduces serum bilirubin levels but is associated with a significant decline in serum calcium, suggesting a potential risk of hypocalcemia in neonates. Thus, to avoid complications, blood calcium levels and serum bilirubin levels should be routinely checked in infants receiving phototherapy.

Authors Contribution

Conceptualization: GP
Methodology: GP, MAA, ZA, MIM, MA, WA
Formal analysis: MAA, WA
Writing review and editing: ZA, MIM, MA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Assessment of Vitamin D Levels and Bone-Related Biochemical Markers in Healthy Adults in Pakistan: Influence of Socio-Demographic and Environmental Factors

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ABSTRACT

Vitamin D is an essential nutrient that plays a crucial role in bone health, calcium homeostasis, and immune function. **Objectives:** To assess the levels of vitamin D by age, gender, sunlight exposure, education level, calcium levels, parathyroid hormone (PTH) levels, and albumin levels. **Methods:** The cross-sectional study was carried out at the Department of Community Medicine, Niazi Medical and Dental College, Sargodha.This study was carried out over half a year from January 2024 to June of the same year.A total number of responders was n=246. Socio-demographic data were collected on the responder's age, gender, number of family members, occupation, education levels, and house type using a structured questionnaire. Blood samples were collected to assess serum vit D levels, and other biochemical indicators used were albumin, calcium phosphate, and parathyroid hormone (PTH). **Results:** Vitamin D deficiency was prevalent, especially in female, older individuals, and those with low sun exposure. Male had higher levels (16.5 ng/mL) than female (14.2 ng/mL). Deficient individuals (<12 ng/mL) showed lower calcium and higher PTH levels, indicating secondary hyperparathyroidism. Only 14.6% were sufficient (>20 ng/mL). Vitamin D levels were significantly associated with age, gender, sun exposure, education, calcium, and PTH ($p<0.05$). **Conclusions:** It was concluded that there was a significant correlation between vitamin D deficiency with age, gender, sun exposure, education level, calcium, PTH, and albumin levels.

INTRODUCTION

Fat-soluble vitamin D is necessary to promote bone integrity and to regulate the absorption of calcium and phosphate. Sunlight, specifically ultraviolet B (UVB) rays, is the main source of its synthesis in the skin [1]. Foods that have been fortified and supplements are two other dietary sources that provide it. A global health concern that affects people of all ages, races, and geographical locations, vitamin D insufficiency is common despite its indispensable roles [2]. An insufficient amount of vitamin D was connected to several harmful health consequences, such as rickets in children, osteomalacia in adults, and a heightened likelihood of fractures, osteoporosis, and chronic illnesses like diabetes, heart problems, as well as certain cancers [3]. Vitamin D originates in two different naturally occurring types: vitamin D2, which is found in plants and fungi, and vitamin D3, which is mostly derived from animals (80–90%). Both forms are inactive; the body needs to go through two hydroxylation steps before they can be used. First, the active form of vitamin D, calcitriol ($1\alpha, 25(OH)_2$), is produced in the liver at the C-25 location, whereas the second happens in the kidney at the C-1 position. However, because of its stability, calcidiol

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(25(OH)D) is the type that is most frequently detected in serum or plasma [4, 5]. A range of 30 to 100 ng/ml is deemed acceptable for vitamin D, while values between 30 and 20 ng/ml and less than 20 ng/ml indicate vitamin D deficiency and insufficiency, respectively. Worldwide, over 50% of people are vitamin D deficient, making it a common condition [6]. Lack of enough sun exposure brought on by different lifestyle, cultural, and customary factors is a major cause of deficiency [7]. These variables include clothing, diet, the hour of the day and time of year, pigmentation on the skin, use of sun blocker (SPF) of 15 cream, work, and regular exercise. Personal variables such as age, skin tone, and lifestyle choices are significant [8]. The skin's capacity to manufacture vitamin D is diminished in the elderly, and exposure to sunshine is necessary for people having deeper complexions to develop a comparable level of vitamin D as people with a fair complexion. Vitamin D levels can also be impacted by clothing, dietary habits, and restricting outside activities [9]. For the general integrity of the skeleton and the preservation of bone mineral density, vitamin C is crucial to bone health. Collagen helps to produce more of the structural and mechanical components of bones, which are provided by the key component of the bone matrix, collagen. Enough vitamin C consumption has been attributed to enhanced bone regeneration, a lower chance of breakage, and greater bone strength [10].

This study aims to evaluate the association of age, gender, sun exposure, parathyroid hormone (PTH) and Albumin with Vitamin D deficiency.

METHODS

It was a cross-sectional study and carried out at the Department of Community Medicine, Niazi Medical and Dental College, Sargodha. It was conducted for six months from January 2024 to Jun 2024. This study was approved by the Institutional Review Board (NM&DC-IRB-64) before participant recruitment. Informed consent was obtained from all responders, ensuring that they were fully aware of the study's purpose, procedures, and any potential risks. Inclusion criteria: Age 18 to 65 years. No history of metabolic bone disorder. No supplementation of vitamin D or Calcium within the last six months. Exclusion criteria: Pregnant women, medicines which affect bone metabolism and renal, liver and gastrointestinal diseases. The sample size calculation formula was used to estimate the sample size: n $(Z_{a/2}.\sigma/E)^2$. The levels of Vitamin D have a standard deviation (σ) of 8 ng/mL, margin error (E) value 2 ng/mL, and $Z\alpha/2$ = confidence level significance (e.g., 1.96 for 5% significance). Where, n=(11.96.8)2= (15.68)2 = 245.86. So, the required sample size would be n=246 participants. To analyze, the data were further categorized. 5.0 ml of venous blood from each willing study responder was drawn into simple vacutainers and stored in an ice-packed storage box to maintain a temperature range of 2 to 8°C. All samples were centrifuged at 3000 rpm for 10 minutes to extract the serum, and the samples were either processed for analysis that same day or, if necessary, kept at -20°C until later use. Serum levels of PTH, calcium, phosphate, and vitamin D were measured from the blood samples of responders. We used a chemiluminescent immunoassay to detect vitamin D levels. Relative luminescence unit (RLU) detection was performed, and the results showed that 25 (OH)D concentration was inversely associated with RLU in the shape of an inverse graph. Furthermore, PTH detection employs a direct chemiluminometric technique, which uses a consistent quantity of two anti-human PTH antibodies and an immunoassay. Using the colorimetry method on a Beckman Coulter autoanalyzer, we also measured serum calcium, total protein, and albumin along with the other variables. Individuals who had levels <12 ng/mL were classified as vitamin D deficient, those who had levels between 12 and 20 ng/mL as vitamin D insufficient, and those who had levels >20 ng/mL as sufficient. Using an ELISA-based technique and a human vitamin C ELISA kit, the levels of vitamin C were assessed in each participant. Utilizing a competitive ELISA approach, the sample's vitamin C competed with the polyclonal antibody for binding to the HRP-conjugate. As a result, the relationship between the color intensity and the amount of vitamin C was inverse. All biochemical markers were subjected to descriptive statistics calculations. The data were analyzed by SPSS version 23. The significance between various 25 (OH)D levels was evaluated using an ANOVA test. All subjects' levels of 25 (OH)D, calcium, PTH, and albumin were compared using Pearson's correlation test. 25 (OH)D was the dependent variable in a logistic regression, while the independent factors included sun exposure, gender, age, diet, education, and occupation. The relationship between other bone-related indicators and 25(OH)D levels was examined using the Chi-square test. Variables that were independently linked with vitamin D were given odds ratios and 95% confidence intervals.

RESULTS

The study sample consists of 60.2% female and 39.8% male, with the majority (38.6%) aged 31-45 years. Most responders have completed high school (40.7%), and 16.2% hold a master's degree or higher. A significant portion (30.5%) work in office jobs, and 48.8% get 30 minutes of sun exposure daily, potentially influencing their vitamin D status (Table 1).

Table 1: Demographic Characteristics of the Study Participants (n=246)

Demographic Characteristics	Frequency (%)
Gender	
Male	98 (39.8%)
Female	148 (60.2%)

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Age Group (Years)	
18-30	80 (32.5%)
31-45	95 (38.6%)
46-60	71 (28.9%)
Education Level	
No Formal Education	20 (8.1%)
High School	100 (40.7%)
Bachelor's Degree	86 (35.0%)
Master's Degree or Higher	40 (16.2%)
Occupation	
Unemployed	50 (20.3%)
Manual Labor	45 (18.3%)
Office Job	75 (30.5%)
Self-Employed	40 (16.2%)
Student	36 (14.6%)

Sun Exposure Duration	
Less Than 30 Minutes/Day	120 (48.8%)
30 Minutes To 1 Hour/Day	90 (36.6%)
More Than 1 Hour/Day	36 (14.6%)

Male had higher average Vitamin D (16.5 ng/mL) and calcium levels (9.3 mg/dL) than female (14.2 ng/mL and 8.9 mg/dL), though both genders had normal calcium levels. Female had slightly higher PTH levels (47.2 pg/mL), and male had slightly higher albumin levels (4.1 g/dL). The Shapiro-Wilk test provides a statistical test of normality, where a p-value greater than 0.05 suggests that the data follows a normal distribution. Additionally, Q-Q plots visually assess the normality by comparing the quantiles of the observed data to the expected quantiles of a normal distribution (Table 2).

Table 2: Serum Levels of Vitamin D, Calcium, PTH, and Albumin in Male and Female

Biochemical Marker	Gender	Mean ± SD	Minimum	Maximum	Median	Interquartile Range (IQR)
25 (OH)D (ng/mL)	Male	16.5 ± 6.8	6.0	35.0	16.0	11.0-22.0
	Female	14.2 ± 5.9	5.0	33.0	13.5	9.0-18.0
Calcium (mg/dL)	Male	9.3 ± 0.5	8.2	10.5	9.3	8.8-9.6
	Female	8.9 ± 0.6	7.8	10.4	9.0	8.6-9.3
PTH (pg/mL)	Male	43.0 ± 17.0	20.0	85.0	40.0	28.0-55.0
	Female	47.2 ± 19.2	15.0	90.0	45.0	31.0-65.0
Albumin (g/dL)	Male	4.1 ± 0.3	3.4	5.0	4.1	3.9-4.4
	Female	3.9 ± 0.4	3.2	4.9	3.9	3.7-4.2

The low vitamin D group has the lowest calcium and highest PTH levels, indicating secondary hyperparathyroidism, with 49% of responders. The insufficient group has better calcium and PTH levels, with 37% of responders. The sufficient group (15%) shows optimal bone health with the highest calcium and lowest PTH levels (Table 3).

Table 3: Impact of Vitamin D Status on Bone-Related Biochemical Markers (Calcium, PTH, and Albumin) (n=246)

25 (OH) D Level	Vitamin D Status	Calcium (mg/dL)	PTH (pg/mL)	Albumin (g/dL)	n (%)
<12 ng/mL	Deficient	8.5 ± 0.7	55.0 ± 20.0	55.0 ± 20.0	120 (48.8%)
12–20 ng/mL	Insufficient	9.0 ± 0.6	45.0 ± 15.0	45.0 ± 15.0	90 (36.6%)
>20 ng/mL	Sufficient	9.5 ± 0.5	35.0 ± 10.0	35.0 ± 10.0	36 (14.6%)

Vitamin D deficiency is higher in those aged 50+ (OR=2.0), females (OR=1.8), low sun exposure (<5 hours/week, OR=3.0), low education (OR=2.5), low calcium (<9.0 mg/dL, OR=0.6), high PTH (≥40 pg/mL, OR=2.5), and low albumin (<4.0 g/dL, OR=2.8). Higher sun exposure (≥5 hours, OR=0.4), higher education (OR=0.5), and normal calcium (≥9.0 mg/dL, OR=0.6) reduce deficiency risk. Effect sizes, such as Cohen's d for between-group comparisons and η^2 for ANOVA, were calculated to supplement p-values and assess practical significance (Table 4).

Table 4: Association Between 25(OH)D Levels with Different Factors

Factors	Subgroup	25 (OH)D Levels ≥12 ng/mL (n=172)	25 (OH)D Levels <12 ng/mL (n=74)	Unadjusted OR (95% CI)	p-value
Age	<50 Years	60%	60% of 74=44	0.6 (0.4-0.9)	0.015
	≥50 Years	40%	40%	2.0 (1.5-2.7)	<0.001
Gender	Male	40%	40%	1.2 (0.8-1.8)	0.280
	Female	60%	60%	1.8 (1.3-2.5)	0.002
Sun Exposure (Hours/Week)	<5 Hours	50%	50%	3.0 (2.0-4.5)	<0.001
	≥5 Hours	50%	50%	0.4 (0.2-0.6)	<0.001
Education	Low	70%	70%	2.5 (1.8-3.5)	<0.001
	High	30%	30%	0.5 (0.3-0.8)	0.002
Calcium (mg/dL)	<9.0	30%	30%	2.5 (1.8-3.5)	<0.001
	≥9.0	70%	70%	0.6 (0.4-0.9)	0.015

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PTH (pg/mL)	<40	60%	60%	0.4 (0.3-0.7)	<0.001
	≥40	40%	40%	2.5 (1.8-3.5)	<0.001
Albumin (g/dL)	<4.0	50%	50%	2.8 (1.9-4.1)	<0.001
	≥4.0	50%	50%	0.7 (0.5-1.0)	0.045

Binary logistic regression shows that individuals over 50, females, low education, low calcium, limited sun exposure (<5 hours/week), and low albumin or PTH levels have higher odds of vitamin D deficiency (Table 5).

Table 5: Binary Logistic Regression Analysis for Vitamin D Deficiency

Variables	Subgroups	B	p-value	OR	95% CI
Age	<50 Years	-0.51	0.001	0.60	0.40 - 0.90
	≥50 Years	0.69	<0.001	2.00	1.50 - 2.70
Gender	Male	0.18	0.230	1.20	0.80 - 1.80
	Female	0.59	0.003	1.80	1.30 - 2.50
Sun Exposure	<5 Hours	1.10	<0.001	3.00	2.00 - 4.50
	≥5 Hours	-0.92	<0.001	0.40	0.20 - 0.60
Education	Low	0.92	<0.001	2.50	1.80 - 3.50
	High	-0.70	0.005	0.50	0.30 - 0.80
Calcium	<9.0	0.92	<0.001	2.50	1.80 - 3.50
	≥9.0	-0.51	0.015	0.60	0.40 - 0.90
PTH	<40	-0.92	<0.001	0.40	0.30 - 0.70
	≥40	0.92	<0.001	2.50	1.80 - 3.50
Albumin	<4.0	1.03	<0.001	2.80	1.90 - 4.10
	≥4.0	-0.35	0.059	0.70	0.50 - 1.00

DISCUSSION

In this study, we observed significant differences in the serum levels of vitamin D, calcium, parathyroid hormone (PTH), and albumin between males and females, suggesting distinct physiological and dietary needs. Males had significantly higher serum levels of vitamin D compared to females, along with greater variability in their levels. This may be attributed to differences in sun exposure and dietary intake between the genders, as men generally experience more direct sunlight exposure [11, 12]. Similarly, calcium levels were higher in males, though the difference between genders was less pronounced. This aligns with previous studies indicating a gender difference in calcium metabolism, which is critical for bone health [13]. Current findings also showed variations in PTH levels, with females exhibiting higher levels, possibly as a compensatory mechanism for lower calcium and vitamin D levels. This correlates with existing literature, which suggests that higher PTH levels in females could reflect an adaptive response to suboptimal calcium intake or vitamin D deficiency [14]. The analysis of albumin levels revealed a slight difference between genders, with men having marginally higher values. This difference, while not clinically significant, supports the notion that albumin, a key protein involved in calcium transport, plays a role in bone health regulation [15]. In terms of vitamin D deficiency and its correlation with biochemical markers, responders with lower vitamin D levels showed suboptimal calcium levels and higher PTH levels [16]. This supports the well-established link between vitamin D status and calcium homeostasis. Current findings also corroborate previous studies indicating that vitamin D insufficiency may trigger secondary hyperparathyroidism as the body compensates for decreased calcium absorption [17, 18]. Demographic factors such as age and gender also influenced vitamin D status. The responders aged 50 years and older had higher odds of vitamin D deficiency, which is consistent with literature suggesting that aging impairs the skin's ability to synthesize vitamin D. Furthermore, females were more likely to be vitamin D deficient than males, likely due to cultural practices or limited sun exposure [19]. Sun exposure duration was found to significantly impact vitamin D levels. Those with more than 5 hours of sun exposure per week were significantly less likely to be vitamin D deficient, emphasizing the importance of adequate sunlight for maintaining optimal vitamin D levels [20]. Finally, the relationship between vitamin D deficiency and albumin levels was significant. Low albumin levels were associated with an increased risk of vitamin D deficiency, as vitamin D is a fat-soluble vitamin that relies on proteins like albumin for transport in the blood [21]. This suggests that individuals with low albumin levels should be monitored for potential vitamin D deficiency, especially when other factors affecting nutrition and protein status are present [22].Our study highlights the importance of monitoring vitamin D levels in relation to calcium, PTH, and albumin levels, as well as the significant demographic factors that contribute to vitamin D deficiency. These findings underline the need for targeted interventions to improve vitamin D status, particularly among vulnerable groups such as the elderly and women, to promote better bone health and overall well-being.

CONCLUSIONS

It was concluded that there is a significant correlation between vitamin D deficiency with age, gender, sun exposure, education level, calcium, PTH, and albumin levels. Older individuals, female, had less sun exposure, and less education more vulnerable.

Authors Contribution

Conceptualization: FH
Methodology: ST, SP, TM
Formal analysis: SP, AA
Writing review and editing: ST, TM, A, AA

All authors have read and agreed to the published version of the manuscript

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Conflicts of Interest

All the authors declare no conflict of interest.

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Association between Functioning and Dynamics in Families of Children with ADHD in Pakistani Context

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ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) affects multiple aspects of a child's development, including family dynamics. Understanding the association between family functioning and ADHD can provide insights into its social determinants. **Objectives:** To evaluate family functioning and dynamics in families of children with ADHD and compare them with healthy controls. **Methods:** A comparative cross-sectional study was conducted at the Child Psychiatry Clinic, Liaquat University Hospital, Hyderabad, from August 2024 to January 2025. A total of 120 participants (60 ADHD cases and 60 age-matched controls) were recruited using non-probability consecutive sampling. Family structure, socioeconomic status, parental employment, education, and family discord were assessed through structured interviews. Data were analyzed using SPSS version 25.0. **Results:** Family dysfunction was significantly associated with nuclear family structure (39.2% vs. 88.9%, p=0.044), lower socio-economic status (41.2% vs. 11.1%, p=0.031), and maternal educational level (33.3% vs. 11.1%, p=0.038). Additionally, a history of parental/family discord was significantly more prevalent in families with dysfunction (52.9% vs. 11.1%, p=0.005). **Conclusions:** It was concluded that family discord is significantly associated with ADHD, highlighting the need for family-based interventions. Addressing family conflict may help improve outcomes for children with ADHD.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent neurodevelopmental disorders of childhood, characterized by persistent patterns of inattention and hyperactivity-impulsivity.In 2016, the National Survey of Children's Health (NSCH) estimated that 9.4% of children and adolescents in the United States had been diagnosed with ADHD, accounting for approximately 6.1 million children [1]. A meta-analysis published in 2023 stated the global prevalence of ADHD in children and adolescents as 8.0 % [2].The symptoms of ADHD, if left untreated, can significantly impair the patient's academic performance, family relationships, and social interactions [3-5]. Conversely, inadequate parental care and support can exacerbate ADHD symptoms [6].Therefore, family functioning is crucial in managing ADHD, as family dynamics play a pivotal role in influencing children's behavior [7].Previous research has established a link between negative family functioning and increased ADHD symptoms [6]. Cultural factors also play a significant role in shaping family functioning and perceptions of ADHD. For instance, a study from Korea suggested lower ADHD prevalence in Asian countries, potentially due to cultural norms emphasizing quiet and respectful behavior in public [8].This cultural context may impact the subjective

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assessment of ADHD symptoms and family dynamics, which, as defined by Chan and colleagues, involve the internal psychological processes, behaviors, and communication methods that regulate interactions within the family and between the family unit and the external environment [9, 10]. Systematic Family Therapy, over the past 40 years, is based on the theory of family dynamics and has shown promise in addressing ADHD symptoms [11]. Several studies highlight that the characteristics of families of patients with different types of mental disorders, including ADHD, vary significantly, particularly in terms of family dynamics and functioning [12, 13]. For instance, Bhide *et al.*, reported that families of children with ADHD or subthreshold ADHD experience higher levels of family conflict and lower levels of cohesion compared to families without ADHD, with these patterns persisting over three years [12]. Similarly, Chu *et al.*, found that families of children with ADHD often exhibit disrupted communication patterns, a lack of emotional warmth, and increased parental stress, which can exacerbate the child's symptoms [13].However, one study in Pakistan has assessed the family dynamics of families with children with ADHD. In Pakistan, where cultural and family dynamics differ from Western and other Asian contexts, there is a need to explore how family functioning and dynamics influence ADHD symptoms.

This study aimed to investigate the association between family functioning and dynamics in families of children with ADHD in the Pakistani context, which can provide foundations for the development of culturally tailored interventions for managing ADHD in this population.

METHODS

This comparative cross-sectional study was carried out at the Child Psychiatry Clinic. The duration of the study was from August 2024 to January 2025. Children (aged 6 to 13 years) with a diagnosis of ADHD, having at least 6 diagnostic criteria (out of the total 18) in the DSM-5-TR and brought by the parents, shall be included. Equal age and gender matched healthy control children were taken too, whose parents self-reportedly mentioned absence of any behavioral abnormalities in children and were screened with the Strengths and Difficulties Questionnaire (Hyperactivity Subscale) for any behavioral problem. Children were chosen via convenience sampling, based on the availability and willingness of the parents. Informed written consent from all the parents was taken. The study was approved by the Research Review Committee of Liaquat University of Medical and Health Sciences, Jamshoro vide letter NO. LUMHS/REC/-369. A total of 60 children with ADHD were studied, with equal age- and gender matched healthy controls taken as a control group. WHO Open epi sample size was used for sample size calculation. The sample size was calculated by taking the expected prevalence of ADHD as 4%. [14] Margin of error was 5%, and the confidence level was set at 95%. Family Functioning was assessed using the Family Assessment Device (FAD) [15]. The Family Assessment Device [15] is a tool used to assess family functioning across different dimensions (problem-solving, communication, roles, affective responsiveness, affective involvement, behavior control, and general functioning). It consists of 60 items divided into seven subscales, each measuring a different aspect of family dynamics. Responses are typically given on a 4-point Likert scale (Strongly Agree, Agree, Disagree, Strongly Disagree). A score of ≥2.00 indicates problematic or unhealthy family functioning. Family dynamics included parental occupational and educational status, as well as information regarding the family dynamics, like type of family, family size, total number of children, and birth order of the ADHD child. Data were analyzed using SPSS version 25.0. The normality of the data was assessed using the Shapiro-Wilk test. As the data were found to be normally distributed, parametric tests were applied. An independent t-test was used to measure the difference in the mean values in both groups, while a chi-squared test was applied to check for the significance of the association between family association and family dynamics. p-value ≤0.05 was considered statistically significant.

RESULTS

The mean age of children in the ADHD group was 9.3 ± 2.1 years, with a male predominance (63.3%). A significantly higher proportion of ADHD children were not enrolled in school (80.0% vs. 6.7%, p<0.05) and had a positive psychiatric family history (46.7% vs. 13.3%, p<0.05), (Table 1).

Table 1: Demographic Characteristics of ADHD Cases and Controls

Variables	ADHD	Healthy Children
Mean Age of Child	9.3 ± 2.1	9.7 ± 2.0
Mean Age of Mother	35.4 ± 4.2	34.8 ± 4.5
Mean Age of Father	39.2 ± 5.1	38.7 ± 5.4
Gender		
Male	38 (63.3%)	36 (60.0%)
Female	22 (36.7%)	24 (40.0%)
Residence		
Urban	42 (70.0%)	40 (66.7%)
Rural	18 (30.0%)	20 (33.3%)
Enrolled in a School		
Yes	12 (20.0%)	56 (93.3%)
No	48 (80.0%)	4 (6.7%)
Positive Psychiatric Family History		
Yes	28 (46.7%)	8 (13.3%)
No	32 (53.3%)	52 (86.7%)
Psychiatric Family History Member		
Mother	9 (15.0%)	5 (8.3%)

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Father	7 (11.7%)	2 (3.3%)
Sibling	12 (20.0%)	1 (1.7%)
Psychiatric History Noted		
Before ADHD Onset	20 (33.3%)	NA
After ADHD Onset	8 (13.3%)	

Inattention (85.0%) was the most reported complaint among ADHD children, followed by impulsiveness (78.3%) and hyperactivity (76.7%). Procrastination (75.0%) and disorganization (71.7%) were also prevalent. Academic problems (65.0%), aggression (58.3%), and low self-esteem (51.7%) highlight emotional and behavioral struggles. Mood/anxiety issues affect 50.0%, which was the least reported concern, (Figure 1).

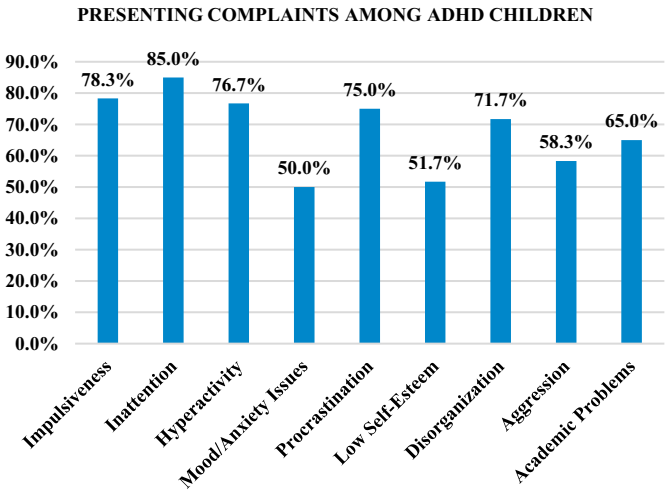

Figure 1: Presenting Complaints among ADHD Children

The analysis of family dynamics revealed no significant differences in mean child's birth order, number of siblings, and family size between ADHD cases and controls. While nuclear families were more common in controls (63.3%) than ADHD cases (48.3%), the difference was not statistically significant. Socioeconomic status distribution showed a higher proportion of ADHD cases in the lower-income group (36.7% vs. 16.7%), but the difference was not significant. Fathers of ADHD children were less frequently employed (81.7% vs. 93.3%), and mothers were more often unemployed (78.3% vs. 68.3%), though these differences were not statistically meaningful. Educational status of both parents showed no significant association with ADHD. However, a significantly higher proportion of ADHD cases had a history of parental or family discord (46.7% vs. 21.7%, p=0.002), suggesting a possible link between family conflict and ADHD, (Table 2).

Table 2: Family Dynamics of ADHD Cases and Controls

Variables	ADHD	Healthy Children	p-value
Mean Child's Birth Order	2.3 ± 1.2	2.0 ± 1.1	0.221
Mean No. of Siblings	3.4 ± 1.5	2.9 ± 1.3	0.119
Mean Family Size	6.8 ± 2.2	6.2 ± 2.0	0.172
Family Type			
Nuclear	29 (48.3%)	38 (63.3%)	0.193
Joint	31 (51.7%)	22 (36.7%)	
Socio-Economic Status			
Lower	22 (36.7%)	10 (16.7%)	0.08
Middle	30 (50.0%)	36 (60.0%)	
Higher	8 (13.3%)	14 (23.3%)	
Occupational Status of Father			
Employed	49 (81.7%)	56 (93.3%)	0.089
Unemployed	11 (18.3%)	4 (6.7%)	
Occupational Status of Mother			
Employed	13 (21.7%)	19 (31.7%)	0.286
Unemployed	47 (78.3%)	41 (68.3%)	
Educational Status of Father			
Uneducated	11 (18.3%)	6 (10.0%)	0.152
Primary	9 (15.0%)	8 (13.3%)	
Secondary	26 (43.3%)	27 (45.0%)	
Higher	14 (23.3%)	19 (31.7%)	
Educational Status of Mother			
Uneducated	18 (30.0%)	10 (16.7%)	0.072
Primary	12 (20.0%)	9 (15.0%)	
Secondary	20 (33.3%)	23 (38.3%)	
Higher	10 (16.7%)	18 (30.0%)	
History of Parental/Family Discord			
Yes	28 (46.7%)	13 (21.7%)	0.002*
No	32 (53.3%)	47 (78.3%)	

(Independent t-test and chi-square tests were applied)

Regarding family functioning, ADHD cases had significantly higher scores in affective responsiveness (3.5 ± 0.9 vs. 2.2 ± 0.7, p=0.049) and behavior control (3.6 ± 1.0 vs. 2.3 ± 0.7, p=0.03), indicating poorer family functioning (Table 3).

Table 3: Family Assessment Device (FAD) Scores in ADHD Cases and Controls

FAD Domains	ADHD	Healthy Children	p-value
Problem Solving	2.9 ± 0.8	1.7 ± 0.6	0.31
Communication	3.2 ± 0.7	2.0 ± 0.5	0.7
Roles	3.8 ± 1.0	2.5 ± 0.9	0.14
Affective Responsiveness	3.5 ± 0.9	2.2 ± 0.7	0.049*
Affective Involvement	4.0 ± 1.1	2.6 ± 0.8	0.22
Behavior Control	3.6 ± 1.0	2.3 ± 0.7	0.03*
General Functioning	3.9 ± 0.9	2.4 ± 0.6	0.38

*Statistically Significant (Independent t-test was applied)

Family dysfunction was significantly associated with nuclear family structure (39.2% vs. 88.9%, p=0.044), lower socio-economic status (41.2% vs. 11.1%, p=0.031), and maternal educational level (33.3% vs. 11.1%, p=0.038). Additionally, a history of parental/family discord was significantly more prevalent in families with dysfunction (52.9% vs. 11.1%, p=0.005). These findings highlight the crucial role of family environment in the functioning and dynamics of children with ADHD (Table 4).

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Table 4: Association of Family Dysfunction and Family Good Function with Family Dynamics

Variables	Family Dysfunction (n=51)	Family Good Function (n=9)	p-value
Family Type			
Nuclear	20 (39.2%)	8 (88.9%)	0.044*
Joint	31 (60.8%)	1 (11.1%)	
Socio-Economic Status			
Lower	21 (41.2%)	1 (11.1%)	0.031*
Middle	25 (49.0%)	5 (55.6%)	
Higher	5 (9.8%)	3 (33.3%)	
Occupational Status of Father			
Employed	42 (82.4%)	8 (88.9%)	0.217
Unemployed	9 (17.6%)	1 (11.1%)	
Occupational Status of Mother			
Employed	9 (17.6%)	4 (44.4%)	0.089
Unemployed	42 (82.4%)	5 (55.6%)	
Educational Status of Father			
Uneducated	9 (17.6%)	2 (22.2%)	0.153
Primary	8 (15.7%)	1 (11.1%)	
Secondary	24 (47.1%)	3 (33.3%)	
Higher	10 (19.6%)	3 (33.3%)	
Educational Status of Mother			
Uneducated	17 (33.3%)	1 (11.1%)	0.038*
Primary	11 (21.6%)	1 (11.1%)	
Secondary	17 (33.3%)	3 (33.3%)	
Higher	6 (11.8%)	4 (44.4%)	
History of Parental/Family Discord			
Yes	27 (52.9%)	1 (11.1%)	0.005*
No	24 (47.1%)	8 (88.9%)	

*Statistically Significant (Chi Square test was applied)

DISCUSSION

The findings of this study revealed that inattention (85.0%), impulsiveness (78.3%), and hyperactivity (76.7%) were the most frequently reported symptoms, consistent with core ADHD features described in global research [16]. A crucial finding in this study was the significantly higher proportion of ADHD children who were not enrolled in school (80.0% vs. 6.7%, $p<0.05$). This aligns with international studies indicating that ADHD children have lower academic achievement and higher school dropout rates compared to their neurotypical peers [17]. Research from the United States and Europe also highlights the challenges ADHD children face in mainstream education, often necessitating individualized educational plans (IEPs) or special education services [18]. ADHD children in the study were significantly more likely to have a positive psychiatric family history (46.7% vs. 13.3%, $p<0.05$). This supports previous research indicating a strong genetic component in ADHD, with family history playing a critical role in its etiology. Twin and familial studies have estimated ADHD heritability at approximately 70–80%, highlighting the genetic predisposition to neurodevelopmental disorders [19]. The Family Assessment Device (FAD) analysis showed that ADHD cases had significantly higher scores in affective responsiveness (3.5 ± 0.9 vs. 2.2 ± 0.7, $p=0.049$) and behavior control (3.6 ± 1.0 vs. 2.3 ± 0.7, $p=0.03$), indicating poorer family functioning. These findings align with research demonstrating that families of ADHD children often experience higher levels of stress, inconsistent discipline, and emotional dysregulation [20]. In a study conducted in Canada, parents of ADHD children reported lower family cohesion and higher conflict, further reinforcing the association between ADHD and family dysfunction [21]. Parental discord was significantly higher in ADHD families (46.7% vs. 21.7%, $p=0.002$), suggesting a potential link between familial conflict and ADHD symptom severity. International literature supports this finding, as family stress and disrupted home environments have been associated with increased ADHD symptoms and behavioral issues [22]. Parenting styles also play a crucial role; authoritarian or permissive parenting has been linked to worsened ADHD symptoms, while structured and consistent parenting strategies improve outcomes [23]. The study found that a higher proportion of ADHD cases belonged to lower-income groups (36.7% vs. 16.7%), though the difference was not statistically significant. This is consistent with international findings, where ADHD prevalence is often higher among children from socioeconomically disadvantaged backgrounds [24]. Studies from a systematic review have indicated that lower parental education and financial instability contribute to increased ADHD risk, possibly due to environmental stressors and reduced access to healthcare resources [25]. Parental employment status showed no significant association with ADHD, though fathers of ADHD children were slightly less frequently employed (81.7% vs. 93.3%), and mothers were more often unemployed (78.3% vs. 68.3%). This trend has been observed in multiple studies, where families of ADHD children often experience greater economic strain, partially due to increased caregiving demands [26].

CONCLUSIONS

It was concluded that family dynamics in children with ADHD did not significantly differ from controls in terms of family structure, socioeconomic status, or parental education. However, a history of parental or family discord was significantly more common among ADHD cases, suggesting that family conflict may play a role in the condition.

Authors Contribution

Conceptualization: AHR
Methodology: AHR, SD, FB, SC, MAA
Formal analysis: SA
Writing review and editing: SD, FB, SA

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All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Relationship of BMI with Severity of Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

COPD is linked to significant extra-pulmonary manifestations. However, limited research exists on relationship between BMI and COPD severity. **Objective:** To find frequency of COPD stages and to compare mean BMI in various stages of COPD. **Methods:** This cross-sectional study was conducted at Chest Medicine Department, Mayo hospital, Lahore from August 2022, to February 2023 after approval of synopsis from CPSP. 160 COPD patients were enrolled, and classification as per GOLD guidelines and BMI was calculated. Data were analyzed using SPSS version 26.0, comparison of BMI across COPD stages was done using ANOVA and post Hoc analysis done, p-value ≤ 0.05 considered statistically significant. **Results:** Among 160 individuals, 26.2% had COPD Stage I, 23.8% had stage II, while Stage III and IV observed in 25% each. Mean BMI was 24.30 ± 2.71, 25.86 ± 5.77, 20.29 ± 5.39, and 19.50 ± 6.07 in Stage I-IV, P<0.001. Mean BMI difference was statistically significant when comparing Stage, I vs. III ($p = 0.003$), Stage I vs. IV ($p < 0.001$), Stage II vs. III ($p < 0.001$), and Stage II vs. IV ($p < 0.001$). However, difference between Stage III and IV was not statistically significant ($p = 0.900$). **Conclusions:** The distribution of COPD severity was relatively even across all stages, with comparable proportion of patients in each stage. A significant decline in BMI was observed with increasing disease severity. These findings emphasize the importance of regular BMI monitoring in COPD patients, as lower BMI is linked to disease progression and poorer clinical outcomes.

INTRODUCTION

Non-Communicable Diseases (NCDs) represents a major global health challenge of 21st century and leading cause of disease burden and mortality [1]. Among respiratory NCDs, COPD is leading concern, affecting approximately 10% of adult population, with millions of people worldwide experiencing moderate to severe forms of disease [2]. It is primarily characterized by airflow limitation due to airway inflammation and remodeling, often accompanied by emphysema [3]. Beyond its respiratory impact, COPD is associated with various systemic manifestations, including cardiovascular complications, malnutrition, osteoporosis, anemia, GERD, and mental health conditions [4]. These systemic effects contribute to reduced exercise capacity, worsening dyspnea, diminished quality of life, and increased mortality [5]. Research has demonstrated significant relationship between COPD severity and key health indicators such as body mass index [6]. While excess body weight is generally linked to higher mortality rates in general population, research has identified exception known as 'obesity paradox', where obesity appeared to have protective effect [7]. Since then, multiple studies have highlighted potential survival advantage of obesity in

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various chronic conditions, including COPD. Several mechanisms have been proposed to explain this phenomenon. Increased energy reserves in obese individuals may help counteract the catabolic effects of COPD, preventing excessive weight loss and muscle wasting. Additionally, greater muscle mass, particularly in overweight individuals, may contribute to improved respiratory function and better overall physical resilience. Furthermore, adipose tissue is thought to exert a potential anti-inflammatory effect, which may help mitigate the systemic inflammation commonly observed in COPD. It was demonstrated that as COPD severity increases, there is progressive decline in both BMI and low BMI is associated with increased risk of COPD exacerbations and reduced survival rates [8, 9]. Several factors contribute to low BMI, including low socioeconomic status, poor overall health, insufficient physical activity, and recurrent illnesses. Maintaining healthy BMI has been suggested as way to reduce the risk of COPD exacerbations and mortality [10]. Therefore, the present study aimed to assess frequency of COPD stages and to compare mean BMI in various stages of COPD.

METHODS

After obtaining synopsis approval from CPSP [CPSP/REU/PUL-2020-062-616], this cross-sectional study was conducted at Institute of Chest Medicine, Mayo Hospital, Lahore. The study duration was six months, from August 2022, to February 2023. A total of 160 patients were included, based on calculated sample size using 95% confidence level, 3.5% margin of error, and expected percentage of stage I COPD as 5.4% [11]. The sampling technique used was non-probability consecutive sampling. Data were collected using pre-designed proforma. Patients of both genders aged between 20-70 years diagnosed with COPD at any stage according to GOLD criteria were included, provided they gave written informed consent. Patients were excluded if they were pregnant, had recent myocardial infarction, active pulmonary TB, malignancy, HIV, or had undergone surgery in preceding four weeks. Written informed consent was obtained before participation. Detailed medical history was recorded, including smoking status. Spirometry was performed using MIR Spirodoc TUKMIR040 (Italy) machine to classify the severity of airflow limitation based on post-bronchodilator FEV_1 as per GOLD guidelines from stage I-IV. Calibration and quality control of the spirometry device were ensured through daily calibration checks using a 3L calibration syringe, adherence to manufacturer-recommended maintenance protocols, and quality control measures as per American Thoracic Society (ATS)/European Respiratory Society (ERS) standards to ensure accuracy and reliability of measurements. BMI was calculated by measuring weight (kg) divided by height (meters squared). To minimize inter-observer variability, height, weight, and spirometry measurements were performed by trained personnel following standardized protocols. Height and weight were measured using calibrated stadiometer and weighing scale, ensuring consistency across measurements. Spirometry was conducted by single trained technician to maintain uniformity. Additionally, periodic cross-checks and quality assurance measures were implemented to ensure reliability and reduce variability in recorded values. All data were entered and analyzed using SPSS version 26.0. Numerical variables, including age, and BMI, were presented as mean ± SD, while categorical variables such as gender and severity of COPD were presented as frequencies and percentages. Comparisons of BMI across different COPD stages were made using ANOVA, and post Hoc analysis was done; p-value ≤ 0.05 considered statistically significant.

RESULTS

As shown in Figure 1 below, among the 160 individuals with COPD, 26.2% were diagnosed with Stage I, 23.8% with Stage II, while Stage III and Stage IV were observed in 25% of patients each.

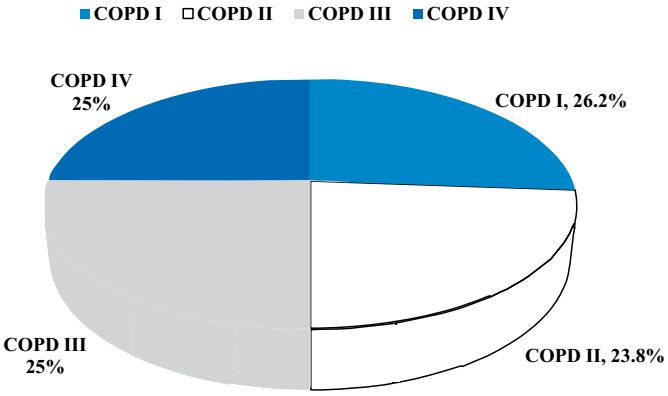

Figure 1: Distribution of Severity of COPD

Stratification of severity of COPD with respect to age, gender and smoking was done. There is significant difference was found between age and severity of COPD. Patient having age >50 years have more severe COPD (stage IV) as compared to age ≤50 years (40% vs 10% p-value <0.001). Moreover, COPD was more severe in male as compared to female (40.5% vs 9.9% p-value <0.001). Furthermore, there is no association was found between smoking and severity of COPD.

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Table 1: Stratification of Severity of COPD with Respect to Age, Gender and Smoking

Variables		Severity of COPD				p-Value
		I Frequency (%)	II Frequency (%)	III Frequency (%)	IV Frequency (%)	
Age	>50 Years	12 (15.0%)	07 (8.8%)	29 (36.3%)	32 (40.0%)	<0.001
	≤50 Years	30 (37.5%)	31 (38.8%)	11 (13.8%)	08 (10.0%)	
Gender	Male	39 (26.9%)	35 (24.1%)	35 (24.1%)	36 (24.8%)	0.844
	Female	03 (20.0%)	03 (20.0%)	05 (33.3%)	04 (26.7%)	
Smoking	No	03 (20.0%)	03 (20.0%)	06 (40.0%)	03 (20.0%)	0.573
	Yes	39 (26.9%)	35 (24.1%)	34 (23.4%)	37 (25.5%)	

As shown in Table 2, mean BMI significantly varied across different stages of COPD ($p < 0.001$). The BMI was found to be 24.30±2.71 in Stage I, 25.86 ± 5.77 in Stage II, 20.29±5.39 in Stage III, and 19.50 ± 6.07 in Stage IV, respectively. Compared to Stage I, the effect size (Cohen's d) was 0.35 for Stage II (small effect), 0.95 for Stage III (large effect), and 1.03 for Stage IV (large effect), indicating a substantial decline in BMI as COPD severity increased.

Table 2: Comparison of mean Body Mass Index with Severity of COPD

Severity of COPD	N	BMI Mean ± SD	95% CI		Cohen's d Effect	p-Value
			Lower Bound	Upper Bound		
Stage I	42	24.30 ± 2.71	23.45	25.14	Reference	<0.001
Stage II	38	25.86 ± 5.77	23.97	27.76	0.35	
Stage III	40	20.29 ± 5.39	18.57	22.02	0.95	
Stage IV	40	19.50 ± 6.07	17.56	21.44	1.03	
Total	160	22.47 ± 5.73	21.57	23.36	-	

The post hoc analysis of BMI across different COPD severity stages, as shown in Table 3, reveals a significant decline in BMI with increasing disease severity. Patients with Stage III and Stage IV COPD had significantly lower BMI compared to those with Stage I and Stage II. Notably, the mean BMI difference was statistically significant when comparing Stage I vs. Stage III ($p = 0.003$, mean difference = 4.00), Stage I vs. Stage IV ($p < 0.001$, mean difference = 4.79), Stage II vs. Stage III ($p < 0.001$, mean difference = 5.57), and Stage II vs. Stage IV ($p < 0.001$, mean difference = 6.36). However, the difference between Stage III and Stage IV was not statistically significant ($p = 0.900$). These findings indicate a progressive reduction in BMI as COPD severity worsens, with Stage IV patients exhibiting the lowest BMI.

