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Antimicrobial Stewardship in Pakistan: Lost in Policy, Weak in Practice

OPEN ACCESS

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Antimicrobial resistance (AMR) is one of the most critical emerging public health threats in this century, jeopardizing decades of success in the treatment of infectious diseases in medical sciences. The discovery and effectiveness of these miracle drugs have now changed into a nightmare due to inefficient regulatory oversight, overprescription, and misuse as a widespread practice. Highly infectious disease-burden countries are poorly performing in stewardship practices, including Pakistan.

Antimicrobial stewardship is considered a fundamental strategy to optimize and rationalize the use of antibiotics. An analysis of antibiotic consumption over the last two decades has risen dramatically, showing a 65% increase between 2000 and 2015, with the fastest growth in LMICs. Pakistan is one of these countries with limited regulatory frameworks and diagnostic capacity [1]. High patient volume, poor microbiological support, patients & families' pressure, healthcare providers' attitude, over-the-counter availability of antibiotics, and delayed diagnostic results are major contributing factors towards high consumption of antibiotics in Pakistan.

Pakistan endorsed the Global Action Plan on AMR by the WHO and developed the National Action Plan (NAP) on AMR in 2017. The NAP emphasizes surveillance, infection prevention and control, rational use of antimicrobials, and multisectoral collaboration using the "One Health" approach through integrating human, animal, and environmental sectors [2]. National institutions such as the National Institutes of Health Pakistan have strengthened surveillance systems and are coordinating national efforts to monitor antimicrobial resistance trends. Now, Pakistan has initiated development of a second national action plan to strengthen provincial implementation mechanisms [3].

The National Institute of Health (NIH) is actively working on policy development and AMR reporting; the national strategies are poorly translated into existing stewardship efforts across Pakistani institutions. Evidence suggests that AMS (antimicrobial stewardship) programs are implemented in only a minority of hospitals, as reported in a study that only 7.6% of paediatricians worked in institutions with functional AMS and merely 15% had received formal training in antibiotic use, AMR, or stewardship principles [4].

Hospital policies and prescribing SOPs and practices further illustrate the level and scale of the challenge. There is substantial antibiotic utilization in hospitals of Pakistan, so a need for structured stewardship interventions to rationalize prescribing patterns [5]. The empirical therapy predominates, while microbiological culture and sensitivity testing remain underutilized.

The change in the use of antibiotics in Pakistan has been in terms of the increase in the number of doses per day used over the past decades, with an approximate of 800 million to over 1.3 billion doses being used daily. Implementation of stewardship is not a universal requirement of accreditation of hospitals, and thus institutional priorities are inconsistent [6].

The Pakistani hospitals do not have specific spreaders of infectious diseases, well-trained clinical pharmacists, and electronic prescription systems, which are normally needed in facilitating successful stewardship programmes. Another

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critical aspect of evidence-based prescribing that impedes it in lower levels of the healthcare system is diagnostic limitations.

However, it is possible to note that academic and tertiary healthcare organizations are forming multidisciplinary stewardship teams that include infectious disease specialists, microbiologists, pharmacists, and infection prevention experts. Such teams have been aiming at interventions like formulary restrictions, antimicrobial review rounds, and the spread of hospital antibiograms. It is indicated that the interventions can enhance the prescribing behaviours and decrease the use of antimicrobials when implemented properly [7].

Education and capacity building are also some of the essential pillars of antimicrobial stewardship. Research in Pakistan has demonstrated that specific training can increase knowledge levels on AMR and stewardship to a great extent [8]. The implementation of stewardship ideas in undergraduate and postgraduate medical, pharmacy, and nursing programs should be adopted as a long-term sustainable approach to enhance the stewardship capacity. CPD programs and institutional training initiatives can further support clinicians in implementing evidence-based prescribing practices.

Beyond hospitals, a broader systems approach is needed for combating AMR. Community prescribing practices, the private healthcare system, and pharmaceutical supply chains all influence antibiotic consumption patterns in Pakistan. Over-the-counter access to antibiotics continues to contribute to self-medication and inappropriate use among the general population. Regulatory oversight of antibiotic dispensing, expanding public awareness campaigns, and improving infection prevention and control practices across healthcare settings need to be strengthened, as these are the essential components of a comprehensive national strategy.

Pakistan is at a critical juncture in its response to AMR, so strengthening stewardship efforts is essential to preserve the effectiveness of existing antimicrobials and to prevent the escalating threat of antimicrobial resistance.

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Original Article

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The Clinical Spectrum of Autoimmune-Mediated Neurological Diseases in Patients Presenting to a Tertiary Care Hospital in Rawalpindi

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ABSTRACT

Autoimmune-mediated neurological diseases (AMNDs) affect the central and peripheral nervous systems through inflammation and demyelination, leading to diverse neurological dysfunctions. Their heterogeneous clinical presentations complicate diagnosis, and epidemiological data in adult Pakistani populations remain scarce. **Objectives:** To determine the frequencies of different AMNDs among adult patients presenting to a tertiary care hospital in Rawalpindi. **Methods:** This cross-sectional study was conducted at the Department of Neurology, Pak Emirates Military Hospital, Rawalpindi, from 1st April to 20th September 2025, including 177 adult patients consecutively presenting with neurological symptoms suggestive of autoimmune etiology. The diagnosis was made on the basis of clinical manifestations supported by MRI, cerebrospinal fluid analysis, and autoantibodies. The analysis was performed using SPSS version 27.0. **Results:** The mean age of the patients was 47.9 ± 11.4 years. The majority of patients were female 108 (61%). Multiple Sclerosis was the most frequent diagnosis (27.1%), followed by autoimmune encephalitis (20.3%), Guillain-Barré syndrome (16.4%), myasthenia gravis (13.6%), and neuromyelitis optica spectrum disorder (10.7%). Anti-ganglioside antibodies showed the highest seropositivity (12.4%), while MRI and CSF abnormalities were observed in 33.9% and 38% of patients, respectively. Significant associations were found between disease type and age (p=0.018), gender (p=0.006), residence (p=0.041), family history (p=0.032), and symptom duration (p=0.014). **Conclusions:** Multiple Sclerosis, autoimmune encephalitis, and Guillain-Barré syndrome are the most prevalent AMNDs in this population, with distinct demographic patterns and variable diagnostic findings. Early recognition and integrated diagnostic approaches are essential to improve patient outcomes.

INTRODUCTION

The disorders that attack and disrupt the central and peripheral nervous systems are the autoimmune-mediated neurological diseases (AMNDs) [1, 2]. The primary cause of these conditions is mostly T-cell-mediated reactions that result in inflammation [2]. The neurons in the results, are killed and cause the development of glioma. The CD8 + T cells associated with neuronal destruction have been observed in the case of anti-Yo paraneoplastic degeneration of cells [3]. The T cell-mediated autoimmune pathophysiology is also identical in Multiple Sclerosis (MS) and autoimmune encephalitis (AE) [4]. Other such conditions, such as anti-NMDA receptor encephalitis, make use of antibodies that cause functional damage rather than direct damage to the neurons [5]. Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) involve infection-triggered immune responses, causing macrophage-mediated nerve demyelination. In contrast, MS and NMO are autoimmune disorders of the central nervous system, while paraneoplastic neurological syndromes result from tumor-related autoantibodies that mistakenly attack nervous tissue, leading to similar

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neurological deficits [6-8]. Due to vague presentation of AMNDs, diagnosis becomes an issue and serological tests comes to play in such situations and additional diagnostic support is provided by cerebrospinal fluid analysis typically revealing an inflammatory CSF profile, MRI of the brain and spinal cord, which often shows T2/FLAIR hyperintense or contrast-enhancing lesions consistent with neuroinflammation and electrodiagnostic studies (EMG and nerve conduction studies) shows demyelinating neuropathy [9]. Early treatment with immunotherapy plays a vital role, and according to one study, A significant response rate of 91.4% to immunotherapy was observed [10]. Immunosuppressive medications like corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis are vital in the treatment of these conditions [11]. Lubarski et al. examined autoimmune neurological disorders in 508 patients, among which 32.4% were positive for antineuronal antibodies. Specific findings included positivity of serum antineuronal antibodies in 25.4%, associated with Autoimmune Neurologic Diseases, Paraneoplastic Neurologic Syndromes, and Autoimmune Encephalitis. Anti-cell surface antibodies were present in 6.69%, associated with Autoimmune Encephalitis [12]. In a study by Kishk et al. Anti-aquaporin-4 (AQP4) was detected in 37.5% of patients being investigated for possible NMOSD [13]. According to a report by Pascual-Goñi et al, in 50% of patients with acute motor neuropathies, anti-GM1 and anti-GD1a IgG antibodies are detected in Guillain-Barré syndrome (GBS) [14]. A study conducted by Rajput et al. in a tertiary-care centre included 204 patients with suspected demyelination, identifying neuromyelitis optica spectrum disorder (NMOSD) in 36 patients (17.6%), while multiple sclerosis accounted for 49.0% of cases. Among NMOSD patients, 88.9% were AQP4-IgG seropositive and 11.1% seronegative; females predominated (72.2%). The mean age was 31.0 ± 10.1 years in seropositive and 28.0 ± 2.5 years in seronegative patients ($p>0.05$), with relapsing disease observed in 75% and longitudinally extensive transverse myelitis (LETM) on MRI in 72.8% of cases [15].

Despite AMNDs, comprehensive adult data from Pakistan, particularly on their clinical spectrum and relative frequencies, remain scarce and fragmented. Overlapping presentations and limited access to advanced serological testing further contribute to delayed diagnosis and suboptimal outcomes. This study aimed to determine the clinical spectrum and frequency of AMNDs at a tertiary care center in Rawalpindi, providing region-specific evidence to support earlier diagnosis, appropriate investigations, and improved patient management.

METHODS

This cross-sectional study was conducted at the Department of Neurology, Pak Emirates Military Hospital, Rawalpindi, including 177 patients from April 2025 to September 2025. Patients were included consecutively based on predefined selection criteria. After obtaining ethical approval from Pak Emirates Military Hospital, Rawalpindi, under ref no: A/28/ERC/31/2025, and written informed consent from patients or guardians, data were collected using a structured proforma capturing demographic details, duration of symptoms, comorbidities, past medical history, and family history of autoimmune or neurological diseases. The sample size was calculated through the WHO sample size calculator, keeping a confidence level of 95%, a margin of Error of 4%, and an anticipated frequency of Neuromyelitis Optica Spectrum Disorder (NMOSD) based on a previous study as 8% [16]. Inclusion criteria were patients of either gender aged ≥18 years presenting with clinical features suggestive of autoimmune-mediated neurological disease. Exclusion criteria comprised patients with confirmed infectious or traumatic neurological conditions, known non-autoimmune neurological disorders (such as stroke or Parkinson's disease), and critically ill patients who were unable to safely undergo required diagnostic investigations. These exclusions were applied to ensure patient safety, ethical compliance, and diagnostic accuracy. Electrophysiological studies (EMG/NCS) were performed selectively in patients with clinical suspicion of peripheral nerve or neuromuscular involvement, in accordance with standardized clinical protocols refer to pre-established, evidence-based guidelines used in the evaluation and management of patients with suspected AMNDs, by specifying the indications for each diagnostic test, such as MRI, cerebrospinal fluid analysis (CSF), antibody testing, and EMG/NCS, based on presenting symptoms and clinical suspicion [17-19]. Final diagnoses were made by a senior neurologist integrating clinical assessment with relevant investigative findings, thereby minimizing potential measurement bias. Co-positivity was recorded, but analyses were conducted according to the principal autoimmune neurological disorder to avoid double-counting in frequency tables. The diseases included Multiple Sclerosis (MS), Autoimmune Encephalitis (AE), NMOSD, GBS, Myasthenia Gravis, CIDP, Stiff-Person Syndrome (SPS), and Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM). Neurological symptoms were defined as motor, sensory, or neuro-electrical dysfunction documented during clinical examination, including limb weakness graded below 5/5 on the MRC scale, reduced sensation confirmed through neurological testing, and seizures diagnosed clinically or via EEG. Diagnostic investigations were done according to the clinical requirements. To test the presence of antibodies or their absence, blood samples were tested in relation to

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anti-AQP4, anti-MOG, anti-NMDAR, anti-ganglioside, paraneoplastic antibodies, and anti-synaptic protein antibodies, with the results registered as positive or negative. Lumbar puncture was done under sterile conditions to test the CSF, cell count, and protein level, and reported normal, high protein, high WBCs, or not done. The MRI of the brain and spine was read in cases of the presence of demyelinating or inflammatory lesion and EMG/NCS were done where necessary to identify patterns of demyelinating, axonal, mixed, or normal neuropathy. A senior neurologist made final diagnoses based on all the clinical findings and the results of the investigations. The analysis of the data was done with IBM SPSS version 27.0. The age and years of the symptoms were tested with the Shapiro-Wilk test to determine normalization and reported as the mean with standard deviation or median (IQR). Frequencies and percentages were used to summarise categorical variables such as gender, antibody positivity, MRI results, EMG/NCS patterns, CSF profiles, as well as the ultimate AMNDs diagnosis. It is stratified by age, gender, residence, family history, MRI, antibody test, CSF test, and electrophysiological patterns with the ultimate clinical spectrum of autoimmune neurological diseases. In cases where it was necessary, chi-square or Fisher's Exact Test was used, and the p-value of 0.05 was regarded as statistically significant.

RESULTS

The study included 177 patients having a mean age of 47.9 ± 11.4 years, ranging from 32 to 87. There were 69 (39%) male and 108 (61%) female. A majority of participants resided in urban areas, 118 (67%), while 59 (33%) were from rural settings. Most were educated, 161 (91%), whereas 16 (9%) were uneducated. A family history of autoimmune or neurological disease was present in 27 (15%) of the participants. The median symptom duration was 5 months (IQR 3–8 months), indicating that most patients presented after a moderate duration of illness (Table 1).

Table 1: Demographic Analysis

Variables	Mean ± SD, n (%)
Age	
32 to 87 Years	47.9 ± 11.4
Gender	
Male	69 (39%)
Female	108 (61%)
Residence	
Urban	118 (67%)
Rural	59 (33%)
Level of Awareness	
Educated	161 (91%)
Uneducated	16 (9%)

Among all these patients, anti-AQP4 antibodies were positive in 17 (9.6%), while anti-MOG antibodies were detected in 11 (6.2%). Anti-NMDAR antibodies were positive in 15 (8.5%), and anti-ganglioside antibodies in 22 (12.4%), which represented the highest seropositivity among the antibody tests. Paraneoplastic antibodies (Hu/Yo) were identified in 8 (4.5%) patients, and anti-synaptic protein antibodies in 6 (3.4%). MRI showed demyelinating lesions in 60 (33.9%) patients, whereas 92 (52%) had no detectable lesions, and MRI was not performed in 25 (14.1%) cases. CSF analysis revealed elevated protein in 50 (28.2%) and elevated WBC in 18 (10.1%), while 84 (47.5%) had normal CSF findings; CSF analysis was not done in 25 (14.1%) patients. EMG/NCS results showed axonal involvement in 36 (20.3%), demyelinating patterns in 26 (14.7%), and mixed changes in 12 (7%), whereas 44 (24.8%) had normal studies; the test was not conducted in 59 (33.3%) patients (Table 2).

Table 2: Diagnostic Findings among Patients (n=177)

Diagnostic Tests	Results	Frequency (%)
Anti-AQP4	Positive	17 (9.6%)
Anti-MOG	Positive	11 (6.2%)
Anti-NMDAR	Positive	15 (8.5%)
Anti-Ganglioside	Positive	22 (12.4%)
Paraneoplastic Antibodies (Hu/Yo)	Positive	8 (4.5%)
Anti-Synaptic Protein Antibodies	Positive	6 (3.4%)
MRI Findings	Demyelinating Lesions	60 (33.9%)
	No Lesions	92 (52%)
	Not Done	25 (14.1%)
CSF Analysis	Elevated Protein	50 (28.2%)
	Elevated WBC	18 (10.1%)
	Normal	84 (47.5%)
	Not Done	25 (14.1%)
EMG/NCS	Axonal	36 (20.3%)
	Demyelinating	26 (14.7%)
	Mixed	12 (7%)
	Normal	44 (24.8%)
	Not Done	59 (33.3%)

MS was the most common autoimmune neurological disorder, diagnosed in 48 (27.1%) individuals. This was followed by AE in 36 (20.3%) and GBS in 29 (16.4%). MG accounted for 24 (13.6%) cases, while NMOSD was observed in 19 (10.7%) patients. Less frequent conditions included CIDP in 14 (7.9%), SPS in 4 (2.3%), and PERM in 3 (1.7%) (Table 3).

Table 3: Distribution of Autoimmune Neurological Diseases (n=177)

Disease	Frequency (%)
Multiple Sclerosis (MS)	48 (27.1%)
Autoimmune Encephalitis (AE)	36 (20.3%)
Guillain-Barré Syndrome (GBS)	29 (16.4%)
Myasthenia Gravis (MG)	24 (13.6%)
Neuromyelitis Optica Spectrum Disorder (NMOSD)	19 (10.7%)

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Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	14 (7.9%)
Stiff Person Syndrome (SPS)	4 (2.3%)
Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)	3 (1.7%)

Significant demographic differences were observed across autoimmune neurological diseases. Age distribution differed markedly (p=0.018), with MS and NMOSD patients predominantly younger (20–40 years), while GBS, MG, and CIDP were more common in older age groups. Gender also showed a significant association (p=0.006): MS and NMOSD occurred mostly in females, whereas AE, GBS, and CIDP showed a higher proportion of males. Residence was significant (p=0.041), with urban predominance seen especially in MS and MG. Family history showed a meaningful association (p=0.032), with MS and NMOSD having higher frequencies of positive family history than other diseases. Symptom duration varied significantly between disease groups (p=0.014): GBS patients mostly presented within <3 months, whereas MS, NMOSD, and CIDP tended to have symptoms lasting >6 months. Education status did not show a statistically significant association (p=0.221) (Table 4).

Table 4: Autoimmune Neurological Diseases vs Demographics

Baseline Characteristics	MS (n=48)	AE (n=36)	GBS (n=29)	MG (n=24)	NMOSD (n=19)	CIDP (n=14)	SPS (n=4)	PERM (n=3)	p-value
Age									
20–40 Years	26 (54%)	10 (27.8%)	5 (17.2%)	3 (12.5%)	12 (63.2%)	1 (7.1%)	0 (0%)	0 (0%)	0.018
41–60 Years	18 (37.5%)	20 (55.6%)	15 (51.7%)	12 (50%)	6 (31.6%)	7 (50%)	2 (50%)	2 (66.7%)	
>60 Years	4 (8.3%)	6 (16.7%)	9 (31.1%)	9 (37.5%)	1 (5.3%)	6 (42.9%)	2 (50%)	1 (33.3%)	
Gender									
Male	14 (29.2%)	22 (61.1%)	18 (62.1%)	6 (25%)	4 (21.1%)	9 (64.3%)	2 (50%)	1 (33.3%)	0.006
Female	34 (70.8%)	14 (38.9%)	11 (37.9%)	18 (75%)	15 (78.9%)	5 (35.7%)	2 (50%)	2 (66.7%)	
Residence									
Urban	34 (70.8%)	20 (55.6%)	17 (58.6%)	18 (75%)	13 (68.4%)	9 (64.3%)	3 (75%)	2 (66.7%)	0.041
Rural	14 (29.2%)	16 (44.4%)	12 (41.4%)	6 (25%)	6 (31.6%)	5 (35.7%)	1 (25%)	1 (33.3%)	
Education									
Status	46 (95.8%)	30 (83.3%)	23 (79.3%)	23 (95.8%)	18 (94.7%)	11 (78.6%)	4 (100%)	3 (100%)	0.221
Literate	2 (4.2%)	6 (16.7%)	6 (20.7%)	1 (4.2%)	1 (5.3%)	3 (21.4%)	0 (0%)	0 (0%)	
Family History									
Present	12 (25%)	4 (11.1%)	3 (10.3%)	2 (8.3%)	4 (21.1%)	1 (7.1%)	1 (25%)	0 (0%)	0.032
Absent	36 (75%)	32 (88.9%)	26 (89.7%)	22 (91.7%)	15 (78.9%)	13 (92.9%)	3 (75%)	3 (100%)	
Symptom Duration									
<3 Months	6 (12.5%)	8 (22.2%)	21 (72.4%)	3 (12.5%)	2 (10.5%)	1 (7.1%)	0 (0%)	0 (0%)	0.014
3–6 Months	18 (37.5%)	17 (47.2%)	6 (20.7%)	10 (41.7%)	6 (31.6%)	3 (21.4%)	1 (25%)	1 (33.3%)	
>6 Months	24 (50%)	11 (30.6%)	2 (6.9%)	11 (45.8%)	11 (57.9%)	10 (71.4%)	3 (75%)	2 (66.7%)	

Note: Here, Multiple Sclerosis (MS), Autoimmune Encephalitis (AE), Guillain-Barré Syndrome (GBS), and Myasthenia Gravis (MG). p-value was calculated through Fisher's Exact Test

DISCUSSION

In this study, MS (27.1%), AE (20.3%), and peripheral demyelinating disorders, including GBS/CIDP (24.3%) were the most common diagnoses, with a notable female predominance in MS and NMOSD. Younger patients (20–40 years) more frequently had MS and NMOSD, while GBS, MG, and CIDP were more common in older age groups. Autoantibody positivity varied by disease, and characteristic MRI, CSF, and EMG/NCS abnormalities were observed. Symptom duration differed significantly across disorders, with acute presentation in GBS and delayed onset in MS, NMOSD, and CIDP. The frequency of MS in this study is consistent with global epidemiological data, where MS affects approximately 2.3 million individuals worldwide [20]. The female predominance in MS and NMOSD aligns with reports showing women are 2–3 times more likely to develop these disorders [21]. NMOSD anti-AQP4 seropositivity in our cohort (9.6%) is lower than previously reported rates (30–40%), reflecting regional variability and diagnostic limitations [13]. The proportion of AE (20.3%) in our study corresponds with prior reports, and the 8.5% anti-NMDAR positivity aligns with literature indicating that approximately two-thirds of AE patients have detectable antibodies [22]. Our findings of GBS and CIDP are comparable with global observations on peripheral demyelinating disorders and anti-ganglioside antibody prevalence, although the antibody rate in our cohort was lower than the ~50% reported in some studies [14]. Rare conditions such as Stiff-Person Syndrome and PERM were

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observed at frequencies consistent with international data [23]. Age-related trends observed in our study mirror global patterns: MS and NMOSD predominance in younger populations and GBS/CIDP in older patients [24, 25]. The urban predominance of MS and MG may reflect better healthcare access, increased disease awareness, and environmental exposures, similar to geographic disease burden variations reported in Germany [21]. Family history associations in MS and NMOSD support literature on autoimmune co-aggregation, including thyroiditis and inflammatory bowel disease [26, 27]. Current study highlights the diagnostic utility of multimodal assessment. Autoantibody testing, MRI, CSF analysis, and electrophysiology all contributed to the diagnosis, supporting the precision-medicine approach emphasized in recent studies. MRI and CSF findings were consistent with known limitations in sensitivity and specificity, and EMG/NCS patterns in peripheral demyelinating disorders reflected expected global trends [28, 29]. Diagnostic delays were evident, particularly for AE, MG, and MS. This aligns with prior literature documenting late or misdiagnoses due to diverse symptom presentations [30, 31]. Chronicity and delayed diagnosis, as observed in our cohort, likely contribute to long-term physical, psychological, and socioeconomic impacts, echoing findings from international studies on MS and other autoimmune neurological disorders [20].

Limited generalization is due to single-centre design, small sample (n=177), incomplete diagnostics (14-33% Missing tests), limited antibody testing, no follow-up, and referral bias. Multicentre registries with standardized protocols, enrich access to multicentre diagnostics, formulate national guidelines, longitudinal outcome investigations, and better training of neurologists and community education on the importance of timely detection of the disease.

CONCLUSIONS

This study provides a detailed account of AMNDs in adults with MS, AE, and GBS, with AMNDs being the most prevalent. Significant associations were observed between disease type and demographic factors such as age, gender, residence, family history, and symptom duration, including female predominance in MS and NMOSD and older age distribution in GBS, MG, and CIDP.

Authors' Contribution

Conceptualization: WWM
Methodology: WWM, FW
Formal analysis: WWM, AR
Writing and Drafting: MM, WWM, HUR, FK
Review and Editing: MM, WWM, HUR, AR, FW, FK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Short-Term Outcomes of Transcatheter VSD Closure Using the MFO Device at a Tertiary Cardiac Centre in Lahore

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ABSTRACT

Transcatheter closure is the commonly used approach to treat congenital ventricular septal defect (VSD), though local outcome data on the use of KONAR-Multi Functional Occluder (MFO) in Pakistan are scarce. **Objectives:** The purpose of this study was to evaluate the short-term outcomes following transcatheter VSD closure with the MFO device and to compare the results in retrograde versus the antegrade methods. **Methods:** Prospective observational research was carried out in the Department of Pediatric Cardiology, Punjab Institute of Cardiology, Lahore. They included patients aged between three years and thirty-one years of age who had previously experienced transcatheter VSD closure using the MFO device between January 2021 and June 2024. There were 30 patients who were enrolled, of whom 20 patients were under retrograde, and 10 patients were under antegrade. The predictors of residual shunt were determined by logistic regression. **Results:** Four patients (13.3) had a residual shunt at discharge, and it reduced to one (3.3) at one-month follow-up. There were three patients with aortic regurgitation in the early post-procedure period (10%). The significance of the ventricular septal defect diameter exceeding six millimeters was only significantly related to residual shunt (odds ratio 4.28, p = 0.04). There were no significant conduction changes or device embolization during hospitalization or 1-month follow-up. **Conclusions:** Short-term success with low complication rates was observed in both methods of Transcatheter closure of VSD with the MFO device. The results demonstrate the safety of this method within a local Pakistani tertiary care environment.