Table 3: Comparison of Mean Body Mass Index with Severity of COPD (Post Hoc Analysis)

(A) COPD-Severity (I)	(B) COPD-Severity (J)	BMI Mean Difference (I-J)	p-Value	95% CI	
				Lower Bound	Upper Bound
Stage I	Stage II	-1.56	0.524	-4.55	1.41
	Stage III	4.00*	0.003	1.06	6.95
	Stage IV	4.79*	<0.001	1.85	7.74
Stage II	Stage I	1.56	0.524	-1.41	4.55
	Stage III	5.57*	<0.001	2.55	8.59
	Stage IV	6.36*	<0.001	3.34	9.38
Stage III	Stage I	-4.00*	0.003	-6.95	-1.06
	Stage II	-5.57*	<0.001	-8.59	-2.55
	Stage IV	0.79	0.900	-2.18	3.77
Stage IV	Stage I	-4.79*	<0.001	-7.74	-1.85
	Stage II	-6.36*	<0.001	-9.38	-3.34
	Stage III	-0.79	0.900	-3.77	2.18

*p-value significant (<0.05)

DISCUSSION

In current study, 26.3% were diagnosed with COPD Stage I, 23.8% with Stage II, while Stage III and IV were observed in 25% patients each. GOLD classification system for COPD categorizes the disease into four stages based on percentage of predicted forced expiratory volume in one second, which is essential for assessing severity and guiding treatment strategies [12]. The distribution of patients across these stages varies, reflecting clinical burden of COPD. Compared to study by Haughney J *et al.*, where Stage II was the most prevalent (52.2%) and Stage IV was least common (5.2%), these findings show more even distribution of COPD severity [13].In current study, there was notable association between age and COPD severity,

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with younger patients (≤50 years) exhibiting more advanced disease (stage IV) compared to older individuals. The condition was also more severe in males than females, but no direct correlation was found between smoking history and disease severity.In contrast, Morena D *et al.*, found progressive increase in COPD severity with age, highlighting that older patients were more likely to have advanced stages of the disease [14].Sørheim IC *et al.*, reported that female COPD patients had higher prevalence of severe disease, with more females classified in GOLD Stage III and IV (50.4% vs. 35.6%, p=0.020) compared to males.These findings not aligning with current results, suggests that female patients may experience more rapid decline in lung function and greater disease severity, potentially due to biological differences, exposure patterns, or healthcare disparities [15].According to current study mean BMI has shown decrimental trend from Stage I to stage IV.Mean BMI difference was statistically significant when comparing Stage, I vs. III ($p = 0.003$), Stage I vs. IV ($p < 0.001$), Stage II vs. III ($p < 0.001$), and Stage II vs. IV ($p < 0.001$). However, difference between Stage III and IV was not statistically significant ($p = 0.900$).Studies have consistently supporting current findings, Suleiman, found that patients with more severe COPD (Stages III and IV) tend to have lower mean BMI compared to those with milder disease [16].A prospective cohort study of 1,755 COPD patients found that prevalence of low BMI and fat-free mass index increased with worsening spirometric stage and dyspnea score [17].In contrast, patients with mild or moderate COPD (Stages I and II) often exhibit higher mean BMI. For example, study by Wang H *et al.*, found that overweight and obese individuals were more likely to have mild COPD compared to underweight individuals [18]. Weight loss in COPD is primarily driven by muscle mass depletion, influenced by increased energy expenditure, reduced caloric intake, and metabolic dysfunction. Pro-inflammatory cytokines like TNF-α and tissue hypoxia contribute to muscle degradation and impaired energy production [19].Low BMI is strongly associated with worse COPD outcomes, but some researchers argue that BMI alone may not accurately reflect nutritional status due to factors like increased total body water, which could obscure the effects of malnutrition [20].

CONCLUSIONS

The distribution of COPD severity was fairly even across all stages, with comparable proportion of patients in each stage and significant decline in BMI was observed as COPD severity increased. These findings highlight the importance of monitoring BMI in COPD patients, as lower BMI is associated with disease progression and worse clinical outcomes.

Authors Contribution

Conceptualization: IJ, AJ, HKD
Methodology: IJ, AJ, ZZ, AU, HKD, MR
Formal analysis: MR
Writing, review and editing: ZZ, AU

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Factors Affecting Sexual Health after Puerperium among Women in Karachi

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ABSTRACT

The puerperium phase represents a critical juncture in a woman's reproductive journey, marked by significant physical, emotional, and relational adjustments. Various factors beyond the mere resumption of sexual activity influence sexual well-being during this period. However, discussions surrounding postpartum sexual health remain limited, particularly in low- and middle-income countries like Pakistan. **Objectives:** To explore postpartum sexual health in Pakistani women, identifying cultural, physical, and emotional factors influencing well-being. **Methods:** A cross-sectional study was conducted at Fazaia Ruth Pfau Medical College (FRPMC) Hospitals in Karachi from August 2022 to July 2023. Within the first three months' post-puerperium, 263 women aged 18 to 45 participated. A comprehensive questionnaire, developed and validated through rigorous processes, assessed socio-demographic, obstetric, and sexual health factors. Statistical analyses, including chi-square tests and Kendall's tau correlation analyses, were employed. **Results:** Participants exhibited diverse socio-demographic and obstetric profiles, with a notable prevalence of resumption of sexual activity (65.1%) and concerns such as dyspareunia (66.5%) and decreased libido (53.2%). Significant associations were found between various socio-demographic and obstetric factors and postpartum sexual health outcomes. Longer marriage duration was associated with higher libido levels, while the mode of delivery and the last baby's birth weight influenced coital frequency. Age, marriage duration, and parity affected postpartum libido, vaginal dryness, and dyspareunia. **Conclusions:** It was concluded that this study provides valuable insights into the complexity of postpartum sexual experiences among women in Karachi, Pakistan. The findings underscore the need for comprehensive, culturally sensitive interventions to support women's sexual well-being during this critical period.

INTRODUCTION

The postnatal phase, commonly referred to as the postpartum period or puerperium, constitutes a transformative stage in a woman's reproductive journey, marked by a multitude of physical, emotional, and relational adaptations [1]. In this crucial time frame, sexual well-being emerges as a complex interplay of factors, extending beyond the mere recommencement of sexual activity [2]. This intricate shift extends beyond the immediate postnatal period, leaving a sustained impact on diverse aspects of a woman's sexual well-being [3]. On a global scale, the examination of sexual health during the postpartum period has gained escalating attention, acknowledging its profound implications for the overall health of women navigating through this pivotal life stage [4]. It is noteworthy that more than fifty percent of postpartum women encounter delayed resumption of sexual activity, emphasizing the significance of addressing sexual health concerns within this demographic [5]. While the World Health Organization (WHO) suggests assessing women 2–6 weeks postpartum, the topic of early resumption of sexual activity in the postpartum period has received limited exploration [6]. Women who have experienced childbirth frequently express lower levels of marital satisfaction compared to those without children [3]. Furthermore, the method of delivery, whether instrumental or via cesarean section, has the potential to impact long-term sexual health, affecting factors like desire and lubrication [7]. The significant influence of childbirth on women's sexuality becomes apparent, resulting in sexual dysfunctions requiring attention and

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intervention [8]. Complications, including pelvic floor disorders, are strongly associated with reduced sexual arousal, infrequent orgasm, and dyspareunia, negatively impacting women's sexual health [9]. Following childbirth, there is a noteworthy increase in sexual morbidity, with a majority of women grappling with sexual issues within the initial three months post-delivery [3]. Despite the acknowledged prevalence, in low to middle-income countries LMICs, including Pakistan, the existing body of knowledge on the sexual health of postpartum women is limited, emphasizing the critical need for expanded research in this field [1]. Pakistan reflects this gap, where discussions around sexual health are infrequent, particularly among females seeking healthcare services, considering it a sensitive and taboo subject [10, 11]. The cultural and societal norms governing female reproductive health in Pakistan require an investigation to shape targeted interventions and strategies. This research endeavors to fill this knowledge gap and advance the understanding of postpartum sexual health within the cultural context of Pakistan.

This study aims to explore postpartum sexual health in Pakistani women, identifying cultural, physical, and emotional factors influencing well-being.

METHODS

This cross-sectional study was conducted from August 2022 to July 2023 at FRPMC Hospital, Karachi, after approval from the ethical committee (IRB/27). The study included 263 women aged 18–45 within 6 months following delivery, visiting post-natal care, vaccination, and family planning clinics. The sampling technique used was non-probability convenience sampling. Women with preterm deliveries, divorced/widowed, diagnosed pre-existing sexual health conditions, or significant psychological disorders were not eligible to participate in the study and thus were excluded. Delineating the intricacies of sample size determination, the study adhered to the WHO sample size calculator 2.0. A 5% margin of error was chosen to strike an appropriate balance between statistical precision and practical considerations (e.g., resource constraints and participant availability). Precision levels were set at a 95% confidence interval, and a conservative estimate for the prevalence of sexual problems post-puerperium in Pakistan, denoted as 24 % [12], was used for calculation. Consequently, a requisite minimum sample size of 257 was ascertained. From the total pool of 325 women, only 263 eligible participants meeting the stringent inclusion criteria were approached. Informed consent was obtained, and trained interviewers conducted face-to-face questionnaires in English and Urdu. The questionnaire assessing post-puerperium sexual health was developed through an extensive literature review and validated by three obstetrics experts specializing in postpartum care. All the items were translated into the National Language, Urdu, and were provided in both English and Urdu to eliminate any potential miscommunication and guarantee that all answers were provided after careful consideration. Each item was rated for relevance on a 10-point scale, and the Content Validity Ratio (CVR) was calculated. Items with a CVR of 0.7 or higher were retained, while those below were revised or removed based on expert feedback. A pilot study with 20 participants from the target population was conducted to evaluate face validity and address issues such as item ambiguity or formatting. Feedback from the pilot test was used to refine the final questionnaire. The study's tool, a comprehensive questionnaire, explores post-puerperium sexual health and its influencing factors. It comprises three sections: Section 1 captures socio-demographic details like age, education, and spousal characteristics. Section 2 focuses on obstetric history, covering parity, birth details, and complications such as episiotomy. Section 3 addresses sexual health, examining coitus resumption, libido, dryness, dyspareunia, lubrication use, and the impact of childbirth on sexual life. Reliability was assessed by measuring the internal consistency of the questionnaire items using Cronbach's alpha, which indicated satisfactory reliability (Cronbach's alpha=0.72). The collected data were systematically stored and analyzed using IBM SPSS version 26.0. Counts and percentages for the entire questionnaire were reported to provide a thorough overview of the dataset. An extensive analysis was conducted to uncover patterns and associations between socio-demographic, obstetric profiles, and post-puerperal sexual health. Comparative analyses were performed using the Chi-square test to examine the relationships between socio-demographic and obstetric factors with sexual health outcomes. Correlation analyses, including Kendall's Tau or Spearman correlation, were utilized to explore the relationships between various variables. Effect sizes for the correlation coefficients (e.g., values <0.3 considered weak, 0.3–0.5 moderate, and >0.5 strong) were reported to clearly illustrate the magnitude of the associations. A significance level of $p<0.05$ was established to determine statistical significance, with p-values below this threshold indicating robust and meaningful associations or patterns within the dataset.

RESULTS

Out of 263 individuals, 62.4% fall within the 20-30 age bracket, and 50.2% have intermediate qualifications. A substantial majority identified themselves as homemakers (73.8%). Regarding parity, 46.4% have 2 to 5 children, and 70% of women have their last childbirth within the last 3 months. Cesarean delivery was conducted in 62.4% of the participants, (Table 1).

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Table 1: Stratification of Severity of COPD with Respect to Age, Gender and Smoking

Variables	Frequency (%)
Age of Patient	
20 –30	164 (62.4%)
31-40	94 (35.7%)
>40	5 (1.9%)
Education of Patient	
Illiterate	28 (10.6%)
Primary	30 (11.4%)
Intermediate	132 (50.2%)
Graduate	73 (27.7%)
Occupation of Patient	
Working	69 (26.2%)
Housewife	194 (73.8%)
Age of Husband	
20-30	89 (33.8%)
31-40	160 (60.9%)
>40	14 (5.3%)
Education of Husband	
Illiterate	7 (2.7%)
Primary	13 (5.1%)
Intermediate	137 (53.3%)
Graduate	100 (40.9%)
Occupation of Husband	
Employed	238 (90.5%)
Unemployed	25 (9.5%)
Duration of Marriage	
1 Year Or Less	26 (9.9%)
2-5 Years	122 (46.4%)
6-10 Years	97 (36.9%)
More Than 10 Years	18 (6.8%)
Satisfaction with Marriage Life	
Yes	231 (87.8%)
No	32 (12.2%)
Parity	
1	77 (29.3%)
2-5	142 (54%)
More Than 5	44 (16.7%)
Last Birth	
<3 months	184 (70%)
3 to 6 months	79 (30%)
Birth Weight of Last Baby	
Less Than 3 Kg	113 (43%)
3-4 Kg	136 (51.7%)
More Than 4 Kg	14 (5.3%)
Mode of Delivery	
Vaginal	99 (37.6%)
LSCS	164 (62.4%)

Out of 263 participants, 65.1% mentioned a return to intimate relations, with husbands being the initiators in 91.7% of cases. The majority of coitus resumption occurred between 6 weeks to 2 months after childbirth (48.6%). However, 34.9% who do not resume sexual relations have concerns about the fear of pain and the absence of their partners. Participants reported distinct changes in sexual patterns as a decrease in libido (53.2%) and dyspareunia (66.5%), (Table 2).

Table 2: Sexual History of study participants

Variables	Frequency (%)
Resumption of Coitus	
Yes	170 (65.1%)
No	91 (34.9%)
Who Initiated Resumption of Coitus	
Husband	188 (91.7%)
Wife	17 (8.3%)
Frequency of Coitus	
Decreased	63 (37.1%)
Same	65 (38.2%)
Increased	42 (24.7%)
Resumption of Coitus in Weeks	
6 Weeks	57 (27.4%)
6 Weeks-2 Months	101 (48.6%)
3 Months	50 (24%)
Libido of Women	
Decreased	140 (53.2%)
Same	117 (44.5%)
Increased	6 (2.3%)
Dryness	
Yes	59 (23%)
No	198 (77%)
Dyspareunia	
No	75 (33.5%)
Superficial	129 (57.6%)
Deep	20 (8.9%)

Reasons for resuming intercourse are analyzed (Figure 1).

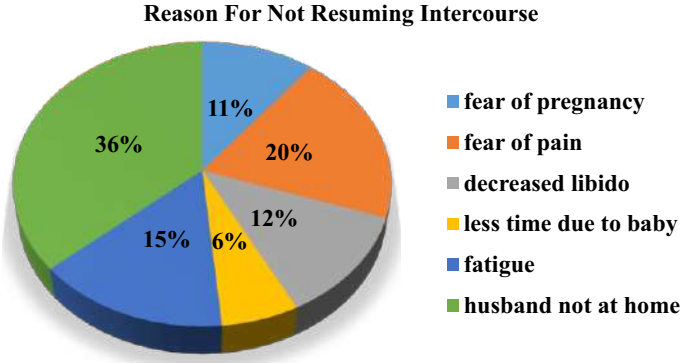

Figure 1: Distribution of Responses for Not Resuming Intercourse

Results show the Influence of Socio-demographic and obstetric profiles on Sexual Health. Socio-demographic factors such as the age of the women, husband's age, husband's occupation, marriage duration, and parity were identified as influential factors impacting coitus resumption ($p<0.05$). Particularly compelling was the robust correlation between marriage duration and

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resumption of sexual activity (r=0.232, p=0.002), alongside the negative correlation observed between the last baby's birth weight and coitus resumption (r=-0.339, p<0.001). Additionally, the husband's age (p=0.032) exhibited a significant association with coital frequency. Marriage duration (p=0.024) emerged as a substantial determinant of coital frequency, while the mode of delivery demonstrates a notable correlation (r=0.254, p=0.010). The age of the patient (r=0.218, p=0.015) and the last baby's birth weight (r=0.377, p<0.001) impacted a positive correlation with resumption time, indicating older age and heavier newborns were associated with delayed resumption of sexual activity.Moreover, marriage duration (p<0.001), marriage satisfaction (p=0.008), and parity (p=0.040) were identified as influential factors affecting postpartum libido, with longer marriage durations associated with higher libido levels (r=0.253, p=0.001), and increased parity correlating positively with libido (r=0.213, p=0.005). Significant correlations were observed between age, dryness (r=0.32, p<0.001) and dyspareunia (r=-0.398, p<0.001). However, marriage duration exhibited a positive correlation with dryness (r=0.296, p<0.001) and a negative correlation with dyspareunia (r= -0.285, p=0.003). A negative correlation was found between parity and dyspareunia(r=-0.331, p=0.001), (Table 3).

Table 3: Chi-Square Test and Kendall's Tau or Spearman Correlation Socio-Demographic and Obstetric Profile with Sexual History

Asked Questions	Coitus Resumption	Coital Frequency	Resumption Time	Libido	Dryness	Dyspareunia
Chi-Square Test (p-value)						
Age of Patient	0.042	0.075	<0.001	0.573	0.001	< 0.001
Education of Patient	0.778	0.513	0.029	0.112	0.138	0.089
Occupation of Patient	0.074	0.913	0.244	0.031	0.834	0.150
Husband's Age	0.046	0.032	0.025	0.062	<0.001	<0.001
Husband Education	0.092	0.244	<0.001	0.695	0.001	0.142
Husband's Occupation Status	0.037	0.219	0.596	0.832	0.258	0.135
Marriage Duration	< 0.001	0.024	<0.001	<0.001	0.056	<0.001
Marriage Satisfaction	0.055	0.321	0.207	0.008	<0.001	0.304
Parity	0.019	0.727	0.001	0.040	0.398	0.072
Duration since Last Birth	0.065	0.104	0.185	0.796	0.459	0.103
Last Baby's Birth Weight	0.662	<0.001	0.122	0.550	0.357	0.236
Mode of Delivery	0.140	0.073	0.011	0.774	<0.001	0.007
Kendall's Tau or Spearman Correlation (p-value)						
Age of Patient						
Correlation Coefficient	0.083	0.009	0.218*	0.123	0.32**	-0.398**
Sig. (2-tailed)	0.256	0.918	0.015	0.09	<0.001	<0.001
Education of Patient						
Correlation Coefficient	0.012	0.159	0.137	0.117	0.085	0.162
Sig. (2-tailed)	0.87	0.085	0.139	0.116	0.257	0.087
Husband's Age						
Correlation Coefficient	-0.035	-0.055	0.166	0.113	0.318**	-0.346**
Sig. (2-Tailed)	0.628	0.538	0.064	0.12	<0.001	<0.001
Husband Education						
Correlation Coefficient	0.046	0.13	0.149	0.004	0.154*	0.127
Sig. (2-Tailed)	0.554	0.171	0.119	0.963	0.048	0.195
Marriage Duration						
Correlation Coefficient	0.232*	-0.068	0.131	0.253**	0.296**	-0.285*
Sig. (2-Tailed)	0.002	0.465	0.159	0.001	<0.001	0.003
Parity						
Correlation Coefficient	0.11	-0.084	0.163	0.213*	0.089	-0.331*
Sig. (2-Tailed)	0.146	0.369	0.118	0.005	0.241	0.001
Duration since Last Birth						
Correlation Coefficient	-0.147	-0.097	0.011	0.031	0.059	0.131
Sig. (2-Tailed)	0.066	0.323	0.913	0.692	0.46	0.196
Last Baby's Birth Weight						
Correlation Coefficient	-0.339**	-0.051	0.377**	-0.056	-0.104	-0.251*
Sig. (2-Tailed)	<0.001	0.605	<0.001	0.475	0.183	0.013

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Mode of Delivery						
Correlation Coefficient	-0.129	0.254**	0.041	-0.05	-0.331**	0.11
Sig. (2-Tailed)	0.107	0.01*	0.675	0.53	<0.001	0.277

**Correlation was significant at the 0.01 Level (2-tailed). **Correlation was significant at the 0.05 Level (2-tailed).

DISCUSSION

Pakistan's complex socio-cultural landscape presents unique challenges that profoundly impact women's reproductive health rights, reinforcing gender disparities and shaping the understanding of sexual health in the postpartum period [13]. Research on postpartum sexual health in Pakistan has several gaps. There is limited focus on postpartum sexual health specifically, with most studies addressing general maternal health. Cultural and religious norms around sexuality, societal taboos, and a lack of open discussion often hinder research [14]. Qualitative insights into women's personal experiences, including communication with healthcare providers, are scarce. Socioeconomic, educational, and psychological factors affecting postpartum sexual health are understudied. Additionally, there is little focus on partner dynamics and access to postpartum sexual health services. These gaps highlight the need for culturally sensitive research and targeted interventions in Pakistan, which we have studied. Our study of 263 women highlights key socio-demographic and obstetric factors affecting post-childbirth sexual well-being. Most participants were aged 20-30, homemakers, and had recently given birth (70% within 3 months), with 46.4% having 2-5 children and 62.4% undergoing cesarean sections. Educational backgrounds vary widely, mostly in the intermediate category (50.2%). It revealed that 65.1% of women resumed intimate relations postpartum, mostly initiated by husbands (91.7%), with 48.6% resuming between 6 weeks and 2 months. Challenges included decreased libido (53.2%) and increased dyspareunia (66.5%). For 34.9%, fear of pain or partner absence delayed sexual activity. Our study identifies key socio-demographic and obstetric factors influencing post-puerperium sexual health. Marriage duration, the husband's age, and the baby's birth weight significantly impacted coitus resumption, libido, and coital frequency. Age and parity influenced dyspareunia and dryness, with longer marriages linked to higher libido and reduced dyspareunia, highlighting complex postpartum sexual dynamics. Current study found that 65.1% of participants wanted to resume intimacy after childbirth, aligning with global trends. Pooled data from 21 studies (4,482 participants) show 67.27% of women resumed sexual activity early postpartum [5]. This observation highlights the significant role of sociocultural norms, values, and beliefs in shaping postpartum sexual activity, with diverse practices influencing women's experiences across different societies worldwide [15]. Current study found that 91.7% of husbands initiate coital resumption postpartum, reflecting cultural norms that position men as primary initiators of sexual intimacy in our society. This dominance of husbands aligns with prevailing cultural norms in Pakistan, where traditional gender roles steeped in gender bias often dictate intimate aspects of marital life [16]. Comparative study shows that men initiate coital resumption 3.5 times more often across cultures [17]. A study conducted in Ethiopia showed that 46.6% had experienced pressure from their husbands to resume sexual intercourse [18]. Current study reveals that younger women and those with high resume coitus earlier postpartum, similar to a study conducted in Ethiopia [19]. Studies conducted in Uganda and Nigeria revealed that Employed women and those with higher incomes also showed earlier resumption, influenced by cultural, economic, and educational factors corresponding to the results of previous research [20, 21]. Similar to the results of previous research, Current study also reflects Husbands' higher education delays coital resumption, emphasizing postpartum health awareness [18]. Current study highlights newborn weight as a significant factor in delayed coital resumption postpartum, aligning with research linking heavier newborns to obstetric injuries, influencing postpartum sexual activity [22-25]. The study reveals that 66.5% of women experienced increased dyspareunia postpartum, aligning with prior research. Addressing dyspareunia through comprehensive care, including pelvic rehabilitation and sexual health counseling, is crucial for improving postpartum well-being [26, 27]. Our study reveals 53.2% experienced decreased libido postpartum, highlighting childbirth's impact on sexual health and the need for comprehensive postpartum support, endorsing the results of previous research [28]. Current findings highlight notable associations between key demographic and obstetric factors with various aspects of postpartum sexual health. Specifically, longer marriage duration demonstrated a significant positive correlation with libido and a negative correlation with dyspareunia, suggesting that as couples spend more time together, they may develop stronger emotional intimacy and sexual compatibility. Future studies, ideally with broader populations and longitudinal designs, are warranted to expand our understanding of these relationships, identify potential confounders, and formulate evidence-based guidelines for optimizing postpartum sexual health. One key limitation of current study is that responses with missing data were excluded but did not apply more robust

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methods (e.g., test-retest reliability, factor analysis) to further ensure consistency and reliability of the questionnaire. Future investigations may benefit from additional psychometric assessments to better validate the instrument and strengthen the overall conclusions.

CONCLUSIONS

It was concluded that our study explores postpartum sexual health among women in Karachi, Pakistan, identifying cultural, physical, and emotional factors influencing well-being. While 65.1% desired coital resumption, challenges like dyspareunia (66.5%) and decreased libido (53.2%) were prevalent. Age, parity, mode of delivery, and socio-cultural norms significantly impacted outcomes. Our findings underscore that socio-demographic aspects such as the woman's age, husband's age, and marriage duration significantly affect the timing and frequency of coital resumption. Obstetric factors, particularly the mode of delivery, birth weight of the last child, and parity, also emerged as key predictors of sexual well-being. These findings highlight the need for culturally sensitive interventions to address multifaceted postpartum sexual experiences.

Authors Contribution

Conceptualization: RM, SAM, AT
Methodology: RM, SAM, AT, ZIK, HM
Formal analysis: RM
Writing review and editing: RM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Evaluation of Glycated Hemoglobin Levels in Cirrhotic Patients Across Different Child-Pugh Classes

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ABSTRACT

Chronic liver diseases can lead to cirrhosis, characterized by structural abnormalities and fibrosis. Diabetes is a significant risk factor for poor prognosis in cirrhotic patients, associated with complications such as ascites, renal dysfunction, and increased mortality. **Objectives:** To evaluate glycated hemoglobin (HbA1c) levels in cirrhotic patients across different Child-Pugh classes, contributing to better management of chronic liver disease. **Methods:** Conducted at Liaquat University of Medical and Health Sciences, this descriptive cross-sectional study enrolled 62 cirrhotic patients (aged 18-60) over six months. Exclusion criteria included known diabetes and recent blood transfusions. Data on demographic characteristics and HbA1c levels were collected and analyzed using SPSS version 24.0. **Results:** The mean age of participants was 52.3 ± 7.5 years, with a mean disease duration of 28.4 ± 12.3 months. The overall mean HbA1c level was 5.3 ± 0.9%. Child-Pugh classification revealed 32% Class A, 40% Class B, and 28% Class C patients. HbA1c levels increased significantly with liver disease severity: Class A (4.9 ± 0.6%), Class B (5.4 ± 0.7%), and Class C (5.9 ± 0.8%), $p<0.05$. Significant associations were found between HbA1c levels and age, disease duration, but not with gender or BMI. **Conclusions:** It was concluded that HbA1c levels are influenced by the severity of liver disease and duration, indicating the need for careful interpretation of HbA1c in cirrhotic patients for effective management.

INTRODUCTION

Liver cirrhosis, which is brought on by chronic liver disorders, results in the transformation of normal liver architecture into structurally aberrant nodules and distinctive tissue fibrosis [1, 2]. Liver cirrhosis is most commonly caused by alcoholic liver disease, nonalcoholic steatohepatitis, and viral hepatitis B, C, and D [3]. Diffuse nodular regeneration encircled by dense fibrotic septa is a histological characteristic of liver cirrhosis, a pathologically defined condition [4]. Hepatic vascular architecture is significantly distorted as a result of the parenchymal extinction and consequent collapse of liver architecture [5]. More than 0.8 to 0.89 million fatalities annually are due to cirrhosis [6]. Because diabetes is linked to serious consequences such as ascites, renal failure, hepatic encephalopathy [7-9], and bacterial infections, it is an independent risk factor for a poor prognosis in individuals with cirrhosis [10]. In patients with chronic liver disease, diabetes also raises the risk of hepatocellular carcinoma and death [11]. About 30% to 60% of individuals with severe cirrhosis develop diabetes, while about 80% of people with cirrhosis have impaired glucose tolerance [12]. Compared to the general population, where the prevalence of diabetes is about 8% and glucose intolerance is about 15%, individuals with cirrhosis have a far greater prevalence of diabetes [13]. The term "hepatogenous diabetes" refers to diabetes resulting from liver

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insufficiency and portal hypertension, as distinct from traditional type 2 diabetes mellitus (T2DM) that is also seen in cirrhotic patients [12]. Reduced hepatic mass and portosystemic shunts are linked to cirrhosis, which affects the liver's ability to clear insulin and causes peripheral insulin resistance as a result of downregulated insulin receptors. Additionally, elevated levels of hypoxia-inducible factors and advanced glycation end products are associated with cirrhosis, which may aid in the development of diabetes [14]. The HbA1c level in cirrhotic patients has been reported as ≥6.1% [15, 16]. Haemoglobin A1c measurement is a standard evaluation tool in diabetes therapy. This study is justified by the fact that diabetes is a common ailment and that diabetes is negatively impacted by chronic liver disease [14]. The purpose of this study is to ascertain how HbA1c levels relate to various stages of liver disease. It will help with early detection, risk assessment, and better chronic liver disease management, all of which could improve quality of life.

This study aims to examine the HbA1c levels of cirrhotic patients across various Child-Pugh classes and to ascertain the HbA1c level in cirrhotic patients who presented to a tertiary care hospital in Jamshoro, Hyderabad.

METHODS

A descriptive cross-sectional study was conducted in the Medical Unit 1 at Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad, over six months starting from February 2024 to July 2024 and non-probability consecutive sampling was used to enroll a sample of 62 cirrhotic patients, as determined by the WHO sample size calculator with a 95% confidence level, an expected HbA1c level of 6.1%, and a precision of 0.2 [16]. Inclusion criteria comprised patients aged 18 to 60 years, of either gender, who had been diagnosed with liver cirrhosis for more than six months. Exclusion criteria included known cases of type 1 or type 2 diabetes, hepatocellular carcinoma, secondary diabetes resulting from steroids, endocrinopathies, or chemotherapy, a history of gastrointestinal bleeding, recent blood transfusion, and patients who did not provide consent to participate. Ethical approval was obtained from the institutional review board (IRB) under the approval number CPSP/REU/. Data collection was initiated following IRB approval. Patients meeting the inclusion criteria and presenting to the outpatient department of Medicine were informed about the study's purpose, procedures, risks, and benefits, and written informed consent was obtained. Confidentiality was strictly maintained. The demographic and clinical data for each participant, including age, gender, and disease duration, were recorded. Height was measured using a wall-mounted scale without shoes, and weight was recorded on an electronic scale with minimal clothing. Body mass index (BMI) was then calculated by dividing weight in kilograms by height in meters squared. Child-Pugh class was assessed using a scoring system based on five clinical and laboratory parameters: total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy. This scoring information was obtained from the patient's record. HbA1c levels were measured using the Uncoated Human HbA1c (Haemoglobin A1c) ELISA Kit (E-UNEL-H0333, Elabscience®, Houston, Texas, 77079, USA) in the institutional laboratory. Prothrombin time was determined using an automated coagulation analyzer, while serum albumin levels were measured using the bromocresol green (BCG) dye-binding method. A 3-cc blood sample was drawn by a trained phlebotomist for HbA1c level measurement in the institutional laboratory. SPSS version 24.0 was used for data analysis. The Shapiro-Wilk test was used to determine whether continuous data were normal. Age, length of illness, height, weight, BMI, prothrombin time, serum albumin, and HbA1c levels were among the continuous variables for which means, standard deviations, medians, and interquartile ranges (IQRs) were computed. Categorical data, including gender and Child-Pugh class, were presented as frequencies and percentages. Comparisons of HbA1c levels across different Child-Pugh classes were conducted using the Kruskal-Wallis test, with p-values≤0.05 considered statistically significant. Potential effect modifiers such as age, gender, disease duration, and BMI were addressed through stratification.

RESULTS

The study involved 62 cirrhotic patients, having a mean age of 52.3 ± 7.5 years and a mean value of disease duration of 28.4 ± 12.3 months. Among these patients, 58% were male (n=36) and 42% were female (n=26). The average BMI was 24.1 ± 3.2 kg/m^2, with a mean prothrombin time of 17.4 ± 4.1 seconds and serum albumin level of 2.9 ± 0.5 g/dL. The overall mean HbA1c level was 5.3 ± 0.9% (Table 1).

Table 1: Demographics and Clinical Features of Cirrhotic Patients (n=62)

Characteristic	Mean ± SD / n (%)
Age (Years)	52.3 ± 7.5
Duration of Disease (Months)	28.4 ± 12.3
Gender	
Male	36 (58%)
Female	26 (42%)
BMI (kg/m^2)	24.1 ± 3.2
Prothrombin Time (Seconds)	17.4 ± 4.1
Serum Albumin (g/dL)	2.9 ± 0.5
HbA1c Level (%)	5.3 ± 0.9

Patients were categorized by Child-Pugh class, with 32% in

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Class A (n=20), 40% in Class B (n=25), and 28% in Class C (n=17)(Table 2).

Table 2: Distribution of Child-Pugh Classes Among Cirrhotic Patients

Child-Pugh Class	n (%)
Class A	20 (32%)
Class B	25 (40%)
Class C	17 (28%)
Total	62 (100%)

Comparison of HbA1c levels across Child-Pugh classes demonstrated a statistically significant difference, with higher HbA1c levels observed as the Child-Pugh class increased. Specifically, Class A patients had a mean HbA1c of 4.9 ± 0.6%, Class B had 5.4 ± 0.7%, and Class C had 5.9 ± 0.8%. A Kruskal-Wallis test confirmed that these differences were significant ($p<0.05$), indicating an association between increasing liver disease severity and elevated HbA1c levels (Table 3).

Table 3: Comparison of HbA1c Levels Across Child-Pugh Classes

Child-Pugh Class	HbA1c (Mean ± SD)	Range
Class A	4.9 ± 0.6	4.2-5.6
Class B	5.4 ± 0.7	4.7-6.2
Class C	5.9 ± 0.8	5.0-6.9
Overall	5.3 ± 0.9	4.2-6.9

A Kruskal-Wallis test showed a significant difference in HbA1c levels across Child-Pugh classes ($p<0.05$).

Further stratification revealed significant associations for HbA1c levels with age and disease duration. Patients aged 41–60 years had a higher mean HbA1c (5.4 ± 0.9%) compared to those aged 18–40 years (5.0 ± 0.8%), with a p-value of 0.03. Additionally, patients with a disease duration of more than 24 months had a higher mean HbA1c (5.5 ± 0.8%) compared to those with a disease duration of 24 months or less (5.1 ± 0.6%), with a p-value of 0.02. No significant differences in HbA1c levels were found based on gender ($p=0.15$) or BMI categories ($p=0.12$) (Table 4).

Table 4: Stratification of HbA1c by Age, Gender, Disease Duration, and BMI

Variables	Category	HbA1c (Mean ± SD)	p-Value
Age (Years)	18–40	5.0 ± 0.8	0.03
	41–60	5.4 ± 0.9	
Gender	Male	5.3 ± 0.7	0.15
	Female	5.2 ± 0.9	
Disease Duration (Months)	≤24	5.1 ± 0.6	0.02
	>24	5.5 ± 0.8	
BMI (kg/m^2)	<25	5.2 ± 0.7	0.12
	≥25	5.4 ± 0.8	

DISCUSSION

Current study findings highlight that HbA1c levels in cirrhotic patients are influenced by liver disease severity, as reflected in the Child-Pugh classification, age, and disease duration. HbA1c levels significantly increased with the progression of liver disease, with Child-Pugh Class A patients displaying lower HbA1c levels (4.9 ± 0.6%) compared to Class C patients (5.9 ± 0.8%) ($p<0.05$). This aligns with prior research, where HbA1c was found to underestimate glycemic control in cirrhotic patients, particularly those with advanced liver disease, as reported by Cacciatore *et al.*, who suggested that cirrhosis itself may impair HbA1c's accuracy as a diagnostic tool due to altered glucose metabolism in such patients [17]. Disease duration was also a significant factor affecting HbA1c levels. Patients aged 41–60 years and those with disease durations longer than 24 months had higher HbA1c levels (5.4 ± 0.9% and 5.5 ± 0.8%, respectively). This concurs with findings by Soni *et al.*, where cirrhotic patients with extended disease duration often displayed lower HbA1c levels relative to their actual glycemic control due to decreased red blood cell lifespan, a common feature in cirrhosis [18]. Despite this, our data revealed no significant HbA1c differences based on gender or BMI, suggesting that while HbA1c might be influenced by liver disease severity and disease duration, other demographic factors may remain relatively unaffected. Notably, we observed higher mean HbA1c levels among cirrhotic patients than the general population, which might reflect systemic changes in glucose metabolism often associated with liver cirrhosis. Nomura *et al.*, work supports this, showing comparable HbA1c levels between cirrhotic and diabetic patients, despite higher fasting plasma glucose in the latter group [19]. Our study also provides valuable insights into the limitations of HbA1c in cirrhotic populations, particularly for patients with moderate to severe anemia, who comprised 63.6% of our study group. This is consistent with English *et al.*, systematic review [20], which identified iron deficiency anemia (IDA) as a factor potentially leading to falsely elevated HbA1c values. Consequently, for diabetic patients with cirrhosis, especially those with anemia, the oral glucose tolerance test (OGTT) remains a more reliable standard. Given that OGTT identified diabetes in 35% of our study population, it remains the preferred diagnostic approach in these cases.

CONCLUSIONS

It was concluded that HbA1c may serve as a valuable tool for assessing glycemic control in cirrhotic patients, particularly regarding liver disease severity and duration. Nevertheless, caution is warranted in interpreting HbA1c levels in this population, especially considering the potential impact of anemia and other confounding factors. Future studies with larger sample sizes and diverse populations are essential to further elucidate the diagnostic utility of HbA1c in cirrhosis and optimize

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diabetes management in this complex patient group.

Authors Contribution

Conceptualization: RQS
Methodology: RQS, MHJ, FS
Formal analysis: AGD, SK
Writing review and editing: IAS

All authors have read and agreed to the published version of the manuscript

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Original Article

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Socioeconomic Determinants of Access to Primary Healthcare in Rural Population of Sindh, Pakistan

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ABSTRACT

Pakistan's rural population lacks access to primary healthcare facilities due to various socioeconomic factors. Investigating these factors is essential to improve healthcare delivery to these people. **Objective:** The Current study explores the socioeconomic determinants that influence the access to primary healthcare services in rural Sindh, Pakistan. **Methods:** This cross-sectional study was conducted in five districts of Sindh: Hyderabad, Thatta, Badin, Tharparkar, and Larkana. A total of 300 participants were surveyed using a structured questionnaire. Demographic data along with education, occupation, Monthly Income, Access to Utilities, Distance to medical facility, Medical services Costs, Waiting Times, Doctor, medicine, and diagnostic facilities. Descriptive statistics and logistic regression were used to analyze the data. **Results:** The study found that 46.8% of respondents had no formal education, and 54.5% reported a monthly household income of less than 20,000 PKR. Barriers to healthcare included long distances to healthcare facilities (72%), lack of transportation (60%), high treatment costs (55%), and long waiting times (50%). Logistic regression revealed that education level, income, and proximity to healthcare services were significant determinants of access to healthcare. **Conclusions:** Socioeconomic factors such as education, income, and geographical distance significantly affect access to primary healthcare in rural Sindh. Targeted interventions, including improving healthcare infrastructure and addressing transportation and affordability issues, are crucial to enhancing healthcare accessibility in these areas.

INTRODUCTION

According to the user's perceived needs, accessibility is defined as "the possibility of the user to obtain the needed health care or the health service in the right place and the right time, and assumes the lack of geographical, economic, financial, social, cultural, organizational, or language obstacles" [1]. Ensuring access to healthcare is a fundamental right, as outlined in the EU Charter of Fundamental Rights, Article 33, which guarantees "the right of access to preventive healthcare and the right to benefit from medical treatment." [2]. Equitable and comprehensive access to a basic package of healthcare services is a necessary condition for a well-functioning and well-organized health system, alongside goals such as general coverage, continuity of care, patient choice, and reasonable medical costs. [3]. Healthcare disparities—differences in health and medical care standards among demographic groups—pose a significant challenge in rural settings. [4]. Utilization of maternal healthcare services is a prominent public health issue, highlighting the importance of understanding factors

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influencing health-seeking behaviour and service utilization at both individual and community levels. [5]. The World Health Organization (WHO) emphasizes that health services must be accessible, socially acceptable, and non-discriminatory, especially for disadvantaged populations. [6]. People in rural areas face difficulties accessing healthcare services due to limited transportation options and a shortage of healthcare providers [7]. Insufficient funding, irregular medication supplies, and a lack of equipment in rural areas of underdeveloped countries severely restrict primary healthcare services.[8]. The lack of universal health coverage in rural areas is a result of the imprecise use of "rural". Due to a lack of more precise methods for dealing with rural contexts, possibilities for action in these places are not well-defined and are only agrarian. The definition of rurality criteria that can differentiate between various realities is still unclear, even in the international debate, particularly when it comes to remote areas [9, 10]. In rural areas, limited education, cultural norms, and economic constraints contribute to the stigma surrounding help-seeking, while concerns about privacy in small communities further discourage individuals from accessing primary healthcare services [11]. Wealthy, continental nations like the US, Canada, and Australia have spearheaded rural health research and discussions [4, 12-14]. Australia, in particular, has become a major player in government programs about rural health [14]. Understanding the tactics outlined in the global discussion on rural health can aid in comprehending this issue, which has not yet gotten much attention. To guarantee adequate access to healthcare and to eradicate disparities, reasonable measures are desperately needed. This study is grounded in Penchansky and Thomas's Access Model, which conceptualizes healthcare access through five dimensions: availability, accessibility, accommodation, affordability, and acceptability. This framework provides a structured approach to analyzing barriers to primary healthcare in rural areas [15].

Using the Access Model as a guiding framework, this study aimed to identify the socioeconomic factors influencing access to primary healthcare in rural Sindh, Pakistan.

METHODS

This cross-sectional study was conducted over three months, starting from September, to December, 2024, following ethical approval from the Ethical Review Committee of Gambat Medical College, Pir Abdul Qadir Shad Jeelani Institute of Medical Sciences, Gambat (Ref No: PAQSJIMS/ORIC/ERC/:35). The study was conducted in the Basic Health Units (BHUs) and Rural Health Centers (RHCs) of five districts of Sindh, Pakistan, including, Hyderabad, Thatta, Badin, Tharparkar, and Larkana. These districts were selected to represent the rural areas of Sindh, considering the healthcare issues in these areas. The adult people aged 18 years and older residing in the selected districts were taken for the study. Individuals with severe mental or physical disabilities that impaired their ability to provide consent or respond to the questionnaire were excluded. 300 participants were selected using a 95% confidence level, a 5% margin of error, and an assumed prevalence of healthcare access issues in rural areas using OpenEpi (Online Calculator). The sample was stratified based on district and socioeconomic status (low -, middle- and high-income groups) to ensure equitable representation. Data were collected using a structured questionnaire designed in English and translated into Sindhi and Urdu for better comprehension. The questionnaire covered demographics (age, gender, marital status), socioeconomic indicators (education level, monthly household income, occupation, and household size), and healthcare access parameters (distance to the nearest facility, transportation availability, service costs, and waiting times). Additional variables included perceived quality of care, encompassing the availability of doctors, medicines, and diagnostic facilities. The questionnaire underwent pilot testing with 30 individuals from a similar demographic to ensure clarity and reliability before being administered in the field. Trained researchers conducted face-to-face interviews, ensuring ethical compliance and obtaining informed consent from participants. The collected data were anonymized and securely stored. Statistical analysis was performed using SPSS version 26.0. Descriptive statistics summarized the demographic and socioeconomic characteristics of the participants. Chi-square tests were used to identify associations between categorical variables, and logistic regression analysis was applied to examine the relationship between socioeconomic determinants and access to healthcare. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study population consisted of 300 participants with a mean age of 38.5 years (±12.7). Males constituted the majority (62.3%), and most participants were married (74.1%). Nearly half (46.8%) of the respondents had no formal education, while only 22.0% had completed secondary or higher education. The majority (54.5%) reported a monthly household income below 20,000 PKR, indicating a predominantly low-income population (Table 1). Agriculture was the most common occupation (42.1%), followed by daily wage labor (28.9%). The majority of participants lived in their own houses (70.3%), and a significant proportion (56.3%) reported owning land. However, access to utilities varied, with electricity being available to 89.0% of households, but only 64.3% had

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access to clean drinking water, and 59.3% had proper sanitation. The average dependency ratio was 1.5, reflecting a high burden of dependents on working individuals. These socioeconomic characteristics highlight significant vulnerabilities that may impact healthcare access in this population (Table 1).

Table 1: Demographic and Socioeconomic Characteristics of Participants

Variable	n (%)
Age (mean ± SD)	38.5 ± 12.7
Gender	
Male	187 (62.3)
Female	113 (37.7)
Marital Status	
Married	222 (74.1)
Single/Widowed/Divorced	78 (25.9)
Education Level	
No formal education	140 (46.8)
Primary education	94 (31.2)
Secondary or higher education	66 (22.0)
Monthly Household Income (PKR)	
<20,000	164 (54.5)
20,000–40,000	98 (32.7)
>40,000	38 (12.8)
Occupation	
Agriculture	126 (42.1)
Daily wage labor	87 (28.9)
Small business	52 (17.3)
Housing Type	
Owned	211 (70.3)
Rented	67 (22.3)
Temporary	22 (7.4)
Source of Income	
Farming	129 (43.0)
Salaried job	88 (29.3)
Remittance	51 (17.0)
Other	32 (10.7)
Land Ownership	
Yes	169 (56.3)
No	131 (43.7)
Access to Utilities	
Electricity	267 (89.0)
Clean drinking water	193 (64.3)
Sanitation	178 (59.3)
Dependency Ratio (mean ± SD)	1.5 ± 0.7
Household Size (mean ± SD)	6.7 ± 2.5

Access to healthcare was significantly influenced by distance to facilities and transportation availability. A substantial proportion (42.7%) of participants lived more than 10 kilometers from the nearest health facility, and 38.4% reported difficulties in accessing transportation. Limited healthcare access due to distance and transportation issues may result in delays in seeking medical care, worsening health outcomes, and increasing the burden of preventable diseases. To mitigate these barriers, potential strategies include establishing mobile health clinics, improving road infrastructure, and implementing community-based transport services to facilitate easier access to healthcare. Service costs were another critical barrier, with 51.3% stating that out-of-pocket expenses deterred them from seeking timely care. Waiting times at healthcare facilities were reported as excessively long by 39.2% of participants (Table 2).

Table 2: Barriers to Healthcare Access

Barrier	n (%)
Distance to Facility (>10 km)	128 (42.7)
Transportation Difficulty	115 (38.4)
Service Costs	154 (51.3)
Long Waiting Times	118 (39.2)

Perceived quality of care also emerged as a significant determinant. Approximately 48.9% of participants reported frequent unavailability of doctors, while 57.1% stated that essential medicines were often out of stock. The unavailability of essential medicines significantly compromises the quality of care, leading to ineffective treatment and poor patient adherence to prescribed therapies. Addressing this issue requires strengthening the supply chain management, increasing government funding for essential medicines, and ensuring adequate stocking at healthcare facilities. Additionally, 45.3% noted a lack of diagnostic facilities at BHUs and RHCs (Table 3).

Table 3: Perceived Quality of Care

Aspect of Care	n (%)
Doctor Availability	
Frequent unavailability	147 (48.9)
Medicine Availability	
Frequent unavailability	171 (57.1)
Diagnostic Facilities	
Lack of facilities	136 (45.3)

The logistic regression analysis revealed several significant socioeconomic factors associated with limited access to healthcare. Participants with no formal education were significantly less likely to access healthcare compared to those with secondary or higher education (OR: 2.34, $p<0.01$). Similarly, individuals with monthly incomes above 20,000 PKR were significantly more likely to access healthcare than those earning less than 20,000 PKR (OR: 2.81, $p<0.01$). Geographical barriers also played a critical role, as participants residing more than 10 kilometers from the nearest healthcare facility were 2.67 times more likely to experience access difficulties ($p<0.01$). Housing type and land ownership also influenced healthcare access; those living in rented or temporary housing and those without land ownership were

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less likely to access healthcare services (OR: 1.85 and OR: 2.14, respectively; both p<0.01). Limited access to clean drinking water further exacerbated healthcare barriers, as those lacking this basic utility were three times more likely to face access issues (OR: 3.02, p<0.01). A high dependency ratio (>1.5) was also associated with reduced healthcare access (OR: 2.25, p<0.01) (Table 4).

Table 4: Logistic Regression Analysis of Socioeconomic Determinants of Healthcare Access

Variable	Odds Ratio (OR)	95% CI	p-Value
Education Level (Secondary or Higher vs. No Formal Education)	2.34	1.52–3.59	<0.01
Monthly Income (>20,000 PKR vs. ≤20,000 PKR)	2.81	1.85–4.27	<0.01
Distance to Facility (>10 km vs. ≤10 km)	2.67	1.78–4.00	<0.01
Housing Type (Rented or Temporary vs. Owned)	1.85	1.19–2.87	0.01
Land Ownership (No vs. Yes)	2.14	1.38–3.33	<0.01
Access to Clean Drinking Water (No vs. Yes)	3.02	1.95–4.66	<0.01
Dependency Ratio (>1.5 vs. ≤1.5)	2.25	1.45–3.50	<0.01

DISCUSSION

According to the findings of this study the 46.8% of participants had no formal education, which is a critical barrier that severely confines health literacy and awareness of available healthcare options. This aligns with the findings of Abbas et al. (2019) [16], who highlighted the role of education in improving access to healthcare services. Education not only raises awareness but also allows individuals to find healthcare systems effectively. The economic landscape also plays an important role in accessing healthcare services. In this study nearly half of the participants belong to the category who earn less than 20,000 PKR monthly. This is another determinant of poor accessibility of healthcare services in these rural areas. Financial constraints in rural areas limit the availability, recruitment, and education of healthcare professionals, making it difficult to develop a strong primary healthcare workforce. Resource shortages hinder proper recruitment and retention, prevent providers from fulfilling their roles, and contribute to burnout [17]. As reported by Khalid and Ali (2020) [18], the high dependency ratio increases poverty, ultimately limiting the utilization of primary healthcare facilities. Distance and poor transportation appeared as significant barriers in this study in utilizing the basic health facilities. A large proportion of participants were residing more than 10 kilometers from the nearest healthcare facility. Distance has long been recognized as a critical determinant of access, as reported by Abbas et al. (2019) [16] who reported that many of the remote areas often lack the necessary transportation to healthcare services. Perhaps one of the most serious findings was the unavailability of healthcare services or poor quality. Nearly half of the participants reported the unavailability of doctors, and a majority reported the unavailability of basic medicines and a lack of diagnostic facilities. Similar observations were also reported by Islam and Amin (2024) [19] in their study pointing out the resource constraints in rural healthcare settings. Basic utilities, such as clean drinking water and sanitation, were also found to be lacking in many households. This not only contributes to the prevalence of preventable diseases but also poses significant challenges for healthcare-seeking behavior. Amri and Sihotang (2023) [20] emphasized that the absence of fundamental utilities exacerbates health vulnerabilities, making access to even primary healthcare an arduous task for rural populations. The study findings resonate with global research on rural healthcare access. For instance, Yar & Yasouri, (2024) [21] noted that rural populations in developing countries face similar patterns of geographic isolation, financial insecurity, and inadequate healthcare infrastructure. The parallels reinforce the universal need for targeted rural health policies, such as the deployment of mobile healthcare units, improved transportation infrastructure, and incentivized rural postings for healthcare professionals. Study limitations include reliance on self-reported data, introducing recall bias, and limited generalizability due to the cross-sectional design. Strengthening PHC with adequate staffing and resources is essential for improving healthcare access in rural areas. To mitigate the impact of essential medicine unavailability (57.1%), future initiatives should focus on strengthening supply chain management, expanding government subsidies for essential drugs, and integrating community-based distribution models to ensure consistent availability. Establishing public-private partnerships and utilizing digital inventory tracking systems can further reduce stockouts and improve medication access. To improve healthcare accessibility for individuals living more than 10 kilometers from facilities (42.7%), mobile health clinics, telemedicine services, and community-based healthcare worker programs should be expanded.

CONCLUSIONS

According to the findings of our study, education, poverty, unavailability of basic medical facilities and transportation are the significant factors that contribute to the poor access to the basic healthcare services in rural areas of the five selected districts of Sindh, Pakistan.

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Authors Contribution

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Methodology: SH, MT, AN, HS
Formal analysis: MT, SS[1]
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All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Histopathological Spectrum of Hysterectomy Specimen in Sonographically Bulky Uterus among Peri and Post-Menopausal Women

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Bulky Uterus, Fibroids, Endometrial Hyperplasia, Endometrial Cancer, Adenomyosis, Hysterectomy Findings

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ABSTRACT

A common sonographic characteristic in peri- and postmenopausal women is a sonographically bulky uterus, often associated with diverse uterine abnormalities, necessitating histopathological evaluation. **Objective:** To assess the histopathological changes in hysterectomy samples of peri- and post-menopausal females with sonographically enlarged uterus. **Methods:** The study participants were 150 postmenopausal women with a bulky uterus by ultrasound. This study was cross sectional and carried out in the Obstetrics and Gynaecology Department of Rashid Latif Meical College, Lahore from February 2022 to January 2024. Histopathological assessment was done on hysterectomy specimens to compare various diseases of the uterus including fibroids, endometrial hyperplasia, endometrial cancer, adenomyosis, and other benign/malignant diseases. Data were analyzed using SPSS version 23.0 and descriptive and comparative analysis methods including chi-square, Fisher exact test and logistic regression. **Results:** The majority of the participants, 53.33 % were peri-menopausal while 46.67 % were post-menopausal. The symptomatic complaints were abnormal bleeding and pelvic pain with rates of 60% and 33.3%, respectively. Uterine size greater than 12 cm was found to be more common in peri-menopausal women 62.5% compared to post-menopausal women 42.86%; p=0.02. Histopathology assessment showed that endometrial hyperplasia 37.5% vs 14.29%, p=0.02 and fibroid 50% vs 28.57%, p=0.02 were higher in peri-menopausal women. There were no statistically significant differences between the two groups for endometrial carcinoma, adenomyosis, cervicitis or atrophic endometrium. **Conclusion:** The women in their peri-menopausal period that had sonographically enlarged uteri had a higher rate of fibroids and endometrial hyperplasia than the post-menopausal women.

INTRODUCTION

The uterus, one of the female reproductive systems, has a number of structural and functional alterations at different stages of a woman's lifetime. These alterations are even more pronounced when uterus is in the transition from the premenopausal to the perimenopausal and postmenopausal periods [1, 2]. The menopause is a stage in a woman's life when she loses her menstrual cycles and experiences a change in the hormonal make up of her body which has an impact on the size and shape of the uterus [3]. Uterine sonography is a valuable diagnostic tool used to diagnose uterine enlargement, which may result from a number of pathologies [4]. Enlarged uterus is a frequent finding in women in their peri- and post-menopausal age group and the most common pathology include fibroid, endometrial hyperplasia, adenomyosis and sometimes cancer such as endometrial cancer [5, 6]. Fibroids, common benign tumours of the smooth muscles of the uterus, affect this population most; endometrial hyperplasia may progress to endometrial carcinoma, if not treated. Endometriosis, which is the growth of endometrial tissue in the muscle of the uterus, is also known to increase during women of childbearing age [7]. These conditions also often produce complaints such as abnormal uterine bleeding, pelvic pain or heaviness, which can be

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particularly debilitating in peri- and post-menopausal women [8]. While there is increasing knowledge of the uterine pathologies in postmenopausal women, there are very limited studies comparing the histopathological features between women in the peri-menopausal and the post-menopausal age groups with sonographically enlarged uterus [9]. Most studies focus on specific diseases like fibroids or certain demographics, often overlooking the subtle differences between perimenopausal and postmenopausal women [10]. However, while sonography is commonly employed to assess for enlarged uteri, the relationship between these sonographic findings and the histopathologic substrates has received little attention [11]. This research seeks to achieve this aim by examining histopathological characteristics of hysterectomy specimens from peri- and post-menopausal women with sonographically enlarged uteri. In this work, the authors attempt to describe the patterns and incidence of uterine pathologies in these different menopausal stages in order to compare the underlying pathologies. This will make it easier to find and treat conditions of the uterus in the pre and post-menopausal women.Although numerous papers demonstrate the incidence of uterine pathologies in peri- and post-menopausal women, little research is available that compares histopathological changes between these two groups with sonographically enlarged uterus. This lack of a clear comparison results in a major gap in the knowledge of how menopausal status affects the types of pathology seen in the uterus, especially in the most common conditions of post-menopausal women. This study fills this gap by comparing the results of histopathological examination of hysterectomy specimens in women of the peri- and postmenopausal age with sonographically enlarged uteri.

The current research also seeked to compare the patterns of uterine pathology during each menopausal phase to gain an understanding of the pathophysiology of these disorders and the implications for practice.

METHODS

This study was comparative cross sectional and carried out in the Obstetrics and Gynaecology Department of Rashid Latif Meical College, Lahore from February 2022 to January 2024. The sample size was determined using the proportion-based formula for cross-sectional studies: n=Z2P(1–P)d2; where Z represents the standard normal variate (1.96 for a 95% confidence level), P = 50% is the estimated prevalence of uterine pathology in peri- and post-menopausal women (based on institutional records), and d=0.05 is the margin of error.A total number of participants was n=150 women.To assess the histopathologic profile of hysterectomy specimens from peri- and postmenopausal women with sonographically enlarged uteri, included women were 40-65 years of age, with an identification of a bulky uterus through ultrasound, either perimenopausal or postmenopausal. The patients had hysterectomy for reasons which include but not limited to abnormal uterine bleeding, fibroids or other gynecological diseases. Patients with history of prior uterine surgeries, pelvic radiation or any co-morbid that may affect uterine pathology were excluded. Information that was collected include age, clinical indication for surgery and ultrasound examination results which include size of uterus. These hysterectomy specimens were subjected to histopathological analysis showing pathology of the uterus such as leiomyomas (fibroids), endometrial hyperplasia, endometrial carcinoma, adenomyosis and any other benign or malignant lesion. All the samples were stained with hematoxylin and eosin (HandE) in order to be analyzed by a pathologist to determine the size, number and position of the fibroids and examine for the presence of other diseases of the uterus such as hyperplasia or malignancy. This study was stratified random sampling was the best technique. Data were analyzed by SPSS version 23.0. The data obtained were analyzed by descriptive statistics in order to present demographic and clinical data, and comparative methods used to compare histopathological data of the peri- and post-menopausal women. Chi-square or Fisher's exact tests was employed in the data for analysis, and logistic regression analysis may be used for the determination of the relationship between clinical variables and histopathological outcomes. In the present study, received ethical approval from the Institutional Ethics Committee (IRB/2022/030). This work aims at presenting the histopathological findings of uterine pathologies in women with sonographically bulky uterus and searching for any possible patterns related to menopausal status. Informed consent was obtained from all participants prior to their inclusion in the study. Each participant was provided with detailed information about the study objectives, procedures, potential risks, and benefits, and consent was obtained in writing before any interventions were administered.

RESULTS

A total number of participants was n= 150, the largest demographic was those in the 51-60 years of age (40%) with those in the 40-50 years of age coming in second at 33.33% and the 61-65 years of age coming in third at 26.67%. The majority of the participants, 53.33 % were peri-menopausal while 46.67 % were post-menopausal. In terms of symptoms, 60% had abnormal bleeding, 33.3 % had pelvis pain and 6.6% had other symptoms.These findings show that abnormal bleeding and pelvic pain are the most common symptoms in peri- and post-menopausal women with a sonographically bulky uteri, see Table 1.

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Table 1: Demographic Characteristics (n=150)

Characteristic	Frequency (%)
Age Group	
40-50 Years	50 (33.33%)
51-60 Years	60 (40.00%)
61-65 Years	40 (26.67%)
Menopausal Status	
Peri-menopausal	80 (53.33%)
Post-menopausal	70 (46.67%)
Symptoms	
Abnormal Bleeding	90 (60.0%)
Pelvic Pain	50 (33.3%)
Others	10 (6.6%)

The sonographic findings in this study reveal several significant differences between peri-menopausal and post-menopausal women.The prevalence of having enlarged uterine size (>12 cm) was also higher in peri-menopausal women at 62.5% than in post-menopausal women at 42.86% (p=0.02). This is in agreement with the findings that more peri-menopausal women had an enlarged size of the uterus pointing to the fact that hormonal changes may cause the uterus to enlarge. In terms of uterine contour, the frequencies of regular and irregular contours were comparable between the two groups with no statistical difference (p=0.55). This suggests that the shape of the uterus was not differing much between the peri- and post- menopausal women in this study.The myometrial echogenicity had a slight variation; more peri menopausal women had homogenous echogenicity (75.00%) compared to post-menopausal women (57.14%) (p=0.05) this was however only statistically significant at the margin.Regarding endometrial thickness, 87.50% of peri-menopausal women had normal endometrial thickness while only 71.43% of post-menopausal women had normal endometrial thickness (p=0.01) this indicates that thickened endometrium 28.57% of post-menopausal women while 12.50% of peri-menopausal women.Lastly, the percentage of women with fibroids was higher in the peri-menopausal group (50%) than post-menopausal women (28.57%) (p=0.02).This means that the presence of fibroid might reduce after menopause perhaps as a result of hormonal change, (Table 2).

Table 2: Sonographic Finding among Peri-Menopausal and Post-Menopausal (n=150)

Sonographic Finding	Peri-Menopausal Frequency (%)	Post-Menopausal Frequency (%)	Chi-square/ Fisher's Test
Uterine Size			
Enlarged (>12 cm)	50 (62.5%)	30 (42.86%)	p=0.02
Normal (≤12 cm)	30 (37.5%)	40 (57.14%)	p=0.02
Uterine Contour			
Regular	65 (81.25%)	55 (78.57%)	p=0.55
Irregular	15 (18.75%)	15 (21.43%)	p=0.55
Myometrial Echogenicity			
Homogeneous	60 (75.00%)	40 (57.14%)	p=0.05
Heterogeneous	20 (25.00%)	30 (42.86%)	p=0.05
Endometrial Thickness			
Normal (≤10mm)	70 (87.50%)	50 (71.43%)	p=0.01
Thickened (>10mm)	10 (12.50%)	20 (28.57%)	p=0.01
Fibroids			
Present	40 (50.00%)	20 (28.57%)	p=0.02
Absent	40 (50.00%)	50 (71.43%)	p=0.02

Comparing the histopathological results between the peri- and post-menopausal women some differences were observed.Endometrial hyperplasia was found to occur more frequently in the peri-menopausal group (37.5%) than the post-menopausal group (14.29%) (p=0.02).On the other hand, fibroids were also noticed to be more prevalent in the peri-menopausal group (50%) than in the post-menopausal group (28.57%), (p=0.02).However, endometrial carcinoma, adenomyosis, and cervical cystic lesions' outcomes did not reveal any significant difference between the two groups with p values >0.05.Also, atrophic endometrium was prevalent in both groups with no statistical variety (p=0.75). The results of this study indicate that some histopathological changes, including hyperplasia and fibroids, are more common in peri-menopausal women, whereas others, including endometrial carcinoma and adenomyosis, are similar in both groups see Table 3.

Table 3: Histopathological Finding among Peri-Menopausal and Post-Menopausal (n=150)

Histopathological Finding	Peri-Menopausal Frequency (%)	Post-Menopausal Frequency (%)	p-Value
Endometrial Hyperplasia			
Present	30 (37.5%)	10 (14.29%)	p=0.02
Absent	50 (62.5%)	60 (85.71%)	p=0.02
Endometrial Carcinoma			
Present	5 (6.25%)	0 (0%)	p=0.09
Absent	75 (93.75%)	70 (100%)	p=0.09
Fibroids			
Present	40 (50.00%)	20 (28.57%)	p=0.02
Absent	40 (50.00%)	50 (71.43%)	p=0.02
Adenomyosis			
Present	15 (18.75%)	10 (14.29%)	p=0.42
Absent	65 (81.25%)	60 (85.71%)	p=0.42
Cervical cysts			
Present	10 (12.50%)	15 (21.43%)	p=0.31
Absent	70 (87.50%)	55 (78.57%)	p=0.31
Atrophic Endometrium			
Present	70 (87.50%)	60 (85.71%)	p=0.75
Absent	10 (12.50%)	10 (14.29%)	p=0.75

The comparison of the sonographic findings with the histopathological diagnoses showed some distinct relations in the peri- and post-menopausal patients.The size of the uterus was found to be larger in women with

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endometrial hyperplasia in peri-menopausal women (50%) than the post-menopausal women (28.57%, p= 0.01); however, fibroids were more frequent in peri-menopausal women (56.25%) than post-menopausal women (21.43% p=0.02). A significant relationship between irregular uterine contour and fibroids was observed in peri menopausal women (r=0.40). Endometrial carcinoma occurred more often in the peri-menopausal group (6.25%) but it did not achieve statistical distinction (p = 0.09). In sum, some USG findings such as the size and the contour of the uterus were more significantly related to the histopathological findings in the peri-menopausal women than the post-menopausal women (Table 4).

Table 4: Correlation between Sonographic Findings and Histopathological Diagnoses among Peri- and Post-Menopausal Women (n=150)

Sonographic Finding	Histopathological Diagnosis	Peri-Menopausal Frequency (%)	Post-Menopausal Frequency (%)	Chi-square/Fisher's Test	Spearman's Correlation
Enlarged Uterine Size	Endometrial Hyperplasia	40 (50%)	20 (28.57%)	p=0.01	r=0.35 (moderate)
	Endometrial Carcinoma	5 (6.25%)	0 (0%)	p=0.09	r=0.25 (weak)
	Fibroids	45 (56.25%)	15 (21.43%)	p=0.02	r=0.45 (moderate)
	Adenomyosis	10 (12.5%)	5 (7.14%)	p=0.35	r=0.15 (weak)
Irregular Uterine Contour	Endometrial Hyperplasia	30 (37.5%)	25 (35.71%)	p=0.75	r=0.10 (weak)
	Endometrial Carcinoma	3 (3.75%)	0 (0%)	p=0.16	r=0.08 (weak)
	Fibroids	35 (43.75%)	20 (28.57%)	p=0.03	r=0.40 (moderate)

The analysis reveals significant differences in sonographic findings between peri- and post-menopausal women. Enlarged uterine size (p=0.01, 95% CI: 1.12–3.87), fibroids (p=0.02, 95% CI: 1.35–5.67), and endometrial hyperplasia (p=0.02, 95% CI: 1.24–4.98) were more common in peri-menopausal women, likely due to hormonal influences. In contrast, adenomyosis (p=0.35, 95% CI: 0.55–3.15) and atrophic endometrium (p=0.13, 95% CI: 0.83–2.74) showed no significant differences, possibly due to insufficient power rather than a true lack of association. These findings align with existing literature, emphasizing the role of estrogen in fibroid and endometrial hyperplasia development, while postmenopausal atrophic changes appear consistent across groups see Table 5.

Table 5: Chi-Square Values among Peri- and Post-Menopausal Women (n=150)

Variable	Peri-Menopausal Frequency (%)	Post-Menopausal Frequency (%)	Chi-Square Value (χ^2)	p-Value	95% CI
Enlarged Uterine Size	40 (50%)	20 (28.57%)	5.21	0.01	1.12–3.87
Irregular Uterine Contour	30 (37.5%)	25 (35.71%)	0.05	0.75	0.72–2.11
Homogeneous Myometrial Echogenicity	20 (25%)	15 (21.43%)	0.32	0.57	0.61–2.38
Thick Endometrial Lining	15 (18.75%)	10 (14.29%)	0.34	0.55	0.58–2.46
Fibroids	45 (56.25%)	15 (21.43%)	7.34	0.02	1.35–5.67
Endometrial Hyperplasia	30 (37.5%)	10 (14.29%)	6.88	0.02	1.24–4.98
Endometrial Carcinoma	5 (6.25%)	0 (0%)	3.42	0.09	0.98–3.51
Adenomyosis	10 (12.5%)	5 (7.14%)	0.91	0.35	0.55–3.15
Atrophic Endometrium	25 (31.25%)	30 (42.86%)	2.29	0.13	0.83–2.74

The sonographic findings in this study exhibit varying levels of diagnostic performance. Enlarged uterine size demonstrated high sensitivity (80%) and moderate specificity (65%), with a balanced predictive value (PPV: 70%, NPV: 75%). Fibroids gave the highest sensitivity (85%) and a high positive predictive value (80%) which shows that fibroids could be effectively used to diagnose the presence of fibroids. Endometrial carcinoma had a specificity of 90% and negative predictive accuracy of 80%, and can be reasonably used to exclude the presence of malignancy. Endometrial hyperplasia also had favorable sensitivity (65%) and specificity (80%) indicating its efficiency in detection. A finding such as homogeneous myometrial echogenicity and thick endometrial lining had moderate sensitivity and specificity making them less reliable predictors. The diagnostic performance of adenomyosis and atrophic endometrium was moderate with reasonably acceptable PPV and NPV, even there is still some potential for improvement (Table 6).

Table 6: Sensitivity, Specificity, and Predictive Values of Sonographic Findings among Peri- and Post-Menopausal Women

Sonographic Finding	Sensitivity (%)	Specificity (%)	**Positive Predictive Value (PPV, %)**	**Negative Predictive Value (NPV, %)**
Enlarged Uterine Size	80	65	70	75
Irregular Uterine Contour	75	60	65	70
Homogeneous Myometrial Echogenicity	60	55	50	60
Thick Endometrial Lining	55	70	62	65
Fibroids	85	75	80	80

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Endometrial Hyperplasia	65	80	72	78
Endometrial Carcinoma	50	90	70	80
Adenomyosis	60	80	70	75
Atrophic Endometrium	60	50	55	60

DISCUSSION

The purpose of this research was to evaluate histopathological characteristics of hysterectomy samples from women with sonographically bulky uterus with emphasis on peri- and post-menopausal women. This research shows that a large number of women attending the outdoor clinic have various benign and malignant diseases which were evident from the histopathological examination of the uterus.These include fibroids, hyperplasia of the endometrium, and carcinoma of the endometrium which are tangible proofs of enlargement of the uterus [12]. Ultrasonography has become an important diagnostic tool in evaluating for abnormalities of the uterus, and the diagnosis of a bulky uterus has been well described in the literature.These findings are in conformity with other studies revealing that a large-sized uterus, particularly in the per- and post-menopausal women, is most likely to be due to benign diseases, including fibroids which are known to enlarge or may even increase in number during the perimenopausal stage of a woman's life due to hormonal changes and which showed that fibroids are the commonest histological diagnosis in such patients [13]. Nevertheless, there was also a high rate of endometrial alterations including hyperplasia and carcinoma.The previous study found that postmenopausal women with a bulky uterus are at risk of endometrial pathology, especially if they are taking unopposed estrogen or are obese.In agreement with this study, endometrial hyperplasia was identified as a histopathological diagnosis in the samples [14]. In the previous study, uterine fibroids were the most prevalent benign tumour in women. Fibroids in post-menopausal women are less common because of the low levels of oestrogen; however, fibroids may continue to exist or even increase in size due to other factors such as hormonal imbalances, obesity or hypertension. These results are in agreement with this assumption that sonographically bulky uteri in peri- and post-menopausal women are likely to be due to fibroids [15].The incidence of endometrial hyperplasia and carcinoma in this study is consistent with those of previous study indicated that a bulky uterus in post-menopausal women could be an indicator of endometrial pathology.The other associated co-morbidities such as obesity, diabetes and hormone replacement therapy were also seen in the cohort. Endometrial carcinoma though not very frequent was also seen and one should be careful while managing women with bulky endometrial thickness, particularly in case of abnormal bleeding [16].The incidence of adenomyosis in peri- and postmenopausal women with large uteri has been a subject of controversy in the literature.In contrast to fibroids, our study gave a lower prevalence of other endometrial pathologies.Several previous works, indicate that adenomyosis is less likely to be diagnosed in post-menopausal women but may sometimes occur, especially in the presence of fibroids.This is in concurrence with these results as adenomyosis was less frequently seen but was present among the patients [17, 18].Thus, the results of this study have significant clinical implications for the treatment of peri- and postmenopausal women with sonographically enlarged uteri.This is particularly the case in the management of conditions such as fibroids which are very common, and where the patient is either symptomatic or has only mild symptoms [19].Still, endometrial pathology, such as hyperplasia or carcinoma should be further evaluated, and possibly managed surgically, as depicted in studies previous literature note that early detection of endometrial cancer can be lifesaving [20]. Moreover, this study is in agreement with the literature regarding the importance of cautious interpretation of sonographic findings.Post-menopausal women with a large uterus should undergo further evaluation for endometrial abnormality if they present with other risk factors such as obesity, abnormal bleeding or use of hormone therapy by doing endometrial biopsy or hysteroscopy.To the best of the authors' knowledge, this is the first study to examine the proposed research questions and as such, it has some limitations.The present study may not have captured the characteristics of the entire peri- and post-menopausal population and future studies with larger sample sizes are needed to confirm the results. Also, the histopathological and radiological examination may be accompanied by inter-observer variability which may affect the results.Similarly, further studies should also be directed towards the evaluation of molecular mechanisms in the pathogenesis of uterine diseases for this age group, especially hormonal factors including estrogen.

CONCLUSIONS

Therefore, this study presents information on the histopathological examination of hysterectomy samples from perimenopausal - and postmenopausal women with sonographically enlarged uteri.This is consistent with the high rate of benign diseases, especially uterine fibroids, but also shows the high proportion of endometrial hyperplasia and less number of cancer.These findings show that there is need for proper examination of women of this age with abnormal vaginal bleeding.This work

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highlights the significance of careful clinical assessment and diagnostic modalities like radiology and histopathology to devise treatment plans in this group.

Authors Contribution

Conceptualization: NK
Methodology: AR, AM, MA, UA
Formal analysis: AM
Writing, review and editing: NK, AM, AR, MA, UA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparative Analysis of Serum Uric Acid Levels and Bone Mineral Density Among Elderly Individuals

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ABSTRACT

Osteoporosis is a major public health concern, particularly in aging populations. Emerging evidence suggests that serum uric acid (SUA) may influence bone mineral density (BMD) due to its antioxidant properties. However, the relationship between SUA levels and BMD remains controversial. **Objectives:** To compare BMD among individuals with low and high SUA levels and to determine the association between SUA and osteoporosis prevalence. **Methods:** This cross-sectional-comparative study was done at Liaquat University Hospital, Hyderabad, from March 2022 to August 2022. A total of 182 participants (≥50 years old) who underwent DEXA scan for BMD assessment were included using a purposive sampling technique.Participants were categorized into low SUA (<5.5 mg/dL) and high SUA (>5.5 mg/dL) groups. BMD at the lumbar spine, total hip, and femoral neck was recorded. Statistical analysis was performed using SPSS v.24, with t-tests, chi-square tests, and Pearson's correlation applied. A p-value of <0.05 was considered significant. **Results:** Participants with high SUA levels had significantly higher BMI (p=0.01). Lumbar spine BMD was significantly lower in the high SUA group (p=0.04), but no significant differences were observed for total hip and femoral neck BMD. Pearson's correlation showed a positive association between SUA and lumbar BMD (r=0.32, p=0.015). **Conclusions:** It was concluded that higher SUA levels were associated with lower osteoporosis prevalence but paradoxically lower lumbar BMD.

INTRODUCTION

The prevalence of osteoporosis increases with age. In Pakistan, where the aging population is steadily growing, osteoporosis and osteoporotic fractures have become a significant public health concern. The burden of osteoporosis is particularly high among postmenopausal women and elderly men, contributing to increased healthcare costs, disability, and mortality [1]. Osteoporotic fractures, particularly hip and vertebral fractures, can lead to severe pain, prolonged immobilization, reduced quality of life, and even death [2]. According to a systematic review, hip fractures in the elderly are associated with a one-year mortality rate of approximately 30%, highlighting the urgent need for effective prevention and management strategies [3]. Additionally, data suggest that osteopenia, a precursor to osteoporosis, significantly increases fracture risk and should also be aggressively managed to prevent future fractures [4]. Uric acid, a byproduct of purine metabolism, has been widely studied for its role in metabolic disorders such as gout, chronic kidney disease, and cardiovascular disease [5]. While hyperuricemia has traditionally been considered a risk factor for metabolic syndrome and inflammatory diseases [6], recent evidence

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suggests that uric acid also has antioxidant properties that may influence bone metabolism [7]. As a potent scavenger of free radicals, uric acid contributes to the body's overall antioxidant defense by neutralizing peroxyl radicals and chelating iron [8]. Since oxidative stress plays a crucial role in bone resorption and osteoporosis, some studies have proposed that higher serum uric acid (SUA) levels may be associated with higher bone mineral density (BMD) and a lower risk of fractures [9]. However, the relationship remains controversial, with some studies reporting no association or even an inverse correlation [10, 11]. Furthermore, much of the existing research has been conducted on women, with limited data available on men. In Pakistan, where malnutrition, vitamin D deficiency, and poor healthcare access contribute to a high prevalence of osteoporosis, understanding metabolic factors that influence bone health is crucial. Body weight and body mass index (BMI) have long been recognized as protective factors against BMD decline, with fat-free mass (FFM) having a stronger association with BMD than body fat mass (BFM) [12]. Some studies suggest that SUA may be positively correlated with both BMD and skeletal muscle mass index (SMI), indicating a potential indirect role in bone health through muscle mass preservation [12, 13]. However, research on the association between SUA and skeletal muscle mass remains limited and inconsistent, particularly in developing countries like Pakistan, where lifestyle and dietary habits differ significantly from Western populations [14].

This study aims to evaluate the relationship between serum uric acid levels and bone mineral density among elderly individuals in Pakistan.

METHODS

This cross-sectional comparative study was conducted at the Department of Orthopedics and Medicine OPD of Liaquat University Hospital, Hyderabad. The study was conducted from March 2022 to August 2022. Men and women aged 50 years and older who had undergone dual-energy X-ray absorptiometry (DEXA) scans for bone mineral density (BMD) assessment were selected through purposive sampling. A 5cc sample of fasting intravenous blood was collected to measure serum uric acid levels using the enzymatic colorimetric method in a standardized laboratory. Both BMD and serum uric acid levels were assessed on the same day. Patients with known metabolic bone diseases, chronic kidney disease, or conditions affecting uric acid metabolism were excluded from the study. The study was approved via the REC of Liaquat University of Medical and Health Sciences vide letter NO.LUMHS/REC/-046. Informed written consent was taken from each participant before enrollment in the study. The study sample included a total of 182 participants, equally divided into two groups: low serum uric acid levels (<5.5 mg/dl) and high serum uric acid levels (>5.5 mg/dl). Sample size was calculated via the Open Epi Sample Size Calculator (mean difference) by taking the mean BMD at the Lumbar spine in the Low Uric Acid group as 1.097±0.152 g/cm2 and in the High Uric Acid group as 1.161 ± 0.156 g/cm2 [15]. Power of study was 80%, and CI was taken as 95%. BMD was assessed at the lumbar spine (L1–L4), total hip, and femoral neck using a DEXA. Osteoporosis was diagnosed based on the World Health Organization (WHO) criteria, with a T-score ≤ -2.5 indicating osteoporosis and a T-score between -1.0 and -2.5 indicating osteopenia. Clinical and demographic data, including age, sex, BMI, smoking status and physical activity, were collected through structured questionnaires and medical records. Statistical analysis was conducted using SPSS v.24. The normality of the data was assessed via the Shapiro-Wilk test. The data were found to be normally distributed, so parametric tests were applied. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Independent t-tests and chi-square tests were used to compare variables between groups. Pearson's correlation analysis was conducted to assess the relationship between SUA levels and BMD. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of participants was comparable between the low uric acid and high uric acid groups (65.3 ± 7.1 vs. 64.8 ± 6.9 years, p=0.65), with a nearly equal distribution of males and females in both groups. However, BMI was significantly higher in the high uric acid group (26.5 ± 4.1 kg/m^2) compared to the low uric acid group (23.1 ± 3.5 kg/m^2, p=0.01), suggesting a possible association between higher uric acid levels and increased body weight. No significant differences were observed in smoking status (p=0.51) or physical activity levels (p=0.32) between the groups.The demographic and clinical characteristics of the study population are presented in Table 1.

Table 1: Demographic and Clinical Characteristics of the Study Population

Variables	Low Uric Acid (n=91)	High Uric Acid (n=91)	p-value
Mean Age (Years)	65.3 ± 7.1	64.8 ± 6.9	0.65
Male	45 (49.5%)	47 (51.6%)	0.75
Female	46 (50.5%)	44 (48.4%)	0.80
Mean BMI (kg/m^2)	23.1 ± 3.5	26.5 ± 4.1	0.01*
Smoking	30 (33.0%)	35 (38.5%)	0.51
Physical Activity	51 (56.0%)	58 (63.7%)	0.32

Participants with high uric acid levels had significantly lower lumbar spine BMD (0.85 ± 0.12 g/cm^2) compared to those with low uric acid levels (0.93 ± 0.15 g/cm^2, p = 0.04). However, BMD differences at the total hip (p=0.25) and

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femoral neck (p=0.67) were not statistically significant. Bone mineral density (BMD) measurements are given in Table 2.

Table 2: Bone Mineral Density (BMD) by Uric Acid Levels

BMD Site	Low Uric Acid (n=91)	High Uric Acid (n=91)	p-value
Lumbar Spine (g/cm^2)	0.93 ± 0.15	0.85 ± 0.12	0.04*
Total Hip (g/cm^2)	0.78 ± 0.16	0.86 ± 0.11	0.25
Femoral Neck (g/cm^2)	0.72 ± 0.9	0.81 ± 0.14	0.67

A significantly higher proportion of osteoporotic patients were found in the low uric acid group (41.8%) compared to the high uric acid group (23.1%, p=0.02). Meanwhile, osteopenia was relatively balanced between the two groups (44.0% vs. 47.3%: p=0.18), while normal BMD was more common in the low uric acid group (29.6% vs. 14.2%: p=0.056). These findings further support the hypothesis that higher uric acid levels might be associated with better bone health and lower osteoporosis risk. The prevalence of osteoporosis and osteopenia across uric acid groups is shown in Table 3.

Table 3: Osteoporosis and Osteopenia Prevalence among Groups

Bone Status	Low Uric Acid (n=91) (<5.5 mg/dl)	High Uric Acid (n=91) (>5.5 mg/dl)	p-value	CI (95%)
Osteoporosis	38 (41.8%)	21 (23.1%)	0.02*	0.01 to 0.16
Osteopenia	40 (44.0%)	43 (47.3%)	0.18	-0.07 to 0.03
Normal BMD	27 (29.6%)	13 (14.2%)	0.056	-0.04 to 0.06

The correlation analysis presented a significant positive correlation between serum uric acid levels and lumbar spine BMD (r=0.32, p=0.015), reinforcing the previous findings of a protective effect of uric acid on bone mass. However, no significant correlation was observed between uric acid levels and total hip BMD (r=0.35, p=0.65) or femoral neck BMD (r=0.40, p=0.08), suggesting site-specific effects of uric acid on bone density, as shown in Table 4.

Table 4: Correlation Between Serum Uric Acid Levels and BMD

Variables	p-value		CI (95%)
Uric Acid vs Lumbar BMD	0.32	0.015*	0.06 to 0.52
Uric Acid vs Hip BMD	0.35	0.65	-0.18 to 0.62
Uric Acid vs Femoral BMD	0.40	0.08	-0.04 to 0.67

DISCUSSION

The present study aimed to analyze the association between serum uric acid levels and bone mineral density (BMD) among osteoporotic and non-osteoporotic patients. Our findings indicate that higher serum uric acid levels are associated with significantly lower lumbar spine BMD (p=0.04), while no significant differences were observed at the total hip or femoral neck BMD sites.Several studies have investigated the potential protective effect of uric acid on bone metabolism.A meta-analysis by Kim *et al.*, suggested that higher serum uric acid levels were associated with greater BMD and lower fracture risk in older adults [16].This was attributed to the antioxidant properties of uric acid, which may reduce oxidative stress and subsequent bone loss. However, our study does not fully support this hypothesis, as lumbar BMD was significantly lower in the high uric acid group, contrary to expectations. Our findings are more aligned with the study by Robles-Rivera *et al.*, which found that elevated uric acid levels were not consistently associated with improved BMD across all skeletal sites [17].They reported that uric acid might exert different effects depending on bone location, which aligns with our observation that lumbar BMD was significantly affected while hip and femoral neck BMD were not. Interestingly, our results showed a significantly higher BMI in the high uric acid group (p=0.01).Obesity and higher BMI are well-documented protective factors against osteoporosis due to the mechanical loading effect on bones and increased estrogen production from adipose tissue [18].Therefore, it is possible that higher BMI rather than uric acid levels contributed to bone health in our study population, making it difficult to isolate the direct effect of uric acid on BMD.This observation is supported by Tu *et al.*, who reported that higher BMI was more strongly correlated with increased BMD than uric acid levels alone [19].In contrast, a study conducted by Tanaka *et al.*, found that hyperuricemia was associated with increased BMD in postmenopausal women [20].Previous research has highlighted that estrogen plays a crucial role in regulating bone remodeling and that postmenopausal women may experience different responses to uric acid compared to men or premenopausal women [21].Our study population included both males and females, which could have influenced the results differently from studies that focused solely on postmenopausal women. Regarding osteoporosis prevalence, our findings indicated that osteoporosis was significantly more common in the low uric acid group (41.8%) than in the high uric acid group (23.1%, p=0.02).This aligns with a study by Yan *et al.*, which reported that low serum uric acid levels were associated with a higher risk of osteoporosis and fractures [22].However, unlike their study, our research found that lumbar BMD was lower in individuals with high uric acid levels, adding complexity to the relationship between uric acid and bone health

CONCLUSIONS

It was concluded that our study provides mixed evidence on the association between serum uric acid levels and bone health. While osteoporosis prevalence was lower in individuals with high uric acid levels, lumbar spine BMD was paradoxically lower in this group, suggesting a complex and site-specific relationship between uric acid and bone metabolism. Additionally, BMI differences between the groups may have confounded the observed associations.