INTRODUCTION

Congenital heart disease remains a major public health challenge in Pakistan and continues to place a significant burden on pediatric cardiac care services [1]. Ventricular septal defect (VSD) is among the most frequently diagnosed congenital cardiac anomalies in the country. Current estimates suggest that approximately 4–6 per 1,000 live births in Pakistan are affected by VSD [2]. Many patients experience delayed diagnosis or limited access to specialized cardiac care, particularly in resource-constrained settings. This delay increases morbidity and places substantial strain on families and tertiary care institutions [3]. A ventricular septal defect is characterized by an abnormal communication between the right and left ventricles, allowing left-to-right shunting of blood. This abnormal circulation may result in pulmonary overcirculation, left ventricular volume overload, recurrent respiratory infections, growth failure, and heart failure if left untreated [4–6]. While spontaneous closure may occur in small defects, moderate to large VSDs often require intervention to prevent long-term complications. Surgical repair has traditionally been the standard treatment for hemodynamically significant VSDs. However, advances in interventional cardiology have led to the increasing use of transcatheter closure as a less invasive alternative in

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selected patients. Recent developments in occluder technology have improved procedural safety and expanded the range of VSD anatomies amenable to percutaneous treatment. The KONAR-Multi Functional Occluder (MFO) is a newer-generation device designed with a flexible nitinol waist and dual-disc configuration, allowing adaptation to a variety of VSD morphologies. Recent studies have evaluated the KONAR-Multi Functional Occluder (KONAR-MFO/KONAR-MF) for transcatheter VSD closure and generally report high procedural success with low rates of major complications. For example, a systematic review and meta-analysis of KONAR-MFO use across perimembranous and muscular VSDs reported overall favorable efficacy and safety outcomes [7]. In addition, single-center and multi-center experiences have described high closure rates with low incidence of clinically significant valve dysfunction or permanent conduction disturbances [8]. A more recent multicenter, prospective experience from India (three centers) reported mid-term follow-up outcomes for perimembranous VSD closure using KONAR-MF, contributing real-world safety data from a large regional cohort [9]. Evidence from South Asia suggests similar short-term success with modern occluders, including KONAR-MF/MFO, although outcomes vary by patient selection, anatomy, and operator strategy [10].

Studies in smaller children and comparative device cohorts have also supported acceptable safety profiles, while emphasizing continued attention to heart block and valve interactions. Despite these encouraging findings, published outcome data from Pakistan remain limited, and local patient factors (late presentation, nutritional status, follow-up access) may affect outcomes and complication detection. Therefore, local short-term outcome data after transcatheter VSD closure using KONAR-MFO are needed to inform practice in Pakistani tertiary-care settings. The main aim of this study was to evaluate the short-term outcomes of transcatheter VSD closure using the MFO device at a tertiary cardiac center in Pakistan and to compare procedural and early post-procedural results between antegrade and retrograde deployment approaches.

METHODS

A prospective observational study was conducted in the Department of Pediatric Cardiology in one of the tertiary cardiac centers in Lahore. The Institutional Review Board of the Punjab Institute of Cardiology, Lahore (Reference No. RTPGME-Research-149-A) gave ethical clearance. The enrolled patients were recruited in sequence, in all patients who came to the department and met the inclusion criteria, and gave informed consent, until the required sample size was reached. The information was gathered in the hospital clinical environment between January 2021 and June 2024. Sample size was estimated using a single-proportion (precision-based) approach, guided by previously reported high procedural success rates (~98%) for transcatheter VSD closure with KONAR-MFO. With a target confidence level of 95%, 5% margin of error, and pragmatic feasibility constraints of a single-center prospective cohort, a sample size of 30 was considered sufficient to provide an initial local estimate of early procedural success and short-term complications [11]. This study was not designed or powered to detect small differences between deployment approaches; subgroup comparisons and regression analyses were performed as exploratory assessments. The eligible patients included patients aged between three and forty years with a hemodynamically significant ventricular septal defect established on transthoracic echocardiography. They were limited to those with appropriate anatomy to sustain transcatheter closure. Patients who were previously surgically repaired or had device closure, were actively infected, had irreversible severe pulmonary hypertension, or aortic valve prolapse were excluded. Exclusion factor was also known allergy to device materials. Clinical interview, hospital record, imaging studies, and catheterization findings were used to collect data. Sociodemographic factors were age and gender. The clinical variables examined were weight, baseline symptoms, previous chest infections, heart failure characteristics, and previous history of infective endocarditis. Vivid E95 (General Electric, USA) was used to perform transthoracic echocardiography to confirm the VSD type, VSD diameter, left ventricular internal diastole and systole inner diameter, and left ventricular ejection fraction. Electrocardiogram and chest X-ray were also examined. Measurements of angiographic defect size and device were taken in the catheterization laboratory. Pediatric interventional cardiologists have conducted procedures in accordance with standard institutional guidelines. The operator decided to apply retrograde or antegrade deployment after the analysis of the defect anatomy, patient size, and ease of access. Anterograde route of device deployment is from the femoral vein to the inferior vena cava and then from the right ventricle via VSD into the left ventricle. The retrograde route involves the femoral artery into the aorta and then LV, and then via VSD into RV. All patients were subjected to the KONAR-MFO device, whose size was determined based on echocardiographic and angiographic measurements. The operator determined whether the device had to be recaptured or repositioned. The bias was minimized through the use of the identical imaging protocol, equipment, and application of standard clinical criteria. The factors that were considered as confounders in the data analysis were age, defect type, and delivery approach

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through stratified assessment. There was anonymity and confidentiality. Each participant or guardian had written informed consent before enrolling. Short-term outcomes were predefined before analysis. Procedural success was defined as successful deployment of the MFO device at the intended position with stable device configuration and no requirement for surgical conversion or device embolization. Residual shunt was assessed using transthoracic echocardiography with color Doppler and categorized as present or absent. Valvular regurgitation (aortic and tricuspid) and conduction disturbances were evaluated by post-procedural echocardiography and electrocardiography. Early adverse events included device embolization, significant valvular regurgitation, new-onset conduction abnormalities, vascular access complications, and in-hospital mortality. All patients underwent clinical assessment, electrocardiography, and transthoracic echocardiography immediately after the procedure, at hospital discharge, and at one-month follow-up. Length of hospital stay was recorded as part of the short-term outcome assessment. The statistical analysis was conducted with the help of Statistical Package of the Social Sciences version 26.0 (IBM Corp., Armonk, NY). The Shapiro-Wilk test, histograms, and Q-Q plots were used to determine the normality of continuous variables, including age, weight, VSD diameter, LVIDd, LVIDs, and LVEF. Age, weight, LVIDd, and LVIDs were normally distributed, and procedure time and Qp/Qs ratio were not. Variables that were normally distributed were summarized as the standard deviation and mean. Non-normal variables were summarized as median and interquartile range. Gender, VSD type, valvular regurgitation, and residual shunt were categorical variables that were represented as frequencies and percentages. An independent t-test was used to compare variables that are normally distributed in subgroups. Non-normal variables were tested using the Mann-Whitney U test. Categorical data were tested using the chi-square test. The normality tests were conducted before the application of parametric or non-parametric tests. The statistically significant p-value was considered to be less than 0.05. Stratification and the use of the right test regulated confounding factors. Prejudice was reduced by standardized data collection methods and operator uniformity over the course of the study.

RESULTS

Thirty patients underwent transcatheter VSD closure using the MFO device, including 20 via the retrograde and 10 via the antegrade approach. Procedural success was achieved in all cases. At discharge, residual shunt was detected in four patients (13.3%) and decreased to one patient (3.3%) at one-month follow-up. No device embolization or major conduction disturbances were observed. Rates of residual shunt, valvular regurgitation, and device recapture did not differ significantly between retrograde and antegrade approaches. The results revealed that the retrograde technique was more common, as it constituted two-thirds of the sample, but the antegrade technique constituted one-third. The age structure was also found to be balanced in both groups, and the gender distribution was almost equal, with no major deviation. Weight was also found to be comparable in groups, indicating that these two methods were used in a broad spectrum of patients and not based on weight. The normality test revealed that age, weight, LVIDd, and LVIDs adhered to normal distribution, whereas procedure time and ratio of Qp/Qs did not. This trend enabled the application of the independent t-tests on most of the continuously measured variables, and Mann-Whitney U tests on procedure time and Qp/Qs ratio. This distribution was confirmed by the Shapiro-Wilk statistics. These findings informed all further statistical decisions. The VSD diameter values remained within the anticipated clinical ranges of transcatheter closure. There were no significant results observed between retrograde and antegrade deployment of echocardiographic defects or angiographic defects. There was also no significant difference in the size of the device. These trends showed that the overall difference in anatomical suitability between groups was not significant. The distribution of VSD types, however, varied considerably and presented the tendency with the retrograde group having more high muscular defects and the antegrade group having more inlet muscular defects. This can be the operator's preference in terms of convenience. Pre-procedural tricuspid regurgitation rate was low, and little regurgitation was left after the closure. The number of residual shunt rates reduced significantly after a month, and the case was one. There was no statistically significant difference in residual shunt in groups before and after the procedure, and that was supported by a Fisher's exact test. Aortic regurgitation was rare, and even distribution between groups was similar. The procedure time was also slightly varied, and the antegrade group was slightly longer, but it did not reach significance. Fluoroscopy time was also in a similar pattern. Recapture events were a little more frequent in the antegrade group. Though this difference was not significant, it did indicate a slight procedural trend that was worth observing. The outcome of correlation analysis revealed a low association between VSD size and residual shunt and a moderate association between device size and procedure time. The latter positive correlation was statistically significant, and the bigger machines were more likely to take longer to deploy. The logistic regression determined that VSD >6 mm was a highly significant predictor of residual shunt. This is supported by the fact

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that the confidence interval did not intersect 1. The additional concept of age, weight, and approach was not found to meaningfully relate in the multivariate model. Categorical group comparisons of the variables did not mostly indicate significant variations except in the case of VSD type. This aided in the outline of the group-based differences and where none existed. These patterns were supported by the chi-square test and Fisher's exact test. Continuous variables comparison also indicated anticipated clinical ranges in transcatheter closure settings. The data indicated uniform reporting of the values of left ventricular dimensions and ejection fraction with no significant differences between the groups. The values were now in normal expectation ranges following closure success. The fact that a single residual shunt remained only after therapy also indicated the anticipated follow-up trend of decreasing the shunt. The findings also matched with some of the South Asian and LMIC reports that showed a high procedural success and a decreasing residual shunt after short-term follow-up. Magnitude and frequency of device performance metrics, such as recapture and valvular regurgitation, also mimicked the international trends. Continuous variables were analyzed in the retrograde (n = 20) and antegrade (n = 10) groups through the variables of age, weight, LVIDd, LVIDs, procedure time, Qp/Qs ratio, and angiographic VSD size. The independent t-tests were used to compare age, weight, LVIDd, and LVIDs, which were normally distributed, but the procedure time and the Qp/Qs ratio were not normally distributed, and the Mann-Whitney U test was used to compare them (Table 1).

Table 1: Comparison of Continuous Variables Between Retrograde (n = 20) and Antegrade (n = 10) Approaches

Continuous Variables	Shapiro–Wilk p-value	Retrograde (n=20) Mean ± SD / Median (IQR)	Antegrade (n=10) Mean ± SD / Median (IQR)	Test Statistic	p-value
Age (years)*	0.41	13.1 ± 7.6	11.0 ± 6.0	t = 0.82	0.42
Weight (kg)*	0.28	33.0 ± 16.2	30.1 ± 15.4	t = 0.32	0.75
LVIDd (mm)*	0.31	42.4 ± 6.1	41.9 ± 6.4	t = 0.22	0.82
LVIDs (mm)*	0.22	27.6 ± 5.4	26.9 ± 5.9	t = 0.36	0.72
Angio VSD Size (mm)*	0.33	5.0 ± 1.5	4.8 ± 1.4	t = 0.29	0.78
Procedure Time (Minutes)	0.01	32 (28–36)	35 (30–40)	U = 71.0	0.19
Qp/Qs Ratio	0.02	1.7 (1.6–1.8)	1.7 (1.6–1.8)	U = 96.5	0.84

*Independent t-test used for normally distributed variables. U = Mann–Whitney U test used for non-normal variables. Significance threshold: p<0.05. Data presented as Mean ± SD or Median (IQR)

The gender distribution, VSD type, pre- and post-procedure tricuspid regurgitation, residual shunt, device recapture, and aortic regurgitation were categorical variables in the retrograde and antegrade groups. The application of chi-square and Fisher's exact test was done, and the test statistics were provided. The majority of categorical variables did not exhibit significant differences between groups, and only VSD type displayed a statistically significant difference in the distribution between retrograde and antegrade approaches. However, low frequencies showed residual shunt, tricuspid regurgitation, and device recapture with non-significant p-values, which showed similar outcomes of the procedures between the two deployment strategies (Table 2).

Table 2: Categorical Characteristics Between Retrograde (n = 20) and Antegrade (n = 10) Approaches

Categorical Variables	Retrograde, n (%)	Antegrade, n (%)	Test Statistic	p-value
Gender (Male)	11 (55%)	5 (50%)	$\chi^2 = 0.07$	0.78
VSD Type	High muscular 12 (60%) / Perimembranous 8 (40%)	Inlet muscular 6 (60%) / Mid-muscular 4 (40%)	$\chi^2 = 8.72$	0.03
Pre-procedural TR	5 (25%)	2 (20%)	$\chi^2 = 0.11$	0.73
Post-procedural TR	1 (5%)	1 (10%)	Fisher p = 0.62	–
Residual Shunt (Discharge)	2 (10%)	2 (20%)	Fisher p = 1.00	–
Residual Shunt (1 Month)	0	1 (10%)	Fisher p = 0.27	–
Aortic Regurgitation	2 (10%)	1 (10%)	$\chi^2 = 0.22$	0.63
Device Recapture	0	2 (20%)	Fisher p = 0.12	–

*Chi-square or Fisher's exact test used for categorical variables. TR = Tricuspid regurgitation. Significance threshold: p<0.05.

The multivariate logistic regression analysis was carried out to determine predictors of residual shunt at discharge, such as VSD diameter, mode of deployment, size of the device, and pre-surgery tricuspid regurgitation. It presented odds ratios, and the 95% confidence intervals, and p-values. The data revealed that the residual shunt was only significantly related to the VSD size of more than 6 mm, but not the deployment mode, the device size, or the pre-procedural tricuspid regurgitation. The adjusted regression model gives a brief picture of what affects the short-term procedural results (Table 3).

Table 3: Multivariable Logistic Regression Predicting Residual Shunt at Discharge (n = 30)

Predictor Variables	Adjusted OR	95% CI	p-value
VSD Diameter >6 mm	4.28	1.07–17.13	0.04
Antegrade Approach	1.64	0.32–8.45	0.54
Device size >8 mm	1.22	0.29–5.08	0.78
Pre-procedural TR	1.31	0.24–7.18	0.74

OR = Odds Ratio. CI = Confidence Interval. Significance threshold: p<0.05

To assess the relationships between continuous variables and subgroups, comparisons were done using correlation analysis of VSD diameter, device size, procedure time, and left ventricular dimensions. Pearson or Spearman

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correlation coefficients using confidence intervals and suitable subgroup statistical tests were used. The outcomes revealed the existence of a weak, non-significant correlation between VSD diameter and residual shunt and a medium, statistically significant correlation between the size of the devices used and the time of procedure. Similar subgroup analyses indicated that there were no significant differences in approaches to left ventricular dimensions, and all the analyses were based on the normality test and appropriate correlation techniques (Table 4).

Table 4: Correlations and Subgroup Comparisons Between Key Variables(n=30)

Variable Pair	Test Used	Coefficient	95% CI	p-value
VSD diameter vs Residual Shunt	Pearson	r = 0.29	0.09 to 0.62	0.11
Device Size vs Procedure Time	Spearman	ρ = 0.41	0.06 to 0.68	0.03
LVIDd Across Groups	t-test*	t = 0.22	—	0.82
LVIDs Across Groups	t-test*	t = 0.36	—	0.72
Procedure Time Across Groups	Mann–Whitney U	U = 71.0	—	0.19

Spearman used for non-normal variables. Significance threshold: p<0.05.

DISCUSSION

The study demonstrated that transcatheter closure of ventricular septal defect (VSD) using the multifunctional occluder (MFO) via either retrograde or antegrade approach achieved comparable short-term outcomes. Procedural success was high in both groups. Age, weight, and baseline left ventricular dimensions did not differ significantly between groups. Residual shunt was uncommon at discharge and further declined by one-month follow-up. Aortic and tricuspid regurgitation remained rare. Larger VSD diameter (> 6 mm) was associated with a higher odds of residual shunt. Device size correlated moderately with procedure time, suggesting that larger devices required longer deployment. VSD type differed significantly between groups (p = 0.033), reflecting operator selection of deployment approach based on defect anatomy and access; therefore, comparisons between approaches should be interpreted cautiously due to potential selection bias. Procedure time, device recapture, and residual shunt rates did not differ significantly between retrograde and antegrade deployment; although recapture and procedure time were numerically higher in the antegrade group, these trends were not statistically significant, likely due to limited sample size. These findings align with previous regional and international studies. A small Pakistani study at a tertiary cardiac center reported safe transcatheter VSD closure with no immediate residual leak, no valve regurgitation, and no device embolization using occluder devices. A recent multicenter South Asian experience of percutaneous closure using modern occluders also described high success and low complication rates in children under 10 kg. In a 2023 international series using MFO, closure at one year was achieved in 95.7% of patients, with only transient heart-block events and no permanent conduction defects [12]. These results broadly mirror the present study, though frequencies of residual shunt and regurgitation here were slightly lower, possibly due to careful patient selection and strict inclusion criteria [13]. When compared with larger international registries, the present study outcomes appear favorable. In a global meta-analysis of percutaneous VSD closure (various devices), a success rate of 96.6% was found, with residual shunt in 25.5% of cases and permanent block in a minority [14]. The present study's lower residual shunt rate may reflect the newer MFO design and meticulous deployment. A European "hybrid" VSD closure study recently reported 93.2% success and low rates of regurgitation or conduction disturbance [15]. The present data seem consistent with the advancing trend toward safer, less invasive VSD closure [16]. Recent scientific literature in the world is in line with the belief that transcatheter VSD closure is emerging as an effective alternative to surgery, particularly in the case of a selected defect [17]. The positive outcomes may be attributed to biological and procedural aspects. The MFO device has a flexible, self-expanding waist of nitinol and a dual disc structure that adjusts to different VSD anatomies, causing less strain on the surrounding structures [18]. This design can decrease the load on conduction tissue and through the valvular apparatus, which reduces the possibility of heart block or valve damage. The average relationship between the device size and the procedure time may lead to the belief that bigger defects should have a higher level of care, yet meticulously arranged deployment can potentially prevent complications [19]. The observed fact that VSD > 6 mm was a predictor of residual shunt is pathophysiological feasible: larger defects could have uneven edges or more than one exit point, making it harder to close them up [20]. The advantages of the research are that it is prospective, the occluder used is modern (MFO), and thorough follow-up with echocardiography and angiography. The entire process was done at one center under the supervision of experienced operators, which had a high level of consistency in method and imaging [21, 22].

This research has a number of limitations, such as a single-center design, a rather limited sample size, and a short follow-up period, which limit the extrapolation of the results and the evaluation of late complications like conduction abnormalities or valve dysfunction. Non-

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randomized deployment approach assignment creates possible selection bias since the approach was selected because of defect anatomy and convenience to the operator. To confirm these findings and determine the long-term performance of the devices, changes during growth, and infrequent adverse effects, larger multicenter studies that have long follow-up will be required. The further study should also investigate standardized parameters in the selection of the antegrade and retrograde methods and evaluate the results in earlier and lighter-weight children as well.

CONCLUSIONS

Transcatheter closure of ventricular septal defect using the KONAR-Multi Functional Occluder demonstrated high procedural success and low rates of early complications in this single-center Pakistani cohort. Residual shunt was uncommon and was primarily associated with a larger defect size. These findings suggest that MFO-based transcatheter VSD closure is a feasible short-term treatment option in carefully selected patients at tertiary-care centers in similar resource-limited settings. Larger, multicenter studies with longer follow-up are required to confirm durability and broader applicability.

Authors' Contribution

Conceptualization: MAA
Methodology: TA, YA, FQ
Formal analysis: YA, AUR
Writing and Drafting: MAA, HA
Review and Editing: MAA, TA, HA, YA, FQ, AUR

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Diagnostic Accuracy of Xpert Mycobacterium Tuberculosis/Rifampicin in Detecting Pulmonary Tuberculosis from Bronchoalveolar Lavage Fluid in Sputum-Negative Patients

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ABSTRACT

Pulmonary Tuberculosis (TB) is also a substantial health issue in high-burden countries like Pakistan. Diagnostic methods such as sputum smear microscopy and culture have limitations in smear-negative cases, necessitating the use of alternative methods. The Xpert MTB/RIF assay is a fast molecular diagnostic option, but its accuracy on bronchoalveolar lavage fluid (BALF) in sputum-negative patients is not well established. **Objectives:** To determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the Xpert MTB/RIF assay on BALF, using culture as the gold standard. **Methods:** This prospective diagnostic validation study was conducted at Lady Reading Hospital, Peshawar, from May 2025 to September 2025, including 679 adult patients with smear-negative pulmonary TB suspicion undergoing bronchoscopy. BALF samples were tested using smear microscopy, culture (gold standard), and the Xpert MTB/RIF assay. Data were analyzed using SPSS version 25.0. **Results:** Most of the patients were male 389 (57.3%). The mean age was 41.3 ± 14.2 years. Among 171 culture-positive cases, 145 were also positive by Xpert. Among 508 culture-negative cases, 490 tested negatives with Xpert. Xpert test showed 84.8% sensitivity, 96.5% specificity, 88.9% PPV, 94.9% NPV, and 93.3% diagnostic accuracy. Stratified analysis showed comparable diagnostic metrics across gender and age groups. The AUC of the ROC curve is 0.91, which indicates that Xpert performed excellently in diagnosing TB. **Conclusions:** Xpert MTB/RIF on BALF provides high diagnostic accuracy for detecting pulmonary TB in sputum-negative patients, with excellent sensitivity, specificity, and predictive values.

INTRODUCTION

Pulmonary tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB), generally affects the lungs and can affect other parts of the respiratory system. According to the WHO, it remains a huge worldwide health concern, accounting for approximately 9.96 million new cases [1]. Globally, the burden by region, demographic characteristics, and underlying health conditions affects almost 25% of the population; more than 8 million people develop active TB each year [2]. About 45% of TB cases globally come from the Asia-Pacific region, with India and Indonesia being among the countries that report the highest burden. The majority of adult men are affected, especially those above 40 years of age, more than women [3]. TB is endemic in Pakistan with an estimated 525,000 new cases annually. According to WHO, Pakistan has the fifth largest TB burden in the world, and fourth among the developing countries in terms of drug-resistant TB [4]. According to a recent study of 2020 - 2023, the prevalence of TB was 25.42% among patients of respiratory symptoms, with annual rates of 23.7%, 24.8%, 28.1%, and

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25.1%, respectively [5]. Effective TB control is very important, and early and correct diagnosis is essential. Although 84% of TB cases involve the lungs, bacteriological confirmation is achieved in only 57% of global pulmonary TB (PTB) cases and about 52% in Pakistan [6]. Diagnostic methods such as smear microscopy and culture have some limitations. Smear microscopy is very rapid and specific (93.94%) but not sensitive (81.8%) in smear-negative and/or paucibacillary disease, especially in tropical settings [7]. Culture, being the gold standard of diagnostic tests, is more sensitive but takes longer and is not so widely available, often needing between 2 and 6 weeks for turnaround times for result interpretation [8]. The Xpert MTB/RIF test, approved by WHO in 2010, is a quick molecular test that can detect TB and rifampicin-resistance in two hours [9, 10]. Although very effective, its diagnostic sensitivity in smear-negative patients, for example, is not very high, at 67% in a study [11].

For patients who are unable to produce sputum or have smear-negative results, bronchoscopy provides access to lower respiratory tract secretions through BALF. This study aimed to evaluate its diagnostic accuracy in sputum-negative suspected pulmonary TB cases to help bridge a key diagnostic gap and enhance patient outcomes by giving the limited evidence on Xpert MTB/RIF performance using BALF.

METHODS

This prospective diagnostic validation study was undertaken at the Department of Pulmonology, Lady Reading Hospital, Peshawar, from May 2025 to September 2025. A total of 679 patients were recruited through consecutive sampling technique, calculated based on previously reported sensitivity and specificity of smear microscopy for pulmonary TB (81.8% and 93.94%, respectively) [5, 7], a national prevalence of 25.42% [5], a confidence level of 95%, and a desired precision of 0.06 using the WHO sample size calculator. The patient was enrolled consecutively in the study based on predefined inclusion and exclusion criteria. This approach was used to reduce selection bias and reflect routine clinical practice. The inclusion criteria were patients of either gender, age ≥18 years, with two consecutive sputum smear results negative for acid-fast bacilli and a clinical suspicion of pulmonary TB, and who were scheduled to undergo bronchoscopy for diagnostic purposes. Patients were excluded if they had a history of TB treatment, were known cases of extrapulmonary TB, or had contraindications to bronchoscopy. After obtaining ethical approval from the IRB committee under Ref No: 527/LRH/MTI, eligible patients were enrolled after informed consent, with assurance of confidentiality and the right to withdraw at any stage. Baseline information like age, gender, height, weight, BMI, education, occupation, socioeconomic status, urban or rural residence, history of TB, comorbidities, presenting symptoms, and body temperature were documented. Radiological assessment with chest X-ray or CT scan was done for each patient. Initial diagnostic evaluation included two sputum smear tests for AFB; those testing negative proceeded to bronchoscopy. BALF was collected under sterile conditions and tested using the Xpert MTB/RIF assay to spot MTB DNA and rifampicin resistance. The same samples were analyzed using AFB smear microscopy and MGIT liquid culture (Becton Dickinson) as the reference/gold standard. Culture results indicating contamination, growth of samples that were unclear, or a lack of viability were censored from the analysis. BALF samples were processed immediately following sample collection. Processing of samples involved digestion-decontamination using the N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH) method followed by centrifugation at 3000 × g for 15 minutes. This resulted in the use of the pellet for smear microscopy analysis, Xpert MTB/RIF analysis, or MGIT culture. Alternatively, if processing in the reference lab was not done immediately, the samples were stored at 2-8°C for a period of a maximum of 24 hours to prevent a decrease in viability and the development of contamination. The trained personnel performed all the laboratory tests using standardized protocols. Xpert MTB/RIF diagnostic performance data were checked against findings of a culture, and rifampicin resistance was reported for clinical management. Data were analysed through SPSS version 25.0. Categorical data were expressed as frequencies and percentages, while continuous variables were summarized as mean ± SD and median (IQR). Diagnostic accuracy measures were derived from a 2×2 contingency table. Subgroup comparisons for diagnostic accuracy across gender and age categories were evaluated using Pearson's Chi-square test. P-values were not adjusted for multiple comparisons, given the limited number of pre-specified, independent subgroup analyses (n=2). Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance of XPERT MTB/RIF using culture as the reference standard. As XPERT MTB/RIF provides a dichotomous result (positive/negative), the ROC plot represents a single operating point. The area under the curve (AUC) was estimated to quantify overall diagnostic discrimination.