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Authors Contribution

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Methodology: NA, SAB, IKM, MFJ, SF
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Writing review and editing: SAB, IKM, RAB, SF
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Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Obstetrical Anal Sphincter Injuries in Nulliparous Women Undergoing Normal Vaginal Delivery in Tertiary Care Hospital at Khyber Pakhtunkhwa

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ABSTRACT

Obstetric Anal Sphincter injury is one of the most devastating complications of vaginal delivery. The incidence is higher in instrumental deliveries, but OASI can be avoided with proper techniques, such as mediolateral episiotomy, and pre-assessment of fetal head position, such as vertex mal-presentation and progress of labour. **Objectives:** To find the frequency of Obstetric anal sphincter injury during normal vaginal deliveries in nulliparous female from August 2023 to September 2024. **Methods:** It was a cross-sectional study conducted in the Gynaecology and Obstetrics Department, Lady Reading Hospital.The study included 162 nulliparous women with Cephalic presentation undergoing Normal Vaginal Delivery, among them the patient with Obstetric Anal Sphincter Injury were identified to find the frequency.The data were collected by a structured questionnaire and analyzed with SPSS version 26.0. **Results:** Out of the total 162 populations, 6 (3.92%) individual had their OASIs. Five individuals had 3rd while one individual had a 4th-degree injury.The mean age was 26.33 years with a standard deviation of 4.73. The oldest mother was 38 years old, and the youngest was 18 years old. BMI from 18.5 to 21.9 (Kg/m2) was more frequent in a population of 67. Regarding the presentation of the fetus's head at birth, 146 presented Cephalic, 5 as transverse and 11 as oblique on presentation. **Conclusions:** It was concluded that the study shows the frequency of Obstetric Anal Sphincter injuries as 6 out of 162 individuals, having injuries of different degrees.

INTRODUCTION

Obstetric anal sphincter injuries (OASIS) occur after vaginal delivery.The internal and external anal sphincter and the anal mucosa are affected by these injuries, in more severe cases, which are referred to as third- and fourth-degree perineal lacerations [1].OASIs are multifactorial among adolescents; it is dependent on maternal as well as fetal conditions. Diabetic mothers were considered at high risk [2]. In mothers of late age at first birth, increased blood pressure and birth weight of the baby were considered independent risk factors [3]. The risk of OASI can be evaluated before delivery by checking the mother's height, performing an ultrasound of the fetus' weight, determining the position of the occiput, and evaluating episiotomy performance [4]. Two independent risk factors in women who have undergone previous vaginal delivery are only one previous vaginal delivery and the weight of the baby. The other risk factors were episiotomy and vacuum-assisted vaginal delivery [5-7]. Fecal incontinence is one of the consequences of OASI. The obstetric anal sphincter injury can be diagnosed with an ultrasound or a patient experiencing anal incontinence [8, 9].To avoid injuring the obstetrical anal sphincter, it is recommended to select a delivery style that reduces the amount of trauma that occurs during the birth process.For instance, select a vacuum delivery rather than a forceps delivery, and take into consideration the mediolateral episiotomy technique

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[10, 11]. Obstetrical anal sphincter injury can be prevented by identifying risk factors. Both antenatal and intrapartum obstetrical practice can lessen the injury, as prenatal massage from the last stage of pregnancy can improve the elasticity of muscles and give the perineum space to stretch [12]. Repair of third- and fourth-degree lacerations should follow a systematic approach, progressing from deep to superficial structures: the anorectal mucosa, anal sphincter complex, rectovaginal fascia, perineal body musculature, perineal skin, and vaginal muscular and epithelium [13].A single continuous stitch is the most effective method of treatment for lacerations of the second degree. Lacerations of the anal sphincter complex require additional expertise, exposure, and lighting; it is recommended that attempts be made to relocate the procedure to the operating room [14]. This study was conducted to cover a population gap, as such a study had not been conducted in our demographics, and to see the frequency of OASIs in our ethnic group. In addition to this, our study has focused particularly on nulliparous women. Normal vaginal delivery was the focus of the current study. This study aims to determine the frequency of OASIS in women who are undergoing the normal vaginal delivery. By taking into consideration the risk factors that have been demonstrated in earlier research, this study also assists in determining which pregnant women are at risk for OASIS.

METHODS

A cross-sectional study was carried out including 162 individuals to assess the frequency of Obstetrical Anal Sphincter Injuries in nulliparous women, in the Department of Gynaecology and Obstetrics, Lady Reading Hospital-MTI, Peshawar. The study was conducted from August 2023 to September 2024. A non-probability consecutive sampling technique was used. The Ethical Approval of this research was obtained from IRB Lady Reading Hospital (LRH) Medical Teaching Institute (MTI), and the reference number was 727/LRH/MTI. The inclusion criteria used include All pregnant women having single intrauterine pregnancy, normal vaginal delivery without instrumentation, only Primary-Gravida, no Previous History of 3rd or 4th Degree Tear, no Previous recto vaginal fistula repair, and patients delivered in Hospital Setting. The Exclusion criteria include the Fetus having a breech presentation, and women not willing to give consent were excluded from the study. Using the WHO sample size calculator, the sample size of the study was found, keeping the confidence interval as 95%, 7% absolute precision and a previously reported frequency of 29.2%. The sample size was 162 patients. After obtaining approval from the ethical committee of the hospital, the patients who were fulfilling the selection criteria, in the Gynaecology and Obstetrics Outpatient Department (OPD), LRH Peshawar. A Consultant Gynaecologist interviewed the patients along with the researcher. The aim of the study was discussed and explained to the patients, and then informed consent was taken. Demographics such as age, weight, height, period of gestation, and parity were noted. A detailed medical history was obtained, and a meticulous physical examination was performed. Relevant baseline labs, including CBC, RFTs, LFTs, ELECTROLYTES, FBS, VIRAL PROFILE, and U/S ABDOMEN, were sent to rule out any other pathology or multiple pregnancies. The researcher collected data and entered it into questionnaires. Confidentiality was ensured by masking the names of patients, and it was used for research purposes. Data entry and analysis were carried out using SPSS version 26.0. For quantitative variables like age, BMI, POG, fetal position during labor, and parity mean and standard deviation were calculated. Frequency and percentage were calculated for categorical variables like gender and type of previous delivery. The BMI, gestational age at delivery, and fetal presentation at birth were stratified and shown in tables. Finally, the mode of induction of labour was measured as frequency.

RESULTS

The mean age of the population was 26.33 with an SD of 4.73. The youngest among the mothers was 18 years old, while the oldest was 38 years old. The weight and height of mothers are used in measuring BMI (Kg / m^2) among them 21 mothers have BMI less the 18.5 (Kg / m2), 67 mothers have BMI from 18.5 to 21.9 (Kg / m^2), 59 have a BMI range from 22 to 24.9 (Kg / m^2), while 12 mothers have BMI of 25 to 30 (Kg / m2). And only one mother has a BMI of more than 30 (Kg / m^2) (Table 1).

Table 1: Demographics Presentation of participants (n=162)

Variables	Mean ± SD/ n (%)
Age (Years)	26.33 + 4.73
Minimum	18.00
Maximum	38.00
BMI (Kg / m^2)	
Less the 18.5	21 (12.96%)
18.5 to 21.9	67 (43.35%)
22 to 24.9	59 (36.41%)
25 to 29.9	12 (7.4%)
More Than 30	1 (0.61%)

Only term mothers were included in the study, which was divided into two groups: those with gestational age at delivery from 37 to 42 weeks, which had 155 individuals, and those with gestational age at delivery more than 42 weeks, which had 7 individuals. The presentation of the fetus's head at birth is shown in Figure 3: 146 presented cephalic, 5 presented transverse, and 11 presented oblique (Table 2).

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Table 2: Gestational Age at Delivery and Fetal Presentation at Birth

Variables		Number of Mothers
Gestational Age at Delivery	37 to 42 weeks	155
	More than 42 weeks	7
Variables		
Fetal Presentation at birth	Cephalic	146
	Transverse	5
	Oblique	11

Out of the total 162, population, 6 (3.92%) individual had their OASIs. 5 individuals had 3rd degree and only one had a 4th-degree injury. So the total frequency of OASI in our study population was 6 out of 162 primigravida mothers (Table 3).

Table 3: Frequency of OASIS

Frequency of OASIS		
Total Number of NVDs (162)	Yes	No
3rd Degree	5	–
4th Degree	1	–
Total	6 (3.92%)	156

DISCUSSION

Our study was conducted on a very specific population i.e. primigravida, full-term having a normal vaginal delivery.It was conducted in a closed, monitored environment.The frequency of total OASIs is 9 out of 162 primigravida mothers.A study by Sørbye *et al.*, shows that women from South Asia had the highest incidence of OASI at 6.2%, followed by those from Southeast Asia, East Asia, and the Pacific at 5.7%, and Sub-Saharan Africa at 5.2% [15].Kwok and fellows studied the prevalence of OASI in nulliparous women as 7.8% undergoing normal vaginal delivery [16]. According to a study by Marschalek, migrant women encounter a novel physical and social environment, where limited language proficiency significantly hinders social integration, leading to inadequate health literacy and suboptimal care post-migration [17].Longo and his co-worker studied risk factors that prone the patient to OASIs undergoing normal vaginal delivery.They observed that the risk was twice for vacuum delivery in nulliparous women and the risk decreased with previous vaginal delivery and also in spontaneous vaginal delivery.Epidural Anesthesia was considered preventive as it lowered the incidence of OASIS.Malpresentation of the fetal head and circumference of the fetal head were considered fetal risk factors [18].Johannesson *et al.*,studied the mixed response of women regarding the role of physiotherapy in recovery from obstetric anal sphincter injury some women felt difficulty and tiresome about therapy, while others were very happy with the outcome and find themselves lucky to have it [19]. A study shows that Anal sphincter rips are frequently overlooked after delivery, and even when they are identified, they are frequently not well healed, leaving a high percentage of residual abnormalities following reconstruction, according to mounting data. Between 25% and 50% of individuals will continue to experience anal incontinence even after initial repair and postpartum diagnosis [20].Antonakou, studied that women suffering from anal incontinence after OASIs feels awkward and ashamed and hesitate to seek medical attention and the condition is termed as OASIs syndrome [21].In a cohort study, Eggebø and fellows, showed that lateral episiotomy is associated with a lower incidence of OASIs in nulliparous women [22].It is a study that mediolateral or lateral episiotomy is preventive for OASIs, decreasing the prevalence by 45%, while Forceps delivery is associated with a higher incidence of OASIs, the risk of OASIs is reduced to half by using vaccume instead of forcep delivery (aOR=1.92, 95% CIs=1.79–2.05)[23].The strength of our study was that it focused on single intrauterine primigravida females delivering babies via normal vaginal delivery in term babies. So, it helps us access the accurate frequency of this group and provides ground for further study.The study's limitation is that it didn't provide an association with BMIs or age, and other confounders were not controlled.

CONCLUSIONS

It was concluded that the frequency of obstetrical anal sphincter injuries in women undergoing normal vaginal delivery for nulliparous women in our study is 6 out of 162, (3.92%). However, further research is required in the field with controlled confounding factors.

Authors Contribution

Conceptualization: NF
Methodology: NF, NA, AS
Formal analysis: NF, PR, AF
Writing review and editing: AF

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Maternal Vitamin A Deficiency in Pregnancy and its Relationship with Maternal and Neonatal Haemoglobin Concentration

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ABSTRACT

Vitamin A Deficiency (VAD) remains a major nutritional concern, particularly in low-income countries, and is associated with maternal anemia and adverse neonatal outcomes. **Objective:** To assesses the correlation between maternal Vitamin A levels and hemoglobin concentrations in both mothers and neonates along with its impact on neonatal health outcomes. **Methods:** A cross-sectional study was conducted at Khyber medical university (Hayatabad Medical Complex, Peshawar), over one year.Pregnant women in their third trimester were recruited based on predefined eligibility criteria. Serum Vitamin A levels were measured using high-performance liquid chromatography (HPLC), and hemoglobin levels were assessed in both maternal and neonatal blood samples. Statistical analyses included t-tests, chi-square tests, and binary logistic regression. **Results:** Among 121 participants, 84% were Vitamin A deficient (<0.70 µmol/L). Maternal hemoglobin was significantly lower in the deficient group (10.38 g/dL vs. 11.83 g/dL, p = 0.001), as was neonatal hemoglobin (13.40 g/dL vs. 14.31 g/dL, p = 0.001). Low birth weight was more common in the deficient group (31.0% vs. 10.8%), though not statistically significant after Bonferroni correction. Logistic regression confirmed Vitamin A deficiency as an independent predictor of low neonatal hemoglobin (AOR = 3.174, p = 0.043). **Conclusions:** Vitamin A deficiency is significantly associated with lower maternal and neonatal hemoglobin levels.These findings highlight the importance of maternal nutrition interventions to prevent anemia-related complications.

INTRODUCTION

Vitamin A deficiency (VAD) is a significant nutritional concern worldwide, particularly in low- and middle-income countries, affecting approximately 19 million pregnant women globally [1]. VAD during pregnancy not only impacts maternal health but is also associated with an increased risk of adverse neonatal outcomes, including low birth weight, preterm birth, and neonatal anemia [2]. Vitamin A plays a crucial role in immune function, cell growth, and hematopoiesis, the process of blood formation. In regions where dietary intake of Vitamin A is inadequate, its deficiency presents a serious public health concern, particularly for pregnant women and newborns [3]. The prevalence of VAD among pregnant women varies across different regions, with higher rates reported in Asia and Africa [1]. In Pakistan, studies indicate a notably high prevalence of Vitamin A deficiency among women of reproductive age, raising concerns about its impact on maternal and neonatal health [4, 5]. Poor dietary diversity, low socioeconomic status, and limited healthcare access contribute to this nutritional deficiency, particularly in vulnerable populations. Given that maternal anemia is common in these regions, it is essential to explore the role

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of Vitamin A in hemoglobin synthesis and anemia prevention. During pregnancy, the maternal demand for essential nutrients, including Vitamin A, increases to support fetal development and physiological adaptations for childbirth [6]. Low serum retinol levels, indicative of Vitamin A deficiency, may impair red blood cell formation and contribute to maternal anemia [7]. Pregnancy-related anemia is associated with increased risks of low birth weight, preterm delivery, and neonatal health complications. Ensuring adequate Vitamin A intake is therefore critical for maintaining optimal hemoglobin concentrations and reducing anemia in both mothers and neonates [8, 9]. Notably, very limited research has specifically examined the role of maternal Vitamin A deficiency in these neonatal outcomes, highlighting a significant gap in the literature. This study hypothesized that Vitamin A deficiency was associated with lower hemoglobin levels in mothers and neonates and increases the risk of adverse neonatal outcomes, including low birth weight and NICU admission. The primary objective of this research was to assess the correlation between maternal Vitamin A levels and hemoglobin concentrations in both mothers and newborns along with its impact on neonatal health outcomes. Additionally, the study aims to determine the prevalence of Vitamin A deficiency among pregnant women, compare hemoglobin levels between Vitamin A deficient and sufficient groups, and evaluate neonatal outcomes such as low birth weight and NICU admission. However, there is a notable lack of research investigating the direct link between maternal Vitamin A status and hemoglobin concentration in both mothers and neonates, further emphasizing the need for studies in Pakistan.

In this study, Vitamin A deficiency is defined as serum retinol levels <0.70 µmol/L, measured using high-performance liquid chromatography (HPLC). This approach provides an accurate and objective assessment of Vitamin A status, distinguishing it from dietary intake assessments or clinical signs, which may be influenced by other factors.

METHODS

This cross-sectional study was conducted at Hayatabad Medical Complex, Peshawar, a tertiary care hospital, affiliated with Khyber Medical University. The study spanned one year (January 22, 2018 – January 22, 2019) to investigate the association between maternal Vitamin A levels and hemoglobin concentration in both mothers and neonates, along with its impact on neonatal health outcomes. Hayatabad Medical Complex provides maternal and child healthcare services, catering to a diverse population. However, since the study was conducted in a tertiary care setting, there is a possibility of selection bias, as hospital-based populations may differ from the general pregnant population in primary healthcare centers or rural areas. Approval for the study was obtained from the Ethics Review Committee (ERC) of Khyber Medical University (Ref No:DIR/KMU-ASandRB/MV/000737).Informed consent was obtained from all participants, ensuring confidentiality and voluntary participation.Participants were informed about the study's objectives, procedures, and potential risks before enrolmentA convenience sampling method was used, recruiting pregnant women from hospital antenatal and delivery units based on eligibility criteria.The inclusion criteria comprised pregnant women in the third trimester (>28 weeks), willingness to provide blood samples, and the absence of chronic illnesses such as diabetes and hypertension.Exclusion criteria included women with multiple pregnancies, those taking vitamin A supplements, and individuals with pre-existing chronic conditions. The sample size was determined using a standard deviation (SD) of 1.75 g/dL for maternal hemoglobin, based on previous studies (Neves *et al.*, 2019) [9]. Using a 95% confidence level (Z = 1.96) and 80% power (Z = 0.84), the estimated required sample size per group was 48 participants, totaling 96 participants. Formula Used: where: $\sigma = 1.75$ g/dL (standard deviation), d = 1.0 g/dL (effect size), Z ($\alpha/2$) = 1.96 (for 95% CI, two-tailed), Z (β) = 0.84 (for 80% power). To account for dropouts and variability, the final sample size was increased to 121 participants. Structured interviews and medical records were used to collect demographic and clinical data, including: Maternal age, education, occupation, monthly income. BMI was calculated using the standard formula (weight in kg/height in m^2), and nutritional status was categorized according to WHO classification: BMI <18.5 kg/m^2 as malnourished and 18.5–24.9 kg/m^2 as normal.

Laboratory Analysis: Vitamin A Measurement (HPLC Protocol). Blood samples were collected after an overnight fast.Serum Vitamin A levels were measured using High-Performance Liquid Chromatography (HPLC), a precise and reliable method for retinol detection.

HPLC Protocol: Serum was extracted using hexane, evaporated under nitrogen gas, and reconstituted in methanol.

Chromatographic Conditions: Column: C18 reverse-phase column

Mobile Phase: Methanol:water (98:2) Detection: UV detector at 325 nm Retention Time: ~4.5 minutes. Participants were classified into two groups based on serum retinol levels: Deficient: <0.70 µmol/L. Sufficient: ≥0.70 µmol/L. Neonatal Hemoglobin Measurement and Consideration of Delivery Factors. Maternal blood samples were collected at the time of admission for delivery, while neonatal cord blood samples were collected immediately after birth using an automated hematology analyzer Sysmex XN-1000 (Sysmex Corporation, Japan). Hemoglobin was measured in grams per deciliter (g/dL). Potential Confounding Factors (Cord Clamping and Delivery Mode). Delayed cord clamping and mode of delivery were

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not specifically accounted for in neonatal hemoglobin measurements. This represents a study limitation as these factors could influence cord blood hemoglobin levels. Data analysis was performed using SPSS version 24.0. The statistical analysis included calculating means and standard deviations for continuous variables like age, BMI, and gestational age, and frequencies for categorical variables such as parity, education, occupation, monthly income, and nutritional status. T-tests, compare maternal and neonatal hemoglobin levels between Vitamin A Deficient vs. Sufficient groups. Chi-square tests: Analyze associations between Vitamin A status and neonatal outcomes(preterm birth, low birth weight, NICU admission, jaundice). Binary logistic regression: Adjusted for maternal anemia, BMI, socioeconomic status, and parity to control for confounders influencing hemoglobin levels. A p-value <0.05 was considered statistically significant, with Bonferroni correction applied for multiple comparisons.

RESULTS

The study population had a mean age of 28.00 years (SD = 4.70) and an average BMI of 24.62 kg/m^2 (SD = 3.393). The mean gestational age among participants was 35.9 weeks (SD = 2.05). In terms of parity, 44.6% of women had one child, while 28.1% were nulliparous. Regarding education, 65.3% had a high school education, and 34.7% attended college. Employment status was nearly evenly split (47.9% employed, 52.1% unemployed). More than half of the participants (52.1%) had a monthly income between 15,000–25,000 PKR. Nutritional status data indicated that 34.7% of women were malnourished, while 65.3% had normal nutritional status(Table 1).

Table 1: Socio-demographic Characteristics of the participants

Characteristics	(Mean ± SD) / Frequency (%)
Age (Years)	28.00 ± 4.70
BMI (Kg/m^2)	24.62 ± 3.393
Gestational Age (Weeks)	35.9 ± 2.05
Parity	
0	34 (28.1%)
1	54 (44.6%)
2	17 (14.0%)
3	16 (13.2%)
Education Level	
High School	79 (65.3%)
College	42 (34.7%)
Occupation	
Employed	58 (47.9%)
Unemployed	63 (52.1%)
Monthly Income (PKr)	
<15000	33 (27.3%)
>15000-25000	63 (52.1%)
>25000- 75000	25 (20.7%)
Nutritional Status	
Malnourished	42 (34.7%)
Normal	79(65.3%)

The majority of participants (84%) were in the Vitamin A deficient group, with a mean vitamin A level of 0.66 µmol/L. Maternal hemoglobin levels were significantly lower in the deficient group (10.38 g/dL) compared to the sufficient group (11.83 g/dL, p = 0.001). Similarly, neonatal hemoglobin levels were lower in the deficient group (13.40 g/dL) than in the sufficient group (14.31 g/dL, p = 0.001). These findings suggest an association between Vitamin A deficiency and lower hemoglobin levels in both mothers and their neonates(Table 2).

Table 2: Maternal Vitamin A and Hemoglobin Levels by Status with P-Values

Vitamin A Status	Participants (%)	Mean Vitamin A Level (µmol/L)	Maternal Hemoglobin (g/dL)	Neonatal Hemoglobin (g/dL)	P-Value (Maternal Hemoglobin and Neonatal Hemoglobin)
Deficient (< 0.70 µmol/L)	84	0.66 ± 0.04	10.38 ± 0.62	13.40 ± 0.73	0.001
Sufficient (≥ 0.70 µmol/L)	37	0.80 ± 0.05	11.83 ± 0.66	14.31 ± 0.69	0.001

Preterm Birth 19.0% of neonates in the Vitamin A deficient group were born preterm, compared to 13.5% in the sufficient group. However, this difference was not statistically significant (p = 0.459, Bonferroni-corrected p = 1.836). The odds ratio (OR = 0.664, 95% CI: 0.224–1.972) further indicates no significant association (Table 3).

Low Birth Weight (<2.5 kg) 31.0% of neonates in the Vitamin A deficient group had low birth weight, compared to 10.8% in the sufficient group. The association was statistically significant before Bonferroni correction (p = 0.018). However, after correction, it was no longer significant (corrected p = 0.072). The odds ratio (OR = 2.863, 95% CI: 1.076–7.621) suggests a potential but borderline association (Table 3). NICU Admission was slightly higher in neonates from Vitamin A deficient mother (19.0%) compared to the sufficient group (10.8%). This difference was not statistically significant (p = 0.261, Bonferroni-corrected p = 1.044). The odds ratio (OR = 0.515, 95% CI: 0.160–1.663) confirms the lack of a significant relationship (Table 3). Jaundice 9.5% of neonates in the deficient group had jaundice, compared to 10.8% in the sufficient group. The difference was not statistically significant (p = 0.827, Bonferroni-corrected p = 3.308). The odds ratio (OR = 1.152, 95% CI: 0.324–4.092) also supported the lack of a significant association (Table 3).

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Table 3: Neonatal Outcomes by Maternal Vitamin A Status with Bonferroni-Corrected p-Values

Neonatal Outcome	Deficient Frequency (%)	Sufficient Frequency (%)	p-value (Before Correction)	p-value (After Bonferroni Correction)	95% CI for Odds Ratio (AOR)	Significant After Correction?
Preterm Birth	16 (19.0%)	5 (13.5%)	0.459	1.836	(0.224 – 1.972)	No
Low Birth Weight (<2.5kg)	26 (31.0%)	4 (10.8%)	0.018	0.072	(1.076 – 7.621)	No (borderline)
NICU Admission	16 (19.0%)	4 (10.8%)	0.261	1.044	(0.160 – 1.663)	No
Jaundice	8 (9.5%)	4 (10.8%)	0.827	3.308	(0.324 – 4.092)	No

To determine whether Vitamin A deficiency independently affects neonatal hemoglobin levels, binary logistic regression was performed, adjusting for maternal anemia, socioeconomic status, dietary intake, and BMI. Vitamin A deficiency was significantly associated with low neonatal hemoglobin levels (AOR = 3.174, 95% CI: 1.038–9.699, p = 0.043). However, maternal hemoglobin, BMI, gestational age, parity, and socioeconomic factors were not significantly associated with neonatal hemoglobin levels (Table 4).

Table 4: Logistic Regression Analysis for Low Neonatal Hemoglobin

Variables	Adjusted Odds Ratio (AOR)	95% Confidence Interval (CI)	p-value	Significant
Vitamin A Deficiency	3.174	(1.038 – 9.699)	0.043	Yes
Maternal Hemoglobin (g/dL)	1.088	(0.730 – 1.624)	0.678	No
BMI (Kg/m^2)	1.047	(0.929 – 1.180)	0.454	No
Gestational Age (Weeks)	0.895	(0.727 – 1.102)	0.297	No
Parity	0.760	(0.500 – 1.155)	0.199	No
Education Level (College vs. High School)	0.899	(0.383 – 2.110)	0.807	No
Occupation (Employed vs. Unemployed)	1.217	(0.549 – 2.697)	0.629	No
Monthly Income (PKR 15000-25000 vs. <15000)	1.095	(0.332 – 3.618)	0.881	No
Monthly Income (PKR 25000-75000 vs. <15000)	0.643	(0.215 – 1.924)	0.430	No
Nutritional Status (Malnourished vs. Normal)	1.765	(0.741 – 4.204)	0.200	No

The forest plot shows the odds ratios (OR) and 95% confidence intervals (CI) for neonatal outcomes associated with maternal Vitamin A deficiency. Low birth weight has the highest OR (2.863) with a wide CI (1.076–7.621), suggesting a borderline association. Preterm birth (OR = 0.664, CI: 0.224–1.972), NICU admission (OR = 0.515, CI: 0.160–1.663), and jaundice (OR = 1.152, CI: 0.324–4.092) show no significant association as their confidence intervals include 1.

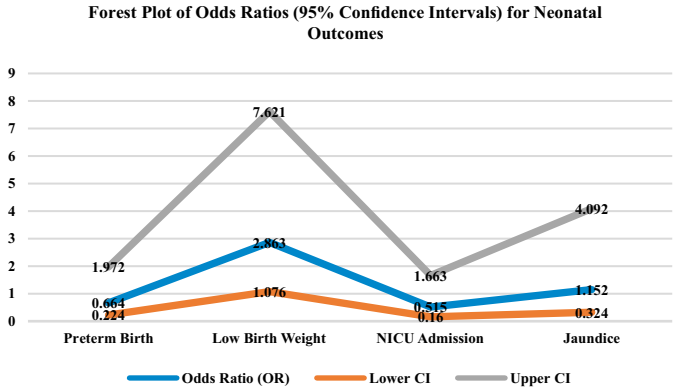

Figure 1: Forest plot of odds ratios (OR) and 95% confidence intervals (CI) for neonatal outcomes associated with maternal Vitamin A deficiency

DISCUSSION

This study investigated the relationship between maternal VAD and hemoglobin concentration in both mothers and neonates, along with its impact on neonatal health outcomes. This study found a high prevalence of Vitamin A deficiency (84%), which was consistent with previous studies conducted in low- and middle-income countries, particularly South Asia, where Vitamin A deficiency remains a major public health concern [10, 11]. Reports from similar settings have documented deficiency rates ranging from 50% to 85% in pregnant women, largely due to limited dietary diversity, micronutrient deficiencies, and socioeconomic constraints affecting nutrition during pregnancy [12, 13]. While these findings align with regional estimates, it is important to consider selection bias, as this study was conducted in a tertiary hospital setting, where pregnant women seeking care may be at higher risk of nutritional deficiencies due to existing health concerns. As a result, the true prevalence of Vitamin A deficiency in the general population of pregnant women may be lower than what was observed in the sample. Mothers with Vitamin A deficiency had significantly lower mean hemoglobin levels than those with sufficient Vitamin A (p = 0.001). This finding supports the biological role of Vitamin A in hematopoiesis, as it contributes to red blood cell production and iron mobilization. Vitamin A deficiency has been linked to impaired hemoglobin synthesis and an increased risk of anemia, which can lead to maternal complications such as fatigue, increased infection susceptibility, and adverse pregnancy outcomes [14, 15]. Similarly, neonates born to Vitamin A deficient mothers had significantly lower

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hemoglobin levels (p = 0.001), suggesting a possible intergenerational effect of maternal nutritional status on neonatal anemia. Neonatal anemia has been associated with higher risks of infection susceptibility and developmental delays [16]. Given that neonatal hemoglobin levels are critical for early growth and immunity, addressing maternal Vitamin A deficiency may contribute to improved neonatal outcomes. Among neonatal health indicators, low birth weight was significantly associated with maternal Vitamin A deficiency before Bonferroni correction (p = 0.018), with a higher prevalence of low birth weight in neonates of deficient mothers (31.0%) compared to those of sufficient mothers (10.8%). However, after Bonferroni correction (p = 0.072), the association became borderline significant, suggesting a potential relationship that warrants further investigation. Since maternal micronutrient deficiencies have been linked to impaired fetal growth, Vitamin A deficiency could contribute to fetal underdevelopment [17], although additional longitudinal studies are needed to confirm a direct causal link. For preterm birth (p = 0.459), NICU admission (p = 0.261), and jaundice (p = 0.827), no statistically significant associations with maternal Vitamin A status were found. However, preterm birth rates were slightly higher among Vitamin A deficient mothers (19.0% vs. 13.5%), and NICU admissions followed a similar pattern (19.0% vs. 10.8%). While these findings were not statistically significant, they align with existing research that maternal micronutrient deficiencies may contribute to pregnancy complications [18-20]. The strengths of this study include its focus on a vulnerable population, the use of laboratory-confirmed Vitamin A levels, and a comprehensive analysis of maternal and neonatal health outcomes. However, certain limitations must be acknowledged. Since this study was conducted in a tertiary hospital, specifically at Hayatabad Medical Complex, Peshawar, there is a possibility of selection bias. Pregnant women seeking care in hospital settings often have existing health concerns, which may have contributed to the higher observed rates of Vitamin A deficiency compared to the general population. Future studies incorporating broader nutritional assessments will be essential to better understand these relationships.

CONCLUSIONS

This study demonstrated a significant association between maternal Vitamin A deficiency and lower hemoglobin levels in both mothers and neonates, as well as a potential link to low birth weight. While other neonatal outcomes (preterm birth, NICU admission, jaundice) were not significantly associated with Vitamin A status, the findings emphasize the importance of addressing Vitamin A deficiency during pregnancy. Incorporating maternal nutrition interventions, including Vitamin A supplementation and dietary improvements, into antenatal care programs could help reduce deficiency-related complications and improve birth outcomes. Further research is required to confirm these associations and identify the most effective strategies for preventing Vitamin A deficiency in pregnant populations.

Authors Contribution

Conceptualization: SAK
Methodology: SJS
Formal analysis: R
Writing, review and editing: SJS, RM, SAK, BSH, NJ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Exploring the Antimicrobial Potential of *Moringa Oleifera* Extracts Against *Acinetobacter Baumannii*

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ABSTRACT

Background setups around the world, especially in Asian countries.Published data explained the situation of extreme drug resistance and left patients with very few antibiotic options against this particular pathogen. Plant and their extracts are well known for their antimicrobial properties. *Moringa oleifera* is one of the prime plants with multiple applications in industries, especially in health care. **Objective:** To determine the antimicrobial activity of *Moringa oleifera* plant extracts against *Acinetobacter baumannii*. **Methods:** In this experimental study, ethanol extracts of *Moringa oleifera* root, stem, and leaves were prepared and tested against *Acinetobacter baumannii* by the well diffusion method and minimum inhibitory concentration method. Four concentrations of all three extracts were prepared as 5mg/ml, 10mg/ml, 15mg/ml, and 20mg/ml. All experiments were tested three times. **Results:** No inhibition was seen at 5mg/ml, a 6mm zone diameter was observed at 10mg/ml, and 11mm was seen at 15mg/ml. **Conclusions:** It was concluded that *Moringa oleifera* showed good inhibition activity against *Acinetobacter baumannii*. This study does not include the quality analysis of extracts; after quality analysis and precise concentrations could create a huge opportunity in dealing with this extremely drug-resistant pathogen.

INTRODUCTION

Infectious microbes, especially bacteria, are the leading cause of death worldwide. The excessive use of antibiotics to treat various illnesses poses a serious threat to health globally, resulting in the development of super-bacteria that are more resistant to antibiotics.These super-resistant bacteria result in multiple epidemics.Some scientific survey predicts that we are now entering in "post-antibiotic era".The misuse of antibiotics results in detrimental effects. Furthermore, bacteria are developing different mechanisms to cope with a broad spectrum of antibiotics [1]. Among those multidrug-resistant bacteria, *Acinetobacter baumannii* is a well-known opportunistic pathogen causing infections in healthcare settings [2].A significant risk to public health because it is becoming more resistant to multiple antibiotics [3].It is a gram-negative bacterium causing nosocomial infections.This

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microbe causes a wide range of infections, including ventilator-associated pneumonia, meningitis, urinary tract infections, and skin-related issues.*A.baumannii* is declared the leading microbe for antibiotic research as it has gained resistance to broad-spectrum antibiotics.It is one of the most important bioweapons due to its vast range of infections, facilitated by diverse mobility of genetic elements, genetic plasticity, integration of foreign determinants, and evolution [4, 5].Recently, there has been an increasing fascination with investigating alternative therapeutic approaches to address infections caused by multidrug-resistant bacteria such as *Acinetobacter baumannii*. From ancient times, a few plants have been suggested to act as medicinal plants due to their therapeutic properties and to treat various illnesses.Even fossil records suggest that humans were using medicinal plants a long time ago. The curative nature of these plants is due to the various organic and inorganic chemicals produced by them. Such plants produce or release a few natural drugs as a result of various metabolic processes. In the current era, medicinal plants have gained special attention due to the antibiotic crisis, i.e. bacteria have developed multidrug resistance.These medicinal plants have a wide range of metabolites, including flavonoids, phenolic compounds, terpenoids, and alkaloids [6, 7]. Among these medicinal plants, a native plant with the old name of "Sohanjna" is a plant that naturally grows in tropical and subtropical areas and is well-known for its wide range of medicinal properties [8].*Moringa oleifera* has its importance in medicine and industry due to the prime compounds produced by its leaves.Because of its high nutritional value, therapeutic properties, and dual function as a vegetable and a seed, the plant is widely capitalized in a variety of cultural traditions. Its significance in increasing the taste and flavor of food is particularly noticeable [9-10]. The *M. oleifera* fresh leaves are edible or otherwise cooked, these can also be stored as dried powder [11]. Previously published studies enlightened the nutritional importance, pharmaceutical importance, and industrial importance of the *Moringa oleifera* plant [12].A well-known property of plants is antimicrobial activity through the production of different antimicrobial chemicals for their defense system, such as alkaloids [13].Alkaloids and phenolic compounds are secondary metabolites of plants with significant antibiotic properties. In a previously published study, the antimicrobial activity of *Moringa oleifera* was successfully evaluated against *Escherichia coli* and *Staphylococcus aureus* [14].The primary reason for the spread of bacterial resistance to antibiotics worldwide is the excessive and unreasonable use of antibiotics.This has resulted in a decline in the efficiency of many common antibiotics against harmful bacteria.The ongoing development of this issue has required the investigation of new antibacterial chemicals.Recent research has emphasized the significance of medicinal plants as a valuable reservoir of natural antimicrobial compounds. Such plant extracts can act directly as antimicrobial agents or may increase the synthetic antibiotic activity via a synergistic effect [5]. A plant of prime importance cultivated for commercial purposes in Egypt as well as other African, American, and many other Asian countries.

This study aims to assess the efficacy of *M. oleifera* for the inhibition of *Acinetobacter baumannii* and its pathogenic effects. More precisely, this study finds the mechanism of *M.oleifera* extract as an antimicrobial agent against A. baumannii and its pathogenesis inhibition. Finding out the antibacterial properties of *M. oleifera* against *A. baumannii* could have great significance for developing a prime therapeutic action plan to manage the rising incidence of multidrug-resistant bacterial infections.

METHODS

This was applied research. Laboratory experiments were performed at the Department of Microbiology, Institute of Molecular Biology and Biotechnology (IMBB), University of Lahore, from July 2023 to Nov 2023. An approval letter was taken from the biosafety management committee of the Institute of Molecular Biology and Biotechnology (IMBB) (CriMM/23/Research/30), University of Lahore, for taking the bacterial samples. *Moringa oleifera* was collected from a nearby nursery to collect fresh stems, leaves, and roots. The plant was washed properly with sterilized distilled water for dirt and debris removal. Later on, it was dried at room temperature in the shade. Stem, Root, and leaves of *M. oleifera* are shown in Figure 1.

Figure 1: Stem, Root, and Leaves of M. Oleifera

Dried parts of the plants, leaves, stems, and roots were converted into powder separately and shown in Figure 2.

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Figure 2: Dried Powder of Stem, Root, and Leaves of *M. Oleifera*

For the extraction of alkaloids from powder of all three parts, a quantity of 10 grams of powdered *Moringa oleifera* was immersed in 50 mL of ethanol (70%) and left to soak for 24 hours at room temperature.The mixture was agitated periodically to promote optimal extraction [15].Finding shows the mixture of powdered stems, roots, and leaves of *M. oleifera* in 70% ethanol, as shown in Figure 3.

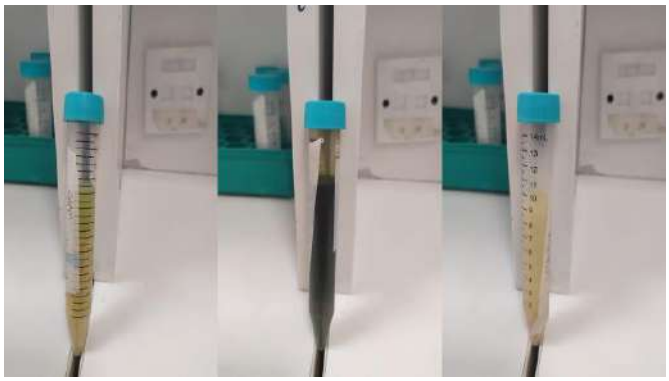

Figure 3: Mixture of Powdered Stem, Root, and Leaves of *M. Oleifera* in 70% Ethanol

Following an average of 24 hours, the extracts underwent filtration using Whatman filter paper with a pore size of 0.22 µm to eliminate any particulates.The liquid samples were condensed by removing excess pressure using a rotating evaporator at a temperature of 40°C [16]. A total of 10 isolates of *Acinetobacter baumannii* were used in this study.For this experiment, the strain of *Acinetobacter baumannii* known as ATCC 19606 was utilized.This strain was obtained from the American Type Culture Collection (ATCC). To get colonies that were free of contamination, the bacterial strain was grown on Mueller-Hinton agar plates and then incubated at a temperature of 37 degrees Celsius for twenty-four hours.To create a bacterial suspension with a concentration of roughly 1.5 × 10^8 CFU/mL, a single colony was introduced into Mueller-Hinton broth and incubated at 37°C with shaking at 150 rpm for 18 hours. Two different methods were used to check antimicrobial activity against *Acinetobacter baumannii.*Well diffusion method and serial dilution method. Well diffusion method: Already isolated *Acinetobacter baumannii* was diluted in sterile normal saline to prepare a 0.5% MacFarland standard. Suspension was spread on Muller Hinton agar by a sterile swab; this is called inoculating. 4 wells were made in each Muller Hinton Plate. 4 dilutions of each extract were prepared, like 25 µl, 50 µl, 75 µl, and 100µl in one ml sterile saline each. One drop was poured into each well of the already loaned MH plate. 4th well was poured with normal saline as a control. After incubation for 24 hours, activity was checked. Serial Dilution Method: Serial dilution tubes were sub-cultured on blood agar plates for growth testing, the highest inhibition was seen on leaves, with no growth after 50 µg/ml, and the least activity was seen on the stem in where 50 µg/ml was not sufficient concentration to inhibit the growth. Descriptive statistics were used to estimate the suitable concentration of *Moringa oleifera's* different parts. Reading and results were obtained in triplets then the results were expressed as mean ± standard deviation(SD).

RESULTS

A total of 10 *Acinetobacter* isolates were obtained from clinical samples such as urine, pus. Wound swab, tracheal aspirate, and blood. The clinical samples used for the isolation of 10 isolates of *A. baumannii* along with the total count in terms of percentage, is given in Table 1.

Table 1: Clinical Samples of *A. baumannii Isolates*

Clinical Samples	n (%)
Urine	2 (20%)
Pus	2 (20%)
Wound Swab	1 (10%)
Tracheal Aspirate	4 (40%)
Blood	1 (10%)
Total	10 (100%)

As per CLSI, the cut-off range for inhibition was as Amikacin=<4.0 µg/mL, Tobramycin=<4.0 µg/mL, Imipenem =<2.0 µg/mL, Meropenem=<2.0 µg/mL, Piperacillin-tazobactam<4.0 µg/mL, Ciprofloxacin = <1.0 µg/mL, Minocycline = <4.0 µg/mL and Tigecycline was from EUCAST guideline as <4.0 µg/mL. Ciprofloxacin was sensitive in only one strain, showing a susceptibility rate of 5%, and was the least sensitive drug, while maximum sensitivity was shown by tigecycline, with 10 sensitive strains, as shown in Table 2.

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Table 2: MIC results for *A. baumannii* Isolates

Amikacin	Tobramycin	Tigecycline	Imipenem	Meropenem	Pipracillin/Tazobactam	Ciprofloxacin	Minocycline
0.75	1	0.5	8	8	32	256	256
16	16	4	16	16	256	256	256
2	1	0.75	2	2	1	2	0.5
32	8	0.5	256	256	256	256	8
256	32	0.5	8	4	16	256	1
256	256	8	8	4	16	256	8
1	2	16	16	4	32	256	256
32	16	2	8	8	256	256	8
256	8	1	1	0.75	1	256	0.25
256	256	1	256	256	256	256	256

MIC unit µg/mL

Well Diffusion Method: After 24 hours of incubation, no antibacterial activity was shown by extracts, the highest activity was shown by leaves with a minimum of 50 µg/ml with an inhibition zone of 22 ± 9 mm, and the least activity was shown by the stem with a minimum 75 µg/ml with inhibition zone 16.5 ± 11 mm. Root extract showed a zone of 19±8 mm. Figure 4 shows the experimentation of the diffusion method for the Inhibition effect of *M. Oleifera* suspension on *A. baumannii* are shown in Figure 4.

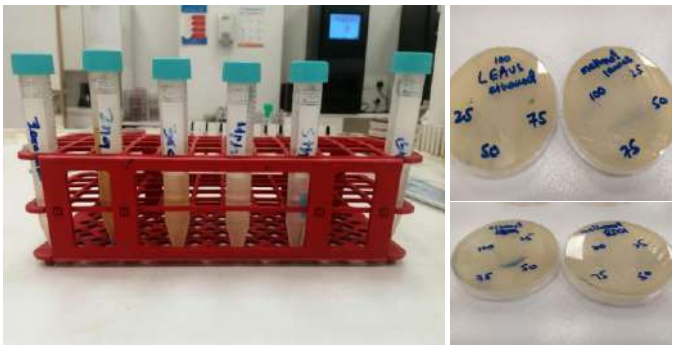

Figure 4: Inhibition Effect of *M. Oleifera* Suspension on *A. Baumannii*

This table narrates the effect of different concentrations of leaves, roots, and stems on 10 different isolates of *A. baumannii* (isolated from different sources as mentioned in methodology) (Results are expressed in descriptive stats, i.e. mean ± Standard deviation). The zone of inhibition is given in Table 3.

Table 3: Effect of Different Concentrations of Leaves, Roots, and Stems of *M. Oleifera* On *A. Baumannii* Isolates

Bacterial #	Leaves				Root				Stem			
	25µg/ml	50µg/ml	75µg/ml	100µg	25µg/ml	50µg/ml	75µg/ml	100µg	25µg/ml	50µg/ml	75µg/ml	100µg
1	0 ± 0	31 ± 0.8	36 ± 0.5	40 ± 0.08	0 ± 0	28 ± 0.4	32 ± 0.3	40 ± 0.2	12 ± 0.5	20 ± 0.3	24 ± 0.3	27 ± 0.2
2	0 ± 0	25 ± 0.6	31 ± 0.08	40 ± 0.3	0 ± 0	16 ± 0.2	21 ± 0.08	40 ± 0.2	0 ± 0	15 ± 0.6	18 ± 0.4	31 ± 0.1
3	0 ± 0	17 ± 0.08	23 ± 0.1	40 ± 0.2	0 ± 0	15 ± 0.3	17 ± 0.2	40 ± 0.08	0 ± 0	13 ± 0.1	15 ± 0.4	28 ± 0.2
4	0 ± 0	16 ± 0.1	18 ± 0.2	40 ± 0.08	0 ± 0	21 ± 0.2	24 ± 0.3	40 ± 0.3	12 ± 0.3	13 ± 0.3	12 ± 0.6	23 ± 0.3
5	0 ± 0	30 ± 0.2	36 ± 0.08	40 ± 0.3	13 ± 0.3	25 ± 0.08	27 ± 0.1	40 ± 0.1	12 ± 0.5	12 ± 0.5	13 ± 0.3	16 ± 0
6	13 ± 0.4	16 ± 0.08	21 ± 0	40 ± 0.1	18 ± 0.3	17 ± 0.6	18 ± 0	40 ± 0.3	0 ± 0	0 ± 0	19 ± 0.3	21 ± 0.4
7	11 ± 0.5	21 ± 0.4	24 ± 0.3	40 ± 0.3	0 ± 0	15 ± 0.5	20 ± 0.2	40 ± 0.08	0 ± 0	12 ± 0.6	15 ± 0.3	16 ± 0.5
8	0 ± 0	24 ± 0.1	27 ± 0.2	40 ± 0.08	11 ± 0.2	20 ± 0	23 ± 0.1	40 ± 0.2	0 ± 0	16 ± 0	19 ± 0.3	23 ± 0.5
9	0 ± 0	21 ± 0.1	23 ± 0.2	40 ± 0.2	12 ± 0.4	17 ± 0.3	21 ± 0.8	40 ± 0.3	12 ± 0.6	15 ± 0.5	18 ± 0.2	19 ± 0.4
10	0 ± 0	19 ± 0.1	21 ± 0.08	40 ± 0.2	12 ± 0.3	16 ± 0.3	18 ± 0.2	40 ± 0.08	12 ± 0.5	17 ± 0.2	12 ± 0.5	13 ± 0.1

The Bar graph shows antimicrobial activity at 25µg/ml vs zone of inhibition. Not much microbial activity was observed from leaves, root and stem extracts, except in isolate 6, root extract shows the maximum inhibition zone, while lesser or no activity was observed in other isolates, as shown in Figure 5.

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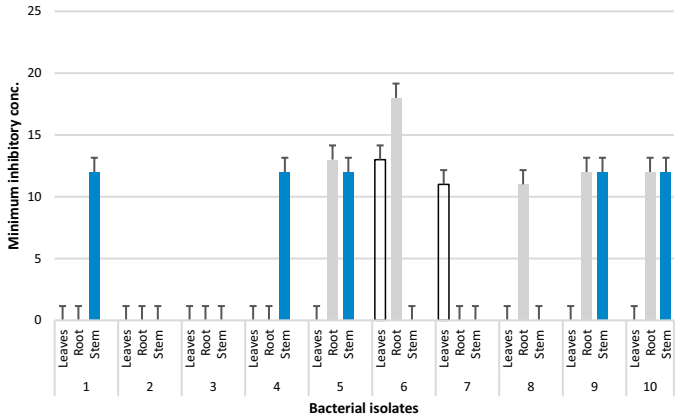

Figure 5: Antimicrobial Activity at 25µg/mL vs Zone of Inhibition

The Bar graph shows antimicrobial activity at 50µg/ml vs zone of inhibition.The leaf extract shows the maximum inhibition zone in all 10 bacterial isolates.Hence, 50µg/ml is declared as the minimum inhibitory concentration for bacterial growth in this work and shown in Figure 6.

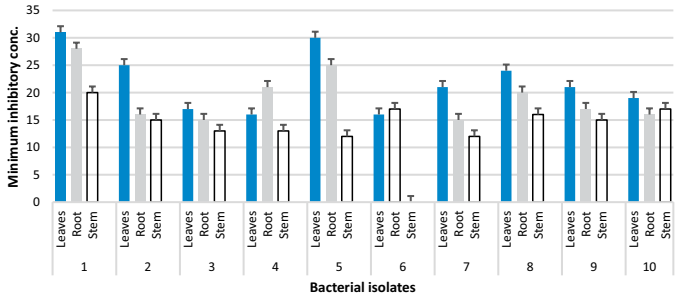

Figure 6: Antimicrobial Activity at 50 µg/ml vs Zone of Inhibition

The Bar graph shows antimicrobial activity at 75µg/ml vs zone of inhibition.Here, the stem extracts show the least antimicrobial activity, while leaves and root extracts show more antimicrobial activity, as shown in Figure 7.

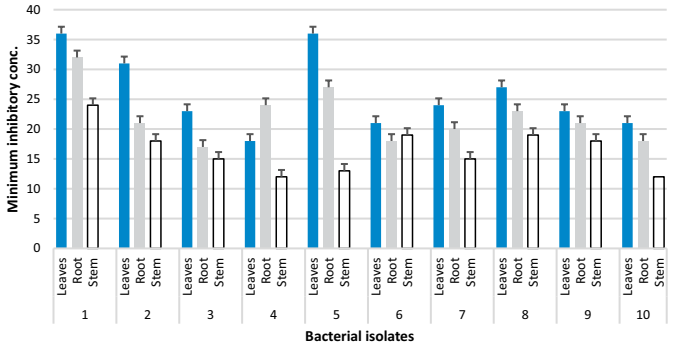

Figure 7: Antimicrobial Activity at 75 µg/ml vs Zone of Inhibition

The Bar graph shows antimicrobial activity at 100µg/ml vs zone of inhibition. Bacterial isolates are inhibited by leaves and root extracts, however, much lesser activity was observed in case of stem extracts, as shown in Figure 8.

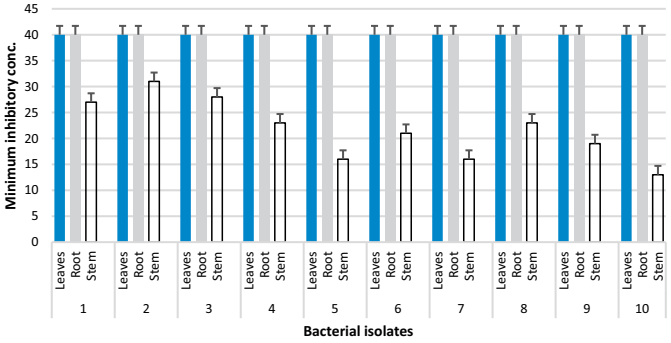

Figure 8: Antimicrobial Activity at 100 µg/ml vs Zone of Inhibition

Serial dilution tubes were sub cultured on blood agar plates for growth testing, highest inhibition was seen on leaves with no growth after 50 µg/ml plate, and the least activity was seen on the stem in which 50 µg/ml was not sufficient concentration to inhibit the growth as shown in figures given below. After 24 hours of incubation, growth was observed only on a 50µl dilution plate. There was no bacterial growth on other dilutions. Finding shows the Serial dilution inhibition effect on blood agar in Figure 9.

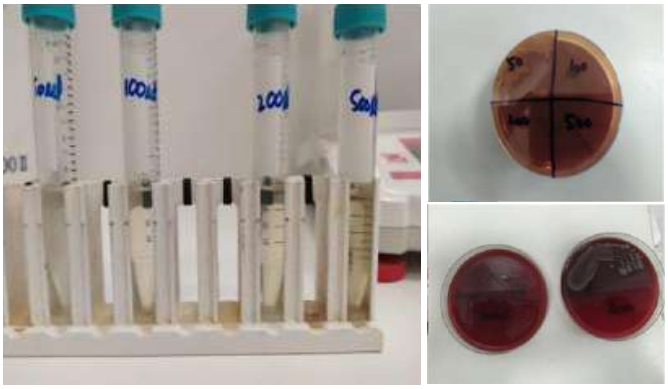

Figure 9: Serial Dilution Inhibition Effect on Blood Agar

DISCUSSION

The present study investigated the antibacterial activity of extracts from different parts of a plant against clinical isolates of *Acinetobacter baumannii,* along with their susceptibility to commonly used antibiotics.This study contributes to finding some alternate sources of antibiotics to overcome the synthetic antibiotics load and minimize drug resistance.The results of this research explained the antimicrobial activity of different parts of the *Moringa oleifera* plant. The extracts obtained from leaves had the most significant action, with a minimum inhibitory concentration (MIC) as low as 50 micrograms per milliliter (µg/ml) and an inhibition zone measuring 22 ± 9 millimeters. On the other hand, stem extracts exhibited the lowest level of activity, indicating a greater concentration (at least 75µg/ml) to achieve inhibition.The root extracts exhibited moderate activity, as evidenced by an inhibition zone measuring 19 ± 8 mm.The same findings were reported in

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previously published studies about plant extract inhibition effects against *A. baumannii* [17]. Our investigations find increased antibiotic resistance among the present study isolates of *A. baumannii.* These isolates were showing resistance against multiple drugs, as shown in Table 1; some were very potent antibiotics like imipenem, meropenem, and ciprofloxacin. Some of these antibiotics, like amikacin and tigecycline, showed good susceptibility. Still, there was some variation among the isolates regarding susceptibility patterns. These findings showed similarity with the common pattern of multidrug resistance observed in isolates of *Acinetobacter baumannii* [18]. A significant association was found between extracts' ability from plants to inhibit bacteria and restrict these bacteria from developing drug resistance. Strains that showed higher resistance to conventional antibiotics were found to be more prone to the plant extract, indicating a possible synergistic or complementary effect between chemicals derived from plants and antibiotics. Multiple previous studies have shown that the combination of plant extracts and synthetic antibiotics enhances their antibacterial efficacy against multiple drug-resistant bacteria [19]. This study also provides valuable and prime evidence of the antimicrobial ability of plant extracts against *A. baumannii.* But still, a precise concentration is very necessary to produce a prime drug, which may require Molecular docking studies, as conducted by [20], could help identify potential targets for synergistic interactions between plant compounds and antibiotics. Additionally, clinical trials are warranted to evaluate the safety and efficacy of plant-derived therapies in human populations.This research outcome gave a way to develop a novel combination therapy for the inhibition of multidrug-resistant *A. baumannii.* Plant extracts have a special amount of flavonoids with prime applications in industry.

CONCLUSIONS

It was concluded that this research described the antimicrobial activity of different parts of the Moringa oleifera plant. The extracts obtained from leaves had the most significant action with a minimum inhibitory concentration (MIC) as low as 50 micrograms per milliliter (µg/ml).

Authors Contribution

Conceptualization: SP
Methodology: AZ, NJ, SS
Formal analysis: UA
Writing review and editing: SMC, IUH, SJ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Coronary Angiographic Profile in Smokeless Tobacco Users in Patients Presenting with Acute Coronary Syndrome at A Tertiary Care Cardiac Center

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ABSTRACT

Smokeless tobacco users with acute coronary syndrome (ACS) at tertiary care cardiac centers are more likely to develop significant coronary artery disease (CAD). With multi-vessel involvement, highlighting its significant risk factor. **Objectives:** To determine the frequency of coronary angiographic profiles in smokeless tobacco users with ACS at a cardiac center. **Methods:** A study involving 159 smokeless tobacco users aged 18-70 with acute coronary syndrome was conducted at the National Institute of Cardiovascular Diseases (NICVD) Karachi from Mar 2022 to Jan 2024, recording demographic data such as gender, age, height, and weight. Before an angiography procedure, the patient's medical history, including hypertension, diabetes, family history, and obesity, was reviewed, along with their smokeless tobacco use, recording type, frequency, and duration. **Results:** A study involving 159 smokeless tobacco users aged 18-70 years, with a mean age of 46.64 ± 10.186, included 134 male (84.3%) and 25 female (15.7%). The study revealed that male accounted for 63 (39.62%) of the total ACS with Single vascular disease (SVD), while unstable angina was typical in 52 (32.70%) cases. The study found a significant association between age groups, ACS type, culprit artery, and tobacco use on the day of ACS (p=0.004, 0.027, 0.044, and 0.024), respectively. However, no significant association was seen between gender, tobacco type, and risk variables. **Conclusions:** It was concluded that smokeless tobacco significantly contributes to ACS, with a high percentage of single vessel blockage involving RCA, and that duration and number of use also contribute to ACS.

INTRODUCTION

Cardiovascular diseases (CVDs) accounted for over one-third of global fatalities in 2021, causing 20.5 million deaths [1]. Acute Coronary Syndrome (ACS) is an umbrella term for various types of coronary artery disease (CAD) caused by plaque formation in coronary arteries, resulting in decreased blood flow to the heart. This condition is characterized by an imbalance in oxygen demand and supply, primarily due to the development of plaques in the coronary artery lumen [2, 3]. Coronary angiographic profiles in acute coronary syndrome (ACS) patients indicate significant trends. Single vascular disease (SVD) is more prevalent in young people, non-diabetics, and smokers [4, 5]. The left anterior descending artery is most commonly implicated. Diabetics are more likely to develop severe triple-vessel disease. Smokeless tobacco users had comparable vascular involvement patterns to smokers, with SVD and left anterior descending artery involvement being common [4-6]. Studies indicate that smokeless tobacco use, including products like Naswar and Snus, can lead to coronary vasoconstriction and increased complication rates during coronary interventions (like re-stenosis) [7]. Smokeless tobacco creates greater nicotine

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levels, which causes sympathetic neuronal activation and immediate cardiovascular consequences [8]. Smoking significantly impacts cardiovascular health by affecting coronary vasomotor tone, endothelial and platelet function, and accelerating atherosclerosis progression through vascular damage, endothelial dysfunction, oxidative stress, thrombosis, lipid changes, and inflammation [9]. Smoking is a significant risk factor for coronary artery disease, but smokeless tobacco has not received considerable attention due to insufficient data on coronary obstructive patterns.Smokeless tobacco product patterns vary regionally, and there are no studies on angiographic patterns in Pakistani patients, and limited global data is available.

This study aims to evaluate coronary obstruction patterns in smokeless tobacco users, enabling the development of targeted preventive strategies for future use.

METHODS

An observational cross-sectional research study was carried out in the Department of Cardiology, NICVD, Karachi, from March 2022 to January 2024. This study was approved by the hospital's ethical review. Committee and the College of Physicians and Surgeons of Pakistan with Ref No: CPSP/REU/PED-2019-195-1995. Participants were informed of the study's purpose and benefits, and consent was obtained.The study involved 18-70-year-old smokeless tobacco users with acute coronary syndrome at the NICVD in Karachi. Demographic details, including gender, age, height, and weight, were obtained at hospital arrival. Medical history was also assessed for hypertension, diabetes, family history, and obesity.Patients were interviewed about their use of smokeless tobacco, recording their type, frequency, and duration. In the study, acute coronary syndrome (ACS) was diagnosed based on two criteria: 1. STEMI (ST-Segment Elevation Myocardial Infarction): Common chest discomfort (>20 min) exacerbated by physical activity or stress, is eased by rest or nitroglycerin. New ST-elevation at the J-point in 2 contiguous leads is present, with cut points ≥1 mm in all leads except leads V2-V3 (cut points male (≥2.5 mm), in females (≥1.5 mm). 2. (NSTEMI) Non-ST-segment elevation myocardial infarction): STEMI is a chest discomfort lasting over 20 minutes, exacerbated by physical activity or stress, and relieved by rest or nitroglycerin. NSTEMI is diagnosed by chest pain lasting over 20 minutes, with ECG showing ST depression, ST elevation, wave inversions, and a rise in cardiac troponin above the normal range. Unstable angina is diagnosed in patients with chest pain, negative troponin results, and ST-segment depression measuring 1 mm on limb leads and 2 mm on chest leads. An angiography procedure was accomplished by a consultant cardiologist with over 5 years of experience. The principal investigator recorded angiographic patterns, disease extent, and the culprit artery on a predesigned pro forma, along with other collected data. In the study, 159 patients were calculated in the sample size by applying the WHO calculator by assuming the prevalence of mid-right coronary artery disease in the smokeless tobacco users, p=28% [10], taking the confidence level (95%) and the margin of error (7%). 159 patients made up the total sample size. In the study, the consecutive sampling method was applied. The study includes both genders, aged 18-70, patients with acute coronary syndrome, and smokeless tobacco users who are chewing or taking any smokeless tobacco such as paan, naswar, gutka, main puri, or mawa with the frequency of at least twice a day for more than 6 months, while exclusion criteria include refusal to give consent, prior cardiac-related surgery history, and patients who have smoked ten or more cigarettes a day for at least 02 years, or five or more cigarettes a day for no less than four years, as well as those who have had any previous heart condition-related surgeries

RESULTS

159 patients, aged 18 to 70, met the study's inclusion requirements and were accepted. The average age, including standard deviation, was 46.64 ± 10.186 years, while other quantitative variables such as age in groups, smokeless tobacco use per day, and year are presented in Table 1.

Table 1: Descriptive Statistics of Different Variables

Variables	Mean ± SD	95%CI (LB-UB)	Median (IQR)	Range	Min	Max
Age						
–	46.64 ± 10.186	50.6 ± 5.213	45 (16)	52	18	70
Age Groups						
18-40 Years	36.81 ± 4.178	35.77-37.86	38 (3)	22	18	40
40-60 Years	36.81 ± 4.178	49.41-51.80	51 (10)	30	41	60
61-70 Years	63.89 ± 3.510	44.04-48.21	63 (6)	10	61	70
Smokeless Tobacco Use Per Day						
–	14.66 ± 5.762	13.76-15.56	15 (06)	28	2	30
Smokeless Tobacco Use in Years						
-	15.25 ± 8.514	13.91-16.58	14 (13)	38	2	40

Frequencies regarding gender were calculated, and it was found that out of the total study subjects, 134 (84.3%) patients were male, while 25 (15.7%) were female while the other qualitative variable such as age in groups, an extension of disease (number of vessels involve), culprit artery involvement, type of ACS, type of tobacco and, risk factors i.e. D.M, hypertension, obesity and family history of CAD detailed is presented in Table 2.

Table 2: Frequency and Percentage of Demographic and Other Related Variables

Variables		Frequency (%)
Gender	Male	134 (84.3%)
	Female	25 (15.7%)

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Age Groups	18-40 Years	64 (40.3%)
	41-60Years	76 (47.80%)
	61-70 Years	19 (11.90%)
Coronary Angiographic Profile	SVD	76 (47.79%)
	2VD	28 (17.61%)
	3VD	55 (34.59%)
Culprit Artery	LAD	42 (26.40%)
	LCX	58 (36.50%)
	RCA	59 (37.10%)
Type of ACS	Unstable	93 (85.50%)
	Angina	31 (19.50%)
	STEMI	35 (22.00%)
Type of Tobacco	Paan	42 (26.42%)
	Naswar	64 (40.25%)
	Gutka	35 (22.01%)
	Main Purri	11 (06.92%)
	Mawa	07 (04.40%)
Risk Factors	Diabetes Mellitus	96 (60.38%)
	hypertension	35(22.01%)
	Obesity	13(08.18%)
	Family History of CAD	15(09.43%)

To determine the relationship, a chi-square test was used to stratify the coronary angiographic profile concerning gender, age group (years), type of ACS, type of risk factors, culprit artery, type of tobacco per day, and type of tobacco per year.A p-value of less than 0.05 was deemed significant.There was a substantial link between age groups. Type of ACS, Culprit artery, and use of tobacco in a day and years have a significant association with ACS (p=0.004, 0.027, 0.044, 0.024, and p=0.057), respectively. While no significant (i.e p=0.900 and 0.842) association with gender, type of tobacco and risk factors was observed, are presented in Table 3.

Table 3: Frequency and Association of Coronary Angiographic Profile with Different Variables (n=159)

Variables		Coronary Angiographic Profile			p-value
		SVD	2VD	3VD	
Age (Years)	18-40 Years	42	07	18	0.004
	40-60 Years	25	17	34	
	61-70 Years	09	04	06	
Gender	Male	63	24	47	0.900
	Female	13	4	8	
Type of Tobacco	Paan	28	02	12	0.094
	Naswar	27	15	22	
	Guttka	13	09	13	
	Mainpuri	06	01	04	
	Mawa	02	01	04	
Culprit Artery	LAD	24	02	16	0.044
	LCX	21	15	22	
	RCA	31	11	17	
Type of ACS	Unstable Angina	52	14	27	0.027
	STEMI	10	10	11	
	NSTEMI	27	11	17	
Risk Factors	Diabetes Mellitus	46	18	32	0.842
	Hypertension	18	06	11	
	Obesity	05	01	07	
	Family history of C	07	03	05	
Use of Tobacco /Day	1-10perday	23	06	07	0. 024
	11-20perday	42	22	38	
	>20 perday	11	00	10	
Use of Tobacco (Years)	1-5 Years	12	00	02	0.05
	6-10 Years	16	07	20	
	11-20Years	31	12	20	
	>20Years	17	09	13	

DISCUSSION

Coronary artery disease (CAD) is a prevalent heart condition characterized by the buildup of atherosclerotic plaque within the arterial lumen.Blood flow impairment reduces oxygen delivery to the myocardium.CAD is the most common cause of major morbidity and mortality in the US and worldwide [11].The present study included 159 patients between 18 and 70 years of age presenting with ACS. Even in the current research, where 84.3% of the patients are men, male sex is one of the most often reported risk factors for CAD in several studies that take into account the skewed gender distribution [12-14].Kaur *et al.*, found that males have more severe coronary artery disease [6]. Joshi *et al.*, found that men under 30 with AMI were significantly more prevalent in angiographic studies, often due to higher smoking rates and estrogen protection in women [13]. With a prevalence of over 60% in the current study, diabetes mellitus is a traditional risk factor for coronary artery disease (CAD). Between 20 and 80 percent of the study cohort in several other studies involving young AMI patients had diabetes [12, 14]. Nevertheless, with a prevalence of 11–15%, obesity was noted as an uncommon cause in the majority of earlier studies [12, 15]. CAD, diabetes mellitus and systemic hypertension well well-established risk factors. In comparison to this study, the studied population had a non-significantly lower frequency of diabetes mellitus (23.4%) and hypertension (12.2%) than this one.Other studies found that the prevalence of hypertension varied from 10 to 44 percent [14, 16]. A higher amount of plaque in the coronary arteries is linked to a favorable family history of early CAD.The results of the current study, which show a prevalence rate of 9.43%, are very similar to other Indian studies that reflect a significantly lower prevalence rate of positive family history of early CAD, which is centered around 10% [12, 17]. In contrast, a small number of Indian research studies suggest a significantly greater prevalence, ranging from 30 to 47% [13, 15].The most preventable cause of death in the world, tobacco use, harms all stages of atherosclerosis.A significant portion of the population under study used smokeless tobacco.Consuming smokeless tobacco is still

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not proven to be a cardiovascular risk factor.However, since it is so common among South Asians, it needs to be thoroughly tested before any particular recommendations regarding STEMI can be made.Events in life that are stressful can make the plaque unstable, which can lead to its rupture and STEMI[13].Following coronary angiography, all 159 patients in the current research had a prevalence of obstructive CAD of 48%, 34%, and 18% for SVD, 2VD, and 3VD, respectively.The above results are further supported by the literature that is currently available, with several studies showing comparable rates of obstructive CAD in their study group, which range from 60 to 70% [18, 19]. El-Rabbat *et al.*, in a comparative angiographic study, found very similar patterns in young adults with ACS: SVD most common, TVD least common [20]. Khan *et al.*, noted that angiographically normal coronaries in young AMI patients might be owing to spontaneous recanalization, thrombosis, or vasospasm, which is consistent with your results[21].Zhang *et al.*, discovered that LAD was the most commonly involved, followed by RCA.Your findings are consistent with past exceptions, such as Kennelly[22].On the other hand, obstructive CAD is far more common (>80%) in several other investigations [15, 17].Before coronary angiography, almost 60% of the patients had thrombolysis, which may have recanalized the artery associated with the infarct. Normal coronary arteries can arise from thrombosis with reperfusion. Common coronary artery spasms in younger individuals and spontaneous recanalization [23].The Glagov phenomenon, characterized by plaque development in the coronary artery and the ability to cause adaptive enlargement while maintaining the luminal area, could not be ruled out since intravascular ultrasonography(IVUS)was not used.[18, 24]. The current investigation found that TVD and DVD were extremely rare. Furthermore, other studies have found a considerable incidence of TVD(18%)and DVD(34%), which suggests that severe coronary involvement is rare in young person's presenting with ACS[25].The majority of research done on juvenile AMI patients shows a prevalence of SVD, which is found in 48% of cases in the current study[18, 26]. Acute coronary syndrome (ACS) is uncommon in young patients under 40 years of age, and these young patients have a different CAD pattern in comparison with older patients[27]. The study aims to investigate the clinical, risk factor, and coronary angiographic features of very young individuals under the age of 30 who present with their first STEMI, as the literature on this topic is quite restricted and particularly lacking in the community[28]. According to the current study, the most often affected artery is the RCA, which is implicated alone in 37.1% of instances, followed by the LCX in 36.5% of cases.The results do not closely match those of earlier studies in which the most often affected vessel was the LAD, followed by the RCA and the LCX, in that order [12, 24]. However, according to Kennelly *et al.*, 1982 study, the most often affected vessel in their sample was the RCA[29]. Remarkably, just 7(17.1%)of the patients had non-culprit vessels diagnosed with an illness, and only 4 (9.75%) of the patients had more than one lesion in the culprit artery, indicating that most of the lesions were non-atherosclerotic[24, 29].

CONCLUSIONS

It was concluded that this study highlights the coronary angiographic profile of smokeless tobacco users with ACS. A significant association was found between ACS and factors like age, type of ACS, culprit artery, and tobacco use frequency and duration, while gender and conventional risk factors showed no significant link. Single-vessel disease (SVD) was most prevalent, with RCA being the most affected artery, differing from prior studies that reported LAD dominance. With the rising use of smokeless tobacco, further research with larger samples and advanced imaging is needed to confirm its role in coronary artery disease. Public health initiatives should emphasize the cardiovascular risks associated with smokeless tobacco to mitigate its impact.

Authors Contribution

Conceptualization: S
Methodology: SH
Formal analysis: VKG
Writing review and editing: SDH, FAM, SU

All authors have read and agreed to the published version of the manuscript

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All the authors declare no conflict of interest.

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Original Article

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Association of Child Pugh Class with Esophageal Varices and Portal Hypertensive Gastropathy in Patients with Cirrhosis

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ABSTRACT

Oesophageal-varices and portal-hypertensive-gastropathy are common in cirrhotic-patients. The Child Pugh-classification, a key measure of liver disease severity, helps assess their association, offering insights into disease progression and management. **Objective:** To determine the association between Childs PUGH class, oesophageal varices and portal hypertensive gastropathy in patients with cirrhosis. **Methods:** This Cross Sectional Study was conducted at the Department of Gastroenterology, LUMHS, Jamshoro, Pakistan. Doppler ultrasound was used to diagnose portal hypertension. Following the ultrasound, endoscopy was performed to diagnose oesophageal varices and portal hypertensive gastropathy. The data collected were electronically recorded for research purposes using the provided proforma. **Results:** Oesophageal varices were noted in 122 (88.4%) patients and portal hypertensive gastropathy in 117(84.8%) patients. In association of Child-Pugh class with oesophageal varices, class A was noted in 9.4%, class B in 23.2%, and class C in 55.8% of patients resulting in a significant p- value of 0.008 whereas in the association of Child-Pugh-class with portal-hypertensive-gastropathy, class A was noted in 8.0%, class B in 23.9%, while class C had 52.9% resulting in a non-significant p- value of 0.122. **Conclusions:** This study found a strong association between cirrhosis severity and the presence of esophageal varices, with the highest prevalence observed in Child-Pugh Class C patients (p = 0.008). However, the association between Child-Pugh class and portal hypertensive gastropathy was not statistically significant (p = 0.122).

INTRODUCTION

Cirrhosis is a chronic liver disease characterized by the histological development of regenerative nodules surrounded by fibrous bands, which can result in Portal Hypertension (PHTN) [1]. The increased pressure within the portal venous system leads to the formation of venous collaterals, contributing to the development of esophageal varices and variceal bleeding—major complications associated with significant morbidity and mortality. Small varices have an annual progression rate of 10%, while the risk of bleeding from small and large varices is approximately 5% and 15% per year, respectively [2, 3]. The six-week mortality rate following an initial variceal bleed is estimated to be around 20% [4]. Portal Hypertensive Gastropathy (PHG) is a common consequence of cirrhotic portal hypertension but can also arise due to non-cirrhotic causes. It is clinically relevant due to its potential to cause acute, massive, or chronic blood loss. Endoscopically, PHG presents as a mosaic-like pattern resembling snake skin, with or without red spots [5]. The reported prevalence of PHG in cirrhotic patients ranges from 20% to 98%, with most cases being mild. Previous studies indicate that mild PHG is present in approximately 60% of patients, whereas

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severe PHG is observed in more than 46% of cases [6]. However, the association between PHG and liver function severity, as classified by the Child-Pugh score, remains inconsistent.Different Studies found a significant correlation between PHG occurrence [7-9] and Child-Pugh classification, whereas El-Kalla *et al.*, did not observe any significant relationship [10]. Tiwari et al., reported that the frequency of esophageal varices in cirrhotic patients was 90.1%. Among those with Child-Pugh class A, 48.3% had varices, whereas 94.2% and 100% of patients in Child-Pugh classes B and C, respectively, presented with varices another study reported the frequency of oesophageal varices 93.8% [9].Similarly frequency of portal hypertensive gastropathy was also 93.8% [11].

Thus the aimed of our study was to find out the association between Child PUGH, oesophageal varices and portal hypertension gastropathy in local population keeping in view of lack of availability of local literature.

METHODS

This cross-sectional study was conducted in the Department of Gastroenterology, LUMHS, Jamshoro, over a period of six months, from February, 2023, to August, 2023. The sample size was calculated using the OpenEpi online sample size calculator, based on a 90.1% frequency of oesophageal varices in liver cirrhosis, a 5% margin of error, and a 95% confidence interval, resulting in a required sample size of 138 [9]. Non-probability, consecutive sampling technique was used. Patients aged 18 to 70 years of either gender, diagnosed with liver cirrhosis and presenting with hematemesis or melena with endoscopy done, were included. Patients with previously diagnosed varices or Portal Hypertensive Gastropathy (PHG), those on prophylactic-β-blocker-therapy, or having hepatocellular-carcinoma, portal vein or splenic vein thrombosis, or hematologic disorders were excluded. Informed written consent was taken from each participant prior to enrollment in the study. The study was approved as dissertation by College of Physician & Surgeon, Pakistan via Letter No. CPSP/REU/GAS-2021-164-1158. Liver cirrhosis was diagnosed on ultrasound based on three or more features: reduced liver lobe size (left <90 mm, right <70 mm), surface irregularity/nodularity, decreased echogenicity compared to the right kidney, ascitic fluid >100 mL, or portal vein diameter >13 mm. Oesophageal varices were identified via endoscopy, showing abnormal tortuous bluish submucosal veins in the lower oesophagus, antrum, or fundus. Portal-hypertensive-gastropathy was diagnosed endoscopically by the presence of erythematous polygonal areas with a whitish-reticular-border in a mosaic-pattern in the gastric-fundus/body. Child-Pugh classification was determined using serum bilirubin, albumin, prothrombin time, ascites, and hepatic encephalopathy, categorizing patients into Class A, B, or C. Data were analyzed using SPSS version 21.0. The normality of the data was assessed using the Shapiro-Wilk test. As the data were found to be normally distributed, parametric tests were applied. Chi square test was applied to check for the significance of the association of Child Pugh Class with Esophageal Varices and Portal Hypertensive Gastropathy. P value ≤ 0.05 was considered statistically significant.

RESULTS

Majority of patients were male (66.7%) and rural residents (55.8%) with mean age of 42.92 ± 15.59 years. The average duration of cirrhosis was 29.54 ± 14.75 months. Hypertension was present in 55.8% of patients, while 44.9% had diabetes mellitus, and 46.4% were smokers, (Table 1).

Table 1: Descriptive Analysis (n=138)

Characteristics	Mean ± SD/Frequency (%)
Mean Age	42.92 ± 15.59
Weight	65.39 ± 14.57
Height	161.97 ± 7.22
Body Mass Index	25.04 ± 5.91
Duration of Cirrhosis	29.54 ± 14.75
Hepatic Venous Gradient Pressure	4.23 ± 2.07
Gender Distribution	
Male	92 (66.7%)
Female	46 (33.3%)
Residential Status	
Urban	61 (44.2%)
Rural	77 (55.8%)
Comorbidity Status	
Presence of Diabetes Mellitus	62 (44.9%)
Presence of Hypertension	77 (55.8%)
Smokers	64 (46.4%)

Regarding disease severity, 10.9% of patients were classified as Child-Pugh Class A, 25.4% as Class B, and 63.8% as Class C. Oesophageal varices were detected in 88.4% of patients, while 84.8% had portal hypertensive gastropathy, (Table 2).

Table 2: Frequency of Child-Pughclass Distribution, Oesophageal-Varices, and Portal-Hypertensive-Gastropathy (n=138)

Category	Frequency (%)
Child-Pugh Class	
Class A	15 (10.9%)
Class B	35 (25.4%)
Class C	88 (63.8%)
Oesophageal Varices	
Present	122 (88.4%)
Absent	16 (11.6%)
Portal Hypertensive Gastropathy	
Present	117 (84.8%)
Absent	21 (15.2%)

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A significant association was observed between Child-Pugh class and the presence of oesophageal varices (p = 0.008). Class C patients were highest (55.8%), followed by Class B (23.2%) and Class A (9.4%).However, the association between Child-Pugh class and portal hypertensive gastropathy was not statistically significant (p = 0.122).Although PHG was more common in Class C patients (52.9%) than in Class A (8.0%) and Class B (23.9%), the difference was not statistically meaningful, (Table 3).

Table 3: Association of Childpughclass with Oesophagealvarices and Portalhypertensivegastropathy(n=138)

Child Pugh Class	Coronary Angiographic Profile		p-Value	Confidence Interval
	Present Frequency (%)	Absent Frequency (%)		
Class A	13 (9.4%)	2 (1.4%)	0.008*	95%
Class B	32 (23.2%)	3 (2.2%)		
Class C	77 (55.8%)	11 (8.0%)		
Portal Hypertensive Gastropathy				
Class A	11 (8.0%)	4 (2.9%)	0.122	95%
Class B	33 (23.9%)	2 (1.4%)		
Class C	73 (52.9%)	15 (10.9%)		

*Statistically Significant (Chi – square test was applied)

DISCUSSION

Oesophageal varices and portal hypertensive gastropathy are major complications associated with cirrhosis due to increased portal vein pressure. Oesophageal varices are dilated, fragile veins in the oesophagus, whereas portal hypertensive gastropathy refers to mucosal changes in the stomach resulting from portal hypertension. Both conditions significantly increase the risk of gastrointestinal bleeding, making their early identification and management crucial for cirrhotic patients [12, 13]. In this study, the mean age of the patients was 42.92 ± 15.59years, which is consistent with prior studies that reported mean ages of 44 ± 12.61 years [14]. The majority of patients in this study were male (66.7%), which aligns with findings from Saleem K et al (53.15% male) [15]. Similarly, Sungkar T *et al.*, reported a male predominance of 71.4% [11]. The prevalence of oesophageal varices in this study was 88.4%, while portal hypertensive gastropathy was present in 84.8% of patients. These findings align with previous studies that reported oesophageal varices in 90.1% and 93.8% of cirrhotic patients [16, 17].The prevalence of portal hypertensive gastropathy varies widely, with reported rates ranging from 20% to 98% [18]. Child-Pugh classification is a critical tool in assessing the severity of cirrhosis, incorporating factors such as bilirubin levels, albumin levels, INR, ascites, and encephalopathy [19].In this study, the association between Child-Pugh class and oesophageal varices was statistically significant (p = 0.008). The distribution of varices across Child-Pugh classes was 9.4% in class A, 23.2% in class B, and 55.8% in class C. Similarly, portal hypertensive gastropathy was found in 8.0% of patients in class A, 23.9% in class B, and 52.9% in class C, with a non-significant p-value of 0.122. These findings contrast with previous studies by Nishino K *et al.*, and Tiwari PS *et al.*, which found a significant association between portal hypertensive gastropathy and Child-Pugh stage [8, 9]. However, El-Kalla F *et al.*, did not observe a significant difference in the prevalence of portal hypertensive gastropathy across different Child-Pugh stages [10].The inconsistency in the association between PHG and Child-Pugh classification arises from variations in patient populations, non-standardized PHG grading, small sample sizes, and inter-observer differences in endoscopic interpretation.Moreover, confounders like H. pylori infection and portal pressure-modifying medications further obscure the relationship.Early detection and management of oesophageal varices and portal hypertensive gastropathy remain essential in preventing severe bleeding events.Endoscopic screening is the gold standard for diagnosing these conditions, with grading systems such as the Baveno criteria guiding treatment strategies [20].Prophylactic measures, including beta-blockers and endoscopic variceal band ligation, are recommended for high-risk patients to reduce the likelihood of life-threatening hemorrhages. Managing cirrhosis holistically, addressing complications such as ascites and hepatic encephalopathy, is crucial in reducing portal hypertension and improving patient outcomes [21]. One of the key limitation of the study is the variability in PHG prevalence due to the potential confounders like differences in patient selection, endoscopic interpretation, liver disease stage and etiology, beta-blocker use, comorbidities, and inconsistent diagnostic criteria across studies. Other limitations included the use of non-probability consecutive sampling which had limited the generalizability of results and the absence of histological confirmation which had limited the diagnostic precision.

CONCLUSIONS

The study found a significant association between Child-Pugh class and the presence of esophageal varices, with the highest prevalence observed in Child-Pugh Class C patients. However, no statistically significant association was found between Child-Pugh class and portal hypertensive gastropathy, suggesting that while cirrhosis severity correlates with esophageal varices, it does not have the same effect on the development of portal hypertensive gastropathy.

Authors Contribution

Conceptualization: SIH
Methodology: MSB
Formal analysis: KHS
Writing, review and editing: SIH, NLS, ARQ, US, KHS, MSB

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All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Efficacy of Combined Intralesional Triamcilone and Cryotherapy for Treatment of Keloid

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ABSTRACT

Keloid treatment remains a challenging task due to the high recurrence rates and limited effectiveness of monotherapies. **Objective:** To determine the efficacy of combining intralesional Triamcinolone Acetonide (TA) with cryotherapy. **Methods:** A quasi-experimental study was conducted at the Dermatology Department, Nishtar Hospital, Multan, over 6 months from 30th June 2024, to December 31, 2024. Eighty patients were enrolled using non-probability consecutive sampling. Baseline characteristics, including keloid dimensions, pain, and itching scores, were documented. Patients received cryotherapy followed by intralesional TA (40 mg/mL) injections for up to six sessions. Treatment outcomes were assessed two weeks post-treatment through reduction in keloid height, length, and Visual Analog Scale (VAS) scores. **Results:** The mean keloid height and length reduced significantly from 4.66 ± 1.37 mm to 1.69 ± 1.18 mm and 6.64 ± 2.23 cm to 2.68 ± 1.79 cm, respectively ($p < 0.001$) post-treatment. VAS pain scores decreased by 2.86 ± 1.96, and VAS itching scores decreased by 3.53 ± 1.39 ($p < 0.001$). Efficacy, defined as ≥50% reduction in keloid dimensions, was achieved in 75% of participants. Common adverse effects included blistering (18.8%) and erythema (15%). **Conclusions:** The combination of cryotherapy and intralesional triamcinolone acetonide demonstrated effective reduction in keloid height and length, with significant improvement in pain and itching scores. Although efficacy varied across demographic and lesion-specific variables, the treatment remains a safe and viable option for keloid management, with manageable adverse effects and promising outcomes.

INTRODUCTION

Keloids are caused by aberrant wound-healing process, due to excessive fibroblast proliferation, persistent inflammation, and dysregulated Extracellular Matrix (ECM) deposition beyond the original wound. They do not regress spontaneously, and often recur after removal [1]. Keloid are frequently observed in the African and Asian population. The prevalence of keloids can varies across different geographical regions, as 0.09% in United Kingdom to as high as 16% in Africa [2]. In addition to cosmetic defect, it can cause substantial discomfort, including itching, pain, and restricted movement. In severe cases, keloids may ulcerate and, rarely, undergo neoplastic progression, making treatment necessary not just for cosmetic reasons but also for medical reasons [2, 3]. Molecular signaling pathways like TGF-β/Smad and JAK/STAT play a key role in keloid progression by activating fibroblast activation, collagen production, and immune responses. TGF-β1, a major cytokine, boosts fibroblast growth, increases Extracellular Matrix (ECM) buildup, and prevents cell death, leading to persistent structural changes. Chronic inflammation from prolonged pro-inflammatory signals worsens fibroblast activity. Mechanical stress and low oxygen levels further aggravate this process. Effective treatments must target fibroblast growth, inflammation, and ECM to prevent proliferation and fibrotic changes [4, 5]. Various therapeutic interventions have been explored,

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including non-invasive methods like silicone gel and pressure therapy to invasive options like intralesional corticosteroids, 5-fluorouracil, cryotherapy, laser therapy, and surgical excision [6]. Intralesional corticosteroids, particularly triamcinolone acetonide, remain a primary treatment for keloid due to their ability to inhibit collagen synthesis, reduce fibroblast proliferation, and relieve symptoms like itching and pain [7, 8]. Cryotherapy treats keloids by applying extremely cold liquid nitrogen, to induce fibroblast apoptosis and reduce collagen synthesis by altering fibroblast phenotype, increasing the type III to type I collagen ratio. Furthermore, through scar tissue softening, it improves corticosteroid penetration. However, the efficacy of cryotherapy as a monotherapy remains questionable, with some studies suggesting a favorable response, whereas others indicate limited benefit [2, 9]. A combination of cryotherapy and intralesional corticosteroids may exert a synergistic effect, achieving better therapeutic outcomes compared to either treatment alone [10]. Despite ongoing progress in skin treatments, managing keloids remains difficult due to their tendency to return and poor response to standard therapies. This study was designed to assess how well a combination of intralesional corticosteroid injections and cryotherapy works for treating keloids. It focused on changes in the size of the lesions, along with improvements in pain and itching.

The goal was to explore whether this combined approach offers better outcomes.

METHODS

This quasi-experimental study was conducted at the Dermatology Department, Nishtar Hospital, Multan, after obtaining approval from the Institutional Review Board (IRB No. 7110), over six months from June 2024 to December 2024. A total of 80 patients were enrolled using non-probability consecutive sampling, with the sample size calculated using the WHO sample size calculator, assuming a 95% confidence level and an anticipated efficacy rate of 71.1%, based on previous studies. The study included adults aged 18 to 60 years with non-flattened keloids (up to 10 cm) present for over six months on various body sites. Preference was given to those with symptoms such as pain, itching, or cosmetic concerns, who agreed to treatment, follow-up, and photography. Patients with conditions such as pregnancy, breastfeeding, allergies to treatment, hypertrophic scars, infections, serious health issues, or recent use of corticosteroids, anticoagulants, or immunosuppressants were excluded. Baseline assessment included a clinical examination by a consultant dermatologist to confirm keloid diagnosis, with documentation of age, gender, keloid duration, site, cause (e.g., trauma, burn, surgery), lesion size, and symptom severity. Pain and itching were assessed using the Visual Analog Scale (VAS), which ranges from 1 (no pain/itching) to 10 (severe pain/itching). Treatment protocol involved the application of Eutectic Mixture of Local Anesthetics (EMLA) cream one hour before cryotherapy to reduce discomfort. Cryotherapy was performed by spraying liquid nitrogen onto the lesion, followed by two freeze-thaw cycles, with intralesional triamcinolone acetonide (40 mg/mL) injection five minutes after cryotherapy. Cryotherapy was repeated weekly for up to six sessions, with patients advised to keep the treated area clean and dry. Adverse effects, including blistering, erythema, ulceration, and skin discoloration, were documented during follow-up visits. The outcome assessment was based on keloid height and length, and efficacy was defined as a ≥50% reduction in keloid dimensions from baseline. Safety assessment involved documenting any adverse effects, and statistical analysis was performed using SPSS version 26.0, with paired t-tests for pre- and post-treatment comparisons. A p-value of ≤ 0.05 was considered statistically significant [11-13].