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RESULTS

A total of 679 adult patients were included, having a mean age of 41.3 ± 14.2 years, body temperature was 37.8 ± 0.9°C, and BMI was 24.5 ± 4.1 kg/m^2 (Table 1).

Table 1: Summary Statistics of Continuous Variables (Adults, n=679)

Variables	Mean ± SD
Age (Years)	41.3 ± 14.2
Body Temperature (°C)	37.8 ± 0.9
Height (cm)	166.5 ± 9.2
Weight (kg)	67.8 ± 13.4
Body Mass Index (BMI)	24.5 ± 4.1

The majority of the study participants were male 389 (57.3%) and were urban residents 410 (60.4%). Regarding socioeconomic status, most participants belonged to the middle socioeconomic group, 317 (46.7%), followed by the low group, 278 (40.9%), and a smaller proportion in the high group, 84 (12.4%). Clinically, 592 (87.2%) individuals were symptomatic, whereas 87 (12.8%) were asymptomatic at presentation. A history of tuberculosis was present in 139 (20.5%) participants. Additionally, 176 (25.9%) had comorbid conditions. Radiological evaluation showed positive findings in 428 (63.0%) participants, while 251 (37.0%) had negative radiological results (Table 2).

Table 2: Baseline Characteristics (n=679)

Variables	Categories	(n) %
Gender	Male	389 (57.3%)
	Female	290 (42.7%)
Residency	Urban	410 (60.4%)
	Rural	269 (39.6%)
Socioeconomic Status	Low	278 (40.9%)
	Middle	317 (46.7%)
	High	84 (12.4%)
Presenting Status	Symptomatic	592 (87.2%)
	Asymptomatic	87 (12.8%)
History of TB	–	139 (20.5%)
Comorbid Conditions	–	176 (25.9%)
Radiological Findings	Positive	428 (63.0%)
	Negative	251 (37.0%)

Out of 171 patients who were positive according to the culture, 145 also tested positive with Xpert (True Positives), while 26 were missed by the test (False Negatives). Among 508 culture-negative patients, 490 were correctly identified as negative by Xpert (True Negatives), and 18 were incorrectly identified as positive (False Positives). An exploratory analysis was conducted to identify possible clinical and radiological factors contributing to discordant Xpert MTB/RIF results. Among the 18 false-positive cases, a substantial proportion had radiological abnormalities suggestive of prior pulmonary tuberculosis and/or a documented history of previous TB treatment, raising the possibility of detection of residual mycobacterial DNA rather than active disease. Among the 26 false-negative cases, most patients had minimal radiological involvement and were clinically less severe at presentation. These cases were also presumed to have a low mycobacterial burden, which is a known limitation affecting Xpert sensitivity. No technical errors were identified during testing (Table 3).

Table 3: Diagnostic Performance of XPERT MTB/RIF Compared to Culture (n=679)

Culture (Gold Standard)	Xpert Positive (Test +)	Xpert Negative (Test -)	Total
Positive (TB Present)	145	26	171
Negative (TB Absent)	18	490	508
Total	163	516	679

The diagnostic performance of the Xpert MTB/RIF test was evaluated against the culture gold standard. The test demonstrated a sensitivity of 84.8% (95% CI: 79.4–90.2%) and a specificity of 96.5% (95% CI: 94.8–98.1%). The PPV and NPV were 88.9% (95% CI: 84.1–93.7%) and 94.9% (95% CI: 93.0–96.8%), respectively. The overall diagnostic accuracy was 93.5% (95% CI: 91.7–95.4%) (Table 4).

Table 4: Diagnostic Performance Metrics of XPERT MTB/RIF

Metric	Calculation	Value (%)	95% CI
Sensitivity	145 / (145 + 26) × 100	84.8	79.4% – 90.2%
Specificity	490 / (18 + 490) × 100	96.5	94.8% – 98.1%
PPV	145 / (145 + 18) × 100	88.9	84.1% – 93.7%
NPV	490 / (26 + 490) × 100	94.9	93.0% – 96.8%
Diagnostic Accuracy	(145 + 490) / 679 × 100	93.3	91.7% – 95.4%

Diagnostic accuracy was high across both gender and age groups, with no statistically significant differences. Males and females showed comparable sensitivity, specificity, and overall accuracy (p=0.521). Similarly, participants aged ≥40 years had slightly higher accuracy than those <40 years, but the difference was not significant (p=0.376). Overall, the test performed consistently across all subgroups (Table 5).

Table 5: Diagnostic Accuracy Stratified by Gender

Variables		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value
Gender	Male	85.7	95.8	89.5	93.5	92.8	0.521
	Female	83.3	97.4	88.1	96.3	93.9	
Age	<40 Years	82.1	95.6	86.7	92.4	91.2	0.376
	≥40 Years	86.5	97.3	91.1	95.7	94.1	

Note: Chi-square was used to calculate the p-value. The p-value<0.05 was statistically significant

The ROC analysis suggests that XPERT MTB/RIF has good discriminatory ability for the detection of tuberculosis when compared with culture. The estimated area under the curve (AUC) was 0.91, indicating a high true-positive rate

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with a relatively low false-positive rate in this study population. These findings are consistent with the observed sensitivity (84.8%) and specificity (96.5%) of the test (Figure 1).

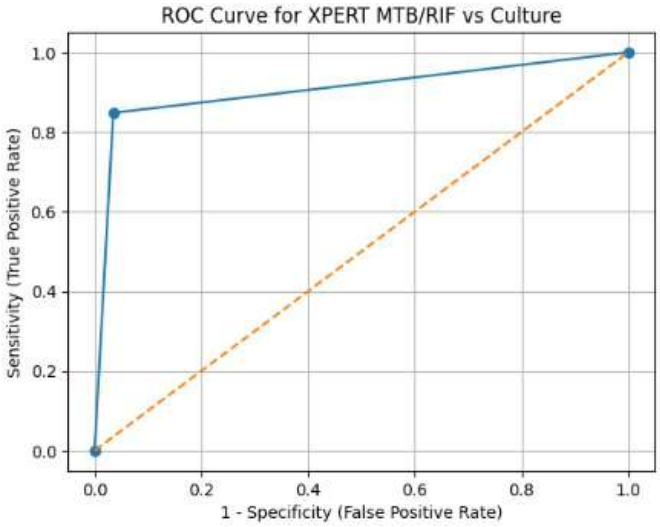

Figure 1: ROC Curve Analysis for Xpert MTB/RIF Versus Culture

DISCUSSION

In the current study, the diagnostic efficacy of Xpert MTB/RIF on BALF samples was compared using culture results as a reference. The results showed a higher sensitivity at 84.8%, specificity of 96.5%, PPV at 88.9%, NPV at 94.9%, and overall diagnostic accuracy of 93.3%. In a study carried out by Rahmati *et al.* in a Pakistani setting with a similar diagnostic objective using Xpert MTB/RIF on patients with smear-negative pulmonary TB, there was a comparable level of sensitivity at 84.5% with a higher specificity at 100% [9]. In a related study carried out on patients with a negligible sputum sample using BALF samples in a Pakistani setting, there was a comparable level of sensitivity at 85.3% with a higher specificity at 94.1% to underscore the diagnostic utility of Xpert [10]. A meta-analysis carried out by Mondoni *et al.* on the diagnostic accuracy of Xpert MTB/RIF on BAL samples revealed a pooled sensitivity and specificity of 87% and 92%, respectively, which closely resembled our values [11]. Xpert was found to have a sensitivity and specificity of 87.2% and 97.7%, respectively, with respect to BAL fluid in patients suspected of having pulmonary TB in a study carried out in China [12-14]. In a similar study carried out in India in patients with sputum scarce and smear-negative samples, Xpert was found to be 81.3% and 73.3% sensitive and specific, respectively, with culture as the reference standard [13]. A retrospective analysis carried out in Colombia revealed a high Xpert sensitivity of 91.7% and specificity of 90.1% using BAL samples [15, 16]. This small variation in both sensitivity and specificity can be explained by differences in sample size, TB prevalence, subjects included in the studies, and processing of the samples. However, the high specificity and NPV in all studies affirm Xpert MTB/RIF's powerful rule-out test and its utility in a high burden of TB countries [17]. Sensitivity of 100% and specificity of 98.81% has been reported in earlier studies, outperforming traditional tests like Ziehl-Neelsen stain [18]. Also, in the current study, the high PPV of 88.9% further confirms the reliability of the test's negative results for not initiating any treatment, as evidenced by studies showing that high PPV aids in early initiation of treatment and successful control of TB infection [19]. Early diagnostic accuracy of tests translates into reduced transmission and improved outcomes, as evidenced by international statistics highlighting the importance of rapid diagnosis and subsequent treatment [20].

One of the key strengths of the current study is its large sample size and the use of BAL samples, which improves diagnostic accuracy in sputum-negative patients. In addition, assessing multiple diagnostic performance measures with culture as the gold standard adds to the reliability of the findings. Although Xpert MTB/RIF performed well in this cohort, its performance may vary across different settings, highlighting the need for ongoing evaluation and, in some cases, the use of complementary diagnostic tools for effective TB control.

CONCLUSIONS

This study's results confirm that Xpert MTB/RIF has high levels of accuracy regarding pulmonary TB in smear-negative patients when using BAL fluid samples. This level of performance is in line with both country and global studies, underpinning its importance as an initial testing methodology within resource-limited and endemic areas.

Authors' Contribution

Conceptualization: AS
Methodology: ZH, MAK
Formal analysis: MKS
Writing and Drafting: AS, ZI, FU
Review and Editing: AS, ZI, ZH, FU, MKS, MAK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Normal Pediatric Kidney Dimensions on Multidetector CT: Defining Standards for Pakistani Children

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ABSTRACT

Kidney size in children is a key marker for detecting congenital abnormalities and conditions that may develop later. In South Asia, CT-based normative data are limited. **Objectives:** To establish CT-derived reference ranges for renal size in Pakistani children and examine their relationship with somatic measurements. **Methods:** This retrospective study examined 15 years of data (2010–2024) from Aga Khan University Hospital, Karachi, focusing on CT scans conducted with GE 128-slice or Toshiba 640-slice scanners. The study included children aged one week to 16–17 years, categorized by age, and utilized both descriptive and inferential statistics. **Results:** Kidney size in children is a key marker for detecting congenital abnormalities and conditions that may develop later in life. The right kidney volume rises from about 19 cm^3 in infants to 146 cm^3 in late adolescence, while the left kidney grows from approximately 21 cm^3 to 146 cm^3. There is a strong correlation between renal size and factors like age, height, weight, and body surface area ($p<0.001$). No significant differences were observed between sexes, and multiple regression analysis confirmed these associations with significant models for both kidneys. **Conclusions:** This study provides the first CT-based reference ranges for renal dimensions in Pakistani children. Renal volume rises consistently with age and strongly correlates with somatic factors, offering valuable benchmarks for clinical assessment.

INTRODUCTION

The understanding of the size of abdominal organs is clinically and diagnostically significant, as changes often indicate underlying pathology. Any deviation in organ dimensions signals the manifestation or progression of disease [1]. The size of organs may be impacted by external factors such as environmental variations, diet, water intake, and high-altitude levels [2]. Childhood is vital period for assessing growth, making renal volumetry critical for diagnosing kidney disease early [1]. Initial normative kidney size data were published 60 years ago, indicating a correlation between anthropometric characteristics and kidney dimensions in children [3]. It is reported that the left kidney tends to be longer and heavier than the right, and renal weight is generally greater in male than in female [4]. Measuring kidney dimensions is crucial for diagnosing renal conditions like acute kidney disease, marked by increased kidney length, and renal hypoplasia [5]. Prompt measurement of kidney volume relative to body surface area (BSA) aids in the early detection and monitoring of chronic kidney disease [6]. Common imaging modalities for assessing renal conditions include CT scan, MRI, and ultrasonography [7]. CT scan and MRI are superior to

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ultrasonography for evaluating kidney volumes and dimensions [6]. CT scan is favored for its quick acquisition time, while MRI offers better tissue contrast but comes at a higher cost and demands careful technical management [8].

Accurate renal size estimation is vital for diagnosing and monitoring pediatric renal disorders. In Pakistan, there are no CT-based standard data for children, leading clinicians to rely on reference standards from other populations or ultrasound-based nomograms. These do not consider local variations, potentially resulting in diagnostic errors. Development of population-specific CT reference values is necessary, as renal dimensions are affected by somatic variables. This study aims to establish CT-derived reference ranges for renal volumetry and to assess how age, height, and weight influence these measurements, to enhance clinical decision making in pediatric nephrology, and to provide a foundation for future regional studies.

METHODS

A retrospective cross-sectional study was conducted in the Department of Radiology at Aga Khan University Hospital, Karachi, Pakistan, involving reviewing pediatric CT scans from January 2010 to December 2024 via the hospital's PACS to identify cases where the kidney was visualized. This study was conducted from March 2025 to April 2025. Approximately 7000 pediatric CT scans were screened, selecting children aged 0-18 who met specific criteria. Demographic data such as age, sex, height, and weight were extracted from medical records, ensuring height and weight were recorded within one month of the scan. Participants were divided into age groups from 0-1 week to 16-17 years for targeted comparisons. No formal sample size calculation was performed; all eligible CT scans meeting the selection criteria (totaling 935 patients) were included to maximize data quality and representativeness. Children included in the study underwent contrast or non-contrast CT imaging for reasons not related to renal or urinary pathology, with only high-quality scans showing normal kidney morphology being included. The exclusion criteria consisted of various renal and systemic conditions affecting kidney size and function, as well as incomplete data. Kidney dimensions were measured from CT images using calipers, with length assessed between poles and diameters noted at the hilum. Renal volume was calculated with the formula: Length × Width × Transverse Diameter × 0.52. Illustration of kidney measurement techniques is shown, with the upper axial section depicting transverse and anteroposterior (AP) dimensions at the renal hilum, while the lower images show the maximum pole-to-pole length of the left kidney and the right kidney measured on sagittal section due to its shorter appearance on the coronal view (Figure 1).

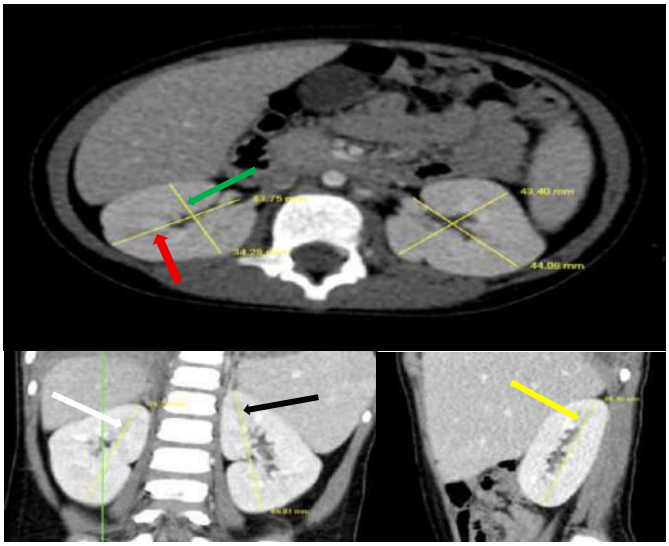

Figure 1: Kidney Measurement Techniques Showing Transverse, Anteroposterior, and Pole-To-Pole Dimensions on Axial and Sagittal Views

Scans utilized Toshiba Aquilion 640-slice and GE Revolution 128-slice CT systems, adhering to standard abdominal protocols and the ALARA principle to minimize radiation while ensuring image quality. Measurements were evaluated on the PACS viewer with consistent settings for accuracy. The study protocol was 2025-10558-34325. Data analysis was performed using SPSS version 25.0, including normality checks via the Shapiro-Wilk test. Descriptive statistics outlined kidney size and volume, while categorical variables like gender and age group were expressed as frequencies and percentages. A simple percentile calculation was done. Independent sample t-tests or one-way ANOVA were used to assess differences in kidney size. Pearson correlation analyzed associations between continuous variables (age and BSA), and linear regression identified predictors of kidney size, setting statistical significance at $p<0.001$.

RESULTS

The mean age of the study population was 6.97 years (standard deviation ± 4.79). Male predominance was noted at 546 (58.34%). The sample's mean weight, height, BMI, and BSA were found to be 23.32 kg, 112.82 cm, 15.98 kg/m^2, and 0.83, respectively. Kidney dimensions increased significantly with age ($p<0.001$), with the cranio-caudal diameter ranging from 46.23 mm in infants to 110.60 mm in teenagers. Other diameters also showed growth, but no significant gender differences in kidney dimensions were observed (Table 1).

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Table 1: Dimensions of the Right Kidney by Age and Gender

Variables	Right Kidney Cranio-Caudal (mm)	Percentile		Right Kidney Transverse (mm)	Percentile		Right Kidney Anteroposterior (mm)	Percentile	
	Mean ± SD	5	95	Mean ± SD	5	95	Mean ± SD	5	95
0–1 Week (n=14)	46.23 ± 13.92	34.60	83.80	26.18 ± 7.44	19.00	48.40	24.35 ± 7.56	17.00	47.70
1 Week–4 Months (n=53)	47.31 ± 6.31	36.10	58.50	26.50 ± 4.82	18.80	34.00	23.84 ± 3.76	17.40	30.00
4–8 Months (n=30)	54.55 ± 8.53	41.10	67.00	27.40 ± 4.19	20.50	33.40	26.92 ± 4.33	20.50	33.00
8–12 Months (n=55)	59.11 ± 7.53	47.90	71.00	31.50 ± 5.18	24.00	40.20	27.74 ± 3.63	21.00	34.00
1–2 Years (n=82)	65.83 ± 7.30	53.50	76.80	33.60 ± 7.52	25.00	42.20	30.53 ± 4.41	25.00	38.00
2–3 Years (n=58)	72.72 ± 7.03	61.00	83.40	36.68 ± 5.43	28.50	45.50	33.40 ± 4.29	27.50	41.00
3–4 Years (n=46)	75.86 ± 8.01	63.00	89.70	38.01 ± 4.07	31.10	42.30	34.17 ± 4.42	27.70	41.00
4–5 Years (n=49)	76.04 ± 10.62	59.00	91.00	37.94 ± 6.50	26.00	47.20	35.30 ± 6.22	23.00	45.10
5–6 Years (n=59)	80.84 ± 9.13	65.30	95.00	39.91 ± 6.71	29.00	50.80	37.71 ± 4.98	29.20	47.90
6–7 Years (n=62)	83.68 ± 11.64	68.00	107.00	41.45 ± 6.75	32.00	54.90	38.42 ± 6.08	30.20	51.30
7–8 Years (n=49)	85.27 ± 9.44	70.00	102.00	41.66 ± 6.40	33.30	51.90	39.00 ± 5.71	30.70	49.00
8–9 Years (n=49)	89.52 ± 10.60	75.40	108.00	44.08 ± 7.26	35.00	58.80	41.13 ± 6.61	32.30	54.00
9–10 Years (n=50)	88.67 ± 7.35	75.20	100.00	44.54 ± 5.92	36.00	54.20	41.01 ± 5.48	32.10	49.00
10–11 Years (n=60)	93.59 ± 8.45	82.50	110.00	45.77 ± 5.93	36.35	55.80	41.25 ± 4.92	34.02	49.80
11–12 Years (n=49)	93.20 ± 8.93	82.00	106.00	47.34 ± 5.73	38.00	57.00	39.98 ± 5.98	32.00	53.60
12–13 Years (n=67)	99.09 ± 10.30	81.00	113.00	49.27 ± 7.20	38.00	60.40	44.01 ± 6.50	35.40	55.00
13–14 Years (n=77)	101.58 ± 9.75	87.00	120.00	51.20 ± 6.32	39.90	61.40	46.14 ± 6.56	35.90	57.40
14–15 Years (n=19)	102.15 ± 8.33	88.00	115.00	47.22 ± 5.23	37.80	55.40	47.29 ± 5.05	41.00	58.00
15–16 Years (n=05)	110.60 ± 7.64	105.00	123.00	52.30 ± 4.71	47.00	59.40	48.82 ± 5.80	40.00	56.00
16–17 Years (n=02)	94.50 ± 2.12	93.00	96.00	43.50 ± 9.19	37.00	50.00	43.50 ± 9.19	37.00	50.00
Male	80.24 ± 18.33	47.50	109.00	40.01 ± 9.19	25.00	56.30	36.84 ± 8.53	23.00	51.50
Female	80.52 ± 18.50	46.30	108.00	40.81 ± 9.96	24.40	56.10	36.72 ± 8.26	23.60	50.00

The average left kidney diameters increase significantly with age, from 26.77 mm in neonates to 52.76 mm in late childhood/adolescence (15-16 years), with all measured diameters showing growth ($p<0.001$). No significant gender differences were observed in these measurements (Table 2).

Table 2: Dimensions of the Left Kidney by Age and Gender

Age group / Gender	Left Kidney Cranio-Caudal (mm)	Percentile		Left Kidney Transverse (mm)	Percentile		Left Kidney Anteroposterior (mm)	Percentile	
	Mean ± SD	5	95	Mean ± SD	5	95	Mean ± SD	5	95
0–1 Week	47.74 ± 17.68	36.00	94.50	26.77 ± 9.20	18.00	55.00	23.81 ± 6.02	17.80	40.00
1 Week–4 Months	47.82 ± 6.96	37.40	61.90	25.28 ± 4.44	18.00	32.00	24.91 ± 3.58	19.90	32.00
4–8 Months	53.98 ± 7.42	43.90	65.40	28.79 ± 4.32	21.70	36.00	27.02 ± 5.10	20.00	34.00
8–12 Months	60.27 ± 7.23	51.00	73.60	29.95 ± 4.86	23.00	39.20	28.60 ± 3.99	22.30	35.50
1–2 Years	67.14 ± 7.92	55.00	81.00	33.02 ± 4.76	25.00	40.20	31.13 ± 3.93	25.00	40.00
2–3 Years	73.69 ± 8.13	62.00	89.00	36.67 ± 5.48	28.00	47.80	33.88 ± 4.45	27.70	41.20
3–4 Years	78.15 ± 8.50	64.70	95.70	37.42 ± 4.66	30.00	46.70	35.35 ± 3.59	30.30	40.70
4–5 Years	78.09 ± 11.08	59.00	94.60	38.06 ± 5.74	32.00	48.30	34.73 ± 5.79	26.00	43.60
5–6 Years	81.74 ± 11.30	63.80	101.00	40.38 ± 6.38	30.00	51.80	37.63 ± 4.87	28.50	45.30
6–7 Years	85.08 ± 11.33	71.30	105.00	41.77 ± 6.14	33.00	52.20	39.38 ± 4.82	33.00	47.90
7–8 Years	84.69 ± 11.02	67.80	101.00	42.51 ± 6.82	30.20	53.00	39.39 ± 4.48	31.80	48.40
8–9 Years	89.70 ± 11.13	73.00	112.00	43.48 ± 8.07	32.10	59.00	41.37 ± 6.75	32.30	55.00
9–10 Years	90.08 ± 8.42	77.00	108.00	44.38 ± 5.86	36.00	55.10	42.22 ± 5.25	33.40	50.30
10–11 Years	94.55 ± 9.01	79.20	110.00	44.99 ± 5.94	36.80	55.75	42.47 ± 5.24	34.00	52.45
11–12 Years	94.40 ± 10.12	83.20	114.00	46.02 ± 6.25	37.00	57.00	43.33 ± 4.52	37.20	51.30
12–13 Years	100.89 ± 10.72	82.00	116.00	49.03 ± 6.39	38.00	59.00	44.22 ± 5.39	36.60	53.00
13–14 Years	101.76 ± 9.16	87.00	117.00	49.82 ± 6.80	38.00	61.70	46.26 ± 5.21	38.00	56.00
14–15 Years	104.02 ± 10.43	85.00	120.00	46.69 ± 5.30	40.00	58.00	47.08 ± 3.80	37.60	53.70
15–16 Years	106.76 ± 9.24	99.80	122.00	52.76 ± 5.64	47.00	61.80	49.54 ± 7.35	42.50	58.00
16–17 Years	92.00 ± 2.83	90.00	94.00	41.00 ± 1.41	40.00	42.00	45.50 ± 6.36	41.00	50.00

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Male	81.01 ± 18.85	49.00	109.00	39.80 ± 9.26	24.00	55.00	37.48 ± 8.05	24.00	50.50
Female	81.82 ± 18.51	46.00	110.00	40.16 ± 9.38	24.50	55.50	37.43 ± 8.25	23.30	50.40

As age increases, kidney volume grows, with the left kidney ranging from 20.74 ± 27.22 cm^3 to 145.58 ± 32.55 cm^3 and the right kidney from 19.26 ± 24.33 cm^3 in infants to 146.32 ± 20.81 cm^3 in teenagers. No significant sex differences were noted (left: p=0.741; right: p=0.684), but kidney volumes varied significantly across age groups (p<0.001) (Table 3).

Table 3: Measurements of Kidney Volume by Gender and Age

Age group / Gender	Right Kidney Volume (mL)	Percentile		Left Kidney Volume (mL)	Percentile	
	Mean ± SD	5	95	Mean ± SD	P-5	P-95
0–1 Week	19.26 ± 24.33	6.68	100.60	20.74 ± 27.22	6.74	108.11
1 Week–4 Months	16.18 ± 6.76	7.78	30.92	16.35 ± 7.19	8.44	26.09
4–8 Months	21.83 ± 8.38	10.30	34.87	22.72 ± 8.55	10.06	35.94
8–12 Months	27.33 ± 8.40	16.36	43.03	27.66 ± 9.69	13.60	48.78
1–2 Years	35.73 ± 12.23	21.73	56.86	36.71 ± 11.68	21.16	59.31
2–3 Years	46.99 ± 13.25	29.33	73.32	48.53 ± 14.95	29.18	84.90
3–4 Years	51.74 ± 12.97	35.76	70.84	54.49 ± 14.42	34.72	86.88
4–5 Years	55.05 ± 20.81	15.86	101.34	56.03 ± 21.82	23.84	89.73
5–6 Years	65.07 ± 22.43	31.05	97.22	66.54 ± 23.29	30.95	115.11
6–7 Years	71.56 ± 27.81	43.71	138.88	75.13 ± 27.43	46.33	125.04
7–8 Years	73.54 ± 23.46	40.23	121.06	76.02 ± 25.55	38.03	119.34
8–9 Years	87.41 ± 35.42	48.54	168.31	87.77 ± 38.13	48.71	172.46
9–10 Years	85.15 ± 22.37	53.85	136.42	88.58 ± 22.73	60.96	137.14
10–11 Years	92.57 ± 21.52	58.14	130.92	95.37 ± 25.45	57.45	144.30
11–12 Years	92.52 ± 23.37	61.05	128.36	98.82 ± 24.70	66.98	145.63
12–13 Years	113.09 ± 33.10	70.96	155.01	115.70 ± 33.35	67.88	171.43
13–14 Years	126.15 ± 33.01	76.64	186.74	123.25 ± 30.28	76.66	177.35
14–15 Years	118.42 ± 19.21	86.49	159.34	119.62 ± 24.73	82.10	175.83
15–16 Years	146.32 ± 20.81	130.97	182.67	145.58 ± 32.55	114.96	195.27
16–17 Years	90.91 ± 2.04	89.47	92.35	89.22 ± 12.81	80.16	98.28
Male	68.96 ± 40.64	14.74	145.63	70.67 ± 41.43	15.25	145.49
Female	70.04 ± 39.44	14.26	142.13	71.56 ± 39.51	15.20	138.58

Significant positive correlations (p<0.001) were observed between kidney volumes and all somatic variables. Age, weight, height, and BSA all showed strong associations with kidney volume, with correlation coefficients ranging from r = 0.82 for the right kidney to r=0.81 for the left kidney. Both right (r=0.383) and left (r=0.381) kidney volumes demonstrated a moderate relationship with BMI (Figure 2).

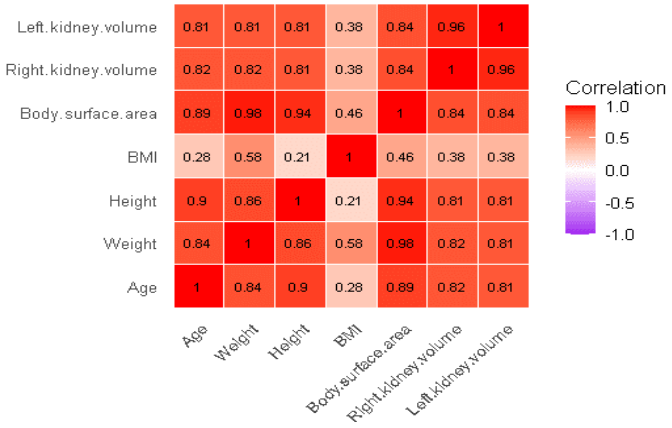

Figure 2: Kidney Volumes and Anthropometric Characteristics are Correlated

Kidney volumes and BSA showed a substantial positive association, according to separate analyses for males and females. There was a similar linear relationship between renal volume and BSA in both genders, with a substantial relation (e.g., r=0.825, p<0.001) (Figure 3).

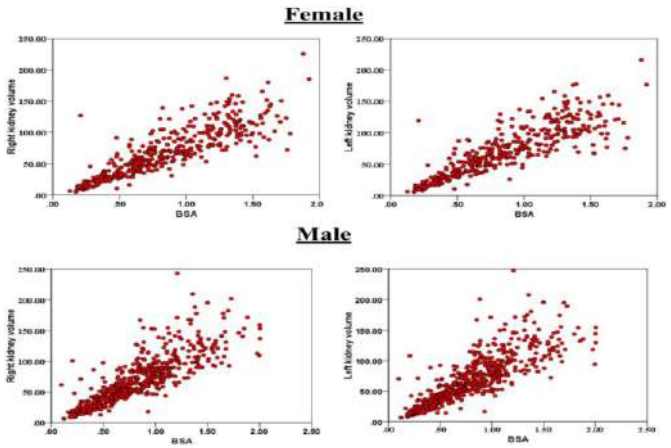

Figure 3: Gender Specific Relationship Between Kidney Volumes and Body Surface Area

Age is the main predictor of right kidney volume (β=0.313,

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p<0.001), with left renal volume also increasing with age, BMI, and BSA. The regression models accounted for approximately 74% of the variation in right kidney volume and 73% in left kidney volume, indicating a robust model fit (Table 4).

Table 4: Analysis of Multiple Linear Regression for Variables Related to the Volumes of the Right and Left Kidneys

Model	Age (β, 95% CI, p)	Gender (β, 95% CI, p)	Weight (β, 95% CI, p)	Height (β,95% CI, p)	BMI (β, 95% CI, p)	BSA (β, 95% CI, p)	Constant (B, 95% CI, p)	R^2 / Adj. R^2
Right Kidney	0.313 (1.92–3.34, <0.001)	0.031 (0.23–5.20, 0.073)	0.118 (1.06–1.66, 0.670)	0.005 (0.51–0.50, 0.983)	0.064 (0.05–1.15, 0.074)	0.650 (29.42–158.26, 0.178)	1.659 (21.75–18.44, 0.871)	0.738 / 0.736
Left Kidney	0.283 (1.67–3.13, <0.001)	0.029 (0.37–5.21, 0.089)	0.508 (0.12–2.68, 0.073)	0.117 (0.39–0.66, 0.605)	0.087 (0.14–1.37, 0.017)	1.156 (19.27–212.32, 0.019)	5.640 (–26.30–15.02, 0.592)	0.729 / 0.727

DISCUSSION

This study utilized CT scans to analyze kidney sizes and volumes in pediatric patients. It was established that kidney dimensions increase with age, with the most rapid growth occurring from infancy to early childhood, followed by a slower growth rate through childhood and teenage years. This growth is closely linked to overall body development during early years, highlighting this period as critical for kidney maturation [9, 10]. Current findings revealed that kidneys showed a consistent increase in size over a span that extended from 0–1 week to around 16–17 years. This pattern was most commonly seen between the ages of 0–2 years and the age of 2–7 years [11]. This initial development and growth indicate that newborns' organs are rapidly developing during this phase, parallel to the whole body. On the other hand, the period between 8 and 13 years showed a comparatively slower rate of increase, which can be explained by puberty, during which hormones influence renal tissue growth as well as renal blood flow [12, 13]. Similar age-related growth patterns have been noticed in both Asian and European which indicate that an increase in kidney growth is associated with the overall growth of the body [14, 15]. Current study findings showed that age is strongly related to the kidney volume more than BSA and BMI. But some published studies are in disagreement with our finding, like Obrycki *et al.* indicate that the BSA is strongly related(r=0.94)with the kidney size [16]. In another study from China, Qin *et al.* found that renal volume is associated with both height and BSA, with a strong correlation (r=0.89) [17]. The finding that age is the strongest predictor in our study might indicate that unique growth patterns depend on the nutritional intake and overall biological development among study participants in this part of the world. Male and female in any age group did not significantly differ in kidney size. This is comparable to the findings of Rongviriyapanich *et al.* and Mohtasib *et al.* who observed no variation before later adolescence [10, 18]. Liu *et al.* noticed that male adolescents tended to have slightly larger kidneys. However, this difference largely disappeared after adjustment for height and BSA [19]. This further indicates that gender alone is not a reliable predictor of kidney size once body dimensions are taken into account. Moreover, our findings are consistent with those reported by Rongviriyapanich *et al.* and Obrycki *et al.* An increase in the renal size is directly associated with the child's age, with only minimal gender differences [10, 20]. This indicates that body size is a reliable predictor for use in local clinical settings. The high R^2 values (around 0.73–0.74) in our regression models indicate that most of the variation in renal volume is attributed to body growth and development. Overall, these findings provide new and valuable data by offering CT-based kidney sizes and volume values specifically tailored to this part of the world. The detailed age-based breakdown enhances the practical utility of these findings for radiologists and pediatric nephrologists and can assist in the early identification of small kidneys, abnormal development, or chronic diseases. However, limitations of the study are that it is a single-center study and the sample size is relatively small, which can limit generalizability. More extensive multicenter research in larger and more heterogeneous groups of patients is required to confirm such reference ranges and to improve further pediatric renal volumetry norms in this group.

CONCLUSIONS

The current study presents uniform data on kidney size and volume in the Pakistani pediatric population, showing a strong correlation with body growth and minimal differences between genders. These insights and prediction models may assist physicians in making accurate diagnoses in pediatric nephrology and radiology, enabling earlier detection of kidney issues and tailored follow-up care.

Authors' Contribution

Conceptualization: MY, WAM
Methodology: MY, WAM, MM, FUI, AR, BZ, MS, MA, AH, MK
Formal analysis: AH, MK
Writing and Drafting: MY, WAM, MMA,
Review and Editing: MY, WAM, MM, FUI, AR, BZ, MS, MA, AH, MK

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

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Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Efficacy of Oral Progesterone Treatment in Women with Unexplained Recurrent First Miscarriages

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ABSTRACT

Recurrent miscarriage in the first trimester is a difficult and emotionally draining problem, affecting nearly 1–2% of women. In many cases, no clear cause can be found. Progesterone is known to help support early pregnancy by stabilizing the endometrium and reducing uterine contractions. **Objective:** To assess how effective oral progesterone is in women who have had repeated unexplained first-trimester miscarriages. **Methods:** This was a prospective, non-randomized single-arm interventional study conducted in the Department of Obstetrics and Gynecology, Combined Military Hospital, Bahawalpur, between August 02, 2024, and February 01, 2025. A total of 152 women aged 20–40 years, each with a history of ≥2 unexplained consecutive first-trimester miscarriages and a confirmed intrauterine viable pregnancy of <12 weeks, were included. All participants received oral dydrogesterone (10 mg twice daily) until completion of 12 weeks' gestation, with follow-up assessments every two weeks. Data were analyzed using SPSS version 26.0. **Results:** Efficacy was defined as pregnancy continuation beyond 12 completed weeks of gestation following therapy; live birth (where available) was recorded as an additional outcome. Associations were examined using chi-square tests and multivariable binary logistic regression, with $p<0.05$ considered statistically significant. **Conclusions:** In this single-arm cohort, oral dydrogesterone was associated with continuation of pregnancy beyond 12 weeks or live birth in 78.9% of women with unexplained recurrent first-trimester miscarriages. As no untreated comparator group was included, this study cannot determine whether dydrogesterone improves live birth outcomes compared with no progesterone therapy; randomized controlled studies are needed to confirm comparative effectiveness.

INTRODUCTION

Recurrent miscarriage (RM) refers to the loss of two or more consecutive pregnancies before twenty weeks of gestation. It affects around 1–2% of women in their reproductive years and is both emotionally and clinically challenging [1]. In almost half of these cases, no clear reason can be found even after a complete work-up [2]. Progesterone, a key steroid hormone that prepares the endometrium for implantation and helps maintain early pregnancy, has long been considered a possible treatment to reduce miscarriage risk [3, 4]. Various progesterone preparations have been used in clinical practice, including oral micronized progesterone and dydrogesterone. Several studies have reported potential benefits of progesterone supplementation in selected women with unexplained RM; however, results have been inconsistent across trials and populations [5, 6]. Progesterone may support early pregnancy through multiple mechanisms, including modulation of immune tolerance, facilitation of trophoblastic invasion, and reduction of uterine contractility processes that are particularly important during the first trimester [7]. The use of progesterone has also been investigated in large randomized controlled trials, such as PROMISE and PRISM. Although the overall effect was small, some subgroups, especially women with early pregnancy bleeding and a history of multiple prior miscarriages, showed higher rates of live births with

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progesterone supplementation [8, 9]. This trend was further supported by a Cochrane meta-analysis suggesting a probable reduction in miscarriage risk, particularly among women with three or more prior losses [10]. Oral dydrogesterone is commonly used due to its convenient oral route and established clinical use in early pregnancy support; however, direct head-to-head comparisons with other progesterone formulations (such as vaginal micronized progesterone) remain limited and have reported mixed findings [6, 11]. In addition, a recent double-blind RCT did not show a statistically significant reduction in miscarriage rates with oral progestogen compared with placebo among women with threatened miscarriage [12].

Taken together, these findings highlight ongoing uncertainty regarding the magnitude of benefit and the populations most likely to respond, indicating the need for further evidence. Recurrent first-trimester miscarriage remains a distressing condition with many contributing factors, and in nearly half of women, no definite cause can be identified. Because progesterone plays a central role in implantation and early pregnancy maintenance, helping stabilize the endometrium, reduce uterine contractility, and regulate immune tolerance, some researchers propose that subtle luteal phase insufficiency may contribute to unexplained RM in a subset of patients. Progesterone supplementation may help support early gestation in such cases. Despite increasing international evidence, data from local populations remain scarce. This study aimed to assess pregnancy outcomes and tolerability among women with unexplained recurrent first-trimester miscarriages treated with oral dydrogesterone, aiming to provide locally relevant evidence to inform clinical practice.

METHODS

This prospective, non-randomized single-arm interventional (quasi-experimental) study was conducted in the Department of Obstetrics and Gynecology, Combined Military Hospital, Bahawalpur, from August 02, 2024, to February 01, 2025. The study was approved by the IRB (EC-6-2023). The sample size was calculated using the standard formula for estimation of a single population proportion: $n = Z^2 \times p \times (1 - p) / d^2$, where Z = 1.96 for a 95% confidence level, p=0.889 (expected efficacy rate of oral progestogen reported by Shinwari *et al.*), and d = 0.05 (margin of error). The calculated sample size was 152 patients [13]. A non-probability consecutive sampling technique was used, and all eligible women presenting during the study period and fulfilling the inclusion criteria were enrolled until the required sample size was achieved. Women aged 20–40 years with a history of ≥2 consecutive first-trimester miscarriages without an identifiable cause and a confirmed intrauterine pregnancy of <12 weeks on ultrasound were included after obtaining informed written consent. Patients with miscarriages due to known causes such as uterine anomalies, chromosomal abnormalities, uncontrolled endocrine disorders, antiphospholipid syndrome, or thrombophilia were excluded. Women with multiple or ectopic pregnancies, those using other hormonal or immunologic therapies, and those with an allergy to progesterone or serious systemic illness were also excluded. Intervention: All enrolled participants received oral dydrogesterone 10 mg twice daily, started at confirmation of intrauterine pregnancy and continued until completion of 12 weeks of gestation. No randomization and no comparator arm were used. Outcome definitions: The primary efficacy outcome was pregnancy continuation beyond 12 completed weeks of gestation following oral dydrogesterone therapy. Pregnancy was labeled effective if it continued beyond 12 completed weeks and not effective if miscarriage occurred before 12 weeks despite treatment. Live birth (where available) was recorded as an additional pregnancy outcome measure. As all enrolled participants received dydrogesterone, no untreated control group was available; therefore, comparative effectiveness versus no progesterone therapy could not be assessed. All eligible participants were identified from antenatal clinics and gynecology wards. After consent, baseline demographic and obstetric information, including age, BMI, gravidity, and parity, was recorded on a structured proforma. Compliance was reinforced through counseling and follow-up every two weeks until 12 weeks of gestation. At each visit, participants were assessed for fetal viability by ultrasound and for adverse effects such as nausea, dizziness, or breast tenderness. Data regarding dose, duration of therapy, gestational age at outcome, and adverse effects were documented. All data were entered and analyzed using SPSS version 26. Quantitative variables such as age, BMI, duration of therapy, and gestational age at outcome were expressed as mean ± standard deviation (SD). Qualitative variables, including efficacy and adverse effects, were presented as frequencies and percentages with 95% confidence intervals (CI). The primary outcome (efficacy) was analyzed as a proportion with 95% CI. For inferential analysis, the association between efficacy and categorical variables such as age group and BMI category was assessed using the chi-square test. For continuous predictors (e.g., duration of therapy), the independent-sample t-test was applied as appropriate. To identify independent predictors of efficacy, binary logistic regression analysis was performed, including relevant demographic and clinical variables. Adjusted odds ratios (AOR) with 95% confidence intervals were reported. A p-value of <0.05 was considered statistically significant.

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RESULTS

A total of 152 women were included in the study. The mean age of the participants was 29.53 ± 5.97 years. The mean BMI was 25.91 ± 4.20 kg/m^2, while the mean duration of progesterone therapy was 10.07 ± 1.42 weeks. The mean gestational age at outcome was 23.72 ± 10.31 weeks. Out of 152 women included in the study, 120 (78.9%) achieved pregnancy continuation beyond 12 completed weeks following oral dydrogesterone therapy (95% CI: 71.8%–84.7%), while 32 (21.1%) experienced miscarriage before 12 weeks (Figure 1).

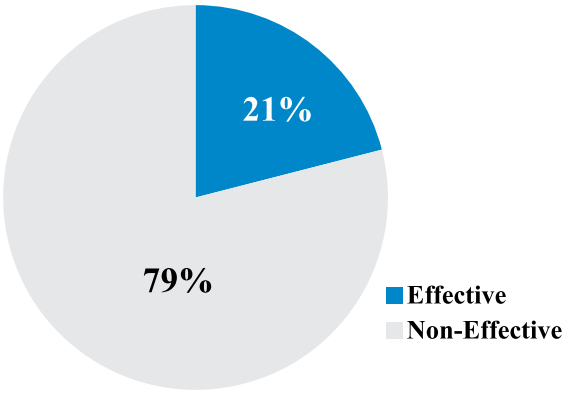

Figure 1: Frequency of Efficacy

The study summarizes the association between baseline/clinical characteristics and treatment efficacy, defined as pregnancy continuation beyond 12 completed weeks among women receiving oral dydrogesterone. Efficacy was numerically higher among women aged ≤30 years (83.1%) compared with those aged >30 years (73.9%); however, this difference was not statistically significant (p = 0.165). Gravidity and parity were not significantly associated with efficacy (p = 0.605 and p = 0.204, respectively). Likewise, BMI category showed no significant association with response (non-obese: 82.8% vs obese: 76.6%; p = 0.365). Women who reported mild adverse effects had a higher observed efficacy rate (88.2%) than those without adverse effects (76.3%), but this difference was also not statistically significant (p = 0.132). Overall, none of the evaluated demographic or clinical variables demonstrated a statistically significant association with efficacy in univariate analysis (Table 1).

Table 1: Association of Demographic and Clinical Variables with Efficacy of Oral Progesterone Treatment (n=152)

Variables	Category	Not Effective n (%)	Effective n (%)	Total	p-value	Odds Ratio (95% CI)
Age Group	≤30 Years	14 (16.9%)	69 (83.1%)	83	0.165	0.58 (0.26–1.26)
	>30 Years	18 (26.1%)	51 (73.9%)	69		
Gravidity	Primigravida	6 (25.0%)	18 (75.0%)	24	0.605	1.31 (0.47–3.62)
	Multigravida	26 (20.3%)	102 (79.7%)	128		
Parity	Nulliparous	11 (28.2%)	28 (71.8%)	39	0.204	1.72 (0.74–4.00)
	Multiparous	21 (18.6%)	92 (81.4%)	113		
Obesity (BMI Group)	Non-obese (<25)	10 (17.2%)	48 (82.8%)	58	0.365	0.68 (0.30–1.57)
	Obese (≥25)	22 (23.4%)	72 (76.6%)	94		
Adverse Effects	No	28 (23.7%)	90 (76.3%)	118	0.132	2.33 (0.76–7.20)
	Yes	4 (11.8%)	30 (88.2%)	34		

Binary logistic regression was performed to identify independent predictors of treatment efficacy (defined as pregnancy continuation beyond 12 completed weeks) among women receiving oral dydrogesterone. The overall model was not statistically significant (χ^2 = 8.34, p=0.303), and the Hosmer–Lemeshow test indicated good model fit (p=0.925). The Nagelkerke R^2 value (0.083) suggested that approximately 8.3% of the variation in efficacy was explained by the variables included in the model. None of the predictors reached statistical significance at p<0.05. Women aged ≤30 years had higher odds of efficacy than those >30 years (AOR = 1.78, 95% CI 0.79–4.00; p=0.162). Gravidity (AOR = 1.43, 95% CI 0.33–6.11; p=0.631), parity (AOR = 0.41, 95% CI 0.12–1.39; p=0.152), obesity (AOR = 1.64, 95% CI 0.68–3.95; p=0.271), duration of therapy (AOR = 0.90, 95% CI 0.68–1.21; p=0.491), and gestational age at outcome (AOR = 1.01, 95% CI 0.97–1.05; p=0.547) were not independently associated with efficacy. With respect to adverse effects, the model used "Yes" as the reference category; therefore, women with no adverse effects had lower odds of efficacy compared with those reporting adverse effects (AOR = 0.37, 95% CI 0.12–1.19; p=0.095), although this was not statistically significant (Table 2).

Table 2: Binary Logistic Regression Analysis for Factors Associated with Efficacy of Oral Progesterone Treatment (n=152

Variables	B	S.E.	p-value	AOR (Exp B)	95% CI for AOR
Age ≤ 30 Years vs > 30 Years	0.577	0.413	0.162	1.78	0.79 – 4.00
Gravidity (Primigravida vs Multigravida)	0.356	0.742	0.631	1.43	0.33 – 6.11
Parity (Nulliparous vs Multiparous)	-0.902	0.629	0.152	0.41	0.12 – 1.39
Obesity (Non-obese vs Obese)	0.494	0.448	0.271	1.64	0.68 – 3.95
Duration of Therapy (Weeks)	-0.101	0.147	0.491	0.90	0.68 – 1.21
Gestational Age at Outcome (Weeks)	0.012	0.020	0.547	1.01	0.97 – 1.05
Adverse Effects (No vs Yes)	-0.997	0.596	0.095	0.37	0.12 – 1.19
Constant	2.603	1.691	0.124	13.50	—

(AOR = Adjusted Odds Ratio; CI = Confidence Interval; Reference categories => 30 years, Multigravida, Multiparous, Obese, Adverse effects = Yes). Model fit: χ^2 = 8.34 (df = 7, p=0.303); Hosmer-Lemeshow χ^2 = 3.14 (df = 8, p=0.925); Nagelkerke R^2 = 0.083.

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DISCUSSION

In this study, oral dydrogesterone was associated with an efficacy rate of 78.9% in women with unexplained recurrent first-trimester miscarriages. This outcome is consistent with previous literature suggesting that progesterone supplementation may support early pregnancy in selected women with recurrent miscarriage. Shinwari *et al.* reported higher success rates with oral progestogens (88.9%) than with vaginal preparations (66.7%) [13]. However, as those findings arise from a different study design and population, and because our study did not include a vaginal progesterone comparator arm, our data do not allow conclusions regarding the superiority of the oral route. Nevertheless, our results indicate that pregnancy continuation beyond the first trimester was observed in a substantial proportion of women receiving oral dydrogesterone in routine clinical settings. Clinical guidance has also discussed the role of oral dydrogesterone in threatened miscarriage and recurrent pregnancy loss. The Thai interest group guideline supports the use of oral dydrogesterone in threatened miscarriage and unexplained recurrent pregnancy loss, primarily citing ease of dosing and tolerability [14]. The guideline also highlights concerns related to variable absorption and patient discomfort with vaginal micronized progesterone when used in high or unnecessary doses [14]. While these recommendations align with common clinical practice, our findings should be interpreted as observational outcomes in a single-arm cohort rather than evidence of preference over alternative formulations. However, not all studies have demonstrated a clear benefit of progesterone in recurrent miscarriage. The PROMISE trial by Coomarasamy *et al.* reported no significant difference between vaginal progesterone and placebo in women with recurrent miscarriage [15]. Such discrepancies across studies may reflect differences in progesterone formulation, route of administration, timing of initiation, dosing regimens, and heterogeneity in underlying patient characteristics. In this context, our findings contribute local data on outcomes among women treated with oral dydrogesterone; however, direct comparisons with vaginal progesterone or placebo cannot be made within this study. Guo and Lu provide mechanistic insight into why dydrogesterone may be beneficial in some patients [16]. They reported that dydrogesterone may promote a more favorable immune environment by increasing anti-inflammatory cytokines (IL-4 and IL-10) and reducing IFN-γ levels. Because immune dysregulation has been implicated in unexplained recurrent miscarriage, this immunomodulatory pathway may partly explain the favorable outcomes observed in some cohorts, including ours. In their meta-analysis, Saccone *et al.* also reported that first-trimester progestogen use may reduce recurrent miscarriage and improve the likelihood of live birth [17]. They discussed the potential role of synthetic progestogens (including dydrogesterone and hydroxyprogesterone caproate) in early pregnancy support. While such findings are encouraging, it remains important to distinguish pooled evidence from individual cohort outcomes and to consider differences in study design and comparator groups when interpreting effectiveness. Pandya *et al.* described potential advantages of dydrogesterone, including good oral absorption, receptor selectivity, and a generally favorable tolerability profile, and noted its use in threatened and recurrent miscarriage [18]. Similarly, Kriplani *et al.* supported its acceptability in clinical practice and reported favorable safety observations [19]. In our cohort, treatment was generally well tolerated, and no major safety concerns were observed, supporting its practical feasibility in this setting. Ranjan *et al.* reported lower miscarriage rates and higher live birth rates among women who received progesterone compared with those who did not [20]. While this supports the broader hypothesis that progesterone may be beneficial in recurrent pregnancy loss, our study design does not permit causal inference or definitive comparison against no progesterone therapy. Influence of BMI on response: In our dataset, the BMI category was not significantly associated with treatment response. Efficacy was 82.8% among non-obese women and 76.6% among obese women ($p = 0.365$). In multivariable logistic regression, obesity was also not an independent predictor of efficacy (AOR = 1.64, 95% CI 0.68–3.95; $p = 0.271$). These findings suggest that the observed pregnancy continuation beyond 12 completed weeks after dydrogesterone therapy was broadly similar across BMI groups in this cohort.