RESULTS

The study included 80 participants, with a majority being female 58 (72.5%), while males comprised 22 (27.5%). The mean age of participants was 35.98 ± 11.22 years. Most individuals were aged 18–39 years 50 (62.5%), while 30 (37.5%) were in the 40–60 years group. Etiologies included surgical wounds in 24 (30%), acne in 21 (26.3%), burns in 13 (16.3%), trauma in 9 (11.3%), and unknown causes in 13 (16.3%). Lesions were most commonly distributed on the abdomen 25 (31.3%), followed by the pubic area and extremities (18 each, 22.5%), armpits (7, 8.8%), and the chest and back (6 each, 7.5%). The mean duration of keloids was 2.50 ± 1.13 years. The mean percentage decrease in height was 68.21 ± 20.58%, while the mean percentage decrease in length was 63.69 ± 18.89%. The average keloid height reduced from 4.66 mm to 1.69 mm, and length from 6.64 cm to 2.68 cm, both showing statistically significant improvement ($p < 0.001$). VAS pain scores dropped from 5.35 to 2.49, and itching scores from 6.46 to 2.94, indicating marked symptom relief following treatment ($p < 0.001$ for both measures) (Table 1).

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Table 1: Comparison of Study Variable Befor and After Treatment

Variable	Pre-Treatment Mean ± SD	Post-Treatment Mean ± SD	Mean Difference Mean ± SD	95% CI (Lower- Upper)	p-Value
Height of keloid (mm)	4.66 ± 1.37	1.69 ± 1.18	2.98 ± 0.65	2.83-3.12	<0.001
Length of keloid (cm)	6.64 ± 2.23	2.68 ± 1.79	3.96 ± 1.07	3.72-4.20	<0.001
VAS pain	5.35 ± 1.61	2.49 ± 1.09	2.86 ± 1.96	2.43-3.30	<0.001
VAS itching	6.46 ± 1.12	2.94 ± 0.77	3.53 ± 1.39	3.21-3.84	<0.001

Improvement in keloid length was observed in 41 participants (51.3%) with a 50-74% reduction, 20 (25%) with a 0-49% reduction, 8 (10%) with a 75-90% reduction, and 11 (13.8%) with more than 90% reduction. Improvement in keloid height was noted in 40 participants (50%) with a 50-74% reduction, 10 (12.5%) with a 0-49% reduction, 12 (15%) with a 75-90% reduction, and 18 (22.5%) with more than 90% reduction.

Efficacy (≥ 50% reduction of keloid height and length from baseline)

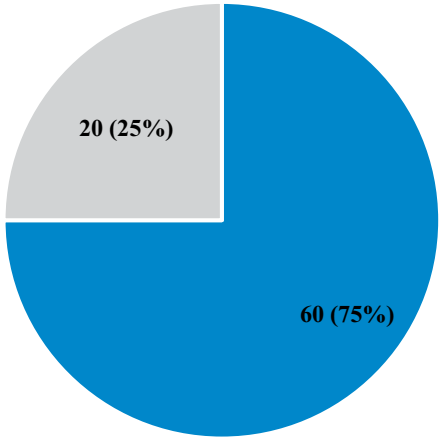

Figure 1: Distribution of Treatment Efficacy (n=80)

The treatment was associated with various adverse effects, as shown in the table 2.

Table 2: Adverse Effects Observed During Treatment

Adverse Effect	Frequency (%)
Blistering	15 (18.8%)
Ulceration	3 (3.8%)
Erythema	12 (15%)
Skin discoloration (hypo-/hyperpigmentation)	6 (7.5%)
Overall adverse effects	20 (25%)

Efficacy was higher in females (79.3%) compared to males (63.6%) with no significant gender association (p = 0.148). Younger participants (18-39 years) showed slightly better efficacy (76.0%) than those aged 40-60 years (73.3%), but the difference was not statistically significant (p = 0.790). Lesion location also showed no significant association with efficacy (p = 0.400), although efficacy was highest for armpit lesions (100%) and lowest for abdomen lesions (64.0%).

Table 3: Stratification of Baseline Variables and Their Association with Treatment Efficacy

Variables	Efficacy		p-Value
	Yes Frequency (%)	No Frequency (%)	
Gender			
Male	14 (63.6%)	8 (36.4%)	0.148
Female	46 (79.3%)	12 (20.7%)	
Age Group			
18-39 Years	38 (76.0%)	12 (24.0%)	0.790
40-60 Years	22 (73.3%)	8 (26.7%)	
Keloid Location			
Chest	4 (66.7%)	2 (33.3%)	0.400
Back	5 (83.3%)	1 (16.7%)	
Abdomen	16 (64.0%)	9 (36.0%)	
Pubic	15 (83.3%)	3 (16.7%)	
Armpit	7 (100.0%)	0 (0.0%)	
Extremities	13 (72.2%)	5 (27.8%)	

DISCUSSION

Managing keloids remains clinically challenging due to their frequent recurrence and inconsistent response to treatment [14].Fibroblast overactivity, collagen buildup, and ongoing inflammation contribute to this complexity. Intralesional corticosteroids like triamcinolone acetonide are commonly used for their anti-inflammatory effects, while cryotherapy helps by damaging abnormal tissue and enhancing drug absorption [2, 15]. Studies have shown that combination therapies are often more effective than single treatments, offering better results by addressing several underlying mechanisms at once [10, 16].In the present study, efficacy was defined as achieving ≥50% reduction in both keloid height and length. Based on this criterion, 75% of patients showed effective improvement.These findings are supported by prior literature.Mutalik S, reported an 87.7% overall improvement with combination therapy, including 1.3% with >90% improvement,46.4% with 75–90%, and 41.2% with 50–74% reduction [17]. Jwa SJ *et al.*, observed a 90.7% non-recurrence rate in 54 patients treated with cryotherapy plus triamcinolone acetonide (TA) after excision [18]. Cohen AJ *et al.*, also demonstrated that 71.1% of patients achieved >50% reduction with combination therapy, versus 43% with TA alone (p = 0.0021) [10].The efficacy of cryotherapy-enhanced intralesional corticosteroid therapy was also supported by Ahsan MQ *et al.*, who observed a 90% improvement rate in their combination therapy group, compared to 83.3% in the TA monotherapy group [16].Similarly, Jannati P *et al.*, compared cryotherapy combined with either TA or verapamil, reporting that 70% of patients receiving TA plus

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cryotherapy achieved complete resolution, while 65% of those treated with verapamil plus cryotherapy showed similar results, suggesting that the addition of cryotherapy significantly enhances therapeutic outcomes [19].The improvement rates observed in this study, where 50% of participants had a 50-74% reduction in keloid height and 22.5% experienced >90% improvement, align closely, found that 46.4% of patients achieved 75-90% improvement, and 11.1% had >90% improvement. Further supporting these findings, Singh PK *et al.*, reported a significantly higher response rate in patients receiving TA and cryotherapy compared to TA alone, with 48% of lesions flattening in the combination group versus only 16% in the monotherapy group [20]. Hewedy ES *et al.*, in a systematic review, highlighted the synergistic effect of cryotherapy, demonstrating that it enhances corticosteroid penetration, promotes fibroblast apoptosis, and reduces local inflammation, complementing TA's anti-inflammatory properties [21].In this study, the mean reduction in VAS pain score was 2.86 ± 1.96 ($p < 0.001$), while the mean decrease in VAS itching score was 3.53 ± 1.39 ($p < 0.001$). This aligns with findings from prior studies demonstrating significant symptomatic relief following combination therapy.A study comparing TA monotherapy to TA combined with cryotherapy reported a notable decrease in pain and itching scores post-treatment, with pain reducing from 5.8 ± 2.1 to 3.2 ± 1.6 ($p = 0.000$) and itching decreasing from 5.8 ± 2.2 to 3.9 ± 2.0 ($p = 0.001$) in the combination therapy group [17]. Cohen AJ *et al.*, study also highlighted that pruritus and pain were significantly reduced [10]. These findings further reinforce these results, where a substantial reduction in both VAS pain and itching scores ($p < 0.001$) was observed.Furthermore, Yosipovitch *et al.*, demonstrated that triamcinolone alone or in combination with cryotherapy resulted in marked pain and pruritus relief, supporting these findings [11].Despite the observed improvements, variations in pain and itching reduction across studies may be attributed to differences in lesion characteristics, treatment protocols, and patient sensitivity to procedural pain [13, 18, 21].The adverse effects observed in this study were consistent with findings from previous literature evaluating the combination of cryotherapy and intralesional Triamcinolone Acetonide (TA) for keloid treatment.In this study, the most common adverse effects included blistering (18.8%), ulceration (3.8%), erythema (15.0%), and skin discoloration (7.5%), with an overall incidence of 25%. Another study comparing TA alone versus TA with cryotherapy found telangiectasia in 29.9% and hyperpigmentation in 11.6% of the control group, whereas blistering (68.6%) and hypopigmentation (25.5%) were significantly higher in the combined therapy group [17]. Similarly, Ahsan MQ *et al.*, observed ulceration in 12.5%, hypopigmentation in 50%, and hyperpigmentation in 34.4% of patients undergoing combination therapy [16]. Yosipovitch *et al.*, reported that hyperpigmentation occurred in only one patient [11].A systematic review by Hewedy ES *et al.*, further corroborated these findings, highlighting that combination therapy increases the likelihood of temporary blistering and pigmentary changes but does not lead to severe or persistent complications [21].The differences in reported adverse event rates across studies may be attributed to variations in treatment protocols and patient skin types.While cryotherapy enhances corticosteroid penetration and keloid regression, it is associated with a higher incidence of transient side effects such as blistering and pigmentary alterations.Previous studies have also assessed how gender, age, and lesion site influence keloid treatment response. Jannati P *et al.*, found higher response rates in females, though not statistically significant.This is similar to these findings, where females showed 79.3 percent efficacy compared to 63.6 percent in males ($p = 0.148$)[19]. Similarly, Singh PK *et al.*, reported better outcomes in younger individuals, which aligns with this data: participants aged 18 to 39 years showed 76 percent efficacy, while those aged 40 to 60 years had 73.3 percent ($p = 0.790$)[20]. Regarding lesion location, Hewedy ES *et al.*, observed better results on the chest and limbs, this study showed highest efficacy in armpit lesions (100 percent) and lowest on the abdomen (64.0 percent) ($p = 0.400$) [21]. Ahsan MQ *et al.*, Additionally, chest keloids demonstrated the highest response (34.6%), whereas back lesions had the lowest (5.8%), a trend consistent with this study findings [16].These findings suggest that although demographic and anatomical variations influence treatment response, they do not significantly alter overall efficacy, reaffirming the consistency of these results with prior research.Limitations of study includes the short follow-up duration which restricts the ability to provide information related to long-term recurrence rates. Future research should focus on larger, multi-center trials with longer follow-up to better evaluate recurrence and refine treatment procedures.Despite these limitations, the findings of this study strengthen the growing evidence that combination therapy offers superior efficacy compared to monotherapy, supporting its continued use in clinical practice.

CONCLUSIONS

This study demonstrates the efficacy of combining cryotherapy with intralesional triamcinolone acetonide for keloid treatment, attaining significant reductions in keloid size along with improvements in symptoms such as pain and itching. The results confirm the therapeutic potential of this multimodal approach, offering a safe option for the

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management of keloids. Demographic factors, such as gender, age, and lesion location didn't report significant associations with treatment efficacy, confirming the broader applicability of combined therapy.

Authors Contribution

Conceptualization: ST
Methodology: ST, RT, N
Formal analysis: MIJ
Writing, review and editing: RT, N, MTS, MS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Determination of Frequency and Risk Factors of Ureteral Stent Encrustations in a Tertiary Care Hospital

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ABSTRACT

Ureteral stent encrustation is a common problem, with incidence rates rising from 9% at 6 weeks to over 75% after 12 weeks of indwelling time. **Objective:** To determine the frequency and associated risk factors of the ureteral stent encrustation in patients with urolithiasis. **Methods:** This was a prospective descriptive study, conducted at the Department of Urology, JPMC, Karachi, Pakistan. All patients who visited to JPMC and fulfilled the inclusion criteria were included in the study after their consent. Stent duration was grouped into ≥ 6 weeks and < 6 weeks. The stent removal was done under general or local anesthesia. All the collected data were entered into the pre-defined study proforma. **Results:** Mean ± SD of age was 39.60 ±12.06 years. In the distribution of gender, 43 (58.9%) were male while 30 (41.1%) were female. Ureteral stent encrustation was noted in 11 (15.1%) patients. In the comparison of urinary tract infection and proteinuria, with and without ureteral stent encrustation was noted as 9.6% v/s 5.5% and 11% v/s 4.1%, and the p-value was found to be highly significant i.e., $p < 0.0001$. **Conclusions:** This study concluded that ureteral stent encrustation was prevalent in patients with urolithiasis. It is significantly associated with urinary tract infection and proteinuria. However, more prospective and well-controlled trials are needed to validate the current findings.

INTRODUCTION

Ureteral stent encrustation remains a noteworthy clinical challenge, with current studies stating a 26.8% incidence rate for stents retained beyond 12 weeks [1].This problem arises from the deposition of minerals on stent surfaces, influenced by several factors such as bacterial biofilm formation, patient-specific metabolic conditions and prolonged indwelling time [2]. The median indigenous time for encrustation-prone stents is 35 days compared to 28 days in non-encrustation cases, highlighting temporal risks [3].Bacterial cultures affect over 90% of long-term indwelling stents, with biofilm-forming pathogens like E. coli enhancing crystal nucleation by pH alterations and urease activity [4].Evolving evidence highlights the multifactorial pathophysiology, where acclimatizing film formation precedes either direct mineral deposition or bacterial culture [5].The current advancements in radiomics and machine learning validate 78.8% specificity to detect encrustations through CT-based texture analysis, contributing promising diagnostic tools [6].The risk factors related to the patient include persistent UTI (urinary tract infection), chronic renal failure, and diabetes mellitus, which modify urinary composition and promote lithogenic conditions [7].Contemporary research emphasizes material innovations, including heparin-

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coated stents and biodegradable polymers, which reduce encrustation by 50% compared to conventional models [8]. These developments emphasize the need for personalized stent selection and indwelling time optimization in tertiary care settings to mitigate encrustation-related complications.

The prevalence of urolithiasis is high in Pakistan due to its geographic location in the stone belt, and several risk factors have been identified in different scientific studies. Data on associated factors of ureteral stent encrustation is also available globally, but from Asia, it's scarce, and from Pakistan, almost non-existent. Different diseases have different prevalences globally, depending on lifestyle modifications, management, diet, socioeconomic conditions, and geographical location. There is no local study available, that figures out the frequency and associated factors of ureteral stent encrustation.

This study was designed to find out the frequency of ureteral stent encrustation and factors associated with patients with urolithiasis.

METHODS

It was a prospective descriptive study, conducted at the Department of Urology, JPMC, Karachi, Pakistan. The study was approved by the Ethical Review Committee of Sindh Institute of Urology (SIUT) with reference number SIUT/CRP/0124. The study was completed within six months from September 2020 to March 2021 after the approval of the synopsis. The sample size was calculated by using a confidence level of 95% (Z-value = 1.96), a margin of error of 5% (0.05) and a proportion of population of stent encrustations of 5% (0.05) and the calculated sample size was 72 and the current study sample size was 73. Data were calculated by using a convenience sampling technique [9]. 73 patients with the ureteral stent in situ in managing urolithiasis were studied. The diagnosis of ureteral stent encrustation was determined by ureteral stent weight before and after treatment with an acidic solution. Patients aged 15-65 years of both genders were included; ureteral stent placement in the stone's management disease. Patients who agreed to participate were involved after signing the consent form and answering a questionnaire performa. Data regarding patients' baseline information, such as age, gender, and duration of stent insertion, was collected. The urine samples were taken for laboratory investigations, including routine examination and Culture and Sensitivity testing. The blood samples were drawn for serum calcium, phosphate, and uric acid testing. After inclusion, stent duration was grouped into ≤6 weeks and >6 weeks. Stent removal was done under general or local anesthesia. After Ureteral stent removal, the outcome variable i.e., ureteral stent encrustation and its associated factor, was assessed by a urology consultant the principal investigator. Data analysis was carried out by using SPSS version 20.0. Mean and Standard deviation were calculated for numerical variables, including age, serum calcium, serum phosphate, serum uric acid, and urinary pH. Calculation of percentage and frequencies was performed for categorical variables i.e, gender, duration of stent placement, ureteral stent encrustation, UTI, and proteinuria. Effect modifiers were controlled through stratification of age, gender, duration of stent placement, serum calcium, serum phosphate, serum uric acid, and urinary pH by appropriate Chi-Square / Fisher's Exact test, considering two-sided P ≤ 0.05 as criterion of statistical significance.

RESULTS

A total of 80 patients with ureteral stent in situ were involved, 73 patients who met the inclusion criteria. 5 patients were excluded because of their ureteral stenting done in the management of neoplasia of the colon, and other excluded patients were owed to insufficient data or termination of the medical follow-up.

Table 1: Characteristics of the Patients

Adverse Effect	Mean ± SD	Percentage (%)
Age (Years)	39.60 ± 12.06	-
Serum Calcium (mg/dl)	10.18 ± 0.53	-
Serum Phosphate (mg/dl)	4.31 ± 0.35	-
Serum uric acid (mg/dl)	4.40 ± 0.67	-
Urinary PH	6.40 ± 0.29	-
Duration of Stent (Weeks)	11.48 ± 20.11	-
Gender	Male	58.9%
	Female	41.1%
Frequency of Stent Encrustation		15%

The mean age of the patients were 39.60 ± 12.06 years. Mostly, patients were male (58.9%) and (41.1%) were female. The mean values were: Serum calcium 10.18±0.53 mg/dl, Serum phosphate 4.31±0.35 mg/dl, serum uric acid 4.40±0.67 mg/dl, Urinary PH 6.40±0.29 and duration of the stent was 11.48±20.11 weeks. Out of 73 patients, 11 patients had ureteral stent encrustation. The frequency of the ureteral stent encrustation in the study was 15%. There were a statistically significant differences about the UTI, proteinuria, age group, duration, serum calcium, serum uric acid, and urinary pH between the patients by means of and short of ureteral stent encrustation, as presented in table 2. Patients with stent encrustation had high serum calcium, serum uric acid, urinary pH, and proteinuria. Patients with encrustation had a higher frequency of urinary tract infections as compared with patients without encrustation. The middle age group (>40 years) suffered more with encrustation when compared with younger age groups (16-40 years). There were no statistical differences regarding serum phosphate and gender, amongst patients with and without encrustation, presented in table 2.

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Table 2: Comparison of Ureteral Stent Encrustation with Associated Factors

Variables		Ureteral Stent Encrustation		p-Value
		Yes Frequency (%)	No Frequency (%)	
Urinary Tract Infection	Yes	7 (9.6%)	4 (5.5%)	0.0001
	No	4 (5.5%)	58 (79.5%)	
Proteinuria	Yes	8 (11.0%)	3 (4.1%)	0.0001
	No	3 (4.1%)	59 (80.8%)	
Age Group (Years)	16-40	4 (5.5%)	44 (60.3%)	0.032
	>40	7 (9.6%)	18 (24.7%)	
Gender	Male	7 (9.6%)	36 (49.3%)	0.500
	Female	4 (5.5%)	26 (35.6%)	
Duration (In weeks)	>6 weeks	3 (4.1%)	42 (57.5%)	0.014
	≤6 weeks	8 (11.0%)	20 (27.4%)	
S.Calcium (mg/dl)	9-10	4 (5.5%)	48 (65.8%)	0.010
	>10	7 (9.6%)	14 (19.2%)	
S.Phosphate (mg/dl)	3-4	2 (2.7%)	48 (65.8%)	0.166
	>4	9 (12.3%)	14 (19.2%)	
S. Uric Acid (mg/dl)	3-4	2 (2.7%)	48 (65.8%)	0.0001
	>4	9 (12.3%)	14 (19.2%)	
Urinary pH	5-6	4 (5.5%)	6 (8.2%)	0.038
	>6	7 (9.6%)	56 (76.7%)	

DISCUSSION

Ureteral stents are devices used for the decompression of the upper urinary tract in the presence or anticipation of the upper urinary tract obstruction. Two types of ureteral obstruction are present i.e., internal and external. Internal obstruction may be due to stone, stricture, and edema after the ureteral intervention; external obstruction can be because of compression by neoplastic growth and retroperitoneal fibrosis. The ureteral stents are also used in rehabilitative urological surgeries to promote healing [10]. These stents help dilate the ureter, decompress the upper urinary tract, and prevent occlusion [11]. However, ureteral stent insertion can also be associated with side effects and complications such as infection, discomfort, lumen occlusion, and ureteral stent encrustation in the urinary tract [12]. These side effects also compromise the excellence of care and become a significant financial burden to healthcare.There are different additional procedures required to remove an encrusted stent; therefore, cases of a kept stent made up 16% of endourology lawsuits [11].In addition to that prolonged stent duration also increased the risk of chronic kidney diseases.These complications lead to hospitalization after stent removal because of sepsis and urinary tract infections. The management of ureteric obstruction has been markedly changed by the use of ureteric stents, which provide relief in renal colic, hydronephrosis, and renal failure.Ureteral stent routine placement can be recommended for the management of urolithiasis but is commonly applied after endourology procedures [13].The encrustation of the ureteral stents might be because of the deposition of the biological layers, uropathogenic and urinary salts.Some studies suggest UTIs are the major culprit in the formation of the organic layer; similar to the study's findings [14].Different designs and materials of ureteral stents experimented but encrustation is yet another concern.Migration, stone formation, and fragmentation of stents are serious complications of long-term forgotten stents which increase with a longer duration of the indwelling stent [15].The etiology of the encrustation is still unclear even after the formation of the hydrophilic coating on stents. Age and gender distribution varied among different studies of ureteral stent encrustation.These study outcomes were based on the adult age group between 39.60 ± 12.06 years of age, whereas Hsu JS *et al.*, study was based on of 60.1 ± 12.1 year's age group [16].We and other similar studies also reported the predominantly male gender for ureteral stent encrustation [17].This study found ureteral stent encrustation in 15.1% of patients, which is close to another study reported from Pakistan, i.e., 10.5% of ureteral stent encrustation cases [18].One of the previous studies reported ureteral stent encrustation in 22% of cases [11]. Waseda Y *et al.*, documented encrustation in 27% of patients from Japan [19]. In the distribution of associated factors of ureteral stent encrustation, 11 (15.1%) were urinary tract infections, while 11(15.1%) were proteinuria. In comparison, urinary tract infection and proteinuria were noted as 9.6% v/s 5.5% and 11% v/s 4.1% among patients with ureteral stent encrustation, having a highly significant p-value of 0.0001. However, Soria F *et al.*, found a large number of urinary tract infections among patients of ureteral stent encrustation [20].Regarding ureteral stent encrustation, we found significant differences in age group i.e., $p = 0.032$, duration of stent placement $p = 0.014$, serum calcium $p = 0.010$, serum uric acid $p < 0.0001$, urinary PH $p = 0.038$ while the insignificant difference was reported in gender $p = 0.500$ and serum phosphate $p = 0.166$.

CONCLUSIONS

This study concluded that ureteral stent encrustation was prevalent among the patients in the middle age group with urinary tract infection, proteinuria, elevated serum calcium, and uric acid, and increased urinary pH. To validate these findings, larger-scale, well-controlled prospective trials are needed.

Authors Contribution

Conceptualization: MM
Methodology: MUS
Formal analysis: MUS
Writing, review and editing: MM, AA, Z, BA

All authors have read and agreed to the published version of the manuscript

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Original Article

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Outcome of Severe Left Ventricle Systolic Dysfunction Patients After Coronary Artery Bypass Grafting

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ABSTRACT

Coronary artery bypass grafting (CABG) has historically been regarded as a high-risk intervention. **Objective:** To evaluate the short-term outcomes of severe left ventricular (LV) systolic dysfunction in patients after CABG. **Methods:** This prospective observational cohort study was done at the Department of Cardiac Surgery, Pervaiz Elahi Institute of Cardiology, Bahawalpur, Pakistan, from August 2022 to September 2024. Patients aged 30–75 years, with confirmed coronary artery disease requiring CABG and ejection fraction (EF) ≤30%, were analyzed. Preoperative variables included demographic information, comorbidities, cardiac function parameters and angiographic findings. Postoperative complications and 90-day mortality were noted. **Results:** In a total of 78 patients, 53 (68%) were male.The mean age was 55.2 ± 9.3 years. The mean baseline EF was 25.4 ± 4.6%.The mean bypass and cross-clamp times were 90.3±16.8 minutes and 51.4 ± 11.6 minutes, respectively.The most common post-surgery complications were arrhythmias, neurological disorders, wound infection, and acute kidney injury, noted in 12 (15.4%), 6 (7.7%), 5 (6.4%), and 3 (3.8%) patients, respectively. At 90 days postoperatively, mortality was reported in 6 (8.7%) patients. Predictors of 90-day mortality included preoperative EF <25% (OR=3.2, 95% CI:1.2–8.5, p=0.014), age ≥65 years (OR=2.8, 95% CI:1.1–7.0, p=0.021), and left main disease (OR=3.6, 95% CI:1.4–9.1, p=0.008). **Conclusions:** In terms of short-term outcomes, CABG in patients with severe LV systolic dysfunction is associated with significant improvements in functional status and EF. Key predictors of mortality included preoperative EF <25%, advanced age (≥65 years), and left main disease, highlighting the need for careful preoperative risk stratification.

INTRODUCTION

Coronary artery disease (CAD) is known to be an important cause of morbidity and mortality worldwide [1]. Ischemic heart disease (IHD) is estimated to affect around 126 million people globally, with a significant proportion experiencing left ventricular (LV) systolic dysfunction (LVSD) [2]. In 2022, it was estimated that there were 315 million CAD cases globally [3]. CAD prevalence is anticipated to be increasing with advanced disease due to delayed access to care in Pakistan [4]. A recent study estimated the prevalence of CAD among adults aged 30-75 years as 34.9%, which seems very high [5]. It has been noticed that around 30% of cases who undergo coronary artery bypass grafting (CABG) have LV dysfunction (LVD), yet their outcomes remain poorly characterized [6]. CABG is a good revascularization strategy in CAD, exhibiting good efficacy in terms of improvement in survival and symptoms, particularly in multi-vessel disease [7, 8]. The outcomes of CABG in patients with severe LVSD remain less clear, especially in resource-limited settings like Pakistan. CABG has historically been nominated as a high-risk intervention for patients with severe LVD (ejection fraction ≤30%) due to the heightened risk of perioperative complications, including arrhythmias, low cardiac output syndrome, and mortality [9, 10]. Despite these risks, data from high-income countries have demonstrated that CABG can offer significant survival and symptomatic benefits if patients are carefully selected [11]. Evidence from trials such as the STICH trial further reinforced the role of surgical revascularization in improving outcomes for these patients [12]. However, in developing countries, barriers such as

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delayed diagnosis, limited access to advanced diagnostic tools (e.g., viability imaging), and lack of surgical expertise in managing complex cases complicate the application of these findings. Contemporary local data has shown a mortality rate of 5% with CABG, while severe LVD is significantly associated with ICU stay and post-operative complications in these patients [13]. This study aims to bridge the gap in evidence and provide insights into the short-term outcomes of CABG in this high-risk cohort, which may inform future policy and clinical decision-making.

This study aims to evaluate the short-term outcomes (post-operative complications, NYHA classification improvement, ejection fraction, and mortality) of severe LVSD in patients after CABG.

METHODS

This prospective observational cohort study was conducted at the Department of Cardiac Surgery, Pervaiz Elahi Institute of Cardiology, Quaid-e-Azam Medical College, Bahawalpur, Pakistan, from August 2022 to September 2024. Ethical approval was obtained from the institutional review board (letter number: 43/IERB/QAMC Bahawalpur). Considering the prevalence of CAD as 9.5% [14], with a 95% confidence level and 8% margin of error, the sample size was calculated to be 68. With the expected loss of follow-up, an additional 15% sample was added, so the final calculated sample size was 78. Non-probability, consecutive sampling technique was adopted. Inclusion criteria were patients of either gender, aged 30–75 years, with confirmed CAD requiring CABG. Patients with concomitant valve surgery, significant congenital or structural heart disease, recent myocardial infarction (<4 weeks), or malignancy were excluded. Severe LVD was defined as an ejection fraction (EF) ≤ 30% [15], assessed via transthoracic echocardiography. Informed consent was obtained from all participants. Preoperative variables included documentation of demographic information, comorbidities, cardiac function parameters, and angiographic findings. Intraoperative data included the surgical technique (on-pump vs. off-pump), cardiopulmonary bypass (CPB), and cross-clamp (IACC) times, number and type of grafts used, and the use of an intra-aortic balloon pump IABP. Postoperative data encompassed complications such as arrhythmias, stroke, acute kidney injury, wound infections, and re-exploration for bleeding. Short-term outcomes were evaluated at 90 days postoperatively. The primary outcomes were all-cause mortality, improvement in functional status (New York Heart Association (NYHA) class), and readmission rates. Secondary outcomes included postoperative complications, and changes in EF. A special proforma was designed to record study data. Data were analyzed using IBM-SPSS Statistics, version 26.0. Continuous variables were summarized as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. An independent t-test was applied to compare continuous variables, and chi-square or Fisher's exact tests were used for categorical variables. Multivariable logistic regression analysis was performed to identify independent predictors of mortality by estimating odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding p-values. A p-value of <0.05 was considered statistically significant.

RESULTS

In a total of 78 patients, 53 (68%) were male. The mean age was 55.2 ± 9.3 years, while 40 (51.3%) patients were aged 45–64 years. The mean BMI was 27.4 ± 3.6 kg/m2. Common comorbidities included hypertension 61 (78.2%), and diabetes mellitus 51 (65.4%). The mean baseline ejection fraction was 25.4 ± 4.6%. Angiographic findings revealed triple-vessel disease in 65 (83.3%) and left main coronary artery disease in 20 (25.6%) patients.Myocardial viability was confirmed in 72 (92.3%) cases.The baseline characteristics of patients are shown in Table 1.

Table 1: Baseline Characteristics (n=78)

Characteristics		Frequency (%)
Gender	Male	53
	Female	25
Age (Years)	18-44	12 (15.4%)
	45-64	40 (51.3%)
	≥65	26 (33.3%)
Body Mass Index (kg/m^2)	Below 18.5	5 (6.4%)
	18.5 to 24.9	18 (23.1%)
	25.0 to 29.9	35 (44.9%)
	Equal Or Above 30	20 (25.6%)
Comorbidities	Diabetes Mellitus	51 (65.4%)
	Hypertension	61 (78.2%)
	Chronic Kidney Disease	14 (18.0%)
NYHA Class	II	12 (15.4%)
	III	44 (56.4%)
	IV	22 (28.2%)
Angiographic Findings	Triple-Vessel Disease	65 (83.3%)
	Left Main Disease	20 (25.6%)
	Viable Myocardium	72 (92.3%)

On-pump CABG was performed in 66 (84.6%) patients. The mean CPB and cross-clamp times were 90.3 ± 16.8 minutes and 51.4±11.6 minutes, respectively.The mean number of grafts per patient was 3.1 ± 0.8. The IABP was used in 13 (16.7%) patients.No mortality was reported intra-operatively.The most common post-surgery complications were arrhythmias, neurological disorders, wound infection, and acute kidney injury, noted in 12 (15.4%), 6 (7.7%), 5 (6.4%), and 3 (3.8%) patients, respectively. Re-exploration for bleeding was performed in 3 (3.8%) patients. Readmission was reported in 10 patients

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during the 90-day post-surgery evaluation period. The most common reasons for readmission were heart failure exacerbation 4 (40.0%), surgical wound infections 3 (30.0%), arrhythmias 2 (20.0%), and pneumonia 1 (10.0%). At 90 days postoperatively, 69 patients completed follow-up. Mortality was reported in 6 (8.7%) patients. Among survivors, 52 (75.4%) showed improvement in NYHA functional class ($p<0.001$). The detailed comparison of the NYHA classification baseline and after 90 days' post-surgery is shown in Figure 1.

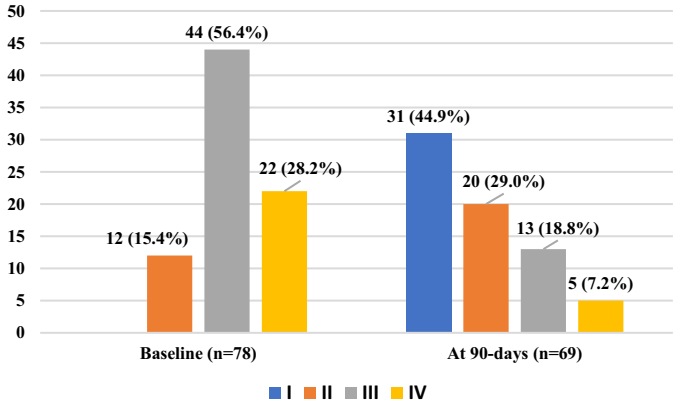

Figure 1: Comparison of Baseline and Post-Surgery 90 Days NYHA Classification

A significant improvement in EF was observed, increasing from a baseline mean of 25.4 ± 4.6% to 35.7 ± 5.2% at 90 days ($p<0.001$), as shown in Figure 2.

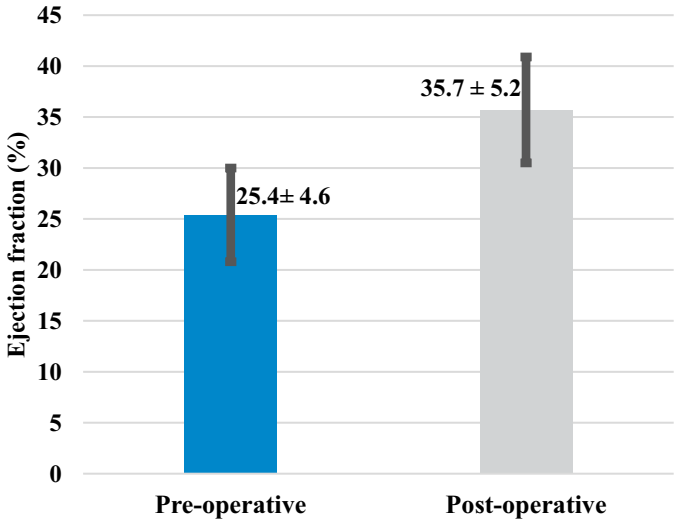

Figure 2: Comparison of Baseline and Post-Operative 90 Days Ejection Fraction (%)

Predictors of 90-day mortality included preoperative EF <25% (OR 3.2, 95% CI: 1.2–8.5, p=0.014), age ≥65 years (OR 2.8, 95% CI: 1.1–7.0, p=0.021), and left main disease (OR 3.6, 95% CI: 1.4–9.1, p=0.008), as shown in Table 2.

Table 2: Multivariable Logistic Regression for Predictors of Mortality at 90 Days

Predictors	Odds ratio (95% CI)	p-Value
Pre-Operative Ejection Fraction <25%	3.2 (1.2-8.5)	0.014
Age ≥65 Years	2.8 (1.1-7.0)	0.021
Left Main Disease	3.6 (1.4-9.1)	0.008

DISCUSSION

The findings of this study indicated that CABG significantly improved functional status, as demonstrated by improvements in NYHA classification and EF at 90 days postoperatively.Hillis *et al.*, demonstrated that patients with EF ≤ 35% undergoing CABG achieved significant survival benefits and functional improvement, with a 3-year survival rate of 81% [16]. Koene *et al.*, found that patients with low preoperative EF (<50%) experienced significant postoperative EF improvement after CABG, with greater gains observed in those with lower baseline EF [17].Current findings align with the published literature, demonstrating substantial EF recovery in a population with severe LVD, reaffirming the physiological benefits of revascularization.While the overall trends in EF improvement and functional recovery after CABG in this study are comparable to international data, the relatively higher complication rates in this study are noteworthy. These rates were a bit higher than those reported in studies from high-resource settings, such as Koene *et al.*, where complication rates were significantly lower [17].This disparity may reflect differences in perioperative care, infection control practices, and patient comorbidity burden.The readmission rate of 14.5% within 90 days, primarily due to heart failure exacerbation and wound infections, underscores the need for improved postoperative management.Despite functional improvements, the observed mortality rate of 8.7% within 90 days highlights the high-risk nature of this population. The observed 90-day mortality rate (8.7%) was higher than rates reported in some high-resource settings, where mortality is often below 5% [18, 19].This study's population had a high prevalence of diabetes mellitus (65.4%) and hypertension (78.2%), which are known contributors to worse surgical outcomes [20].Resource constraints in South Punjab, such as limited access to advanced diagnostic imaging and perioperative care, may have influenced outcomes.Studies by Yang *et al.* and Sun *et al.* highlighted the role of adjunct procedures like surgical ventricular reconstruction (SVR) and advanced imaging in improving CABG outcomes, but these were not feasible in our setting [21, 22]. Preoperative EF < 25%, age ≥65 years, and left main disease were significant predictors of 90-day mortality in our cohort.Nardi *et al.*, identified reduced preoperative EF and advanced age as independent predictors of perioperative and long-term mortality [23].

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Left main disease, associated with a higher ischemic burden and hemodynamic instability, has also been consistently linked to poorer outcomes in prior studies [24, 25].The findings of this study also align with findings from the STICH trial, which underscored the importance of myocardial viability assessment in predicting CABG success [12].However, in our cohort, viability was assessed using basic imaging rather than advanced modalities like cardiac MRI, potentially impacting patient selection and risk stratification.The identification of key predictors of mortality, including preoperative EF <25%, advanced age, and left main disease, underscores the need for rigorous preoperative risk stratification.This can guide surgical decision-making and patient counseling, ensuring appropriate resource allocation for high-risk cases. Patients with borderline EF or significant comorbidities may benefit from adjunct therapies, such as preoperative optimization with mechanical circulatory support or intraoperative strategies to minimize ischemic burden [26].The high rates of postoperative complications observed in this study emphasize the importance of strengthening perioperative care protocols.Targeted interventions, such as enhanced infection control measures, standardized perioperative anticoagulation protocols, and improved post-extubation care, could help mitigate these complications.Early detection and management of arrhythmias, along with structured cardiac rehabilitation programs, may further reduce morbidity and readmissions.Investment in staff training, perioperative hemodynamic monitoring, and postoperative critical care resources could also improve outcomes in resource-limited settings.These findings suggest a need for multidisciplinary collaboration, involving cardiologists, surgeons, and intensivists, to optimize outcomes for these patients [27].These findings suggest a need for multidisciplinary collaboration, involving cardiologists, surgeons, and intensivists, to optimize outcomes for these patients.By focusing on a high-risk population in South Punjab, Pakistan, the present findings address a critical gap in the literature and provide evidence to guide clinical practice in similar settings.This study highlights the potential for significant functional recovery and survival benefits, even in resource-constrained environments, when CABG is performed with careful patient selection and perioperative care.

CONCLUSIONS

It was concluded that in terms of short-term outcomes, CABG in patients with severe LVSD is associated with significant improvements in functional status and EF. Key predictors of mortality included preoperative EF <25%, advanced age (≥65 years), and left main disease, highlighting the need for careful preoperative risk stratification. These findings emphasize the importance of optimizing perioperative management strategies to improve short-term outcomes in this high-risk population. While complications and readmissions remain a challenge in resource-limited settings, the observed benefits highlight the value of CABG as a viable treatment option for this high-risk population.

Authors Contribution

Conceptualization: MM[1], HA
Methodology: MM1, HA, MM[2]
Formal analysis: HA, MM[2]
Writing review and editing: Mm[2]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Comparison of Trichoscopic Features of Alopecia Areata before and after Treatment with Intralesional Steroids

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ABSTRACT

Alopecia Areata is a common form of non-scarring hair loss. Utility of trichoscopy helping in diagnosis and monitoring therapeutic response in challenging cases. **Objectives:** To compare the change in frequency of trichoscopic features of Alopecia Areata before and after treatment with intralesional steroids. **Methods:** This descriptive longitudinal study was carried out in the Department of Dermatology, Sahiwal Teaching Hospital, Sahiwal. Patients between age 18 to 60 of either sex, having Severity of Alopecia Tool (SALT Score) of less than 50 were enrolled. Intralesional triamcinolone acetate (5mg/ml with lignocaine) was infiltrated at a dose of 0.1 ml /cm2 into the dermis. Trichoscopic features were recorded using Heine Delta 30 digital Dermatoscope at baseline and after 12 weeks. **Results:** Age was 28.19 ± 8.54. There was statistically significant decrease in mean of SALT Score before (9.91 ± 6.77) and after (4.94 ± 4.04) treatment. The frequency of black dots, exclamation mark hairs and yellow dots at baseline was 91%, 81% and 23%. After treatment these frequencies reduced significantly to 8%, 7%, and 9% respectively (p-value<0.001). While the proportion of short vellus hair and circle hair at baseline (63%,12%) increased to 99% and 70% after treatment respectively (p-value<0.001). **Conclusions:** It was concluded that clinical improvement in Alopecia Areata after treatment with intralesional steroids can be demonstrated with disappearance of yellow dots, black dots, exclamation mark hair and appearance of circle and short regrowing hair on Trichoscopy. Thus, highlighting the utility of Trichoscopy as a valuable tool for monitoring therapeutic response in Alopecia Areata.

INTRODUCTION

Alopecia areata is a common autoimmune disease of hair follicles and nails that clinically manifests as non-scarring hair loss ranging from circumscribed patches to involvement of the whole scalp when it is called Alopecia Totalis [1]. The worldwide prevalence of alopecia areata is 2% and prevalence is lower in adults than children [2, 3]. The interplay of immune, genetic and environmental factors causes Alopecia Areata. Hair follicles, which are normally protected from immune responses due to immune privilege, can become the target of immune attack due to generation of autoantigens and increased expression of major histocompatibility complex Class I molecules [4, 5].Various treatment modalities are available ranging from topical corticosteroids, calcineurin inhibitors and contact immunotherapy to intralesional and systemic corticosteroids. The most appropriate first-line therapy in adults when Severity of Alopecia Score (SALT) is 0-30% is intralesional corticosteroids and when SALT score is 31-50% both oral or intralesional alone, or in combination are recommended. Intralesional steroids are found to be more effective and potent than other routes [6]. Alopecia areata is usually diagnosed on clinical examination and the presence of exclamation mark hairs on trichoscopy. Since the last decade trichoscopy has emerged as a useful non-invasive tool to examine the scalp skin and hair, thus helping to confirm the diagnosis in difficult cases [7, 8]. Ganjoo and Thappa, reported presence of yellow dots, black dots, broken hairs and tapering hairs before treatment, and >75% reduction in these features were observed in all study subjects after treatment with

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intralesional steroids [9].Another study found that a 100% response was seen on trichoscopy appearing as short vellus hair or circle hairs, in all patients after using intralesional steroids [10].While another study found that success (short vellus hair or terminal hair on trichoscopy) was observed in 42.9% cases and mean SALT score was reduced from 4.24 ± 4.4 to 1.37 ± 0.84 (change=2.87 ± 3.56) after using intralesional steroids [11]. Various studies have been carried out to evaluate different trichoscopic features in alopecia areata but very few research articles are available that report the alterations in trichoscopic features after treatment with various therapies.The main rationale for carrying out this study was the paucity of data regarding determining the change in trichoscopic pattern of alopecia areata with intralesional corticosteroids in the local population. Furthermore, we wanted to compare our study's results with international studies.

This study aimed to compare the changes in trichoscopic features of Alopecia Areata and SALT score before and after treatment with intralesional steroid.

METHODS

This descriptive longitudinal study was carried out after approval from Sahiwal Teaching Hospital Ethical Review Board (S.No 66/IRB/SLMC/SWL) and Research Evaluation Unit of the College of Physicians and Surgeons, in the Department of Dermatology, Sahiwal Teaching Hospital from March to August, 2024. Sample size was calculated by using WHO calculator, taking 95% confidence level, effect size (d) of 0.07 and mean decrease in SALT score 2.87 ± 3.56 after using intralesional steroids for alopecia Areata [11]. Patients of either sex, age between 18 to 60 years, and having SALT Score of less than 50 were selected using non-probability consecutive sampling. After taking written informed consent a performa containing information like demographic data, duration of disease, baseline SALT score and trichoscopic features was filled. Trichoscopy was done by using Heine Delta 30 Dermatoscope with 10x magnification (Heine Optotechnik, Germany). Intralesional injection using triamcinolone acetonide (5mg/ml with lignocaine) was then infiltrated at a dose of 0.1 ml /cm2 into the dermis. A total of three injections at one-month interval each were given, and patients were followed up after one month of completion of treatment.SALT score and trichoscopic features were reassessed again at the 12 week. Success was labeled if short vellus hair or circle hair were observed on trichoscopy.Data analysis was done using SPSS version 27.0. Quantitative variables such as age, duration of disease and SALT score (before and after) were presented as mean and standard deviation. Qualitative variables such as gender and trichoscopic features were presented as frequency and percentages. Kolmogorov-Smirnov test indicated that the data followed a normal distribution. So to compare SALT Score before and after treatment paired sample t-Test was used and for comparison of trichoscopic features, paired sample proportions test was used.Age, gender and duration of disease were used to make stratified groups of the data. An independent sample t-test was applied to calculate mean decrease in SALT Score in stratified groups.Statistical significance was determined at p value ≤0.05.

RESULTS

In a total of 100 Alopecia Areata patients, the mean and standard deviation of age was 28.19 ± 8.54 years (95% C.I: 26.4, 29.8). The majority (72%) of study participants belonged to 18-37 years of age. There were 47% male and 53% female participants with male-female ratio of 1:1.13. The mean disease duration was found to be 9.5 ± 14.17 months (95% C.I: 6.7, 12.4). A statistically significant decrease in the mean of SALT Score before (9.91 ± 6.77), and after (4.94 ± 4.04) treatment was noted. Patients with disease duration of less than 12 months showed a statistically significant reduction in their mean SALT Score compared to those with a longer disease duration (>12 months)(Table 1).

Table 1: Mean Difference of SALT Score Between Stratified Groups

Variables	Group	Frequency	Mean ± SD	95% C. I	p-value
Age (Years)	18-37	72	5.14 ± 3.97	(4.2, 6.0)	0.470*
	38-57	28	4.50 ± 3.80	(3.0, 5.9)	
Gender	Male	47	4.19 ± 3.35	(3.2, 5.1)	0.06*
	Female	53	5.64 ± 4.27	(4.4, 6.8)	
Disease Duration (Months)	<12 Months	80	4.28 ± 3.37	(3.5, 5.0)	<0.001*
	>12 Months	20	7.67 ± 4.78	(5.4, 9.9)	
SALT Score	Baseline	100	9.91 ± 6.77	(8.5, 11.2)	<0.001**
	12 Week		4.94 ± 4.04	(4.1, 5.7)	

*Independent sample t-test statistics, **paired sample t-test

On trichoscopic evaluation, the frequency of black dots (91%), exclamation mark hairs (81%), and yellow dots (23%) decreased significantly after treatment (8%, 7%, 9%) respectively. On the other hand, the proportion of short vellus hair (63%) and circle hair (12%) at baseline increased to 99% and 70% after treatment, respectively. Picture I and 2 depict two patients of Alopecia Areata showing change in trichoscopic features at baseline and at 12 weeks(Table 2).

Table 2: Difference in Proportions of Trichoscopic Features before and After Treatment

Trichoscopic Features	Baseline	At 12 Weeks	p-value
Black Dots	91%	8%	<0.001
Exclamation Mark Hair	81%	7%	<0.001
Short Vellus Hair	63%	99%	<0.001
Yellow Dots	23%	9%	<0.001
Circle Hairs	12%	70%	<0.001

Paired sample proportion test statistics

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Baseline: (a) Naked eye examination finding (b) Trichoscopic findings: Blue arrows show exclamation mark hair, green arrows yellow dots, red arrow black dot (10x magnification).At 12th week (c) Naked eye examination finding (d) Trichoscopic findings: Blue arrows show pigtail hairs(10x magnification),(Figure 1).

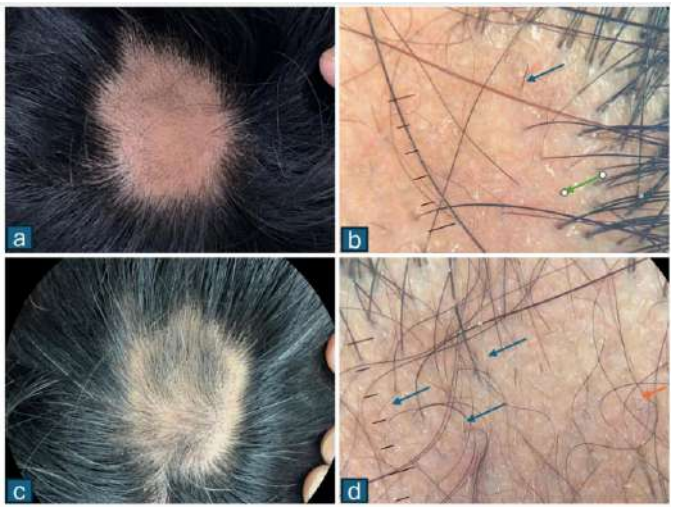

Figure 1: Alopecia Areata in A 30 Year Old Female, Naked Eye and Trichoscopy Examination

Baseline: (a) Naked eye examination finding (b)blue arrow shows exclamation mark hair and green arrow shows black dot (10x magnification). At 12th week: (c) Naked eye examination findings(d)Trichoscopic findings: Blue arrows show vellus hair orange arrow shows pigtail hair (10x magnification)(Figure 2).

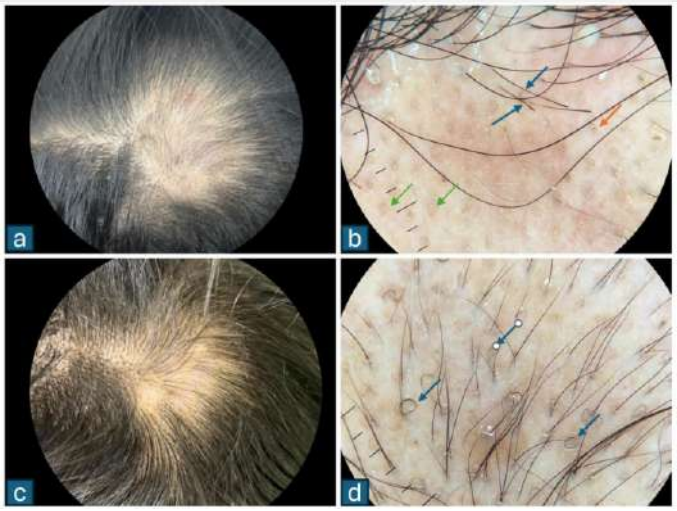

Figure 2: Alopecia Areata in A 30 Year Old Male, Naked Eye and Trichoscopy Examination

DISCUSSION

Alopecia Areata is the most common autoimmune cause of non-scarring hair loss. At times it becomes a challenging task for the dermatologist to determine the efficacy of various treatment modalities.Previously clinical improvement and SALT Scoring were used but with the advent of technology, digital trichoscopy has emerged as a useful tool for therapeutic monitoring.In our study, Alopecia Areata was observed mostly in the 3rd decade of life and the mean disease duration was 10 months.These findings were consistent with the previous studies [9, 12]. The participants of this study belonged mostly to the female gender.In contrast, the male gender predominates in the studies carried out previously [10, 12]. This disparity can be attributed to the demographic, cultural and methodological factors.Severity of Alopecia Tool (SALT Score) is an objective method to calculate severity of Alopecia Areata [13]. In the current study, the mean SALT score was 9.91 ± 6.77 at baseline and decreased significantly after treatment (4.94 ± 4.04). Fawzy *et al.*, and Ageeba *et al.*, reported an analogous pattern of decrease in SALT score from baseline (4.68 ± 3.54 and 4.24 ± 4.4) to final SALT Score (0.55 ± 0.58 and 1.37 ± 1.84) respectively [11, 14]. Trichoscopic features of Alopecia Areata can be divided into signs of active disease, chronic disease and regrowth signs. Signs of active disease are black dots, exclamation mark hair, broken hair and less commonly, pohl-pinkus constrictions and coudability hairs [15, 16].Yellow dots are mostly seen in chronic disease and short regrowing hair and circle hair are signs of regrowth [17, 18]. Broken hairs are formed due to the increased fragility of the hair shaft and when they break at scalp level, it forms black dots. They are mostly seen in the active phase of disease and tend to disappear in the re-growing phase [7].In our study, they were the most common finding, seen in 91% of patients which subsequently decreased significantly to 8% after treatment.Ganjoo *et al.*, reported black dots in 84% of patients and their frequency decreased to nil at 12 weeks of treatment [9].Similarly, a significant reduction was noted after treatment from 85.7% and 68 % to 14.3% and 12% in previous studies [11, 14].These findings were in concordance with our results. Exclamation mark hair forms due to rapid conversion to telogen phase from anagen phase.They are tapered proximally close to scalp surface. They are the most specific finding of Alopecia Areata present in active disease but can also be observed in trichotillomania, chemotherapy-induced alopecia, anagen effluvium, etc [7].In the present study, their frequency significantly decreased from 81% at baseline to 7% after treatment.This finding is consistent with the previous literature showing a significant decrease in their proportion after treatment [19].Due to the prolonged telogen phase, hair follicle infundibula tend to be filled with

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keratin or sebum, forming yellow dots [15]. Yellow dots were seen in 23% of patients at baseline and decreased to 9% in our study. A similar frequency (28%) was reported by Ageeba *et al.*, [14]. In contrast, the reported frequency in the existing literature ranges from 80-95% [9, 20]. Short vellus hairs are short regrowing hypopigmented hair. They appear for a short time and with change to pigmented regrowing terminal hair. They represent the regrowth phase of Alopecia Areata. In the current study, the frequency of short vellus increased significantly from 63% at baseline to 99% after treatment. Likewise, a significant increase from 56% to 100% of short vellus hair was noticed in a previous study [10]. Circle hair or pigtail hairs are a sign of regrowth in Alopecia Areata. These are short, coiled hairs with tapered ends. In our study, 12% of patients had them at baseline but their proportion increased to 70% after treatment. There is a significant correlation between regrowth and the frequency of circle hairs observed in a study carried out by Fawzy *et al.*, [11]. Trichoscopy is a non-invasive diagnostic tool that aids in establishing diagnosis and monitoring disease severity. Trichoscopic features of active disease and regrowth signs of hair in response to the therapy may augment the cutaneous examination. This study emphasizes the need to consider trichoscopic examination as an aid to cutaneous examination for diagnosis and optimal management of Alopecia Areata.

CONCLUSIONS

It was concluded that clinical improvement in Alopecia Areata after treatment with intralesional steroids can be demonstrated with disappearance of yellow dots, black dots, exclamation mark hair and appearance of circle and short regrowing hair on Trichoscopy. Thus, highlighting the utility of Trichoscopy as a valuable tool for monitoring therapeutic response in Alopecia Areata.

Authors Contribution

Conceptualization: SH, ZR
Methodology: SH, ZR, SAAG, HK
Formal analysis: SH, ZR, SAAG
Writing review and editing: SAAG

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Determination of Diagnostic Accuracy of ACR-TI-RADS in Detecting Malignancy in Thyroid Nodules On Ultrasonography, Keeping Bethesda Cytological Score at FNAC as Gold Standard

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ABSTRACT

Thyroid nodules are a common clinical concern, requiring precise evaluation to differentiate benign from malignant cases. **Objective:** To compare the diagnostic accuracy of the ACR TI-RADS with the Bethesda System, the gold standard for thyroid cytopathology. **Methods:** This cross-sectional study was carried out within the Diagnostic Radiology Division of Mayo Hospital Lahore between August and November 2024, and included 224 patients who had thyroid nodules on ultrasonography and were planned for fine needle aspiration cytology (FNAC). A radiologist assessed the ACR-TIRADS scores after data were accumulated employing a standardized case report form.The FNACs were categorized utilizing the Bethesda framework. SPSS was used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the ACR TI-RADS system. **Results:** Their study had a total of 224 patients, with a prevalence of female (186, 83.0%). The sensitivity of ACR TI-RADS in identifying malignant nodules was 87.5% (SE=0.049, 95% CI (77.9%, 97.1%)), while specificity was lower at 31.6% (SE=0.039, 95% CI (23.9%, 39.3%)). The PPV and NPV were 33.6% and 86.5%, respectively. Overall, the accuracy of ACR TI-RADS was 47.4%. **Conclusions:** It was concluded that the ACR TI-RADS system showed excellent sensitivity but low specificity in identifying malignant thyroid nodules. This implies that ACR TI-RADS is more useful for excluding cancer than identifying malignant instances. To improve the ACR TI-RADS system's predictability across a range of populations, more research is required.

INTRODUCTION

Thyroid nodules, also known as incidentalomas, are frequently encountered in routine clinical practice, with their prevalence varying based on the screening method and population studied. Research indicates a prevalence of 2–7% through palpation, 19–68% via ultrasound, and 8–65% in autopsy findings [1-3].While over 90% of detected nodules are benign and clinically insignificant, they hold clinical significance due to the potential risk of malignancy, with thyroid cancer observed in approximately 4.0% to 10% of cases [2, 4]. Thus, accurately distinguishing between benign and potentially malignant nodules is crucial for clinicians, as early identification of malignancy can significantly improve patient prognosis [5, 6]. A robust system for stratifying nodules based on malignancy risk is therefore essential. B-mode ultrasound has proven effective in detecting thyroid nodules [1].The American

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College of Radiology (ACR) created the ACR Thyroid Imaging Reporting and Data System (TI-RADS) to aid in precise risk assessment. Based on certain ultrasonography characteristics, counting as composition, echogenicity, shape, borders, and echogenic foci, ACR TI-RADS classifies nodules into five grades (I through V), with higher numbers indicating a greater chance of malignancy [7, 8]. This efficient approach makes a difference radiologist quickly identify and report knobs which will warrant advance examination. For thyroid nodules, Fine Needle Aspiration Cytology (FNAC) is regularly utilized as a preparatory symptomatic strategy. The Bethesda System for Reporting Thyroid Cytopathology (TBS) remains the most widely recognized standard for evaluating FNAC data [9, 10]. This framework categorizes nodules into six levels (I through VI), from benign (category II, with no danger chance) to highly suspicious (category VI, with up to a 99% threat chance) [9, 10]. TBS, moreover, helps in clinical decision-making, from suggesting follow-up for benign cases to proposing thyroidectomy for high-risk cases. Given its unwavering quality, the Bethesda framework has been broadly embraced by pathologists [9-11]. The ACR-TIRADS scoring system is extensively utilized in local practice in Pakistan to categorize thyroid nodules and guide decisions on the need for further cytological assessment. Research gives limited data on the effectiveness of the Bethesda System and TI-RADS in detecting malignant thyroid nodules within the Pakistani population.

This study aims to examine and assess the sensitivity of the TI-RADS risk stratification tool by directly contrasting its results with Bethesda, the "Gold Standard,". By assessing its alignment with biopsy outcomes, we can accurately gauge the sensitivity of the imaging system, thereby strengthening clinicians' confidence in its use. With limited local studies on this topic, our findings will contribute valuable insights to both national and international literature.

METHODS

This cross-sectional study was conducted in the Diagnostic Radiology Department of Mayo Hospital Lahore from August to November 2024 after approval from the Institutional Review Board of King Edward Medical University, CPSP/REU/RAD-20Z 7-066-3343. 224 cases were chosen using a non-probability sampling technique for this cross-sectional survey-based investigation; the sample size was determined to be 224 with a 95% confidence level and a 5% margin of error, using an online sample size calculator (calculator.net). This estimation was based on a 16.58% prevalence of goiter in the Pakistani population, with an expected sensitivity of 80 ± 13% and specificity of 92.7 ± 5% [12]. Data were collected using a structured case report form. Informed consent was taken from all patients. Patients of any gender who presented with thyroid nodules found on B-mode ultrasonography and were scheduled for fine-needle aspiration cytology (FNAC) at the Mayo Hospital Radiology Department were the focus of the inclusion criteria. Participants with biopsy-confirmed thyroid cancer (Bethesda 6) or those with a normal thyroid ultrasound scan were not included in this study. A radiologist with at least a fellowship certification performed an ultrasound scan on each patient for ACR-TIRADS assessment. Scoring was done by assessing the parameters outlined by the TIRADS scoring system, with nodules assessed for their composition, echogenicity, shape, margins and echogenic foci. Each parameter received a minimum score of zero and a maximum score of three. These individual parameter scores were added to achieve the final TIRADS grade. All patients who underwent ultrasound examination for thyroid nodules had FNAC. Ultrasound-guided FNACs were performed by a fellowship-qualified radiologist. The samples were air dried, then sent to a pathologist for staining and further evaluation. The pathologist determined the cytological features of each sample under a microscope and assigned the relevant Bethesda category. ACR-TIRADS subcategories were removed to streamline the analysis, and scores were arranged as follows: TR3, TR4, and TR5 were categorized as "Malignant," whilst TR1 and TR2 were categorized as "Benign". Similarly, Bethesda categories I and II were classified as "Benign", while categories III to VI were categorized as "Malignant". The results from TIRADS and Bethesda were summed up into these two broad categories, and then compared in a 2 x 2 table. True Positive (TP), False Positive (FP), True Negative (TN) and False Negative (FN) were assessed from this table. Further tests were applied to calculate the Positive Predictive Value (PPV), Negative Predictive Value (NPV) and the Diagnostic Accuracy. For data analysis, SPSS version 29 was used to evaluate the accuracy, sensitivity, and specificity of the ACR-TIRADS score relative to the Bethesda cytology scoring. Frequencies and percentages were reported for categorical variables, such as gender. Data were stratified by age and gender, and associations with ACR-TIRADS and Bethesda scores were assessed.

RESULTS

A total of 224 patients were enrolled in the study, with 186 female and 38 male. The age of the participants ranged from 17 to 77 years, with a mean age of 40.12 ± 11.135 years in females and 47.32 ± 17.96 years in males.The age distribution across genders is detailed in Table 1.

Table 1: Frequency of Gender in Each Age Group

Age Groups	Female	Male	n (%)
16-25 Years	15	6	21 (9.3%)
26-35 Years	55	4	59 (26.3%)

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36-45 Years	66	8	79 (33.6%)
46-55 Years	26	9	35 (15.6%)
56-65 Years	19	0	19 (8.4%)
66-75 Years	1	8	9 (4.0%)
76-85 Years	0	2	2 (0.8%)
Total	186	38	224

The results for frequency of benign versus malignant lesions as per the Bethesda classification are shown in Figure 1

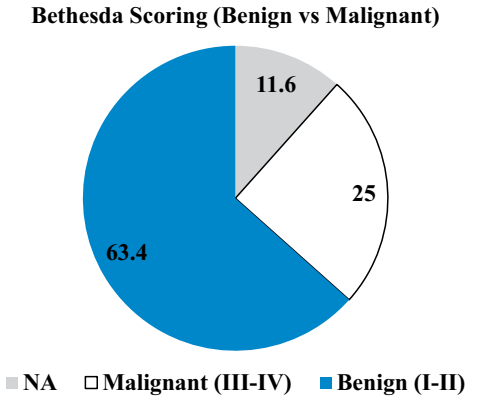

Figure 1: Frequency of Benign versus Malignant Lesions as per the Bethesda Classification

The results for the frequency of benign versus malignant lesions as per ACR-TIRADS classification are shown in Figure 2.

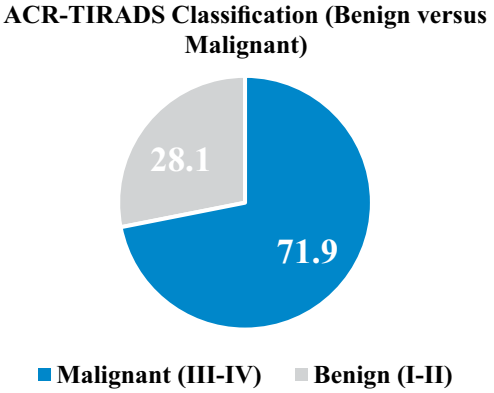

Figure 2: Frequency of Benign versus Malignant Lesions as per ACR-TIRADS Classification

Results present a 2×2 contingency analysis comparing the ACR TI-RADS classification with the Bethesda System for reporting thyroid cytopathology, categorizing nodules into benign and malignant groups, as shown in Table 2.

Table 2: 2 x 2 Contingency Analysis for ACR-TIRADS Classification versus Bethesda

Bethesda Class	ACR-TIRADS Class		Total
	III-V	I-II	
III-VI	49 (TP)	7 (FN)	56
I-II	97 (FP)	45 (TN)	142
Total	146	52	198

TP = True positive, FN = False negative, FP = False positive, TN = True Negative.

The diagnostic performance of the ACR TI-RADS classification in identifying malignant cases compared to the Bethesda classification was evaluated. The sensitivity of the ACR TI-RADS was found to be 87.5% (SE=0.049, 95% CI (77.9%, 97.1%)), indicating a high probability of correctly identifying malignant lesions. However, the specificity was lower at 31.6% (SE=0.039, 95% CI (23.9%, 39.3%)), reflecting a limited ability to accurately identify benign lesions. The positive predictive value (PPV) was calculated at 33.6% (SE=0.038, 95% CI (26.1%, 41.1%)), suggesting that a notable proportion of positive results may not indicate true malignancy. In contrast, the negative predictive value (NPV) was observed to be 86.5% (SE=0.047, 95% CI (77.3%, 95.7%)), indicating that a substantial majority of negative results accurately reflected the absence of malignancy. Overall, the accuracy of the ACR TI-RADS classification in this sample was 47.4% (SE=0.035, 95% CI (40.5%, 54.3%)), having minimal physical performance.

DISCUSSION

The precise preoperative diagnosis of thyroid nodules requires the use of both ultrasonography and fine needle aspiration cytology (FNAC). Since most of the nodules are painless, it is crucial to choose nodules carefully for FNAC to prevent needless invasive operations. Thyroid ultrasonography, the main imaging modality, is essential for the first evaluation of these nodules, and the ACR TI-RADS grading system offers an evidence-based method for classifying cancer risk and offering therapeutic recommendations [13]. Ultimately, ACR TI-RADS aims to improve patient care by reducing unwarranted FNACs and minimizing over-surveillance of low-risk nodules [14, 15]. A study evaluated US TI-RADS while comparing results with Bethesda scoring, reporting values of 70.6% and 90.4%, respectively [16]. Another study done in 2022 observed a similar sensitivity of 72.3% but a lower specificity of 66.7% [17]. In our study, ACR TI-RADS showed a higher sensitivity of 87.5%, indicating a robust ability to detect true positives. However, the specificity in our study was lower at 31.6%, suggesting a higher rate of false positives compared to these studies. Variability in specificity across studies may reflect differences in patient populations, ultrasound interpretation criteria, or diagnostic thresholds, underscoring the importance of context-specific evaluations when implementing ACR TI-RADS in clinical practice. In terms of diagnostic accuracy, a study reported a 60% accuracy for US TI-RADS in predicting malignancy in thyroid nodules [16]. Another study found a higher accuracy of 85.7% [17]. By comparison, our study showed a diagnostic accuracy of 47.4% for ACR TI-RADS, indicating lower precision in malignancy prediction. This discrepancy may result from variations in patient populations, nodule

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characteristics, or ultrasound interpretation methods. These findings suggest that TI-RADS accuracy may vary based on clinical setting and demographic factors, and further studies are required to refine TI-RADS criteria and improve predictive reliability across diverse populations. While studies directly comparing TI-RADS scores with biopsy results are limited, most research has relied on comparing scores with FNAC rather than definitive histopathology from resected specimens. Our study uniquely compared the ACR TI-RADS classification system with the Bethesda scoring system, providing a comprehensive evaluation of both ultrasound-based risk stratification and cytological assessment in thyroid nodule management. For instance, a study done in 2019 from Pakistan compared ultrasonography with FNAC in managing thyroid nodules and found high concordance between the two. On FNAC, 1.6% of the 124 patients whose nodules were determined to be benign by ultrasonography were discovered to be malignant, while 98.38% of them were confirmed to be benign. On the other hand, FNAC revealed benign results in 44.4% of nine individuals whose lesions were classified as malignant by ultrasonography and confirmed malignancy in 55.6% of them. They concluded that ultrasonography is a highly effective non-invasive diagnostic technique that has significant diagnostic accuracy in differentiating between benign and malignant nodules [18]. Our study consists of a comparison of ACR TI-RADS and Bethesda systems, further aiming to clarify each system's strengths, enhancing clinical decision-making accuracy. In a comparable study conducted in Pakistan, 201 patients' TI-RADS scores and FNAC results were compared. They reported a 76.1% overall diagnostic accuracy for predicting malignancy, with a TI-RADS sensitivity of 77.8%, specificity of 75.5%, positive predictive value (PPV) of 53.8%, and negative predictive value (NPV) of 90.2% [19]. In comparison, our study observed a lower PPV of 33.6% but a similarly high NPV of 86.5%. This difference in PPV suggests that, while ACR TI-RADS effectively rules out malignancy in benign nodules, its ability to predict malignant cases accurately may be limited. These findings highlight the need for further research to refine the ACR TI-RADS criteria and enhance its predictive capabilities in diverse clinical settings. A 2023 hospital-based cross-sectional study included 132 patients with thyroid nodules to evaluate the diagnostic accuracy of ACR TI-RADS. The system showed a strong correlation with cytology findings and high sensitivity and specificity. It proved to be a reliable, noninvasive tool for thyroid nodule assessment, reducing unnecessary fine-needle aspirations and supporting its use as a standardized screening method, particularly in resource-limited settings [3]. In another study, ACR TI-RADS had the highest sensitivity, at 94.5%, when the relative accuracy of five distinct TI-RADS systems was assessed on 939 thyroid nodules. The study concluded that ACR TI-RADS performs well in recognizing threat and is the foremost brief strategy for thyroid nodules of all sizes. When compared to histopathology results, it was seen that ACR TI-RADS appeared higher in efficiency than the Bethesda system, suggesting its value as a preliminary diagnostic approach [20]. Our study found a similarly high sensitivity for ACR TI-RADS at 87.5%, aligning with the findings of a study done in Goztepe City Hospital of Turkey [20], and reinforcing its reliability in thyroid nodule assessment. These results support the integration of ACR TI-RADS as an effective component of diagnostic workflows, particularly when emphasizing sensitivity in the early detection of malignancy.

CONCLUSIONS

It was concluded that compared to the Bethesda classification, the ACR TI-RADS scoring system demonstrated high sensitivity but low specificity in detecting malignant thyroid nodules.This indicates that while ACR TI-RADS is useful for ruling out cancer, its positive predictive value suggests it may not accurately diagnose malignant cases. Further research is needed to enhance the predictive accuracy of the ACR TI-RADS system across diverse populations.

Authors Contribution

Conceptualization: TBK
Methodology: TBK, RA, WZ, TK
Formal analysis: SA
Writing review and editing: TAS, SM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Assessing the Etiology and Pathogenesis of Pyogenic Granuloma in Gingival Tissues

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ABSTRACT

Pyogenic granuloma is a benign, rapidly growing vascular lesion commonly found on mucous membranes. Although its demographic distribution is well documented, the specific etiology and pathogenesis of pyogenic granuloma in gingival tissues remain poorly understood. **Objectives:** To evaluate the etiology and pathogenesis of pyogenic granuloma in gingival tissues. **Methods:** Databases including PubMed, Google Scholar, Cochrane Library, Springer, and Science Direct were searched from January 2009 to February 2024. Prisma guidelines were followed and 20 studies meeting the criteria were included in the systematic review. **Results:** These results indicate the significant role of etiological factors such as poor oral hygiene, trauma, local irritation, and hormonal factors in the development of pyogenic granuloma. Patients with pyogenic granuloma showed gingival inflammation, thick bundles of collagen fibers, proliferating endothelial cells, overexpression of vascular molecules and CD4+ cells, and a plethora of neutrophils. **Conclusions:** It was concluded that pyogenic granuloma in gingival tissues is predominantly associated with local irritants, poor oral hygiene, chronic trauma, and hormonal imbalances. These factors trigger inflammatory responses and vascular proliferation, suggesting that targeted interventions such as enhanced oral care and management of hormonal levels could improve prevention and treatment outcomes for gingival pyogenic granuloma.

INTRODUCTION

Pyogenic granuloma (PG) is a benign, non-neoplastic proliferation of connective tissue characterized by granulation tissue hyperplasia. It is a common soft tissue lesion, particularly affecting skin and mucous membranes While first described in 1844 by Hullihen, it was Poncet and Dor who, in 1897, coined the term "botryomycosis hominis" for similar vascular tumors. The current term, "pyogenic granuloma," was introduced by Hartzell in 1904 [1]. PG can manifest in two forms: lobular capillary hemangioma (LCH) and non-lobular capillary hemangioma (non-LCH). It can occur at any age but is most prevalent in young adults, with a higher incidence in females, especially during pregnancy. Hormonal factors, particularly increased estrogen and progesterone levels may contribute to its development during pregnancy by stimulating angiogenesis [2]. Clinically, PG presents as a raised, smooth, exophytic mass

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with a reddish, hemorrhagic appearance. It can be either sessile or pedunculated, with the majority being sessile [3]. The lesion progresses through three phases: cellular, capillary, and involutionary. Its colour can vary from pink to reddish-purple, depending on vascularity. Early lesions are often pink, while advanced lesions become increasingly red or purple. Typically, PG grows slowly and is asymptomatic [4]. However, in some cases, it can grow rapidly and stabilize at a certain size. The lesion size can range from a few millimetres to several centimeters, with the marginal gingiva being a more common site than the alveolar part [5]. Diverse factors have been implicated in developing pyogenic granulomas (PGs), which affect the skin and oral cavity. Historically, bacterial infections were considered the primary cause. However, recent findings suggest a different etiology, as PGs are not associated with infection and lack pus or complete granulomas on histological examination. Potential contributing factors include chronic low-grade trauma, physical injury, hormonal influences, microorganisms, and certain medications. Oral PGs, which constitute 75% of cases, are often linked to local irritants such as dental calculus, and foreign bodies lodged in the gingiva [6]. Gingival PG is the most common tumor-like growth in the oral cavity mostly developing around the anterior teeth and is considered to be neoplastic. The majority of gingival PGs develop at the marginal gingiva. Gingival PGs are more common in the second and third decades of life [7]. The International Society for the Study of Vascular Anomalies (ISSVA, 2022) classifies some PGs, such as Langerhans cell histiocytosis (LCH), as vascular tumors. Angelopoulous AP proposed "hemangiomatous granuloma" as a more accurate descriptor, reflecting the histopathological similarity to hemangiomas and the inflammatory nature of PGs. Definitive diagnosis relies on histopathological examination. Therapeutic options for PGs include surgical excision, which is the standard approach [8]. Additional treatments may involve carbon dioxide laser therapy, pulsed dye laser therapy, cryosurgery, electrodessication, and intralesional corticosteroid injections. While the risk of malignant transformation is generally low, recurrence rates can be as high as 16%, necessitating re-excision [9]. Recurrence may be attributed to incomplete excision, persistent underlying causes, or re-injury to the lesion site [10, 11]. A comprehensive review of existing literature reveals a lack of high-quality evidence on the underlying causes and mechanisms of PG in gingival tissues. The literature is particularly lacking in studies that delve into various etiologies and pathogenic processes of PG.

This study aims to comprehensively assess the etiology and pathogenesis of PG in gingival tissues.

METHODS

A comprehensive literature search was conducted using PubMed and Google Scholar to identify relevant studies published between January 2009 and February 2024. The search strategy adhered to the PRISMA guidelines and employed the following keywords: "pyogenic granuloma," "gingival tissue," "pathogenesis," and "etiology." The primary focus was on original research articles that evaluated the etiology and pathogenesis of pyogenic granuloma in gingival tissues. Reference lists of included studies were manually searched to identify additional eligible studies. Studies were included or excluded based on predefined criteria (Table 1).

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Papers published between January 2009 to February 2024	Duplication publication
Directly linked to the etiopathogenesis of PG in gingival tissues	Not directly linked to the etiopathogenesis of PG in gingival tissues
English language	Not written in English
Papers mentioning the evaluation of the etiology and pathogenesis of PG in gingival tissues	Not mentioning the etiology and pathogenesis of PG in gingival tissues.
Full-text systematic reviews, case reports, case series, meta-analyses, RCTs, prospective studies, cohort studies, case reports, observational study	Editorials, conference papers, letters to the editor, short communications, meeting abstracts

Initially, 6,582 studies were identified. After screening titles and abstracts, 2,000 potential studies were selected for full-text review. Ultimately, 20 studies met the inclusion criteria and were included in the qualitative synthesis. The inclusion and exclusion criteria were developed following PRISMA guidelines to make sure that only high-quality studies that were relevant to the research question were selected. As a result, irrelevant, outmoded, and methodologically defective studies were excluded while defining population, intervention, comparison, outcomes, and study designs (PICOS). A systematic and structured approach was implemented to ensure data accuracy and consistency. Two reviewers independently extracted relevant data such as study characteristics, participant demographics, interventions, and outcomes using a standardized spreadsheet developed specifically for this review. Before full data extraction, the reviewers conducted a calibration exercise on a sample of studies to ensure that key variables were consistently identified and recorded. Discrepancies between the reviewers were resolved through discussion, and when necessary, a third reviewer was consulted to reach a consensus. Furthermore, periodic cross-checks were performed against the original articles to verify data accuracy. This rigorous process aimed to minimize Identification of Studies Via Databases bias and enhance the reproducibility

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of our findings (Figure 1).

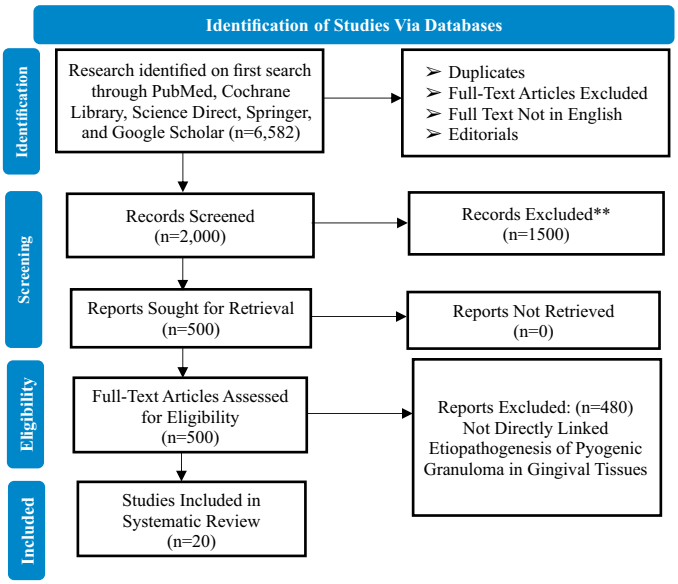

Figure 1: Screened Studies Included in the Systematic Review

RESULTS

This systematic review yielded a total of 20 studies, of which, nine were case reports, and five were comparative studies. The remaining studies were a literature review, narrative review, and retrospective study. A combined total of 3,374 patient samples included in the studies have been evaluated in this systematic review. The analysis of the papers indicated that 10 studies are from India, two studies are from Iran, two are from Mexico, remaining are from Columbia China, Nepal, Brazil, and Greece. The country that evaluated the etiopathogenesis the most was India as per the systematic review. Eight studies reported poor oral hygiene, calculus in the mouth, chronic irritation by food impaction, hypersensitivity reactions to certain drugs, and hormonal factors as common PG etiological factors. Eight studies examined the pathogenesis of PG and revealed that a plethora of inflammatory infiltrate cells, bundles of collagen fibers, hemorrhage stroma, and proliferating endothelial cells contributed majorly to developing PG in the gingival. The remaining studies evaluated the role of higher proliferation in LCH type of PG, excessive infiltrate of neutrophils, microorganisms in lesions, overexpression of COX-2, IL-10, and IL-4, bone resorption, and tissue destruction (Table 2).

Table 2: Summary of Study Findings Evaluated

Sr. no	Study Design	Country	Total Participants	Etiopathogenesis	Evaluation Method	References
1	Case report	India	1 male patient	Calculus in the mouth, engorged blood vessels, inflammatory cells, thick collagen fibers	Histopathological report	[12]
2	Case report and literature review	Mexico	3 female patients	Ulcerated surface, local irritants, diffused lymphoplasmacytic type inflammatory infiltrates, stromal hemorrhage	Histological examination	[13]
3	Case series	Nepal	4 patients	Proliferating perivascular inflammatory infiltration, thick bundles of collagen fibers widespread in the stroma	Histopathological investigation	[14]
4	Narrative review	Mexico	Not specified	Hypersensitivity to certain drugs, hormonal factors, gingival inflammation	Histopathological report	[15]
5	Case report	India	30-year-old male patient	Proliferating endothelial cells, lymphatic vessels	Histopathological investigation	[16]
6	Case report	India	28-year-old female patient	Increased estrogen and progesterone levels	Clinical examination	[17]
7	A series of case reports	India	6 female patients	Excessive infiltrate of neutrophils	Histopathological investigation	[18]
8	Case report	India	1 year-old child	Excessive infiltration of neutrophils, poor oral hygiene	Histopathological investigation	[19]
9	Case report	India	Not specified	Ulceration, hyperplasia	Histopathological investigation	[20]
10	Case report	India	18-year-old female patient	Chronic irritation, peripheral ossifying fibroma,trabeculae vascular	Histopathological investigation	[21]
11	Literature review	India	1 patient	Excessive infiltrate of neutrophils	Histopathological examination	[22]
12	Retrospective study	China	2971 epulis cases	Excessive infiltrate of neutrophils	Medical records	[23]

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13	Comparative study	Iran	70 samples	Higher levels of immune-histochemical expression of ICAM-1, VCAM-1, CD34 levels	Immunohistochemistry staining, paired t-test	[24]
14	Comparative study	Iran	10 PG cases	Higher proliferation in LCH	Mann-Whitney U-test	[25]
15	Comparative study	Greece	30 PG cases	Higher proliferation in LCH	Mann-Whitney U-test	[26]
16	Retrospective study	Brazil	169 samples	Higher proliferation in LCH	Histopathological investigation	[27]
17	Comparative study	Columbia	46 samples	Lesion evolution, inflammatory infiltrate masses, overexpression of IL-4, bone resorption, tissue destruction	Histopathological investigation	[28]
18	Literature review	India	Not specified	MOs in lesion	Not specified	[29]
19	Comparative study	Columbia	57 oral PG cases	Increased immune-expression of COX-2 and IL-10	Immunohistochemically assessment	[30]
20	Literature review	India	2 patients	Nonspecific infection, over-hanging restorations, cheek biting	Histopathological investigation	[31]

PG, pyogenic granuloma; LCH, lobular capillary hemangioma; IL-4, interleukin 4; MOs, microorganisms; IL-10, interleukin-10; COX-2, cyclooxygenase-2

DISCUSSION

Pyogenic granuloma (PG) is a common benign, non-neoplastic overgrowth of skin and oral tissues. Despite its name, it is not associated with pus formation or infection. Histologically, it presents as a vascular lesion rather than a granulomatous one. A case report by Gomes *et al.*, identified several potential etiological and pathological factors contributing to PG development in a 22-year-old Indian male. These included poor oral hygiene, calculus accumulation, engorged blood vessels, and the presence of inflammatory cells and collagen fibers, as revealed by histopathological examination [12]. The presence of bacteria such as *Bacteroides melaningogenicus, Prevotella intermedia, Fusobacterium, Staphylococcus aureus*, imbalanced angiogenesis enhancers and inhibitors such as angiopoietin-1, ephrin-B2 are the major contributors to exacerbating etiopathogenesis of PG [13]. Marla and colleagues presented a case series involving four young Nepalese patients (three women and one man) diagnosed with PG. Their histopathological findings revealed a common pattern across all four cases: proliferating inflammatory cells surrounding blood vessels and dense collagen fiber bundles infiltrating the stromal tissue [14]. A narrative review conducted by Lomeli *et al.*, in Mexico in 2023 found that PG condition can occur following hypersensitivity reactions to certain drugs such as calcineurin inhibitors, phenytoin, and antiretroviral drugs. They also reported that hormonal changes particularly estrogen and progesterone rapidly promote the development of PG by elevating levels of already present gingival inflammation in blood vessels, increasing the adhesion of platelets and leukocytes. The results of the study found ulcerated surface, bleeding on touch, local irritants, history of lesion evolution, diffused lymphoplasmacytic type inflammatory infiltrates, large masses of fibroblasts, and stromal hemorrhage among all 3 patients [15]. Panseriya and Hungund described a unique case of pyogenic granuloma (PG) linked to a periodontal abscess and bone loss in a 30-year-old Indian male. Histopathological analysis of the lesion revealed proliferating endothelial cells and lymphatic vessels, along with thickened blood vessels and areas of pseudo-epitheliomatous hyperplasia [16]. Debnath and Chatterjee reported that hormonal changes during the third trimester of pregnancy were the main etiological factor attributable to recurrent PG twice within 2 years in the same area [17]. Adusumilli *et al.*, (2014) presented six case reports from India involving six female patients. Their findings indicated that etiological factors, including local irritants, traumatic injuries, and hormonal influences, were implicated in all six cases. Furthermore, the histopathological examinations showed ulcerated surfaces filled with excessive infiltration of neutrophils, polymorphonuclear leukocytes (PMNs), lymphocytes, and proliferation of fibroblasts [18]. Surprisingly, similar histological features were also observed in a one-year-old child as reported by Thomas *et al.*, in India in 2024. They also highlighted the etiological factors found in this case such as repeated trauma by brushing or food impaction, and failure to remove tissues causing lesions [19]. Hunasgi *et al.* reported that ulceration and hyperplasia were most commonly found in PG [20]. Lalremtluangi and fellows, assesed a female patient with long-standing PG in India.The results of the study found that poor oral hygiene, chronic irritation caused by calculus, peripheral ossifying fibroma, and trabeculae vascular were associated with reactionary bone changes in long-standing PG [21]. Meshram *et al.*, and Zhao *et al.*, independently conducted literature reviews and

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retrospective studies, respectively, in India and China [22, 23]. A comparative study consisting of 70 samples was carried out by Seyedmajidi *et al.*, in Iran. Their findings revealed significantly elevated levels of ICAM-1, VCAM-1, and CD34 in periodontal pockets compared to healthy gingival tissues ($p<0.001$ for all comparisons). These vascular adhesion molecules and endothelial cell markers were identified as potential biomarkers for periodontal disease pathogenesis [24]. Rezvani *et al.*, demonstrated that Langerhans cell histiocytosis (LCH) is associated with increased endothelial cell proliferation compared to non-LCH cases [25]. Another comparative study conducted by Epivatianos *et al.*, in Greece found that non-LCH PG (86.4%) compared to LCH was associated more frequently with the PG etiological factors [26]. Ribeiro *et al.*, conducted an 18-year retrospective study in Brazil and reported comparable outcomes [27]. González-Pérez *et al.*, reported that lesion evolution, inflammatory infiltrate masses, overexpression of IL-4, bone resorption, and tissue destruction may act as predictors of gingival PG [28]. Sharma *et al.*, found that trauma is usually the causative factor for PG in buccal mucosa, lips, tongue, and palate.They also revealed various mechanisms of pathogenesis such as the plethora of inflammatory angiogenesis factors such as persistent injury by faulty filling and food impaction, and increased estrogen or progesterone levels [29].Isaza-Guzman and colleagues performed a comparative study of 57 oral squamous cell carcinoma cases in Colombia.Their immune-histochemical analysis revealed elevated expression of both cyclooxygenase-2 (COX-2) and interleukin-10 (IL-10) in all cases [30].Verma *et al.*, conducted 2 PG case series (consisting of 1 male and 1 female aged <30 years) in India and concluded that nonspecific infection, overhanging restorations, and cheek biting may lead to the underlying fibro-vascular connective tissue-promoting formation of PG in all 6 cases [31].According to our study, the development of PG is multifactorial, being dependent on both, independent and interrelated factors. Factors that can independently trigger PG development include trauma (cheek biting, brushing injuries,etc) hormonal changes (elevated estrogen and progesterone levels), hypersensitivity to drugs, bacterial infections, and genetic markers (e.g., ICAM-1 and VCAM-1 expression) while interrelated factors work together towards the development of PG and include chronic irritation (e.g.,calculus accumulation), inflammatory processes, and abnormal angiogenesis (mediated by inflammatory markers and endothelial proliferation).This suggests a complex interconnection of these causative factors where inflammation initiates the pathogenesis while hormonal changes and bacterial overload in the oral cavity exacerbate the condition [32]. The role of CD4 cells and neutrophils was observed in the pathogenesis of gingival pyogenic granuloma [33]. CD4+ cells release cytokines (IL-4 and IL-10) contributing to chronic inflammation and dysregulated fibro-vascular proliferation which is seen in gingival pyogenic granuloma. Whereas neutrophils, being the first responders of the innate immune system, play their role by secreting reactive oxygen species, matrix metalloproteinase and pro-inflammatory cytokines ultimately leading to tissue degradation and remodeling, setting up a background of vascular engorgement and endothelial cell proliferation which are the characteristic features of PG pathogenesis [34]. CD4+ cells and neutrophils make a feedback loop of inflammation and vascular remodeling leading to the exacerbation of gingival PG lesions [35]. Prevention options include maintaining good oral hygiene, avoiding local irritants such as overhanging dental restorations and food impactions, and dose adjustments or changing the drugs that are known to trigger PG to other alternatives [36]. Treatment includes non-surgical and surgical interventions, hormonal management and pharmacological treatment. Initial management includes scaling and root planning to remove calculus which reduces inflammation and lesion size [37]. Complete excision of the lesion is the gold standard [38]. Diode laser excision offers less bleeding and faster healing [39]. Cryotherapy, electrodessication and pulse dye laser therapy can also be considered [40]. Local steroid application can be considered in some cases [8, 9]. In pregnancy-related cases, postpartum regression is observed so surgical treatment should be delayed until there is any complication. Hence, a multidisciplinary approach including expertise from periodontists and general practitioners should be used for optimal management of PG [10, 11]. This review identified multiple studies that evaluated correlations regarding hormonal factors across genders and age groups. For instance, Koo *et al.*, found that oral PG occurs mostly in the first and third decade of life in males and fourth to fifth decade in females. So there is a statistically significant difference in occurrence between genders across different age groups($p<0.05$)[11]. Although our review is narrative, these findings suggest that hormonal variations may play a role in the pathophysiology of the conditions under review. However, heterogeneity in study design and sample characteristics limits our ability to generalize these findings. Future research employing a meta-analytical approach could help clarify these associations further.