Limitations of the Study: Non-randomized, single-arm, no control group, single-center, short follow-up (12 weeks), no blinding, lack of confounder adjustment, and subjective measure of adherence. Future Recommendations: Multicenter RCTs with placebo comparators, longer postpartum follow-up to live birth, blinding, and oral versus vaginal progesterone should be carried out. Add subgroup analysis of the previous number of miscarriages, age, and BMI.

CONCLUSIONS

In this cohort of women with unexplained recurrent first-trimester miscarriage who received oral dydrogesterone, 78.9% of pregnancies continued beyond 12 weeks or resulted in live birth, and adverse effects were generally mild. However, because this study lacked an untreated control group, a definitive comparison with no progesterone therapy cannot be made. Comparative trials are recommended to confirm whether oral dydrogesterone

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improves live birth outcomes versus no treatment and to identify subgroups most likely to benefit.

Authors' Contribution

Conceptualization: MUAZ
Methodology: MUAZ
Formal analysis: SZ
Writing and Drafting: SZ
Review and Editing: MUAZ, SZ

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparative Effect of Green and Blue Filters on Near Point of Accommodation among Emmetropes and Myopes

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ABSTRACT

Coloured filters are optical devices that selectively transmit certain wavelengths of light while absorbing others. Green and blue filters can reduce glare and improve contrast. **Objectives:** To determine the effect of green and blue filters on relieving excessive near point of accommodation among emmetropes and myopes. **Methods:** This analytical cross-sectional study was conducted at the Rashid Latif Khan University, Lahore, Pakistan, from May 2023 to January 2024. 110 participants of both genders, aged 15-30 years, were included. The participants were divided into emmetropes and myopes, with 55 participants in each group. The near point of accommodation (NPA) was assessed objectively using the RAF rule. Both groups were examined initially without any filter and then using green and blue filters. Data were analysed using SPSS-24. A repeated-measures ANOVA test was applied to compare the effect of green and blue filters in emmetropes and myopes. **Results:** Mean NPA ± SD without filter, with green filter, and with blue filter in emmetropes was 14.89 ± 1.64, 12.07 ± 1.15, and 12.25 ± 1.03, respectively, with ($p<0.001$) while, mean NPA ± SD without filter, with a green filter, and with a blue filter in myopes was 13.92 ± 1.68, 11.92 ± 0.58, and 12.53 ± 0.55, respectively, with ($p<0.001$) suggesting that both green and blue filters contribute to a reduction in excessive accommodation among emmetropes and myopes. **Conclusions:** The use of green and blue filters could decrease excessive NPA both in emmetropes and myopes (mild to moderate myopes).

INTRODUCTION

Myopia is the most prevalent type of refractive error. Recently, myopia has become more common in young adolescents, particularly in East and Southeast Asia [1, 2]. According to recent estimates, 49.8% of the population will have myopia in 2050 [3]. Uncorrected myopic error contributes significantly to visual impairment and reduces the quality of life. Children with myopia usually read at a closer distance than emmetropic children. Furthermore, it has been observed that myopia development in children is considerably faster at closer work distances [4-6]. Children often view objects at closer distances, which get smaller as they focus more intently. When spatial frequencies increase, this causes larger accommodation lags and lowers vision quality [7]. The ability of the eye to adjust the lens's refractive power to focus on objects at different distances is known as accommodation. The retina is imaged clearly at various viewing distances by a complex series of sensory, neuromuscular, and biophysical events that alter the refracting power of the eye [8]. Myopia causes poor distance vision, which can be corrected by

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using visual corrective aids like spectacles, contact lenses, and refractive surgeries. Wearing glasses can improve vision and academic performance [8]. Tinted glasses and coloured overlays are commonly used to support individuals experiencing reading difficulties linked to increased retinal sensitivity to specific light wavelengths. By modifying the light that reaches the retina, tinted filters help create a more stable and visually comfortable environment that allows users to focus for longer periods with less effort [9]. Green and blue filters are among the most frequently used options, each offering distinct optical benefits based on their selective transmission of specific wavelengths [10, 11]. Green filters transmit light around an optimal wavelength of approximately 531 nm, which corresponds to the sensitivity of the eye's M-cones, located centrally in the retina. Thus, provides comfortable vision, improving clarity, easing eye strain, and creating a soothing visual experience that supports extended reading, especially in bright or high-contrast environments [12]. In contrast, short-wavelength blue light in the 450–500 nm region is absorbed by blue-blocking filters [13]. Overexposure to blue light, especially from digital screens, has been linked to glare sensitivity, visual tiredness, and irregular sleep patterns [14]. Blue-blocking filters diminish pain during prolonged near work, lessen digital eye strain, and promote healthy sleep by reducing blue-light interaction with circadian rhythms by limiting these wavelengths [15].

There is limited evidence comparing the differentiation effect between green and blue filters of the near point of accommodation (NPA), particularly on emmetropic and myopic groups. Over-accommodation leads to visual fatigue and can also increase the rate of myopia in people with spectacles, but relatively little has been done to understand the relative effectiveness of a green and a blue filter in reducing the accommodative demand of myopes with spectacles and emmetropes. This study aimed to assess and compare the effect of green and blue filters on excessive accommodation in emmetropes and optically corrected myopes.

METHODS

This analytical cross-sectional study was conducted at Rashid Latif Khan University, Lahore, Pakistan, in the period from May 2023 to January 2024, after obtaining technical and ethical approval from the Ethical Review Board (IRB/RLIAHS/860/2024). The sample size was 110, calculated according to Robert Masson's equation: $N=Z^2PQ/d^2$ where N is the required sample size, Z is the standard normal deviate corresponding to a 95% confidence level (Z = 1.96), P is the estimated population proportion assumed to be 0.5 in the absence of prior data, Q is (1 – P) and therefore equal to 0.5, and d is the allowable margin of error. The margin of error (d) was set at 0.093, as margins between 5% and 10% are considered acceptable and consistent with the literature [16]. Participants of both genders aged 15-30 years were included in the study through the purposive sampling (non-probability) technique. Purposive sampling was used to include participants with specific refractive error (myopia) and those without it (emmetropia), ensuring the sample is relevant to research objectives. Emmetropic and mildly to moderately myopic (BCVA 6/6) subjects with excessive accommodation (>10 dioptres) were included in the study. All ocular diseases, extraocular muscle instability, tropias, amblyopia, uncorrected myopes, myopia greater than 6 dioptres (D), hypermetropic patients, astigmatic patients, contact lens users, mentally retarded patients, and those suffering from any systemic diseases were excluded from the study. The procedure was explained to the eligible participants, and informed written and verbal consent was obtained. The data collection was done through a self-designed examination-based proforma approved by the technical and ethical committee of the institute. The questionnaire contained history taking (personal data, past medical and ocular history), a thorough ocular examination including best corrected visual acuity (BCVA), refractive error, near point of accommodation (NPA) with and without green and blue filters, and detailed anterior and posterior segment slit lamp evaluation. Subjects were divided into two groups, i.e., emmetropes and myopes, with 55 participants in each group. NPA was assessed using the Royal Air Force (RAF) rule at three instances in both groups: initially without any filter, then using green filters, and lastly using blue filters. RAF was a 50-centimeter-long rule featuring a slider that rotates and holds a four-sided cube with a distinct target. The patient was instructed to focus on the letters that were slowly moving closer to their nose until he/she could no longer maintain a clear focus on the letter or symbols. The NPA is obtained when the letters get blurred, initially without using any filter, then using green and blue filters separately at each turn. The near point of accommodation was taken in diopters (D). Descriptive and inferential statistical analyses were performed using SPSS for Windows version 24.0 (SPSS Inc., Chicago, IL, USA). Data were reported as frequency and mean ± standard deviation (SD). The data were normally distributed, and a parametric test (repeated measure ANOVA) was applied. The repeated measure ANOVA was applied as NPA was assessed three times in the same participants (without filter, with green filter, and with blue filter) in both myopic and emmetropic groups. A p-value of <0.05 was considered statistically significant with a 95% confidence level.

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RESULTS

Data of a total of 110 patients, divided into two groups: emmetropes and myopes, with 55 participants in each group, is presented. The mean age was 21.78 ± 4.37 in emmetropes and 21.00 ± 2.78 in myopes. Among 55 emmetropes included in the study, 21 (38.2%) were male, and 34 (61.8%) were female, whereas among 55 myopes, 28 (50.9%) were male and 27 (49.1%) were female (Table 1).

Table 1: Demographics of Participants

Parameters	Emmetropes (n=55)	Myopes (n=55)
Age		
Mean ± SD	21.78 ± 4.37	21.00 ± 2.78
Gender		
Male	21 (38.2%)	28 (50.9%)
Female	34 (61.8%)	27 (49.1%)

Based on the level of refractive error, the myopic group was divided into two groups: mild and moderate. 40 participants, or around 72.8% of the myopic population sample, fell into the mild refractive error group, which included -0.50D to -2.75D. However, 15 individuals, or around 27.3% of the myopic population, showed a moderate degree of myopic refractive error (-3.00D to -6.00D). This data suggests a higher prevalence of mild myopic refractive error as compared to moderate in the study population (Figure 1).

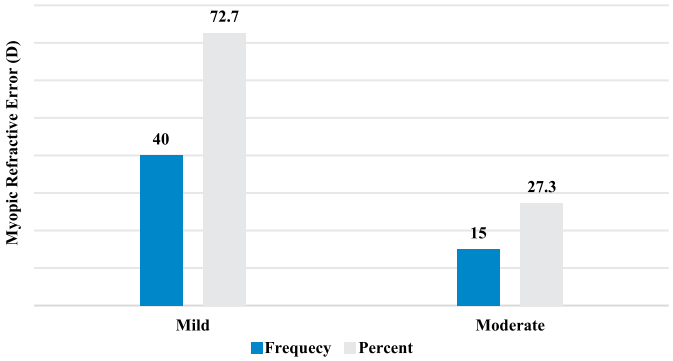

Figure 1: Distribution of Myopic Refractive Error Based on the Degree of Error

The Shapiro-Wilk test was employed to evaluate whether the data are normally distributed. The results of the normality test indicate that for both the near point of accommodation in emmetropes and myopes, the p-value was greater than 0.05, suggesting that the data were normally distributed. A repeated-measures ANOVA test was applied to compare the effect of green and blue filters on excessive accommodation. The mean ± standard deviation without filter, with green filter, and with blue filter in emmetropes was 14.89 ± 1.64, 12.07 ± 1.15, and 12.25 ± 1.03, respectively, with a significance of ($p<0.001$), suggesting that both green and blue filters reduce excessive accommodation in emmetropes, however no significance difference was found when the effect of both fiters were compared ($p=0.190$), although mean value of green showed superior effect (Table 2).

Table 2: NPA of Emmetropes with and Without Green and Blue Filters by Repeated Measure of ANOVA

Variables		Mean ± SD	Sig. (p-value)
NPA Without Filter vs with Green Filter	No Filter	14.890 ± 1.640	<0.001*
	Green Filter	12.072 ± 1.156	
NPA Without Filter vs with Blue Filter	No Filter	14.890 ± 1.640	<0.001*
	Blue Filter	12.254 ± 1.031	
NPA With Green Filter vs Blue Filters	Green Filter	12.072 ± 1.156	0.190
	Blue Filter	12.254 ± 1.031	

(*) indicates statistical significance at $p\leq0.05$

The mean ± standard deviation without filter, with a green filter, and with a blue filter in myopes was 13.92±1.68, 11.92±0.58, and 12.53±0.55, respectively ($p<0.001$), suggesting that both green and blue filters contribute to a reduction in excessive accommodation. Furthermore, the green filter showed a superior effect to blue filters in relieving excessive accommodation among corrected myopes (Table 3).

Table 3: NPA Myopes with and without Green and Blue Filters by repeated measure of ANOVA

Variables		Mean ± SD	Sig. (p-value)
No Filter vs Green Filter	No Filter	13.927 ± 1.687	<0.001*
	Green Filter	11.927 ± 0.588	
No Filter vs Blue Filter	No Filter	13.927 ± 1.687	<0.001*
	Blue Filter	12.536 ± 0.559	
Green Filter vs Blue Filter	Green Filter	11.927 ± 0.588	<0.001*
	Blue Filter	12.536 ± 0.559	

(*) indicates statistical significance at $p\leq0.05$

DISCUSSION

Filters function by blocking a certain region of the colour spectrum, thus greatly enhancing the remaining wavelengths of light. Coloured filters have been extensively utilized for the past fifteen years as a safe remedy for visual stress, and their effectiveness has been proven over time [17]. This study was carried out to assess the near-point of accommodation with green and blue filters in optically corrected myopic patients. Myopia is the most prevalent condition, affecting 2.9% of the global population and up to 52% of the school-age population. People 65 years of age and older have a 46% increased risk of developing myopia [18]. A previous study indicated that participants with an AC/A ratio of 5.84 or above were 22.5 times more likely to develop myopia within the next year ($p<0.001$) [19]. Thus, it was determined that the AC/A ratio was a significant risk factor for the onset of myopia [19]. To the best of our knowledge, no study was conducted in Pakistan that

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showed the effect of coloured filters on excessive accommodation, asthenopia symptoms, and eye fatigue. This study aimed to highlight the positive effect of coloured filters in this domain, which may result in the prevention and/or improvement of refractive error, strabismus, and other visual anomalies. A previous study was conducted in 2023 on the effect of green and red filters on high and low AC/A ratios among emmetropes. It was found that the mean ± SD of low AC/A was 3.48:1 Δ ±0.72 by using green filters, whereas the mean ± SD of high AC/A ratio was 5.57:1 Δ ±0.49 with green filters. It was found that both green and red filters significantly improved the AC/A ratio in emmetropes ($p<0.001$) [20]. In the current study, the near point of accommodation (NPA) with green and blue filters in optically corrected myopes as well as in emmetropes was assessed. It was found that in emmetropes, the mean ± SD without any filter, then using green and blue filters were 14.89 ± 1.64, 12.07 ± 1.15, and 12.25 ± 1.03, respectively. Whereas, in myopes, the mean ± standard deviation without filter, with green filter, and with blue filter was 13.92 ± 1.68, 11.92 ± 0.58, and 12.53 ± 0.55, respectively. The results were statistically significant with both green and blue filters ($p<0.001$). It was concluded that the excessive accommodation was relieved with both green and blue filters in optically corrected myopic patients and emmetropes. However, the green filter significantly improved excessive accommodation as compared to the blue filter in optically corrected myopic patients. The findings of this investigation corroborate a Simmers study that found increased ocular accommodation during near-target but decreased when using tinted lenses. This is because, in the absence of a lens, the target's total brightness is at its highest, producing the maximum amplitude of response [20]. Filters result in a dilation of the pupil, which happens naturally in reaction to a drop in light levels specific degree of pupillary dilation [17]. The lens flattens when the pupil dilates, resulting in a relaxation of accommodation. This study emphasizes the use of filters for more comfortable eyesight in optically corrected myopic patients.

The cross-sectional design of the study did not allow for evaluating long-term filter effects; the samples were restricted to mild-to-moderate myopes and high myopes, and other refractive errors were not included; possible confounding factors like digital screen usage and near work habits were not controlled. The longitudinal studies ought to determine the long-term impacts of using filters on accommodation and myopia progression. High myopes, hypermetropies, and astigmats should also be studied, and the effect of the filters on visual comfort and digital eye strain should be investigated both in the real-world environment.

CONCLUSIONS

It was concluded that the use of green and blue filters could decrease excessive near point of accommodation (NPA), thus proving that filters are an effective tool for managing eye strain, especially in today's digital world. Furthermore, the green filter showed a more significant effect than the blue filter on decreasing NPA in the myopes.

Authors' Contribution

Conceptualization: RBE, MMN
Methodology: SS, RBE, MMN, MA, TS, EI
Formal analysis: RBE, MMN
Writing and Drafting: SS, TS, EI
Review and Editing: SS, RBE, MMN, MA, TS, EI

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Left Ventricular Ejection Fraction among Patients with Acute Myocardial Infarction

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ABSTRACT

After an acute myocardial infarction (AMI), the LVEF may be used for prognosis and therapy purposes. Despite the importance of left ventricular ejection fraction (LVEF) testing as a performance indicator for AMI patients, nothing is known about the current rates of in-hospital assessment or how it relates to therapeutic utilization. **Objective:** To ascertain the prevalence of LVEF patterns in individuals with AMI. **Methods:** It was a cross-sectional descriptive study conducted at the Department of Cardiology, King Edward Medical University/ Affiliated Hospital, Lahore, from March 2025 to September 2025 under IRB number 783/RC/KEMU. A total of 110 patients were enrolled through nonprobability purposive sampling. Data analysis was done on SPSS version 26.0. Quantitative variables were presented as mean ± S.D. Qualitative variables, i.e., gender, types of myocardial infarction (STEMI/ NSTEMI), and patterns of left ventricular function (Abnormal/ moderately to severely impaired) were presented as frequency and percentage. **Results:** The average age of the cases in this study was 52.74 ± 8.08 years. There were 72 (65.5%) males and 38 (34.5%) females enrolled in this study. The mean BMI, LVEF, and duration of MI were 27.62 ± 4.27 (kg/m2), 35.30 ± 7.88 (%), and 176.18 ± 5.65 (minutes). There were 35 (31.8%) patients diagnosed with STEMI and 75 (68.2%) diagnosed with NSTEMI. There were 40 (36.4%) patients found with abnormal LVEF patterns and 70 (63.6%) with moderately to severely impaired LVEF. **Conclusion:** The results of this study showed that the majority of patients with acute MI had moderately to severely impaired LVEF.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the major causes of morbidity and mortality throughout the world. Several recent studies have highlighted a fall in acute and long-term mortality following ST-elevation myocardial infarction (STEMI) in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention. Unfortunately, STEMI mortality rates are still too high [1]. The measurement of left ventricular ejection fraction (LVEF) after acute myocardial infarction (AMI) has both prognostic and therapeutic implications and is a class I clinical practice guideline recommendation, as well as a core AMI performance measure recommended by the American College of Cardiology (ACC) and American Heart Association (AHA) [1, 2]. Reduced LVEF is associated with greater mortality among patients with coronary artery disease [3] and predicts increased risks of early all-cause mortality [4], as

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well as sudden cardiac death [5] after AMI. Improvement of LVEF with revascularization is associated with improved long-term survival among AMI patients [6]. Clinical practice guidelines provide several therapeutic recommendations for both the acute and long-term post-discharge management of AMI based on LVEF. Specifically, indications for angiotensin-converting-enzyme inhibitor (ACE-I), angiotensin receptor blockers (ARB), and aldosterone antagonists are LVEF dependent [6]. Given that assessment of primary prevention implantable cardioverter-defibrillator candidacy after AMI is also determined primarily by LVEF, patients with reduced LVEF during the AMI hospitalization require appropriate follow-up care to avoid missed prevention opportunities [7, 8]. In a previous study, as per the pattern of left ventricular ejection fraction, the abnormal LVEF was found in 45.6% patients, and moderately to severely impaired LVEF was found in 22.6% patients [4].

By providing insight into the frequency and risk factors of acute left ventricular dysfunction in individuals who have had myocardial infarction, this research aims to influence future treatments and management techniques. This study aimed to determine the frequency of patterns of left ventricular ejection fraction among patients with acute myocardial infarction.

METHODS

The research was a cross-sectional descriptive study done at the Department of Cardiology, King Edward Medical University/Affiliated Hospital, Lahore, over a period of six months from 15 March 2025 to 15 September 2025 under IRB number 783/RC/KEMU. The sample size of 110 individuals was determined using a 95% confidence level, an 8% margin of error, and an anticipated frequency of moderately to severely reduced LVEF at 22.6% [4]. (8% margin was chosen to achieve a feasible sample size (n=110), given practical constraints (time, budget, patient availability). The wider margin still provides a statistically acceptable confidence interval for the exploratory nature of the study, balancing precision with logistical feasibility. VT (Ventricular Tachycardia) /VF (Ventricular Fibrillation) episodes were not assessed as an outcome in the present study; therefore, effect modification of age or BMI in relation to VT/VF could not be evaluated. Since the study objective was descriptive, focused solely on LVEF patterns, no stratified or interaction analyses for VT/VF were undertaken. This study enrolled male and female patients of age 18-60 years presenting with myocardial infarction (as per operational definition) within 24 hours of the start of symptoms. Patients having permanent atrial fibrillation were excluded from the study. Patients with creatinine concentration > 176.8 mmol/L by laboratory test and history of cardiogenic shock on admission were excluded from the study. Myocardial infarction: It was defined as symptoms of ischemia and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block or development of pathological Q waves in the ECG), rise and or fall of cardiac biomarkers, evidence of new loss of viable myocardium or new regional wall motion abnormality or evidence of fresh thrombus by coronary angiography [9]. Patterns of left ventricular ejection fraction (LVEF): It was described in terms of Abnormal. It was labeled if LVEF < 50% on echocardiography. Moderately to severely impaired: it was defined as LVEF < 40% on echocardiography [9]. One hundred and ten patients from the cardiology and Emergency Departments at King Edward Medical University/Affiliated Hospital in Lahore met the inclusion criteria and were recruited for the research. All patients were asked to provide their informed consent. All patients underwent echocardiography. Chamber dimensions, myocardial wall thickness, and LVEF parameters: LVEF is calculated using the biplane disc method in both four-chamber and two-chamber views. The wall motion score index is the result of dividing all scores by the number of segments seen using the 16-segment LV segmentation model. Normokinesia, hypokinesia, akinesia, and dyskinesia are each assigned a score of 1, 2, 3, and 4 points, respectively [9]. The operational definition was used to identify the patterns of LVEF. Data analysis was done on SPSS version 26.0. Quantitative variables, i.e., age and BMI, were presented as mean ± S.D. Qualitative variables, i.e., gender, types of myocardial infarction (STEMI/ NSTEMI), and patterns of left ventricular function (Abnormal/ moderately to severely impaired) were presented as frequency and percentage. Normality of continuous variables was assessed using the Shapiro–Wilk test. All variables (age, BMI, LVEF, and MI duration) demonstrated non-significant results ($p>0.05$), confirming that the data were normally distributed. Post-stratification chi-square test was applied. Chi-square assumptions were verified for all contingency tables. Whenever any expected cell count fell below 5, Fisher's Exact Test was automatically applied. A p-value of <0.05 was considered significant.

RESULTS

The average age of the cases in this study was 52.74 ± 8.08 years. There were 72 (65.5%) males and 38 (34.5%) females found in this study. The mean BMI, LVEF, and duration of MI were 27.62 ± 4.27, 35.30 ± 7.88, and 176.18 ± 5.65. There were 35 (31.8%) patients diagnosed with STEMI and 75 (68.2%) diagnosed with NSTEMI. There were 40 (36.4%) patients found with abnormal LVEF patterns and 70 (63.6%) with moderately to severely impaired LVEF (Table 1).

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Table 1: Examining Demographic and Clinical Factors

Demographic and Clinical Factors		Mean ± SD, n (%)	CI
Age	(95% CI)	52.74 ± 8.08	51.23 – 54.25
Gender	Male	72 (65.5%)	–
	Female	38 (34.5%)	–
BMI (kg/m^2)	(95% CI)	27.62 ± 4.27	26.82 – 28.42
LVEF (%)	(95% CI)	35.30 ± 7.88	33.83 – 36.77
Duration of MI	(Minutes)(95% CI)	176.18 ± 5.65	175.12 – 177.24
Type of MI	STEMI	35 (31.8%)	–
	NSTEMI	75 (68.2%)	–
Pattern of LVEF	Abnormal	40 (36.4%)	–
	Moderately to Severely Impaired	70 (63.6%)	–

The stratification of STEMI and NSTEMI patients according to gender, age, and BMI did not show any significant difference, i.e., p-value 0.969, 0.826, and 0.504, respectively (Table 2).

Table 2: Stratification According to Age, Gender, BMI, and Types of MI

Variables		STEMI	NSTEMI	p-value
Gender	Male	23 (65.7%)	49 (65.3%)	0.969
	Female	12 (34.3%)	26 (34.7%)	
Age (Years)	18-28	0 (0%)	1 (1.3%)	0.826
	29-39	2 (5.7%)	4 (5.3%)	
	40-50	13 (37.1%)	23 (30.7%)	
	51-60	20 (57.1%)	47 (62.7%)	
BMI	< 30	24 (68.6%)	56 (74.7%)	0.504
	≥ 30	11 (31.4%)	19 (25.3%)	

DISCUSSION

When it comes to risk-stratifying individuals with AMI, left ventricular ejection fraction is one measure that the guidelines advocate using [10, 11]. Heart failure, sudden cardiac death, cardiovascular and overall mortality, and reduced EF after myocardial infarction have all been linked in many investigations [12]. The patients with improved ejection fractions after leaving the hospital had a reduced risk of cardiovascular events and a higher quality of life, according to many studies [13-15]. Patients who have had heart failure in the past with a low ejection fraction and now have a LVEF more than 40% are considered to have the phenotype of heart failure with improved ejection fraction, as newly acknowledged by the recommendations [16-18]. The average age of the cases in this study was 52.74 ± 8.08 years. There were 72 (65.5%) males and 38 (34.5%) females found in this study. The mean BMI, LVEF, and duration of MI were 27.62 ± 4.27, 35.30 ± 7.88, and 176.18 ± 5.65. There were 35 (31.8%) patients diagnosed with STEMI and 75 (68.2%) diagnosed with NSTEMI. There were 40 (36.4%) patients found with abnormal LVEF patterns and 70 (63.6%) with moderately to severely impaired LVEF. The majority of patients were diagnosed with NSTEMI (68.2%), reflecting contemporary trends in MI presentation. Importantly, a substantial proportion of patients 70 (63.6%) demonstrated moderately to severely impaired LVEF, highlighting the high burden of left ventricular systolic dysfunction in this cohort. These findings emphasize the continued clinical relevance of early and accurate assessment of LVEF in post-MI patients, particularly in populations with a high prevalence of cardiometabolic risk factors, as reflected by the elevated mean BMI in this study. A prior study also found that between 25% and 40% of individuals had acute anterior MI at the time of hospitalization [19]. The proportion of patients with significantly reduced LVEF in our cohort aligns with prior studies reporting that a considerable number of MI patients present with impaired systolic function at the time of hospitalization [19]. Previous literature indicates that pulmonary congestion or left ventricular systolic dysfunction occurs in approximately 13–32% of MI cases and is associated with a two- to threefold increase in the risk of subsequent mortality or heart failure–related hospitalization. Furthermore, earlier studies have demonstrated that nearly two-thirds of MI patients have LVEF values below 40%, reinforcing the prognostic importance of ventricular dysfunction in this population [19]. Information about left ventricular systolic function after MI is lacking, as ejection fraction (EF) was not typically measured. Just 73% of patients with STEMI and 61% of patients without had their EF evaluated in the 25 European countries that took part in the Euro Heart Survey, which looked at MI therapy [20]. As a result, there is a chance that the data presented contains selection bias. Patients with pulmonary congestion or left ventricular systolic dysfunction, which occur in 13–32% of MI cases, are two to three times more likely to die later or be admitted to the hospital as a result of heart failure. According to earlier research, 39% of patients had left ventricular ejection fractions (LVEFs) between 41% and 55%, 6% had LVEFs between 55% and 70%, and 65% of patients had LVEFs below 40% [19]. The study has a focused aim to determine the prevalence of LVEF patterns in AMI patients, which guides the research design and analysis. It investigates an important clinical parameter (LVEF) in AMI, providing data on STEMI/NSTEMI distribution and LVEF impairment, which can inform therapeutic decisions.

Using a non-random sampling technique may introduce selection bias, limiting the generalizability of the results to the broader AMI population. The study captures data at a single time point, so causal relationships between AMI types and LVEF patterns cannot be established. The study reports age and gender but lacks other potential confounders (e.g., comorbidities, medications) that could

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influence LVEF. A single-center setting (KEMU Affiliated Hospital, Lahore) may restrict the applicability of findings to other populations or settings. VT/VF was not assessed as an outcome variable in this study; therefore, effect modification analysis between age/BMI, MI type, and VT/VF could not be conducted. The study did not evaluate VT/VF incidence; therefore, no association could be drawn between LVEF category, MI type, and VT/VF risk. Use probability sampling in future studies to improve representativeness and reduce bias. Conduct a cohort design to assess changes in LVEF over time and its relation to therapeutic outcomes. Include additional variables such as comorbidities, treatment protocols, and echocardiographic details to enable multivariate analysis. Extend the study to multiple centers to increase sample diversity and external validity of the results. Investigate how LVEF patterns influence treatment choices and patient prognosis to bridge the knowledge gap mentioned in the background.

CONCLUSIONS

The results of this study showed that in patients with acute myocardial infarction, most of them (63.6% of the patients) had moderate-to-severe left ventricular ejection fraction (LVEF). Such results reveal the high prevalence of left ventricular dysfunction among this group and the urgent need to conduct routine, in-hospital LVEF evaluation to inform prognosis and maximize the effectiveness of evidence-based therapy.

Authors' Contribution

Conceptualization: AT
Methodology: MN, ZA, NS
Formal analysis: ZI, ZA, NUS, UGC, NS
Writing and Drafting: ZI, NS
Review and Editing: MN, ZI, ZA, NUS, UGC, NS, AT

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Comparison of Pain Intensity After Laparoscopic Cholecystectomy Between Patients with and Without Periportal Lidocaine Infiltration

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ABSTRACT

Early postoperative pain after laparoscopic cholecystectomy (LC) is largely related to port-site trauma. Peri-portal lidocaine infiltration is a simple technique used to reduce this discomfort, but evidence from local clinical settings remains limited. **Objectives:** To compare postoperative pain intensity between patients receiving peri-portal lidocaine infiltration and those undergoing LC without local anesthesia at a tertiary hospital in Karachi, Pakistan. **Methods:** This prospective cohort included 148 adults undergoing elective LC who were allocated to receive either periportal infiltration of 10 mL 2 % lidocaine (n=74) or no local anaesthetic (n=74). Pain at rest was assessed on a 10-cm visual analogue scale immediately post extubating and at 3, 6, 12, and 24 h. Secondary outcomes were time to ambulation, time to oral intake, and length of hospital stay. SPSS version 23.0 was used to analyze the data. **Results:** Pain scores were significantly lower in the lidocaine group at the immediate (3.42 ± 0.64 vs 4.38 ± 0.85, p=0.001), 3-hour (2.83 ± 0.63 vs 3.76 ± 0.63, p=0.001), and 6-hour assessments (1.95 ± 0.67 vs 2.53 ± 0.92, p=0.001). Patients receiving lidocaine mobilized earlier (4.43 ± 1.57 h vs 6.32 ± 2.37 h, p=0.001), resumed oral intake sooner (6.18 ± 1.52 h vs 7.70 ± 1.84 h, p=0.001), and had a slightly shorter postoperative stay (9.31 ± 1.57 h vs 9.99 ± 0.07 h, p=0.001). **Conclusion:** Peri-portal lidocaine infiltration effectively reduces early postoperative pain after LC.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is the procedure of choice for symptomatic cholelithiasis, offering distinct advantages over open cholecystectomy, such as smaller incisions, reduced blood loss, earlier ambulation, and shorter hospital stay [1-3]. LC, introduced in the mid-1980s, has become the standard surgical approach for symptomatic gallstone disease because it offers clear advantages over open surgery [4]. Even though LC is less invasive, it doesn't prevent postoperative complications, and pain is reported very frequently [1]. Parietal pain arises from the port-site incisions, visceral pain occurs from peritoneal irritation and dissection of the gallbladder from the hepatic bed, and referred shoulder pain arises in several patients because of phrenic nerve irritation due to residual carbon dioxide used during pneumoperitoneum [4-6]. This often results in a wide spectrum regarding the

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intensity of pain [1, 5]. In one study, Zedan et al. reported VAS scores ranging from 2 to 9 at 24 hours, underlining how patient experience can vary depending on operative technique and perioperative analgesia [7]. Nonsteroidal anti-inflammatory drugs, opioids, intraperitoneal local anesthetics instillation, transverse abdominal plane block, and subhepatic drainage are some analgesic maneuvers that have been utilized in the process to reduce this pain [7-10]. However, one or more of these methods may be limited by their side effects, inconsistent efficacy, or resource issues, especially in low- and middle-income countries (LMICs). Among them, infiltration with local anesthetics like lidocaine at the periportal site has gained attention as an easy, less expensive technique that can directly target parietal pain at port sites [4, 10]. This randomized trial, by Kiany et al. showed subcutaneous lidocaine injection at port sites was associated with a measurable reduction in postoperative opioid use when compared to instillation at the gallbladder bed [4]. Similarly, patients receiving 0.25% bupivacaine at port sites demonstrated significantly lower mean pain scores at 12 hours postoperatively (4.1 ± 1.21) compared to controls (7.95 ± 0.6) and thus described the clinical efficacy of local infiltration techniques [2]. Although promising in the international literature, there is a paucity of evidence from Pakistan that assesses the role of periportal lidocaine in enhancing postoperative pain and recovery in LC. Locally, Asad et al. compared day-case with conventional LC and demonstrated no difference in the intensity of pain on VAS; however, they identified early resumption of activity. The use of local anesthetics was not explored in this study [11].

This study among a Pakistani population will also test the feasibility and effectiveness of lidocaine use in public sector hospitals, where resource limitations are an important reason for pragmatic yet evidence-based interventions. This study aimed to identify the difference in postoperative pain intensity measured on the VAS in patients with and without periportal lidocaine infiltration after undergoing laparoscopic cholecystectomy.

METHODS

This was a prospective cohort study conducted at the Department of General Surgery in a tertiary care teaching hospital in Pakistan over a period of six months (June to December 2024). Ethical approval was obtained from the Institutional Review Board (IRB) of the respective institution, and the study was conducted in accordance with the Declaration of Helsinki (3507). The sample size of 74 participants per group (148 total) was calculated using the WHO sample size calculator, by considering 95% confidence interval, 80% power, pain score at 12 hours in the instillation group as 1.18 ± 0.39 and the infiltration group as 1.05 ± 0.22 post-laparoscopic cholecystectomy [4]. Eligible participants included adult patients aged 18–60 years scheduled for elective laparoscopic cholecystectomy for uncomplicated symptomatic cholelithiasis. All patients were classified as American Society of Anesthesiologists (ASA) physical status I or II. Exclusion criteria included patients with acute cholecystitis, gallbladder perforation, common bile duct stones, conversion to open cholecystectomy, allergy to lidocaine, coagulopathy, or significant comorbidities such as uncontrolled diabetes, cardiovascular disease, or renal or hepatic insufficiency. Written informed consent was taken. Samples were selected using a non-probability consecutive sampling technique. Patients were divided into two groups based on the anesthetic plan at the discretion of the attending surgeon. Group A (Intervention Group): Received periportal infiltration of 5 mL of 2% lidocaine at each port site immediately after creation of pneumoperitoneum, before trocar insertion. Group B (Control Group): Did not receive any local anesthetic at the port sites. All procedures were performed by consultant general surgeons with a standardized technique using four ports under general anesthesia. Pneumoperitoneum was established with CO_2, maintaining intra-abdominal pressure between 12 and 14 mmHg. No intraperitoneal or intramuscular analgesics were administered intraoperatively apart from standardized anesthesia. Postoperative pain intensity was assessed using the Visual Analogue Scale (VAS), with scores ranging from 0 (no pain) to 10 (worst imaginable pain). VAS scores were recorded at 3, 6, 12, and 24 hours postoperatively by nursing staff who were not involved in the surgical procedure and were unaware of group allocation. The lidocaine infiltration was conducted before the observer entered the operating area, and postoperative charts did not indicate intervention status. This approach ensured single-blind outcome assessment to minimize observer bias. Analgesic consumption was also recorded within the first 24 hours. Rescue analgesia in the form of intravenous diclofenac sodium (75 mg) was administered on the patient's request [12], and the total number of doses required within the first 24 hours was documented. Time to ambulation, time to oral intake, and total length of hospital stay were also recorded. Data were analyzed using SPSS version 23.0. Normality of continuous variables was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated with Levene's test. As assumptions were met, continuous variables were summarized as mean ± standard deviation and compared between groups using the independent t-test. Repeated-measures ANOVA was applied to evaluate changes in pain scores over time and interaction effects between time and group. Categorical variables were compared with the chi-square test. Effect sizes and 95%

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confidence intervals were calculated for between-group mean differences. A p-value <0.05 was considered statistically significant.

RESULTS

Out of 148, the mean age was 39.76±11.73 years, and the mean BMI was 26.09 ± 3.45 kg/m^2. About 97 (65.5%) were female, and 51 (34.5%) were male. ASA class II was reported in 89 (60.1%) participants. Hypertension was present in 36 (24.3%) participants, diabetes mellitus was present in 27 (18.2%) participants, and 13 (8.8%) participants had both conditions. Group-wise distribution of baseline characteristics is displayed in table 1.

Table 1: Baseline Characteristics of Study Participants (n=148)

Variables	Overall (n=148)	Lidocaine (n=74)	Control (n=74)	p-value
Age				
Years	39.76 (11.73%)	39.23 (11.41%)	40.30 (12.09%)	0.582
BMI (kg/m^2)	26.09 (3.45%)	25.88 (3.69%)	26.31 (3.20%)	0.458
Gender				
Male	51 (34.5%)	27 (52.9%)	24 (47.1%)	0.604
Female	97 (65.5%)	47 (48.5%)	50 (51.5%)	
ASA Status				
I	59 (39.9%)	25 (42.4%)	34 (57.6%)	0.131
II	89 (60.1%)	49 (55.1%)	40 (44.9%)	
Comorbid				
Hypertension	36 (24.3%)	19 (54.3%)	17 (47.2%)	0.755
Diabetes	27 (18.2%)	15 (55.6%)	12 (44.4%)	
Both	13 (8.8%)	5 (38.5%)	8 (61.5%)	
None	72 (48.6%)	35 (48.6%)	37 (51.4%)	

Data presented as Mean (SD) or n (%), BMI=Body Mass Index

Immediately after surgery, the lidocaine group reported a lower mean VAS score than controls (3.42 ± 0.64 vs 4.38 ± 0.85), with a mean difference of −0.95 (95% CI: −1.20 to −0.71; p=0.001). At 3 hours, pain remained lower in the lidocaine group (2.83 ± 0.63 vs 3.76 ± 0.64), corresponding to a mean difference of −0.93 (95% CI: −1.14 to −0.72; p=0.001). This difference persisted at 6 hours (1.95 ± 0.68 vs 2.53 ± 0.92), with a mean difference of −0.58 (95% CI: −0.85 to −0.32; p=0.001). By 12 hours, VAS scores had converged between groups (1.08 ± 0.47 vs 1.14 ± 0.32), with a non-significant mean difference of −0.05 (95% CI: −0.18 to 0.08; p=0.409). At 24 hours, pain levels were similarly low in both groups (0.99 ± 0.39 vs 0.95 ± 0.37), with a mean difference of 0.05 (95% CI: −0.08 to 0.17; p=0.463). A repeated-measures ANOVA demonstrated a significant overall within-subjects effect of time (p=0.001), indicating a steady decline in postoperative pain across all assessment points. Trend analysis showed a strong linear effect (p=0.001), consistent with progressive pain reduction throughout the first 24 hours. The between-subjects effect was also significant (p=0.001), confirming that, across all timepoints, patients who received lidocaine experienced lower overall pain scores than those in the control group. Postoperative pain scores were assessed at five predefined intervals and are illustrated in figure 1.

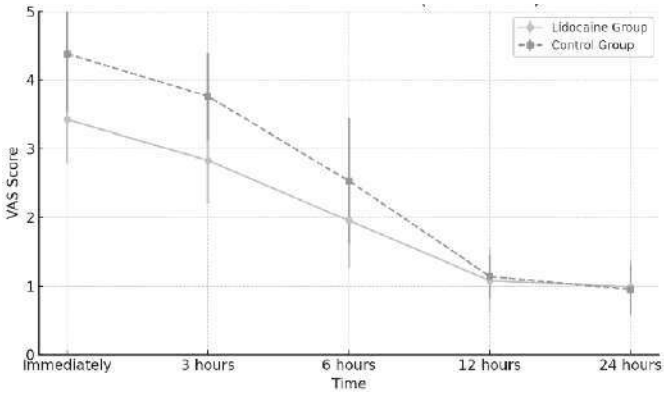

Figure 1: Comparison of Pain Scores at Five Time Points Between Both Groups (n=148)

Mean time to ambulation was 4.43 ± 1.57 hours in the lidocaine group and 6.32 ± 2.37 hours in the control group (p=0.001). Time to oral intake was 6.18 ± 1.52 hours in the lidocaine group compared to 7.70 ± 1.84 hours in the control group (p=0.001). Mean hospital stay was 9.31 ± 1.57 hours in the lidocaine group and 9.99 ± 0.07 hours in the control group (p=0.001), as shown in table 2.

Table 2: Comparison of Time to Ambulation and Oral Intake and Hospital Stay Between Both Groups (n=148)

Variables	Group	Mean ± SD	p-value
Time To Ambulation (Hours)	Lidocaine	4.43 ± 1.57	0.001*
	Control	6.32 ± 2.37	
Time To Oral Intake (Hours)	Lidocaine	6.18 ± 1.52	0.001*
	Control	7.70 ± 1.84	
Hospital Stay (Hours)	Lidocaine	9.31 ± 1.57	0.001*
	Control	9.99 ± 0.07	

*Significant at 5% level of significance

DISCUSSION

This cohort demonstrates that subcutaneous peri-portal infiltration of 2% lidocaine provides an early but time-limited analgesic benefit after laparoscopic cholecystectomy. Pain scores were significantly lower in the lidocaine group during the immediate (Δ=0.96) and 3-hour (Δ=0.93) assessments (both p=0.001). By 9 hours, differences between groups had narrowed substantially, and no significant advantages were observed at 12 or 24 hours. Despite the short pharmacologic duration of lidocaine, the reduction in early parietal pain was sufficient to produce clinically relevant functional gains, including earlier ambulation by nearly two hours, faster resumption of oral intake, and a modest reduction in postoperative stay. These improvements may be particularly valuable for enhancing patient turnover in resource-constrained public hospitals. The pattern observed here aligns with findings

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from a recent double-blind Iranian randomized trial in which subcutaneous lidocaine improved early pain scores without affecting 24-hour outcomes [4]. Studies evaluating longer-acting local anesthetics show a more prolonged effect. A Bangladeshi study using 0.25% bupivacaine reported significantly lower pain scores up to 12 hours [13], while a Turkish cohort demonstrated reduced pain at one hour but no advantage beyond 12 hours when bupivacaine was used at port sites [14]. Combined parietal–visceral techniques appear to extend analgesic duration. Ahmed *et al.* reported greater pain reduction when bupivacaine infiltration was paired with intraperitoneal irrigation of the gallbladder bed [15], and Egyptian data indicate that gall-bladder-bed lidocaine can effectively reduce visceral discomfort throughout the first postoperative day [16]. Collectively, these studies support the concept that addressing both somatic and visceral nociception may provide broader analgesic coverage than port-site infiltration alone. Our functional gains mirror systemic-lidocaine data. A Pakistani randomized trial of perioperative intravenous lidocaine recorded VAS 2.0 ± 0.49 versus 3.93 ± 0.94 at 12 h (p=0.001) and 0.73 ± 0.82 versus 2.2±0.61 at 24 h (p<0.001) and earlier ambulation (5.57 ± 1.55 h vs 7.30 ± 1.90 h; p=0.001) [17]. Local infiltration avoids infusion pumps and monitoring, therefore offering a low-cost alternative that aligns with enhanced-recovery targets [18-21]. Adjunct modalities could further prolong analgesia: reducing pneumoperitoneum pressure to 7–8 mm Hg halved postoperative opioid demand and lowered pain intensity in a 100-patient double-blind study [5], and sodium-bicarbonate peritoneal lavage decreased 24-h VAS by more than two units in a controlled study [7]. This study has several strengths. Its prospective design reduced recall bias, pain assessment was conducted by blinded nursing staff, and all procedures followed a uniform four-port technique performed by the same surgical team, minimizing operative variability. Baseline demographic and clinical variables were balanced between groups, enhancing comparability. Moreover, the inclusion of functional outcomes like ambulation time, oral intake, and length of stay provides a more comprehensive picture of postoperative recovery than pain scores alone. The setting of a high-volume government hospital increases the applicability of these findings to similar environments, where simple, low-cost analgesic strategies are particularly valuable. Future research should prioritize randomized controlled designs to reduce allocation bias and strengthen causal interpretation. Exploration of combined parietal–visceral blocks, such as port-site infiltration plus gall-bladder-bed instillation, may yield more sustained analgesia. Trials comparing lidocaine with longer-acting agents (e.g., bupivacaine, ropivacaine, or liposomal formulations) or adjuncts like dexamethasone would clarify whether extended coverage enhances functional recovery. Incorporating dynamic pain assessments, opioid usage, and patient-reported outcomes could offer a broader view of postoperative comfort. Finally, dedicated health-economic analyses are needed to determine whether improvements in early mobility and oral intake translate into meaningful cost savings in high-volume public-sector hospitals.

CONCLUSIONS

Peri-portal lidocaine infiltration provides meaningful early analgesic benefit after LC and contributes to faster immediate recovery milestones. Although its effect is time-limited, its simplicity, low cost, and ease of integration into routine surgical practice make it a useful component of postoperative pain management, particularly in resource-limited settings.

Authors' Contribution

Conceptualization: WNZ, MG
Methodology: WNZ, MG, MA, MDH
Formal analysis: WNZ
Writing and Drafting: WNZ, MA, ZS, MZ, MDH
Review and Editing: WNZ, MG, MA, ZS, MZ, MDH

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Association of TLR7 Variants with Secondary Bacterial Pneumonia in COVID-19 Patients

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ABSTRACT

Variations in the TLR7 gene have been linked to impaired immune signaling, which may increase a person's risk of developing secondary infections and developing severe COVID-19. **Objectives:** To investigate the relationship between variations in the TLR7 gene and the prevalence of co-infections and secondary bacterial pneumonia among hospitalized COVID-19. **Methods:** A case-control study was a hospital-based study done among 200 RT-PCR-confirmed COVID-19 patients. The secondary bacterial pneumonia (SBP) was determined as another type of clinical deterioration that appeared over 48 hours of admission and was proven by radiological infiltrates and the increase of inflammatory factors; the microbiological confirmation was viewed as supportive but not obligatory. Hardy-Weinberg equilibrium of the female control group was checked, and the genotype was determined with the help of Taqman SNP assays. **Results:** The average age of the participants was 45.6 ± 12.3 years, and 60 percent of them were men. Among the SBP cases, 85% had microbiological confirmation, while 15% fulfilled predefined clinical, radiological, and inflammatory marker-based criteria for SBP despite negative cultures. Hence, pathogens in SBP cases were *Klebsiella pneumoniae* 25%, as well as *Staphylococcus aureus* 35%. **Conclusions:** TLR7 gene polymorphisms were substantially linked to a roughly three-fold higher risk of secondary bacterial pneumonia in this cohort of hospitalized COVID-19 adults, ages 18 to 65. These results imply that bacterial superinfection may be predisposed by compromised TLR7-mediated antiviral innate responses.

INTRODUCTION

Coronavirus is one of the most important disease-causing organisms, specifically infections in adults and children associated with the upper respiratory tract [1]. Coronavirus outbreaks have been associated with Pneumonia, Middle East respiratory disease (MERS), severe acute respiratory syndrome (SARS), and an emerging coronavirus that originated in Wuhan, China [2, 3]. These early investigations either reported very few cases, found no cases at all, or failed to note the presence of secondary infections or co-infections [4, 5]. Though host factors such as age, comorbidity, mechanical ventilation, and corticosteroid use are reported risk factors that regulate the occurrence of SBP in COVID-19, there is little information regarding how the host genetic susceptibility regulates the susceptibility to secondary infections by bacteria. The X-linked toll-like receptor 7 (TLR7) is a vital part of early antiviral immunity, detecting single-stranded RNA viruses and triggering type I interferon responses, which are required to initially clear viruses and regulate immunity. Research using both human and murine models shows that TLR7 loss-of-function or deficiency variants are linked to worse COVID-19, higher

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viral loads, and impaired interferon activation [6]. The role of the innate immune system in regulating the intensity and course of viral infections has been highlighted by the COVID-19 pandemic [7]. To recognize the receptor on the pattern, a Toll-like receptor 7 (TLR7) on the X chromosome is a very important requirement against RNA viruses for the host's defense [8]. Hence, type I interferon (IFN) responses depend on Antiviral immunity, which is usually triggered when single-stranded RNA is detected by TLR7 [9]. TLR7 genetic variants assist in overcoming the interference in IFN signaling and render the individual vulnerable to a severe form of COVID-19 and secondary infections, which disrupts the signaling of interferon and prolongs the viral replication [10]. A recent study revealed that variants in the TLR7 gene have been linked to the severity of COVID-19. A study conducted by Zhang *et al.* revealed that inborn errors were observed in type I IFN immunity [11]. As a result, the early antiviral response is affected, leading to increased chances of secondary bacterial infections, such as pneumonia, which ultimately leads to death and is one of the causes of morbidity among patients of COVID-19 [12]. Hence, an association exists between bacterial co-infections and higher mortality rates among COVID-19 patients, emphasizing that initial identification of disease is essential along with definitive care [13]. The host immune system is weakening, leading to serious infections of the respiratory tract due to a combination of various viral and bacterial pathogens. Understanding of genetic variables, specifically those that cause secondary infections are essential as they help to develop treatment regimens [14].

According to physiological principles, a lack of early antiviral defense may allow for prolonged viral replication, epithelial damage, and dysregulated innate immunity, all of which are favorable conditions for bacterial colonization and superinfection. It is of great interest to evaluate TLR7 genetic variation as a risk factor for SBP in COVID-19 because of this biological plausibility and the clinical implications. The study aimed to determine the connection between functional TLR7 single-nucleotide polymorphisms (rs179008, rs179009, rs179010), specific TLR7 gene polymorphisms, and incidence of secondary bacterial pneumonia in patients with COVID-19 aged 18 to 65 years who had controlled the known clinical risk factors.