CONCLUSIONS

It was concluded that this study highlighted the various etiopathogenesis factors of gingival PG such as poor oral hygiene, calculus, hypersensitivity reactions to certain drugs, chronic irritation caused by food impaction, trauma by forceful tooth-brushing or cheek biting, a bundle of inflammatory masses, overexpression of immune-histochemical, angiogenesis and hormonal factors, the proliferation of endothelial cells, stromal hemorrhage, gingival inflammation in blood vessels, and abundance of

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anaerobic and aerobic bacteria. This systematic review underscores the importance of practicing preventive measures which include oral hygiene, avoiding trauma to gingiva and drugs known to trigger PG. This study provides insights into the etiopathogenesis of PG that can help clinicians in designing targeted treatment strategies, highlighting the need for a multidisciplinary treatment approach to reduce lesion recurrence and improve clinical outcomes.

Authors Contribution

Conceptualization: AK
Methodology: AK, ME, DN
Formal analysis: DN
Writing review and editing: UT, A, SSH, AA, SM, SA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Assessment of the Efficacy and Safety of Enhanced Recovery After Surgery (ERAS) Protocols in Patients Undergoing Bariatric Surgery: A Meta-Analysis

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ABSTRACT

In modern era bariatric surgeries, the use of several tools of the Enhanced Recovery after Surgery (ERAS) protocols are highly accepted and associated with reduced peri-operative rate of complications and robust recovery. **Objectives:** To evaluate the impact of application of ERAS protocols in bariatric surgeries, with relevance to postoperative recovery period, postsurgical complications, length of hospital stay and cost effectiveness. **Methods:** Various randomized controlled trials (RCTs), reviews and observational studies implementing ERAS protocols in bariatric surgeries were included in this meta-analysis after performing a comprehensive search over databases up to August 2024. **Results:** This meta-analysis affirmed that ERAS protocols significantly reduced the post-operative length of hospitalization by an average of 1.5 days, reduced opioid consumption by approximately 30.7%, and also led to a decreased incidence of major complications(mean 4.16%). The readmission rates remained low (mean 4.16%) in the ERAS group, and overall complication rates were also reduced in studies implementing an increased number of ERAS protocol elements.Subgroup analysis revealed that Sleeve Gastrectomy (SG) was associated with shorter recovery period and fewer complications when compared to Roux-en-Y Gastric Bypass (RYGB). **Conclusions:** It was concluded that this meta-analysis favors the implementation of ERAS principles in improving outcomes in bariatric surgeries, including shorter hospital stays, reduced recovery period, less need of opioid analgesia and increased patient satisfaction.

INTRODUCTION

Enhanced Recovery After Surgery (ERAS) protocols have revolutionized perioperative care in bariatric surgery by the implementation of multimodal strategies to optimize patient outcomes, reduce complications and surgical stress associated with bariatric surgery [1]. This meta-analysis aims to assess the efficacy and safety of ERAS protocols in patients undergoing bariatric surgery by evaluating postoperative outcomes, complication rates, and recovery. Bariatric surgery(BS) is a trending treatment choice for people who suffer from severe morbid obesity (BMI greater than 35kg/m2) associated with major comorbid conditions, in whom other non-surgical weight loss measures have failed to give fruitful results [1]. Bariatric surgery has not only had a direct impact on weight loss, but also improves overall quality of life and several other health parameters, including metabolic syndrome [2]. On the other hand, such procedures are difficult because often patients have complex medical histories and metabolic syndromes, which increase perioperative risks, and thus there is a crucial need to optimize perioperative care to enhance patient outcomes [3]. Hence, the application of Enhanced Recovery after

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Surgery (ERAS) principles is particularly relevant. The ERAS protocol is a multidisciplinary approach, has shown promising results in reducing hospital stays, postoperative complications and enhancing recovery in various surgical specialties, thus making it an area of significant clinical interest[4].

This study aimed to utilize evidence from various studies to evaluate the impact of ERAS protocols on perioperative outcomes in bariatric surgery, thus providing a comprehensive assessment of its efficacy and safety. By utilizing the data available, we can also identify areas where further improvement is needed and whether ERAS protocols can be considered a standard of care in other surgical specialties as well, besides bariatric surgery.

METHODS

This meta-analysis was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. Various randomized controlled trials (RCTs), reviews and observational studies comparing ERAS protocols with standard care (SC) in bariatric surgeries were included in our meta-analysis after performing a comprehensive search over databases like PubMed, Cochrane Library, Google Scholar and Web of Science, up to August 2024. The search strategy combined both Medical Subject Headings and free-text terms. The search was conducted in English language and the main keywords used in our search were "Enhanced Recovery After Surgery" or "ERAS", "Weight loss or Metabolic surgery" or "Bariatric Surgery", "Roux-en-Y Gastric Bypass" or "Sleeve Gastrectomy", "Perioperative Care", "Duration of Hospital Stay" or "Peri- and Post-Operative Complications." Only studies published in the English language were included. Duration of hospital stay was the primary outcome measured across studies included in our analysis, and secondary outcomes were overall morbidity and peri-operative and post-operative complication rates (bleeding, leakage, infection, cardiopulmonary), mortality rates and readmissions. Three researchers (JMA, IM and AA) independently carried out the process of selection of studies. The selection was then compared, and any discrepancy, if found, was settled by mutual discussion. The first 3 authors independently determined the eligibility of the relevant articles, and included studies evaluating ERAS protocols in patients undergoing bariatric surgery (Sleeve Gastrectomy SG, Roux-en-Y Gastric Bypass RYGB or both). Randomized controlled trials, case-control studies, cohort studies and observational studies comparing ERAS and Standard Care in bariatric surgery were included. Only studies published in English were considered. Studies conducted in different geographic regions were included to assess the generalizability of ERAS protocols, and also with clearly defined methodology and outcome measures to minimize reporting bias. Studies reporting perioperative outcomes like duration of hospital stay, post-operative complications, readmissions, and mortality rates were also included. Only the latest and highly comprehensive data were included. Reviews, editorials, abstracts, and case reports were not included in this meta-analysis. Non-comparative studies, i.e., ERAS vs. standard care and studies on other surgical specialties without specific reference to bariatric surgery, were not added. Animal and in vitro studies and those without a clear description of ERAS principles were also excluded. Studies that failed to distinguish between ERAS and conventional perioperative care were not included. A careful review of all the eligible full-text articles was done before adding them to the meta-analysis, and data extraction was based on pre-defined criteria. The abstracts, methodology and results were independently screened by two reviewers. Data extraction was done in tabulated form highlighting study demographics i.e., authors, country, study design, sample size, follow-up period; patients baseline demographics i.e., gender, age, BMI, type of surgery and comorbidity; clinical outcome indicators like duration of hospital stay, post-operative complications, readmission, cost of hospitalization, mortality rates and ERAS protocol principles. A comprehensive, structured approach was ensured to carry out a robust meta-analysis report on the efficacy and safety of ERAS in bariatric surgery patients. The random effects model was used to assess for variability across various studies, reflecting the differences in sample sizes, study designs and populations. This model is appropriate while dealing with heterogeneous studies, as it assumes that individual studies estimate variable but related treatment effects. This provided a more generalized interpretation of the results. In cases where the population of interest constituted a subset of the study population, only the readings or values about the population of interest were selected. If the extraction of the values of the population of interest was not possible, then the study was excluded from the meta-analysis. The data extraction records us maintained with the authors and will be used to refer back to the process of data extraction if needed. This meta-analysis used descriptive statistics to find out the impact of ERAS protocols and the Standard Care group on surgical outcomes (Fisher's exact test). The continuous outcomes, e.g., duration of hospital stay, mean differences (MD) or standardized mean differences (SMD) were calculated, with data pooled utilizing a random effects model to account for variability among included studies. The dichotomous outcomes, i.e., post-operative complications, odds ratios (OR) or relative risks with 95% confidence intervals, were

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calculated and pooled using a random-effects model. Results were carefully interpreted while considering both statistical significance ($p<0.05$) and clinical relevance, with reliability of conclusions assessed by sensitivity analyses and consideration of potential biases. Statistical heterogeneity was evaluated by using the I^2 statistics, which determines the percentage of variability due to heterogeneity rather than chance. It is crucial to identify heterogeneity in meta-analysis as it determines the confidence in the pooled results. Sensitivity analyses were carried out to determine the resilience of the obtained results. These analyses assessed the influence of excluding studies with high risk of bias, as well as the impact of varying methodological quality across the studies included in ours. Studies were not included that seemed methodologically weak, and the consistency of overall outcomes was determined, ensuring the reliability of the pooled estimates. The statistical analysis was conducted using the Rev-Man software tool, a standard tool for meta-analyses. The risk of bias from missing results was assessed by several methods, which include: The Forest plots tool was used to identify publication bias by plotting effect sizes against their standard errors, and Egger's test was carried out to statistically assess the overall symmetry of the plot. The initial literature search yielded 380 citations; 325 remained after the exclusion of duplicate publications; 21 studies were eventually included after meeting the pre-defined inclusion criteria of our meta-analysis (Figure 1).

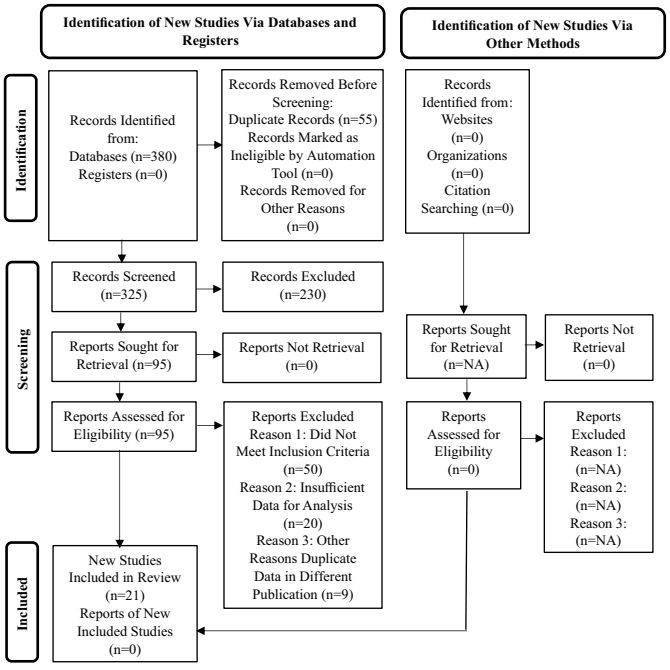

Figure 1: Study Selection for This Research

RESULTS

A total of 21 studies met the inclusion criteria of our meta-analysis, and it includes a vast range of study designs, including randomized controlled trials (RCTs), cohort studies, retrospective studies and systematic reviews. The studies included in our meta-analysis involve a significant number of patients undergoing various bariatric surgical procedures, i.e.,SG and RYSG, and thus allow a comprehensive analysis of the ERAS principle's impact on post-operative outcome. A substantial total sample size of 9899 patients was included in our analyses.The largest sample size was seen in the study by Małczak *et al.*, [6] i.e., 3475 patients and the smallest in Schmoke *et al.*, [7] with only 21 patients in the ERAS group. A study by Stenberg *et al.* [8] met the inclusion criteria, but it was excluded after reviewing because the quality of evidence for many ERAS elements remains relatively low, especially in the context of bariatric surgery.Many recommendations are based on evidence assumed from other types of surgeries rather than bariatric-specific studies.A broad range of bariatric surgeries, i.e., laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass, and randomized controlled trials, retrospective cohort studies and observational studies were included in our paper, which enhances the generalizability of our meta-analysis findings.Our meta-analysis included studies up to August 2024, which is important for analyzing current era practices and patient outcomes (Table 1).

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Table 1: Characteristics of Studies Included

References	Country	Study Design	Patients Number	Gender (M/F)	Age (Years)	BMI (Kg/m^2)	Follow-up (days)	Type of Surgery	ERAS Adherence
[9]	Brazil	Cross-sectional	150	41/109	37	41.9	30	SG	Full
[10]	Luxembourg	RCS	103	26/77	42.1 ± 11.84	44.8 ± 5.9	30	RYGB	Partial
[11]	Not Specified	RCT	374	Not Specified	Not Specified	Not Specified	Not Specified	Mixed	Full
[12]	Netherlands	RCT	110	12/98	42.7 ± 10.5	42	30	SG	Full
[13]	United States	Review	435	Not Specified	Not Specified	Not Specified	Not Specified	SG	Full
[6]	Poland	Review	3475	Not specified	Not specified	Not specified	Not specified	Mixed	Full
[14]	USA	RCS	134	11/123	44	44	30	RYGB	Full
[15]	UAE	RCS	1602	572/1030	30.41	43.95 ± 5.60	30	SG	Full
[16]	India	RCT	56	14/42	36.21	42.33 ± 7.01	30	SG	Full
[17]	China	RCS	237	58/179	32.61	38.38 ± 6.78	30	RYGB	Full
[18]	United States	Retrospective	657	77.6% Female	45	45.4	Not specified	SG	Partial
[19]	France	RCS	232	47/185	43.07	40.67 ± 6.87	30	SG	Full
[20]	Italy	RCS	1019	277/742	41.3	44.8 ± 67.4	30	RYGB	Full
[21]	Spain	RCT	180	90/90	NA	NA	NA	RYGB	Full
[22]	Turkey	Cohort Study	216	NA	NA	Not Specified	Not Specified	SG	Partial
[23]	America	RCS	282	NA	43.9	46.4	30	SG	Full
[24]	America	RCS	90	17/73	42	46.3	30	SG	Full
[7]	New York	LCS	21	10/11	17.5	46.3	-	SG	Full
[25]	USA	RCS	173	47/126	50.2	43.6 ± 6.1	90	RYGB	Full
[26]	United Kingdom	Retrospective Analysis	288	Not specified	Not specified	Not specified	30 days	Mixed	Partial
[27]	America	RCT	65	11/54	38.0	44.6	30	SG	Full

ERAS, enhanced recovery after surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; M, male; Mini, minimally invasive (both laparoscopic and robotic surgeries); RCS, retrospective cohort study; RCT, randomized controlled trial; SC, standard care.; Vertical Sleeve Gastrectomy VSG.

The mean age and BMI of patients in the ERAS group were 39.07 years and 43.70 kg/m^2. The gender ratio of male to female was approximately 0.40. Differences in patient population demographics, such as age, sex, BMI, and comorbidities, can lead to variability in outcomes, as adolescent patients or those with lesser comorbidities may have faster recovery, thus impacting overall heterogeneity. A study by Schmoke *et al.*, showed better outcomes in adolescent age group bariatric surgeries, which may differ from studies focusing on older age group populations [7]. The Forest plot showed symmetrical distribution of studies included, which indicates low risk of publication bias, but minimal asymmetry was seen in studies with smaller sample sizes, thus suggesting the potential influence of missing studies. Egger's Test was employed to evaluate the symmetry of the forest plot (p-value for Intercept (Egger's Test) approximately 0.000000019).It suggested some degree of publication bias or systematic differences in effect sizes reported by smaller studies. The risk of bias due to selective reporting was measured as low across mostly included studies. All included studies reported relevant outcomes, thus reducing the possibility of selective outcome reporting(Figure 2).

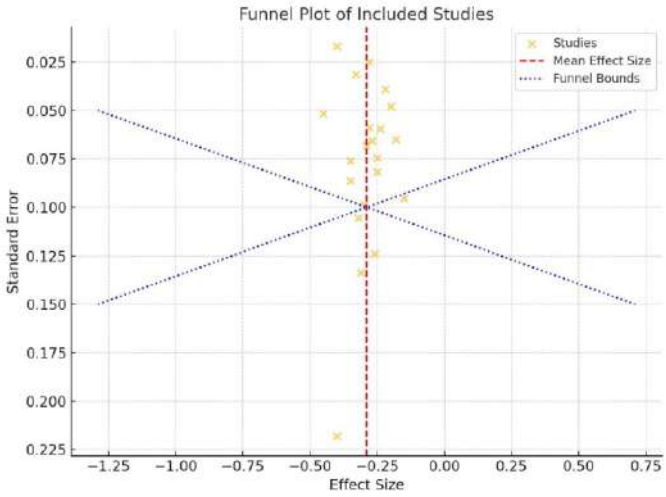

Figure 2: Funnel Plot of Included Studies Distribution

The primary and secondary outcomes across the included studies are given(Table 2).

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Table 2: Outcomes Across Selected Studies

References	Length of Hospitalization (LOH) mean	Overall Complications	Major/Severe Complications	PONV (GI Complaints)	Wound Infections	Intra-abdominal Bleed	Anastomosis Leaks	30 Days Readmission	Revision surgery	Cost	Opioid Discharge Rate
[9]	2.03 days	57.3%	Bleeding 1.3%, Respiratory distress 2.6%	Nausea 21.3%; PONV prophylaxis 95%	NA	1.3%	NA	7.3%	0.6%	NA	NA
[10]	1.79 days	1.9%	13.5%	NA	NA	NA	NA	12.5%	8.8%	€5424.09 (surgery), €775.07 (recovery)	NA
[11]	1.24 days; 86.1% discharged on Day 1	2.9%	Hemorrhage 1.6%, Leak 0.5%, Portal Vein Thrombosis 0.8%	NA	NA	1.6%	0.5%	2.1%	1.3%	NA	NA
[12]	ERAS: 17.4 hours	7.3% (Clavien-Dindo Grade ≥ II)	IIIb: 2.7%	ERAS: Controlled in 1.2 hours (p=0.042)	NA	NA	NA	6.4%	2.7%	NA	NA
[13]	1.2 days	4%	NA	NA	NA	NA	NA	1.5%	NA	NA	NA
[6]	Significant reduction (SD. MD=-2.4, p=0.002)	ERAS 10.1%	ERAS 5%	NA	NA	2.4%	0.8%	6.5%	NA	NA	NA
[14]	1 day shorter than control group	NA	NA	NA	NA	NA	NA	NA	1.3%	3.8% increase	NA
[15]	LSG: 3.2 to 1.5 days, LRYGB: 3.5 to 1.7 days	LSG: 13.8% to 0.8%, LRYGB: 4.2% to 3.0%	LSG: Significant decrease, LRYGB: Similar	NA	NA	NA	NA	LSG: 2.9% to 2.6% and LRYGB: 0% to 4.8%	LSG: 0.7% to 0.5% and LRYGB: 0 to 2.4%	NA	NA
[16]	1.36 days	NA	NA	10.71%	NA	NA	NA	NA	NA	NA	NA
[17]	2.2 days	2.1%	0.4% (ERAS)	Reduced with ERAS	0%	NA	0%	1.3%	NA	NA	NA
[18]	1 day	6.4%	NA	NA	NA	NA	NA	5.4%	2.7%	NA	7.1%
[19]	2.47 days	13.8%	1.3%	6%	2.6%	3.5%	0.9%	6.5%	1.3%	NA	NA
[20]	2.1	3.5%	3.5%, Clavien-Dindo grade III and above	82% PONV free	NA	2.3%	0.5%	0.9%	0.8%	NA	NA
[21]	1.7 days	NA	NA	8.9%	NA	NA	NA	NA	1.1%	NA	NA
[22]	1.2	3.3%	NA	NA	NA	NA	NA	0.9%	NA	625.2 USD	NA
[23]	1.48 days	3.33%	NA	NA	NA	NA	0%	3.74%	0%	NA	44.9% did not need opioids /narcotics
[24]	1.36	3.33%	NA	0%	NA	NA	0%	0%	0%	NA	11%

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[7]	1.5 days	NA	NA	NA	NA	NA	NA	0%	NA	NA	Reduced opioid discharge rate in ERAS group (18.2 vs 97.0 MME)
[25]	1 day	1.7%	1.7%	Significantly lower PONV	NA	NA	NA	8.1%	NA	NA	NA
[26]	81% of patients were discharged by POD 1	NA	NA	NA	NA	NA	NA	6% represent-ation within 30 days	4 patients returned to theatre	NA	NA
[27]	28 hours ERAS	NA	NA	NA	NA	NA	NA	NA	NA	NA	Fewer ERAS patients need opioids/ narcotics in the hospital, 72.3%

Length of hospital stay also had a weak positive correlation with overall complications (r = 0.35) and opioid use reduction (r = 0.28). The LOH was variable across the included studies, with most studies reporting an average stay of approximately 1 to 3 days. A study by Blanchet *et al.*, reported that 86.1% of patients were discharged on the first post-operative day [11], while studies like Mannaerts *et al.*, showed reductions in hospital stay by up to 50% [15].Thus implementation of ERAS protocols reduces hospital stays, which suggests that ERAS is effective in standardizing quicker recovery periods. The average length of hospitalization (LOH) was approximately 1.46 days, with moderate variability (SD=0.47) (Figure 3).

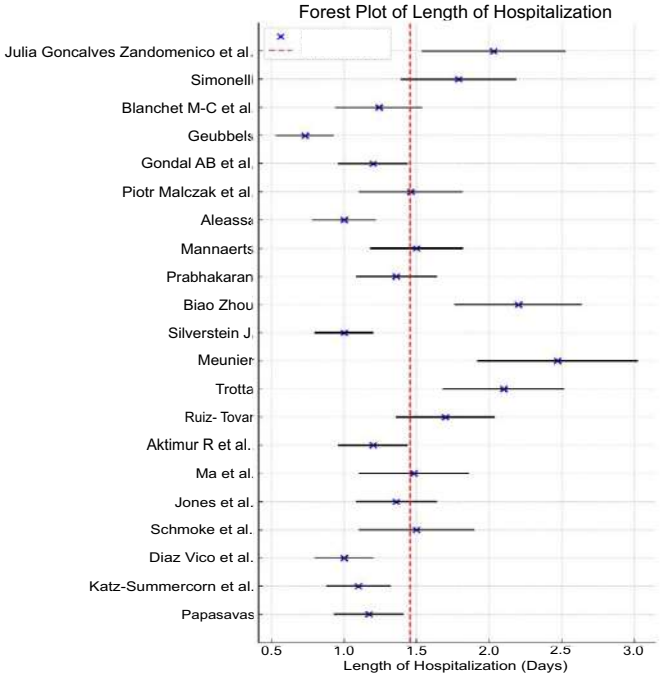

Figure 3: Forest Plot of Length of Hospitalization across Included Studies

The heterogeneity in mixed studies also emphasized the need for clear reporting and separate analysis of SG and RYGB. The subgroup analysis revealed that consistently shorter LOH across the SG subgroup compared to RYGB also supported its use as a low-risk bariatric surgery option for quicker recovery (Figure 4).

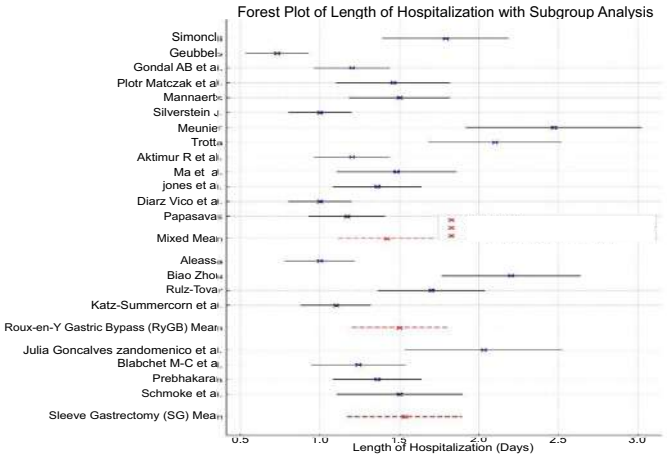

Figure 4: Forest Plot of Subgroup Analysis between SG and RYGB

A study by Zandomenico *et al.*, reported a high incidence of PONV, i.e., 21.3%, but also had a high rate of prophylactic medicine use [9]. Wound infections and anastomotic leaks were not commonly reported across studies but were generally low, as 0% reported by Zhou *et al.* and Jones *et al.* in an ERAS setting [17, 24].The rates of intra-abdominal bleeding were relatively low across studies, 2.4% in Małczak *et al.*, [6] and 1.6% in Blanchet *et al.*, [11], but perioperative monitoring is important in complex bariatric surgeries. The need for revision surgery appears low when ERAS protocols were followed, as Mannaerts reported

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rates of 0 to 2.4% [15]. Katz-Summercorn *et al.*, found that revisional procedures were managed similarly to primary procedures in an ERAS setting without a significant increase in complications [26]. This suggests that ERAS pathways are effective even in more complex surgeries. The readmission rates were low in the majority of studies, between 1% and 6%. Studies like Zhou *et al.*, reported 1.3% [17] and Geubbels [12] 6.4%, low readmission rates with ERAS protocols.

Table 3: Key Metrics of Included Studies

Metric	Studies Count	Mean ± SD	Min	25%	50%	75%	Max
Length of Hospitalization	20	1.46 ± 0.47	0.73	1.13	1.36	1.72	2.47
Overall Complications (%)	15	8.10 ± 14.01	1.7	2.50	3.33	6.85	57.3
Major Complications (%)	8	4.16 ± 4.63	0.4	1.30	2.15	4.88	13.5
30-Day Readmission (%)	16	4.16 ± 3.52	0.0	1.20	3.79	6.43	12.5
Opioid Use Reduction (%)	5	30.70 ± 27.54	7.1	11.00	18.20	44.90	72.3

The complication rates also varied significantly across studies, with some reporting very low rates, e.g., Simonelli *et al.*, with 1.9% [10], and others reporting higher rates, that is, 57.3% by Zandomenico *et al.*, [9]. Studies employing ERAS protocols generally reported lower complication rates e.g., study by Zhou *et el.*, 2.1% [17]. Such variability suggests that surgical techniques, patient selection, comorbidities and the implementation of standardized protocols like ERAS play a significant role in postoperative outcomes. Sleeve Gastrectomy had relatively lower complication rates with a narrower confidence interval as compared to RYGB. The included studies' complication rate (blue dot) and its 95% confidence interval (horizontal line) are displayed (Figure 5).

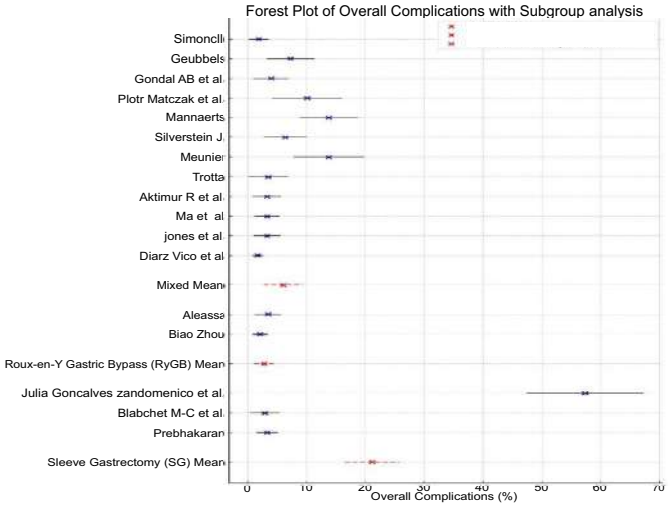

Figure 5: Forest Plot of Overall Complications with Subgroup Analysis

Major complications like anastomosis leakage also showed variability. Simonelli et al. had a relatively high rate of major complications, i.e., 13.5% [10], while others like Małczak and Zhou *et al.*, reported much lower rates below 5% [6, 17]. Katz-Summercorn *et al.* state that revision surgeries were managed similarly to primary in an ERAS setting without a significant increase in complication rates [26], suggesting that ERAS protocols are effective even in more complex bariatric surgeries.Our analysis showed a weak positive correlation (r=0.35) between length of hospitalization and overall complications, which suggests that as complication rates increase, there is a slight tendency for patients to stay longer in the hospital (Table 4).

Table 4: Correlation Analysis of Outcomes

Variables	LOH (Days)	Overall Complications	Major Complications	30-Day Readmission	Opioid Use Reduction
Length of Hospitalization	1.000	0.35	-0.13	0.00	0.28
Overall Complications (%)	0.35	1.000	-0.28	0.24	-0.37
Major Complications (%)	-0.13	-0.28	1.000	-0.18	0.20
30-Day Readmission (%)	0.00	0.24	-0.18	1.000	-0.26
Opioid Use Reduction (%)	0.28	-0.37	0.20	-0.26	1.000

Our analysis showed a moderate negative correlation, r=-0.37, between overall complications and reduction in opioid use, which suggests that hospitals with greater reduction in opioid use tend to have a lower overall complication rate.Opioid use varied across included studies; the study by Ma *et al.*, reported that 44.9% of patients did not require narcotics post-surgery [23]. ERAS protocols were associated with reduced opioid need, as seen in studies like Papasavas *et al.*, [27].The ERAS protocol significantly lowers the use of morphine equivalents for pain management (18.2 mg vs. 97.0 mg; p<0.01) reported by Schmoke *et al.*, [7]. It also reflects the benefit of multimodal analgesia techniques, which reduce opioid dependence and potentially reduce complications associated with opioid use, like nausea and respiratory depression. In our meta-analysis, the overall trend supported a substantial reduction in opioid use across included studies that implemented ERAS protocols

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(Figure 6).

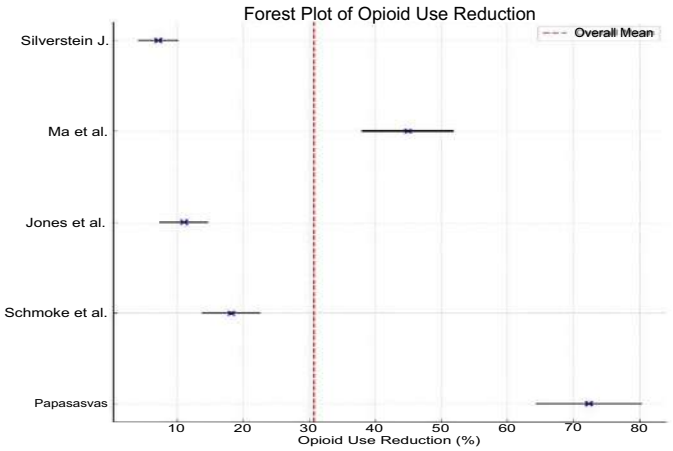

Figure 6: Forest Plot of Opioid Use Reduction

Although direct costing data were not reported by many studies, reduced LOH and complication rate associated with the ERAS protocol were likely to result in reduced overall healthcare budgets.The type of bariatric surgical procedure performed, e.g., laparoscopic sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) may also have resulted in different outcomes, e.g., study by Mannaerts *et al.*, showed variability in outcomes based on the type of surgery performed, with SG generally resulting in shorter recovery periods when compared to RYGB [15]. The heterogeneity observed in our meta-analysis was affected by differences in demographics, surgical techniques and ERAS protocol adherence.The major contributor to heterogeneity in our analysis was driven by variability in the number and type of elements implemented across included studies (Figure 7).

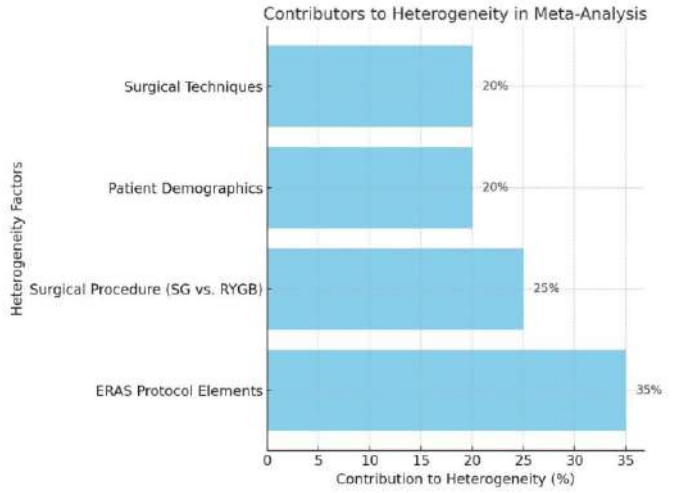

Figure 7: Heterogeneity Contributors in Our Analysis

The regression model was unable to detect any significant relationship between the independent variables (complication rates, readmission rates) and length of hospitalization (dependent variable). This analysis interpreted that reducing complications by 10-30% has a positive impact on reducing hospital stay and improving opioid reduction rates, and it suggests that effective and prompt management of complications significantly accelerates the recovery period and reduces the need for opioids/narcotics post-surgery (Figure 8).

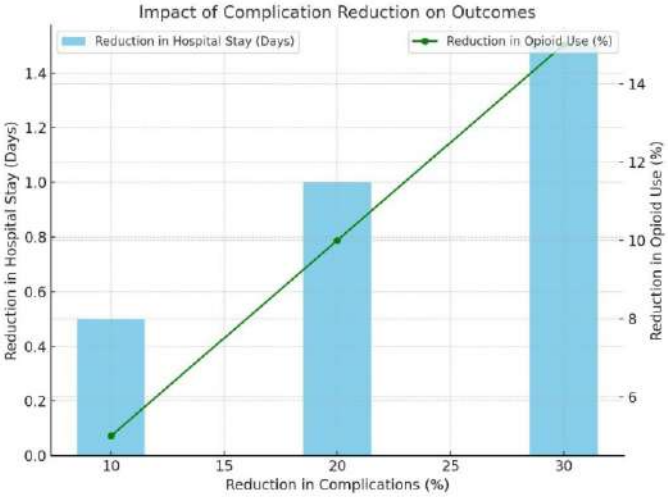

Figure 8: Sensitivity Analysis of Impact of Complication Reduction on Outcomes

DISCUSSION

Enhanced Recovery After Surgery (ERAS) was first introduced in 1995 and refers to a collection of multimodal evidence-based perioperative management strategies which include the following core components, i.e., pre-operative patient preparation and education, nutritional analysis, intraoperative anesthesia protocol, surgical methods and analgesia strategies post-operatively [28]. The ERAS protocol aims to improve surgical outcomes, reduce the perioperative stress response and complications, increase patient satisfaction rates, and have a robust postoperative recovery period [29].This meta-analysis includes evidence from 21 studies, carried out in different countries and ethnic groups, to assess the impact of ERAS principles on bariatric surgery outcomes. These meta-analytic findings support the superiority of ERAS protocols over conventional care in reducing hospital stays and post-operative recovery. Studies included in this meta-analysis, like Blanchet *et al.*, and Mannaerts *et al.*, show a reduction in hospitalization by up to 50%, hence emphasizing the ERAS protocol's effectiveness in standardizing quicker recovery periods [11, 15]. In this meta-analysis, a significant correlation was found for the weak positive relationship (r=0.35) between LOH and overall complication rates, revealing that high complications slightly extend hospital stays.This observation is also supported in a study by Małczak *et al.*, [6], in which a complication rate of 10.1% was associated with longer LOH. In contrast, studies with low complication rates, 2.1% in Zhou *et al.*, [17], generally reported shorter recovery periods. Study by Thorell *et al.*, [30]. On ERAS in bariatric surgery, also reported significant reduction in

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hospital stays, with most patients being discharged within 1 to 3 days, which is comparable to our analysis.Thorell *et al*, also reported an overall complication rate of around 7.5% with implementation of ERAS protocols [30], similar to 8.10% in this analysis.This meta-analysis also highlights a moderate negative correlation (r =-0.37) between overall complications and opioid reduction rate, which reveals that hospitals utilizing more multimodal analgesia techniques central to ERAS elements experienced fewer complication rates.A study by Feldheiser *et al.*, reported that opioid sparing protocols led to reductions of 40-70% in opioid consumption, similar to our analysis findings [31].This meta-analysis is comparable with other analyses, i.e., with Awad *et al.*, [32] and Stenberg *et al.*, [8], but the main difference lies in the quality of evidence.Our analysis included a broader range of recently conducted studies, allowing for a more comprehensive evaluation of ERAS effectiveness in bariatric surgery, while their studies excluded several bariatric surgery-specific key ERAS elements due to low evidence quality and thus led to heterogeneity.The study by Trotta *et al.*, [20], published in 2024 and conducted in high-volume centers, provides more valuable insights into the implementation of ERAS principles in diverse settings. A study by Schmoke *et al.*, [7].Conducted in 2024, focused on adolescent age range bariatric surgeries and improved outcomes,suggested that ERAS protocols are beneficial across various patient demographics.This diverse variety of included studies in our meta-analysis supports the applicability and versatility of ERAS protocols in different patient demographics and ethnic populations.The ERAS protocols not only reduce hospitalization duration but also improve utilization of ICU resources as evident in a meta-analysis by Davey *et al.*, [33], who quantify reductions in ICU stay (MD: 0.70, p=0.02) and time to mobilization (MD: -3.78, p<0.001). Besides, Davey *et al.*, observed no significant statistical difference in overall (11.8%) and major complications (3.4%) between the ERAS and SC group [33].The findings of another study by Huh and Kim [34] aligns with this meta-analysis, demonstrating that ERAS protocol implementation significantly lessens postoperative pain (mean difference [MD]:−1.2, 95% confidence interval [CI]: −2.0 to −0.4, p=0.003), nausea and vomiting (odds ratio [OR]: 0.55, 95% CI: 0.32–0.91, p=0.021), and length of hospital stay (MD:−0.8 days, 95% CI:−1.1 to −0.5, p<0.001) without increase in morbidity. Their study also highlights opioid-sparing multimodal pain management strategies and optimal goal-directed postoperative fluid therapy as structural key elements in optimizing robust recovery, which is consistent with this meta-analysis. The study by Doshi *et al.*, [35] demonstrated that the implementation of the ERAS protocol in patients who underwent bariatric surgery resulted in a significant reduction in length of hospital stay (LOS) by 1 day (p=0.001) and median cost reductions of $2230 per patient (p<0.001). The exact data on cost savings were not explicitly analyzed in this meta-analysis, making it difficult to quantify and compare the exact financial impact.The Italian Consensus Statement on Enhanced Recovery After Bariatric Surgery (ERABS) also concludes that ERAS implementation significantly reduces length of hospital stay compared to conventional bariatric surgery protocols [36].The Consensus also highlights the multimodal analgesia strategy as a fundamental key element, thus aligning with this meta-analysis, which demonstrates a significant reduction in opioid consumption and opioid-related adverse events. Despite the overall positive outcomes, this meta-analysis revealed significant heterogeneity among the included studies, particularly in ERAS protocol components and implementation practices.This variability suggests a need for standardized ERAS guidelines tailored to bariatric surgery specifically to enhance consistency in patient outcomes.Our meta-analysis also included different study designs, while most included were RCTs, others were retrospective or observational studies that may cause bias and influence the study outcomes. Few studies also lacked sufficient blinding and detailed methodology, hence making it difficult to fully assess their quality.Many studies included were conducted in high-volume surgical centers where ERAS implementation was better established, which may not reflect outcomes in low-volume settings. Currently, developing countries are facing many healthcare challenges and resource constraints, but the implementation of ERAS protocols could significantly improve surgical postoperative outcomes, enhance patient satisfaction rates and reduce healthcare budgets. Future large-scale RCTs should be conducted to identify the most impactful and uniformly consistent core elements of ERAS protocols to ensure optimal applicability across different clinical settings and surgical techniques.

CONCLUSIONS

This meta-analysis concluded that ERAS protocols' implementation in modern-era bariatric surgeries supports the positive role of these protocols due to short hospital stays, decreased recovery periods, and increased patient satisfaction. The findings affirm that ERAS protocols lead to shorter hospital stays (by an average of 1.5 days), reduced post-operative complications, and low opioid consumption, thus contributing to faster recovery periods.

Authors Contribution

Conceptualization: MAJ
Methodology: MI, AA, MH, NF
Formal analysis: MI, NF
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All authors have read and agreed to the published version of the manuscript

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Conflicts of Interest

All the authors declare no conflict of interest.

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