METHODS

The study took place in Ziauddin University Hospital, Karachi, Pakistan, from June 2022 to March 2023 as a case-control study at a hospital. Ziauddin University Ethical Review Committee granted ethical approval to the study (Reference Code: 5360522BKBC). Informed consent of all the participants was carried out in written form, and the confidentiality of patient information was upheld during the study. Consecutive enrolment of 200 COVID-19 patients admitted to the hospital and confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) was used. The conventional formula to compute sample size was n=Z2P(1-P)/ d 2, where prevalence is assumed to be 42 percent among COVID-19 patients hospitalized with secondary bacterial pneumonia (SBP), where Z=1.96 is a 95 percent confidence interval, and d=5 represents the margin of error. Operationally, secondary bacterial pneumonia was defined as a clinical deterioration that was new, more than 48 hours after admission, and had new or progressive radiologic infiltrates, with an increase in the level of inflammatory markers. Microbiological culture positivity was regarded as supportive and not obligatory in the diagnosis of SBP, especially in patients who had prior experience with broad-spectrum antibiotics, which are known to lower the bacterial culture yield. Patients who met these clinical and radiological criteria were included in the cases, and COVID-19 patients who never developed SBP during hospital stay as controls. Those patients who showed a case of bacterial infection in the first 48 hours of admission were classified as co-infected and were disqualified from the study. Patients more than 65 years, patients with pre-existing immunodeficiency disorders, patients who had received systemic antibiotics in the 48 hours before admission, and patients who had bacterial co-infection documented at admission were excluded to reduce the confounding factors. It included patients aged between 18 and 65 years as the final study population. Hospital medical records were used to gather demographic and clinical data, such as age, sex, comorbidities (diabetes mellitus and hypertension), smoking status, intensive care unit admission, mechanical ventilation, steroid use, as well as the severity of the disease based on World Health Organization criteria, on a structured data collection form. In suspected patients of SBP, aseptic collection of sputum and /or blood samples was done after 48 hours of admission to the hospital and subjected to processing in the microbiology laboratory by the use of standard culture techniques. The identification of bacteria was done through Gram staining, morphology, and biochemical identification through the API 20E system (bioMérieux). The Kirby-Bauer disk diffusion test was used to perform the antibiotic susceptibility test in line with Clinical and Laboratory Standards Institute guidelines. Genetic analysis of approximately 3 mL of peripheral blood in EDTA tubes was done on each participant. The QIAamp DNA Mini Kit (Qiagen) was used to extract the genomic DNA according to the directions of the manufacturer. The Nanodrop spectrophotometer was used to determine the concentration and purity of DNA. TLR7 SNP genotyping. Geno-typing of TLR7 SNP genotyping assays, including pre-

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designed TaqMan SNP genotyping assays, was completed on a QuantStudio 5 Real-Time PCR System. The assays involving the primer and probes are highly confidential and thus are not publicly revealed. The thermal cycling conditions were as follows: denaturation at 95 °C/10 minutes, 40 cycles of denaturation at 95 °C/15s and annealing/extension at 60 °C/1min with a final extension at 72 °C/5min. QuantStudio Design and Analysis Software was used to perform allelic discrimination and genotype calling. The fluorescence signal clustering was used to assign genotypes and categorize them as homozygous wild-type, heterozygous, or homozygous variant. The samples that had unclear amplification curves or low levels of fluorescence intensity were resampled, and only the sample with a conclusive genotype was incorporated into the final analysis. Since TLR7 is an X-linked gene, the Hardy-Weinberg equilibrium was evaluated in female-only participants who were considered as controls. There was no major difference in the Hardy-Weinberg equilibrium. The independent t-test was used when comparing continuous variables, and the chi-square or Fisher's exact test was used to compare the categorical variables, depending on the type. TLR7 polymorphic variations of developing secondary bacterial pneumonia were assessed using logistic regression analysis and adjusted in the presence of appropriate confounding variables. Additive and dominant models of genetic interactions were used. Multiple testing was corrected by Bonferonni test, the statistical significance of which was $p < 0.017$. There were odds ratios and 95 percent confidence intervals.

RESULTS

The total number of patients included was 200 hospitalized RT-PCR-confirmed COVID-19 patients, including 100 cases of secondary bacterial pneumonia (SBP) and 100 controls who did not have SBP. Among the 100 SBP cases, 85 patients (85%) were microbiologically confirmed bacterial pneumonia, and 15 patients (15 percent) had predefined clinical, radiological, and inflammatory marker-based criteria of SBP even in negative cultures. The average age of the study population was 45.6 ± 12.3 years, and there was no significant variance in age between the SBP cases and the controls (46.2 ± 11.9 vs. 45.0 ± 12.7 years; $p > 0.05$) (Table 1).

Table 1: Clinical and Demographic Characteristics of COVID-19 Patients (n=200)

Variables	Cases (n=100)	Controls (n=100)	Total (n=200)
Age (Mean ± SD)	46.2 ± 11.9	45.0 ± 12.7	45.6 ± 12.3
Male Sex, n (%)	62 (62%)	58 (58%)	120 (60%)
Hypertension, n (%)	38 (38%)	32 (32%)	70 (35%)
Diabetes Mellitus, n (%)	30 (30%)	26 (26%)	56 (28%)
Smoking History, n (%)	20 (20%)	16 (16%)	36 (18%)
Severe/Critical Disease, n (%)	35 (35%)	25 (25%)	60 (30%)

The identification of the bacterial pathogen was conducted only among culture-confirmed cases of SBP (n=85). The most isolated ones were *Staphylococcus aureus* (35%), *Klebsiella pneumoniae* (25%), then *Pseudomonas aeruginosa* (15%), and *Escherichia coli* (10%) (Table 2).

Table 2: Microbiological Profile of Culture-Confirmed SBP Cases (n=85)

Variables	p-value
Staphylococcus aureus	30 (35%)
Klebsiella pneumoniae	21 (25%)
Pseudomonas aeruginosa	13 (15%)
Escherichia coli	9 (10%)
Others	12 (15%)

Variants of TLR7 were much more common in SBP cases than in the controls (21% vs. 7%, p=0.004). The most common SNP identified in the analysis is the most common variant; 12 per cent of the cases of SBP carried the SNP rs179008. Female control genotype was in Hardy-Weinberg equilibrium (kh^2=0.49, p=0.48) (Table 3).

Table 3: Distribution of TLR7 Variants in COVID-19 Patients (n=200)

SNP	Cases n (%)	Controls n (%)	p-value
rs179008	12 (12%)	4 (4%)	0.037
rs179009	4 (4%)	2 (2%)	0.420
rs179010	5 (5%)	1 (1%)	0.090
Any TLR7 Variant	21 (21%)	7 (7%)	0.004

The multivariate logistic regression analysis revealed that the presence of the TLR7 variant was directly linked with a secondary bacterial pneumonia, with the possibility to control the potential confounders (adjusted OR=3.2, 95% CI 1.5-6.8, p=0.002). Mechanical ventilation and ICU admission were also important predictors; age, sex, diabetes, hypertension, and steroid use were statistically not important (Table 4).

Table 4: Multivariable Logistic Regression Analysis of Factors Associated with SBP

Variables	Adjusted OR	95% CI	p-value
Presence of TLR7 Variant	3.2	1.5–6.8	0.002
ICU Stay	2.3	1.1–4.8	0.028
Mechanical Ventilation	2.9	1.3–6.6	0.011
Age (>50 years)	1.4	0.8–2.4	0.210
Male Sex	1.1	0.6–2.0	0.790
Diabetes Mellitus	1.6	0.8–3.1	0.170
Hypertension	1.4	0.7–2.8	0.290
Steroid Use	1.2	0.6–2.5	0.590

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DISCUSSION

This study assessed the relationship between secondary bacterial pneumonia development and polymorphisms of the X-linked receptor gene TLR7 in hospitalized COVID-19 patients. To improve generalizability and evaluate age-related immune effects, future research involving senior populations is necessary. The fact that there are clinically diagnosed cases of SBP that are not culture-confirmed is indicative of what is happening in the real world of the diagnosis of SBP in hospitalized COVID-19 patients. The carriers of any of the three assayed SNPs (rs179008, rs179009, rs179010) had significantly higher odds (adjusted OR 3.2, 95 % CI 1.5–6.8, p=0.002) of developing secondary bacterial pneumonia after adjusting for known confounders (age, sex, diabetes mellitus, hypertension, ICU stay, mechanical ventilation, steroid use). The genotype frequency in cases (21%) was substantially higher than in controls (7%). These results imply that in the context of a severe viral respiratory infection, TLR7 genetic variation may increase susceptibility to bacterial super-/secondary infection. When single-stranded RNA viruses are detected, the endosomal pattern recognition receptor TLR7 initiates the production of type I interferon (IFN-α and IFN-β), which is crucial for antiviral defense [10]. This gene's variations may affect the antiviral response, resulting in delayed viral clearance and heightened susceptibility to bacterial infections [11]. The most common TLR7 variant in our cohort was rs179008, which was present in 12% of patients. According to the analysis, even after controlling for comorbidities, age, and sex, patients with TLR7 variants had more than three times the chance of getting secondary bacterial pneumonia than patients without variants (OR=3.2, 95% CI: 1.5–6.8, p=0.002). analysis. According to earlier research, rare TLR7 mutations make people more vulnerable to severe COVID-19 outcomes because they impair type I IFN responses. These findings are in line with those findings [15, 16]. According to previous studies, the high prevalence of Gram-positive and Gram-negative co-infections in severe COVID-19, *Staphylococcus aureus* (35%) and *Klebsiella pneumoniae* (25%), made up most secondary bacterial infections [17, 18]. Significantly, 40% of the bacterial isolates showed signs of antibiotic resistance, highlighting the need for targeted antimicrobial therapy and the clinical difficulties in treating co-infections. The impaired TLR7-mediated type I IFN signaling can enhance early antiviral responses, which prevent epithelial injury and bacterial colonization and therefore augment the probability of secondary pneumonia [19, 20]. Notably, SBP inclusion was intentional and predefined. This is true to the reality of hospitalized COVID-19 patients, as it is difficult to diagnose in the real world, where previously exposed antibiotics cause the culture yield to decrease substantially. The same diagnostic methods have been generally adopted within the research of hospital-acquired and ventilator-associated pneumonia, especially in the case of critically ill patients. These findings suggest that genetic predisposition plays a significant role in the clinical course of COVID-19 and highlight the significance of TLR7 as a crucial modulator of both antiviral and antibacterial defense pathways [21, 22].

This study has some limitations as the sample size of the study was less due to which the results may not be as broadly applicable. Another limitation of the study design itself due to which the causal relationship between TLR7 variants and secondary bacterial pneumonia was not possible. Furthermore, a thorough assessment of the host's genetic characteristics, environmental exposures, and viral load that could influence susceptibility to co-infections was lacking. Due to the limited number of TLR7 variants that were analyzed, additional polymorphisms or epigenetic modifications might also increase the risk of developing a disease. These findings allow for several recommendations. Furthermore, the study protocol specifically included clinically diagnosed, culture-negative SBP cases to replicate actual diagnostic procedures. This method has been extensively employed in comparable clinical investigations and is in line with recognized diagnostic standards for hospital-acquired and ventilator-associated pneumonia in critically sick patients. Hence, routine genetic screening for TLR7 variants may help identify hospitalized COVID-19 patients who are more susceptible to secondary bacterial infections, particularly those who are at risk of severe illness. Early intervention strategies like timely antiviral and targeted antibacterial therapy may be beneficial for patients with harmful TLR7 variants.

CONCLUSIONS

The study concludes that the carriers of TLR7 gene polymorphisms showed a notably higher predisposition to secondary bacterial pneumonia in patients with COVID-19 infection hospitalized between 18 and 65 years. These data points on the correlation between defective antiviral innate immunity and vulnerability to bacterial superinfection. Although the findings highlight how host genetic factors may play a significant role in disease development, it will take additional large-scale, multicenter research before TLR7 genotyping is factored into a regular clinical risk assessment or customized antimicrobial treatment plans.

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Authors' Contribution

Conceptualization: BK, SB
Methodology: HF, AB
Formal analysis: BK, FA, AJ
Writing and Drafting: SB, HF
Review and Editing: BK, SB, FA, HF, AJ, AB

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Psychological Impact of Infertility on Couples: A Cross-Sectional Study of Coping Strategies

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ABSTRACT

Infertility is not only a biomedical concern but also a source of considerable psychological stress for both partners, affecting emotional health and relationship functioning. The distinct emotional and coping processes of infertile couples necessitate understanding emotional distress for the planning of structured psychosocial support. **Objective:** To evaluate the psychological effect of infertility and find the coping mechanisms employed by infertile couples attending Maqsood Medical Complex and General Hospital, Peshawar. **Methods:** This cross-sectional descriptive study was carried out from April 1st, 2025, to September 30, 2025, on 130 infertile couples. Data were gathered on sociodemographic characteristics, the Hospital Anxiety and Depression Scale (HADS), and the Brief COPE inventory. The means ± SD were calculated for continuous variables, the frequencies were calculated for categorical variables, while the associations of coping strategies with psychological distress were handled using chi-square and Pearson correlation tests. **Results:** Of the 130 couples studied, 61.5% reported clinically significant anxiety and 49.2% reported depressive symptoms. Female partners consistently had higher mean scores for anxiety and depression than their male counterparts. Problem-focused coping (planning, active coping, and positive reframing) was related to lower levels of distress, while avoidant and emotion-focused coping were associated with higher anxiety and depression. **Conclusions:** Infertility carries a significant emotional burden, especially for women, and emotional coping strategies have a strong bearing on the psychological impact. It is critical that couple-focused psychosocial support and stress-management counseling be integrated into the psychosocial aspects of infertility care.

INTRODUCTION

Infertility is not only a biomedical condition but also a profound psychosocial stressor that affects both members of a couple across emotional, relational, and social domains. The impacts of infertility often correlate with increased feelings of anxiety, depression, grief, and self-loathing; these psychological impacts usually surface at the time of diagnosis and tend to linger during the course of treatment or attempts at conception thereafter [1]. Recent global reviews more than confirm the presence of anxiety and depression along with reduced quality of life, reinforcing the presence of infertility as a global issue for mental health and not just a problem limited to certain contexts [2]. It is the couple, and not just one person, who bears the brunt of the impact: partners' emotional responses and coping mechanisms are bidirectionally interdependent, with one spouse's maladaptive coping worsening the other's psychological distress as well as the relational dyad's functional construct [3]. Longitudinal and cross-sectional studies have shown that some modalities, such as meaning-based and problem-focused coping, tend to protect the quality of the marriage, while avoidance and self-blame are reliably associated with heightened distress [4, 5]. It is clear that because infertility is a mutual stressor, dyadic approaches that examine both partners' coping and interactions are more clinically useful than approaches that focus on one partner. The sociocultural environment

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greatly influences the psychological burden of individual constituents. Stigmas associated with infertility in women is amplified in cultures where motherhood is conferred with social standing. This stigma, in turn, amplifies emotional distress and causes women to avoid seeking help [6]. The situational factors of the context clearly define the acceptable coping strategies, such as religion and social disengagement. Considering the clear evidence of the interdependence between psychological symptoms and the unfolding of interpersonal relationships, the practice of routine psychosocial assessment, as well as psychosocial treatment of the couple, has been integrated into the standard approach of international policies on sexual and reproductive health [7, 8]. There is emerging evidence in favor of brief psychotherapies and couple counseling that center the couple as the main therapeutic agents, focusing on adaptive coping and reducing the persistent ruminative self-blame, and poor inter-partner dyadic communication [9]. These well-being-enhancing strategies are also treatment adherence-promoting interventions. The goal of the current cross-sectional study is to quantify distress and the coping methods utilized by couples who come for fertility assessment to our center and examine the dyadic interdependence of coping and mental health. Stress and coping frameworks, alongside qualitative methods, will be employed to make our conclusions not only relevant to the context but also aligned with the international body of work.

Although it has been established that infertility is a psychosocial stressor that is shared, much research and clinical interest are yet to be conducted on dyadic coping and psychological interdependence, especially when dealing with diverse sociocultural backgrounds. The study aimrf to evaluate the psychological distress and coping in couples who refer to fertility assessment, and also investigate the interdependent nature of couples' coping strategies and mental health outcomes.

METHODS

This cross-sectional study with psychological impact of infertility and coping strategies used by couples went on from (April 1st, 2025 – September 30 2025) at Maqsood Medical Complex General Hospital, Peshawar. For the fulfillment of this objective, clinic-based surveys were used to collect data from couples visiting the clinic for infertility assessment and treatment. Both partners were invited to partake in the study, and the couple-level data were collected along with individual data after the couple-level informed consent was attained. The inclusion criteria consisted of heterosexual couples who had ≥12 months of regular unprotected intercourse and were seeking to have an infertility evaluation. Women between 18 and 45 years and men between 18 and 55 years of age were considered for the study. However, couples were not considered for the study if either partner had a 'major psychiatric illness' such as schizophrenia or bipolar disorder and was currently undergoing psychiatric treatment, or if the woman was at the stage of physiological gestation during the recruitment process. Couples who did not actively experience infertility and already had a biological child were not considered as those with severe illness or linguistic obstacles that hindered them from completing the questionnaire. The sample size was calculated a priori for the primary comparison of psychological distress between female and male partners (paired design) using a two-sided α=0.05 and 80% power. Based on prior literature showing small-to-moderate gender differences in anxiety/depression among infertile couples, an effect size of d=0.40 was assumed [10]. As the primary objective was to compare psychological distress between female and male partners using a paired design, the sample size calculation was based on the expected standardized mean difference rather than the estimation of depression prevalence. Under these assumptions, the minimum required sample was approximately 50–70 couples (depending on the within-couple correlation), and after inflating for incomplete/non-response data, a target of ~80 couples was set. We therefore recruited 130 couples (260 individuals) to ensure adequate power for paired comparisons and to support multivariable analyses. The non-probability convenience (consecutive) sampling technique was used in sampling, whereby all eligible and willing couples present in the infertility clinic within the time period of the study were approached and sampled. Structured questionnaires administered by the interviewer in a confidential environment were used as a method of collecting data. The partners were also interviewed individually to avoid influencing each other. The questionnaire contained three parts, namely sociodemographic and clinical data, clinical assessment with the help of the validated tool like the Hospital Anxiety and Depression Scale (HADS), and the assessment of coping strategies with the help of the Brief COPE inventory [11, 12]. Psychological distress and coping were measured using validated instruments. The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire (7 anxiety, 7 depression) with the items scored on a 0-3 scale to generate subscale scores of 0-21; the scores were interpreted as 0-7 normal, 8-10 borderline abnormal, and 11-21 abnormal with a cut-off of ≥8 on any of the subscales, used to indicate clinically significant anxiety or depression. The Brief COPE (28-item) was used to measure coping strategies in terms of 14 subscales (2 items) rated 1-4, where a higher score indicated a correspondingly higher use of the given coping strategy, and the subscales were

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then subjected to the analysis in terms of broader domains (problem-focused, emotion-focused, and avoidant coping). Suitable original validation sources were found in the case of HADS and Brief COPE. All participants received a comprehensive account of the study purpose and procedures, and provided written informed consent. Ethical approval was obtained from the Hospital Research & Ethics Committee of Maqsood Medical Complex General Hospital (reference #62/MMCGH03/25), and for the entire study, confidentiality was upheld. Couples exposed to considerable psychological distress were referred for counseling and additional evaluation to an appropriate mental health professional.

Data entry and subsequent analyses were conducted using SPSS version 26.0. Data were summarized using descriptive statistics by calculating means and standard deviations for continuous variables as well as frequencies and percentages for categorical variables. Comparisons between male and female partners were evaluated using paired statistical tests, while factors associated with anxiety, depression, and coping styles were assessed using logistic and linear regression analyses. The threshold for statistical significance was set at $p<0.05$.

RESULTS

We utilized a sample of 130 infertile couples, which corresponds to 260 individuals. The women had a mean age of 31.4 ± 5.8 years, while men had a mean age of 35.7 ± 6.4 years. The sample population was made up of participants mostly from urban regions, which was 61.5%, while 70% of couples had a household income of less than PKR 100,000. The majority of women, 113, which forms 78.5%, were unemployed, while 66.2% of men were employed as skilled workers and above. Out of the total sample population, primary infertility was recorded from 84 couples, which corresponds to 64.6%, while the remaining 46 couples, which is 35.4%, had secondary infertility. The mean duration of infertility was 4.2 ± 2.1 years (Table 1).

Table 1: Sociodemographic and Clinical Characteristics of the Study Participants

Variables	Female Partner, n (%)	Male Partner, n (%)
Mean Age (Years)	31.4 ± 5.8	35.7 ± 6.4
Residence		
Urban	80 (61.5%)	80 (61.5%)
Rural	50 (38.5%)	50 (38.5%)
Occupation		
Employed	28 (21.5%)	86 (66.2%)
Housewife or Unemployed	102 (78.5%)	44 (33.8%)
Monthly Household Income < PKR 100,000	91 (70%)	91 (70%)
Type of infertility		
Primary	84 (64.6%)	–
Secondary	46 (35.4%)	–
Duration of infertility (Years, Mean ± SD)	4.2 ± 2.1	–

Clinically significant findings of anxiety were recorded according to the Hospital Anxiety and Depression Scale (HADS), and documented anxiety levels of women were 38.5%, while those of men were 24.6%. The population diagnosed with depressive symptoms was 32.3% of women and 18.5% of men. Women had a mean anxiety score of 10.6 ± 3.8, which was statistically higher than men with a score of 8.4 ± 3.2 ($p < 0.001$). Being less than the defined alpha threshold statistically confirms the result. Women again were able to report higher mean scores of depression, which was 9.8 ± 3.6, compared to the men with a score of 7.9 ± 3.3 ($p = 0.002$) (Table 2).

Table 2: Psychological Distress Among Male and Female Partners (HADS Scores)

Variables	Female Mean ± SD	Male Mean ± SD	p-value
Anxiety Score	10.6 ± 3.8	8.4 ± 3.2	<0.001
Depression Score	9.8 ± 3.6	7.9 ± 3.3	0.002
Anxiety Present (HADS ≥ 8)	50 (38.5%)	32 (24.6%)	0.010
Depression Present (HADS ≥ 8)	42 (32.3%)	24 (18.5%)	0.008

According to problem-focused coping (active coping, planning, positive reframing), the Brief COPE Inventory is the most frequently used by both genders, although more frequently used by men. On the other hand, more females used emotion-focused coping (seeking emotional support, religion, acceptance). Avoidant coping (denial, disengagement, and substance use) was identified in 28.5% of men and 34.6% of women, and with a significant association to raised anxiety and depression scores ($p<0.05$) (Table 3).

Table 3: Coping Strategies Used by Infertile Couples (Brief COPE Subscale Scores)

Variables	Female Mean ± SD	Male Mean ± SD	p-value
Problem-focused coping	24.6 ± 5.2	25.8 ± 4.7	0.120
Emotion-focused coping	26.9 ± 4.9	23.5 ± 5.1	<0.001
Avoidant coping	18.2 ± 4.3	16.7 ± 3.9	0.030

Given the strong inverse association of anxiety ($r = -0.42$) and depression ($r = -0.38$) with problem-focused coping, it could be said that these results demonstrate the change in problem-focused coping to anxiety and depression. In contrast, avoidant coping was related to anxiety ($r=0.49$) and depression ($r=0.45$). A positive correlation was also found with emotion-focused coping. In this case its religious and acceptance self-blame and venting with the distress (Table 4).

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Table 4: Correlation between Coping Strategies and Psychological Distress

Variables	Anxiety (r)	Depression (r)	p-value (Anxiety)	p-value (Depression)
Problem-Focused Coping	-0.42	-0.38	<0.001	<0.001
Emotion-Focused Coping	0.15	0.12	0.090	0.160
Avoidant Coping	0.49	0.45	<0.001	<0.001

[After controlling for the age, duration, and type of infertility, the multivariate regression analyses identified avoidant coping (β=0.36, p<0.001) and female gender (β=0.29, p=0.002) as significant contributors to increased psychological distress.]

The study observed a moderate positive correlation (r = 0.54, p < 0.001) between partners' coping styles, which suggested mutual influence among spouses regarding coping behaviors. Couples' discordancy on coping, relative to concordancy on problem-focused coping, was associated with marked increases in joint distress (Table 5).

Table 5: Concordance of Coping Strategies between Partners and Mean Distress Scores

Coping Strategy	Low Anxiety / Depression (n=66)	High Anxiety / Depression (n=64)	χ^2	p-value
Problem-Focused Coping (Active Coping, Planning, Positive Reframing)	45 (68.2%)	21 (32.8%)	10.92	0.001
Emotion-Focused Coping (Acceptance, Religion, Emotional Support)	14 (21.2%)	25 (39.1%)	4.66	0.031
Avoidant Coping (Denial, Behavioral Disengagement, Self-Blame)	7 (10.6%)	18 (28.1%)	6.84	0.009

DISCUSSION

The outcomes of the study indicate the stark reality of the psychological impact of infertility on couples, especially women, who suffer from depression and anxiety. In addition, the outcomes indicate that distress was lower among those who practiced problem-focused coping, and higher psychological morbidity was found among avoidant copers. These outcomes support the evidence being generated from different parts of the world on the psychosocial aspects of infertility. The overall prevalence of anxiety and depression among women in this study, 38.5% and 32.3%, respectively, is not different from other studies in the region and abroad. Simionescu *et al.* for example, found that close to a third of infertile women suffer from clinically significant psychological distress [13]. This emphasizes the need to view infertility as a chronic stressor, not a medical issue, a position taken by many. Similarly, Cousineau *et al.* recognize infertility as one of the more distressing life events concerning emotional reaction, on the same par as chronic illnesses such as cancer and HIV [14]. The disparity in the anxiety and depression scores in our sample, with women faring worse, is consistent with the results of Peterson *et al.* who found that women undergoing infertility treatment showed more emotional self-blame, in contrast to men who stayed quiet and were emotionally withdrawn [15]. Hasanpoor-Azghdy *et al.* have illustrated that in the South Asian and Middle Eastern settings, the emotional and marital conflicts that arise due to infertility are disproportionate in women due to the existence of a strong stigma directed socially towards women, especially in the case of infertility [16]. Inferring the same set of sociocultural factors, in our study, an expectation of early pregnancy and the stigma of infertility being of female origin are likely factors in the disproportionate psychological stress that women endure throughout the process. In this study, the problem and emotion-focused coping strategy prevalence mirrors the findings of Mohammadi *et al.* who noted that positive reframing, stress planning, and religious coping are characteristic of infertile couples [17]. Analogously, the study of Gourounti *et al.* has shown that the use of active coping and positive reinterpretation during assisted reproduction is beneficial in stress reduction, stressing the importance of adaptive coping [18]. In contrast, the findings of our study relating avoidant coping to high levels of anxiety and depression are in line with the findings of Reisi *et al.* who showed that avoidant coping in one partner negatively influences both partners' psychological well-being through dyadic interdependence [19]. The value of moderate concordance found between partners' coping styles (r = 0.54, p < 0.001) reinforces the idea that coping behaviors among couples are interdependent. This observation is in line with the dyadic stress model of Falconier *et al.* who argue that couples' responses to infertility are interdependent, and supportive communication lessens the ache [20]. Current findings also indicated that couples with shared problem-focused coping styles reported the lowest combined distress, highlighting the need for couple-based approaches as the primary form of intervention, rather than individual counseling. The mean duration of infertility (4.2 years) in the present study was in line with what has been reported by Hwang *et al.* in which the prolonged duration of infertility has been associated with progressive emotional exhaustion and a dwindling adherence to the treatment [21]. The inverse association between problem-focused coping and psychological distress signals, improving the case for psychological counseling, to which Braverman *et al.* have been a strong advocate for the mental infertility care framework, in which mental healthcare is embedded in the everyday practice of infertility care [22]. Overall, the study's findings support the notion that infertility is a shared emotional experience, and addressing the psychological component alongside medical treatment

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can improve outcomes and quality of life for both partners. Also, the findings of the study suggest that distress and avoidant coping should be identified as problems that require early intervention and counselling. This may suggest that in our context, the stigma of emotions and the gendered expectations would be strongest in those contexts, which is why couple therapy that emphasizes communication, joint conflict resolution, and emotional control may help the most.

This study has several limitations. It used a cross-sectional design, so relationships between coping and psychological distress were examined at one point in time. The sample was recruited from a clinical setting and included mostly urban participants, which may limit representation of the wider infertile population. Psychological distress and coping were assessed through self-report questionnaires rather than clinical diagnostic interviews. In addition, some relevant psychosocial factors and the emotional interdependence between partners were not fully included in the analysis.

CONCLUSIONS

The results analysis indicates that infertility has adverse psychological effects on both partners, with greater vulnerability in women towards anxiety and depression. The type of coping strategy adopted is instrumental in predicting emotional well-being; couples using problem-focused coping exhibited better adjustment compared to avoiding and emotion-centered coping. These results reinforce the need for infertility to be treated as a medical and psychological problem simultaneously.

Authors' Contribution

Conceptualization: MY
Methodology: UU, LS
Formal analysis: NR
Writing and Drafting: UU, NR, LS
Review and Editing: MY, UU, NR, LS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Safety and Efficacy of Intravenous Brivaracetam versus Levetiracetam in the Management of Status Epilepticus in Children

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ABSTRACT

Status epilepticus (SE) is one of the most common pediatric neurological emergencies and a major cause of all pediatric epilepsy-related hospital admissions. **Objectives:** To compare the safety and efficacy of intravenous (IV) brivaracetam versus levetiracetam in the management of SE in children. **Methods:** This randomized controlled trial was performed at the Department of Pediatric Neurology, Institute of Child Health, Multan, Pakistan, from January to September 2025. A total of 152 children (76 in each group), aged 1 month to 16 years with SE, were randomly assigned to receive IV brivaracetam (2 mg/kg) or levetiracetam (40 mg/kg). Seizure cessation within 30 minutes of infusion, time to cessation, recurrence, hospitalization duration, and adverse events were documented. Data were analyzed using SPSS v26.0, with $p<0.05$ considered significant. **Results:** In a total of 152 children, the median age was 6.2 years (IQR 3.4–10.7), and 84 (55.3%) children were males. Seizure cessation within 30 minutes was noted in 65 (85.5%) children receiving brivaracetam and 55 (72.4%) receiving levetiracetam (p=0.047). The median time to cessation was 4.5 (IQR 3.0–7.0) minutes in bivarectam, vs. 6.0 (IQR 4.0–9.5) minutes with levetiracetam (p=0.009). The median hospital stay was 4.0 (IQR 3.0–6.0) days vs 5.5 (IQR 4.5–7.0) days (p=0.034) in brivarecetam and levetiracetam groups, respectively. Adverse events occurred in 10 (13.2%) children in the Bivaracetam group vs. 14 (18.4%) with levetiracetam (p=0.374), while no mortality was documented. **Conclusions:** IV brivaracetam achieves faster and more effective seizure cessation compared with levetiracetam in children with SE, with lower rates of adverse effects.

INTRODUCTION

Status epilepticus (SE) is one of the most common pediatric neurological emergencies, with an estimated incidence of 10-27 per 100,000 children per year, and accounts for nearly 20% of all pediatric epilepsy-related hospital admissions [1-4]. The longer the seizure persists, the greater the risk of neuronal injury, systemic complications, and poor neurodevelopmental outcomes [5]. Early and effective intervention is therefore crucial to reduce morbidity and mortality. First-line treatment typically consists of benzodiazepines; however, up to 30-40% of patients develop benzodiazepine refractory SE (RSE), necessitating the use of second-line antiseizure medications (ASMs) [6,7]. Traditionally, phenytoin, valproate, and phenobarbital have been used, but their variable efficacy, narrow therapeutic index, and risk of cardiopulmonary or hepatic adverse effects limit their utility in the acute pediatric setting [8]. In recent years, newer ASMs like levetiracetam and brivaracetam have emerged as promising alternatives owing to their favorable pharmacokinetic profiles, safety, and intravenous (IV) formulations [9]. Levetiracetam, an SV2A ligand, is one of the most commonly employed 2nd-line agents in SE. IV levetiracetam offers good efficacy and tolerability, a fast onset of action, and minimal drug-drug interactions, making it especially suitable for critically ill children [10]. Documented response rates of levetiracetam in seizure

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cessation rates vary between 40-70% [11]. Relatively higher affinity of brivaracetam is expected to result in more potent and quicker seizure cessation rates [12, 13].

Although IV brivaracetam is increasingly being studied in adult SE populations, evidence in pediatric patients remains sparse, with only limited case series and observational studies reporting favorable outcomes. There is a pressing need for safe and effective options in pediatric SE. There is also a lack of head-to-head data comparing IV brivaracetam with levetiracetam, particularly in children. The findings of this study may guide safe and effective options in managing paediatric SE. This study aims to compare the safety and efficacy of IV brivaracetam versus levetiracetam in the management of SE in children.

METHODS

This randomized controlled trial (NCT07163572 at https://clinicaltrials.gov/study/NCT07163572) was conducted at the Department of Pediatric Neurology, The Children's Hospital, Multan, Pakistan, from January 2025 to September 2025, following approval from the Institutional Review Board (letter: 2361). A sample size of 152 (76 in each group) was calculated using the Open Epi online sample size calculator. Because no head-to-head pediatric randomized trial comparing IV brivaracetam and levetiracetam in convulsive status epilepticus was available to inform the expected effect size, the study conducted a pilot study in 40 children (20 per group) to estimate event rates for the primary endpoint (seizure cessation within 30 minutes of study drug administration). In the pilot, seizure cessation within 30 minutes occurred in 16 (80.0%) of children receiving brivaracetam versus 13 (65.0%) receiving levetiracetam, indicating an absolute difference of 15%. Using Open Epi for comparison of two independent proportions with two-sided α=0.05 and 80% power, the required sample size was 152 children (76 per group). Written informed consent was obtained from parents or legal guardians before enrollment. The inclusion criteria were children aged one month to 16 years, presenting with SE. The exclusion criteria were children who had already received IV antiseizure medication for the current episode before presentation, had known hypersensitivity to study drugs, or were hemodynamically unstable, requiring inotropic support before administration. SE was defined as continuous seizure activity lasting > 5 minutes or recurrent seizures without recovery of consciousness. The study adhered to CONSORT 2010 guidelines (Figure 1).

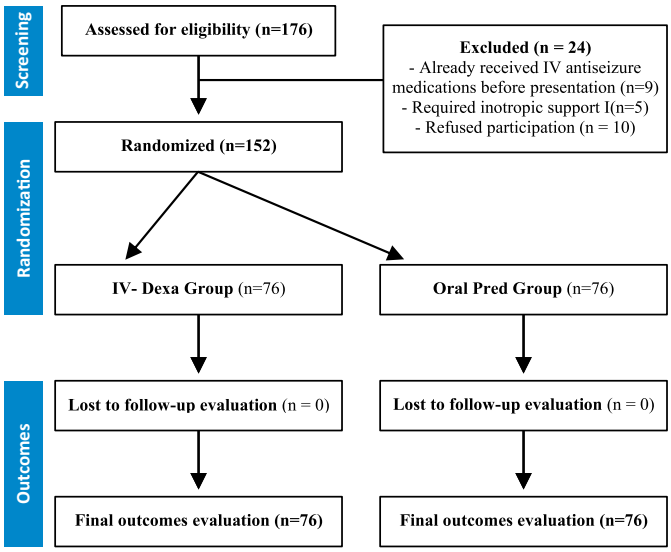

Figure 1: CONSORT Flow Diagram

Baseline demographic data on gender, age, weight, and clinical variables like seizure duration before drug administration were recorded. Baseline demographic and clinical characteristics were recorded at enrollment, prior to study drug administration, using caregiver interviews, standardized clinical assessments, and review of emergency/medical records. Data for the etiology of status epilepticus were obtained from patients' records. Participants were randomized in a 1:1 ratio to receive either IV brivaracetam or IV levetiracetam. A computer-generated randomization sequence was used. To maintain allocation concealment, allocations were enclosed in sequentially numbered, opaque, sealed envelopes. The treating team and outcome assessors were blinded to the drug allocation since the drugs were prepared and labeled by a pharmacist who did not participate in the care of the subjects. Patients in the brivaracetam group received a loading dose of 2 mg/kg (maximum 100 mg) diluted in 100 ml of normal saline infused over a period of 10 minutes, while the patients in the levetiracetam group received a loading dose of 40 mg/kg (maximum 3000 mg) similarly diluted and infused. All patients were continuously monitored during infusion and for 30 minutes after infusion for any acute adverse effects. Efficacy was the primary outcome, which was labelled as the cessation of clinical seizures within 20-30 minutes of infusion without the need for additional antiseizure medication. Secondary outcomes included time to seizure cessation, recurrence of seizures (within 24 hrs, 72 hrs, or 7 days), need for additional antiseizure medication, duration of stay in hospital or intensive care in days, and in-hospital mortality (yes/no). Safety was assessed in terms of recording drug-related adverse events like hypersensitivity reactions, cardiovascular instability, respiratory depression, gastrointestinal intolerance, and CNS depression, which were actively

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looked for.

Statistical analysis was performed using "IBM-SPSS Statistics" version 26.0. For the continuous variables, means and standard deviations (SD) or medians and interquartile ranges (IQR) were computed, depending on the data's normal distribution. Comparison between the two groups was done using the student's t-test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using chi-square or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among 152 children, the overall median age was 6.2 years (IQR 3.4–10.7), and 84 children (55.3%) were male. In terms of identified etiologies, febrile seizures were noted in 43 (28.3%), idiopathic epilepsy in 40 (26.3%), central nervous system infection in 34 (22.4%), post-hypoxic events in 22 (14.5%), and metabolic or structural causes in 13 (8.6%) cases. The median seizure duration before study drug administration was 24 minutes (IQR 18–31) (Table 1).

Table 1: Comparison of Baseline Demographic and Clinical Characteristics Between Study Groups (n=152)

Characteristics		Bivaracetam (n=76)	Levetiracetam (n=76)	p-value
Gender	Male	43 (56.6%)	41 (53.9%)	0.744*
	Female	33 (43.4%)	35 (46.1%)	
Age in Years	Median (IQR)	6.0 (3.5-10.5)	6.3 (3.3-10.9)	0.715^
Weight in kg	Median (IQR)	21.0 (15.4-28.2)	22.6 (15.5-29.5)	0.603^
Etiology of Status Epilepticus	Febrile Seizures	20 (26.3%)	23 (30.3%)	0.953*
	Idiopathic Epilepsy	19 (25.0%)	21 (27.6%)	
	Central Nervous System Infection	18 (23.7%)	16 (21.1%)	
	Post-Hypoxic	12 (15.8%)	10 (13.2%)	
	Metabolic/Structural	7 (9.2%)	6 (7.9%)	
Seizure Duration Before Drug in Minutes	Median (IQR)	24.0 (15.5-30.0)	25.0 (19.0-32.5)	0.528^

*Chi-square test applied; ^Mann-U Whitney test applied

Clinical seizure cessation within 30 minutes of infusion was achieved in 65 (85.5%) children in the brivaracetam group, and 55 (72.4%) children in the levetiracetam group (p=0.047). The median time to cessation was significantly shorter in patients receiving brivaracetam, recorded at 4.5 minutes (IQR 3.0–7.0), compared with 6.0 minutes (IQR 4.0–9.5) with levetiracetam (p=0.009). No patient required discontinuation of infusion due to acute intolerance or hemodynamic instability. Seizure recurrence within 24 hours occurred in 8 (10.5%) cases in the brivaracetam group, and 13 (17.1%) in the levetiracetam group (p=0.240). Recurrence within 72 hours was observed in 11 (14.5%) and 17 (22.4%) children, respectively (p=0.209), and within 7 days in 13 (17.1%) and 20 (26.3%) children, respectively (p=0.168). The requirement for a rescue anti-epileptic drug was recorded in 9 (11.8%) cases receiving brivaracetam, and in 18 (23.7%) receiving levetiracetam (p=0.056). No mortality was reported during the study period. The median duration of hospitalization was 4.0 days (IQR 3.0–6.0) in patients treated with brivaracetam and 5.5 days (IQR 4.5–7.0) in those treated with levetiracetam (p=0.034) (Table 2).

Table 2: Comparison of Treatment Outcomes Between Study Groups

Characteristics		Bivaracetam (n=76)	Levetiracetam (n=76)	p-value
Seizure Cessation	< 30 Minutes	65 (85.5%)	55 (72.4%)	0.047
Time to Cessation in Minutes	Media (IQR)	4.5 (3.0-7.0)	6.0 (4.0-9.5)	0.009
Seizure Recurrence	Within 24 Hours	8 (10.5%)	13 (17.1%)	0.240
	Within 72 Hours	11 (14.5%)	17 (22.4%)	0.209
	Within 7 Days	13 (17.1%)	20 (26.3%)	0.168
Need for Rescue Anti-Epileptic Drug	–	9 (11.8%)	18 (23.7%)	0.056
Intensive Care Unit Admission	–	28 (36.8%)	33 (43.4%)	0.385
Duration of Hospitalization in Days	Media (IQR)	4.0 (3.0-6.0)	5.5 (4.5-7.0)	0.034

With respect to safety outcomes, 10 (13.2%) cases in the brivaracetam group, and 14 (18.4%) in the levetiracetam group experienced adverse events (p=0.374). The most frequent adverse event was somnolence, observed in 5 (6.6%) cases in the Bivaracetam group, and 7 (9.2%) cases with Levetiracetam (p=0.547). Vomiting was noted among 3 (3.9%) children in Bivaracetam, and 4 (5.3%) children's patients respectively (p=0.699). Mild hypotension was reported in 2 (2.6%) children receiving brivaracetam, and in 3 (3.9%) with Levetiracetam (p=0.649). No serious adverse events or life-threatening complications were documented in either treatment group. None of the children in either group developed rash, hypersensitivity, or respiratory depression during or after infusion (Table 3).

Table 3: Comparison of Adverse Events Observed within 30 Minutes Following Bivaracetam and Levetiracetam Infusion

Characteristics	Bivaracetam (n=76)	Levetiracetam (n=76)	p-value
Somnolence	5 (6.6%)	7 (9.2%)	0.547
Vomiting	3 (3.9%)	4 (5.3%)	0.699
Mild Hypotension	2 (2.6%)	3 (3.9%)	0.649
Behavioral Agitation	–	2 (2.6%)	0.155
Overall Adverse Events	10 (13.2%)	14 (18.4%)	0.374

DISCUSSION

The rate of seizure cessation within 30 minutes was significantly higher in the brivaracetam group at 85.5% compared with 72.4% with levetiracetam. Contemporary literature describing brivaracetam's pharmacological properties highlights it to have a more rapid blood–brain

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barrier penetration and greater receptor selectivity compared with levetiracetam, explaining its more potent antiepileptic effect in both clinical and experimental models [14, 15]. The median time to seizure cessation in this trial was 4.5 minutes in the brivaracetam group and 6.0 minutes in the levetiracetam group. Although seizure control was achieved within a clinically acceptable timeframe with both agents, this difference has important therapeutic implications, given that longer seizure duration is directly associated with neuronal injury and poorer outcomes in children. A recent meta-analysis of levetiracetam compared with other antiseizure medications reported that levetiracetam shortened the time to seizure cessation in comparison to phenytoin or fosphenytoin, but that the duration remained longer than the values observed for brivaracetam in the present study [16]. This difference indicates that brivaracetam may have a specific pharmacological advantage in terms of limiting seizure exposure time, a factor highly relevant to preventing refractory progression and intensive care requirements. Recurrence rates were consistently lower in the brivaracetam group in all time intervals measured; however, the difference did not reach statistical significance. These findings are supported by the systematic review performed by Moalong *et al.* in which 48% of patients with SE responded to IV brivaracetam, but recurrence intervals were variable depending on etiology and disease chronicity [12]. Orlandi *et al.* from Italy, documented a seizure freedom rate of 58% within 24 hours after the administration of brivaracetam, in comparison to conventional agents, and reported lower risks of evolution to SE [17]. The recurrence pattern seen in the present study reinforces the possibility that early seizure termination could provide extended postictal stabilization, even if the data did not show a full statistical difference. The need for rescue antiseizure medication was almost twice as frequent among children treated with levetiracetam (23.7%) compared with those treated with brivaracetam (11.8%). This finding mirrors the observations of Martellino *et al.* who reported that IV brivaracetam achieved sustained seizure control in over half of the treated patients within 24 hours, reducing the need for additional agents [18]. Besli *et al.* also demonstrated that levetiracetam required fewer secondary interventions compared with phenytoin, suggesting a favorable efficacy gradient among newer antiseizure drugs [19]. The duration of hospitalization in this study was significantly shorter among children receiving brivaracetam, with a median stay of four days compared with 5.5 days in the levetiracetam group. The link between faster seizure control and shorter hospitalization is a reasonable interpretation, but not a statistically proven causal pathway. In the meta-analysis by Alsabri *et al.* levetiracetam was found to reduce ICU stay compared with phenytoin, indicating that agents with a better safety margin and shorter seizure resolution time facilitate quicker recovery [16]. Regarding safety, adverse events were uncommon, and their rate was similar in the two treatment groups. During the double-blind period, adverse effects occurred in 13.2% of children assigned to brivaracetam and in 18.4% of those assigned to levetiracetam; this difference is not statistically significant. The most common adverse event was somnolence, observed in 6.6% and 9.2% of children in the respective groups. Vomiting and mild hypotension were infrequent and self-limiting. No serious hypersensitivity reactions, respiratory depression, or hemodynamic instability occurred. Song *et al.* reported that treatment-emergent adverse events occurred in 39% of pediatric patients receiving brivaracetam, with somnolence being the most frequent and behavioral symptoms being less common than with levetiracetam [20]. Sivadasan *et al.* reported that behavioral adverse effects were more prominent with levetiracetam [21]. The present trial reinforces the view that both agents possess favorable safety profiles, but that brivaracetam may offer improved behavioral tolerability in prolonged therapy or recurrent seizure scenarios. Both brivaracetam and levetiracetam act on the SV2A receptor; however, brivaracetam has a 10-30-fold higher affinity and a more rapid receptor occupancy rate, resulting in faster antiepileptic activity with fewer off-target effects [15, 22]. Steinhoff and Sttack highlighted that brivaracetam's selective SV2A binding minimizes psychiatric and behavioral complications, whereas levetiracetam has been associated with irritability and agitation in a subset of pediatric patients [9]. Evidence regarding the use of brivaracetam in pediatric SE remains limited. Most published literature has focused on adult or mixed populations with either refractory epilepsy or SE. This makes the trial unique due to the paucity of pediatric data and provides direct, comparative evidence of brivaracetam versus levetiracetam in a controlled pediatric cohort. The findings extend our current understanding of seizure management in children and suggest that early use of brivaracetam may enhance seizure control without compromising safety [23, 24].

Several limitations are recognized. The trial was performed at a single tertiary care center. The follow-up period was confined to the duration of acute hospitalization, restricting assessment of long-term outcomes such as seizure recurrence, cognitive development, and behavioral effects. Relatively modest sample size may have underpowered the actual differences in effect sizes in the provided statistics, so further studies with larges sample size should be conducted to verify these findings. To

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confirm long-term effectiveness and safety, future research should focus on large-scale, multicenter trials that employ long follow-ups. Besides, cost-effectiveness studies and studies on optimal dosing of specific groups of children are required to inform the practice. Evidence-based treatment guidelines must be updated using these findings.

CONCLUSIONS

IV brivaracetam achieves faster and more effective seizure cessation compared with levetiracetam in children with SE, without increasing adverse effects. The results support brivaracetam as a promising therapeutic alternative where rapid seizure control is essential.

Authors' Contribution

Conceptualization: MZA
Methodology: IUR, MZA, AT
Formal analysis: IUR
Writing and Drafting: IUR
Review and Editing: IUR, MZA, AT

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Prevalence of Childhood Unintentional Injuries Presenting to the Emergency Department of a Tertiary Care Hospital

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ABSTRACT

Childhood unintentional injuries are one of the leading public health concerns worldwide. These injuries need immediate medical attention to prevent any adverse outcomes. **Objectives:** To determine the prevalence, types, severity, and outcome of unintentional injuries in children presenting to the Emergency Department at Shalamar Hospital, Lahore. **Methods:** This cross-sectional study was conducted at the Department of Pediatrics, Shalamar Hospital, Lahore. Non-probability consecutive sampling was used to include a total of 242 children with unintentional injuries up to 12 years of age. Validated questionnaires filled out by attending doctors, covering demographic details, injury type, injury setting and circumstances, primary caregiver, and clinical outcomes were used to collect the data. SPSS version 25.0 was employed to analyze the data. **Results:** Out of 242 children, males accounted for 55% of the cases. The mean age of children was 6.5 ± 3.2 years. 35% of the injuries were transport-related injuries, followed by falls, which accounted for 30% of injuries. Minor injuries (40%) were most frequent, followed by moderate (35%) and severe injuries (25%). The average time between injury and hospital presentation was 3.2 ± 1.5 hours. 45% of the children presented within 1st hour of the injury, and 25% presented after 3 hours. There was no significant difference in injury severity by gender. C**onclusions:** Transport-related injuries and falls are the leading causes of unintentional injuries, which are more common in boys, occurring more frequently among young children.

INTRODUCTION

Unintentional injuries are unexpected and violent events affecting children with or without a visible lesion requiring urgent medical assistance. These injuries may be diverse, resulting from drowning, animal bite, fall, poisoning, road traffic injuries, burns, or electrocution [1]. Injury is a physical damage that occurs when the human body is subjected to an amount of energy that exceeds the physiological threshold or is deprived of any vital element, such as oxygen. The energy can be mechanical, thermal, chemical, or radiant [2]. According to the World Health Organization, out of 4.4 million injury-related deaths, 81.8% fatalities occur due to unintentional injuries, the majority of which belong to the less than 12-year age group [3]. A mini review by Emad et al. conducted in Karachi revealed that 1.1 million unintentional injuries occur in children annually; 72% to 84.4% of injuries occurred at home, out of which 54% were contributed by fall from height, 21.5% to 77.0% due to poisoning, drowning was responsible for 3% of injuries and RTA injuries accounted for 31.7% of all injuries among children aged 0-14 years [4]. Due to the exploratory nature of toddlers, unintentional injuries are far more common in preschool children. According to a vast data

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collection in tertiary care hospitals of China, 64.6% children with unintentional injuries are less than 6 years old. Results showed that unintentional fall was the most common reason for unintentional injuries among both genders, accounting for 72.2% cases [1]. Research on injuries in Pakistan remains limited, and data are scarce. Certain factors, such as poverty, political instability, frequent natural disasters, lack of legislation, paucity of preventive measures, lack of awareness and knowledge, make the Pakistani population more vulnerable to injuries [5]. The purpose of this study is to determine the prevalence of children less than 12 years of age who present with unintentional injuries to the emergency room of a tertiary care facility. This study helps to document socio-demographic risk factors, patterns, and types of unintentional injuries so that a proactive and preventive approach can be formulated to reduce the mortality and long-term morbidity in Pakistan's pediatric population [6].

There is no national data on childhood unintentional injuries in Pakistan, and the majority of the literature is single-center studies with a non-probability sampling that makes generalization not very broad. There is no long-term follow-up, multicentric studies, and research is related to prevalence rather than an evaluation of preventive measures. Sampling bias (out of convenience sampling), recall bias (out of caregiver-reported data), and observer bias (because of multiple clinicians gathering data) are the primary methodological problems. Research is descriptive and lacks data on the community level and standardized procedures, thus impacting reliability and inhibiting testing of the preventive remedies. This study aimed to determine the prevalence, types, severity, and outcome of unintentional injuries in children presenting to the Emergency Department at Shalamar Hospital, Lahore.

METHODS

This cross-sectional study was conducted at the Department of Pediatrics, Shalamar Hospital, Lahore, from July 2024 to January 2025. The study was approved by the Institutional Review Board (IRB Number: 0491) and Ref no: SMDC-IRB/AL/2024-070 at Shalamar Medical and Dental College, Lahore. Informed consent was obtained from the parents or guardians of the participating children. A total of 242 children of both genders and ages up to 12 years presenting with unintentional injury (as per operational definition) were included in the study via non-probability consecutive sampling assuming the prevalence of transport injuries as 4.1% at 95% confidence interval and 2.5% margin of error (calculated by formula $n=Z2 \cdot p \cdot (1-p)/d2$, where n = required sample size, Z = Z-score corresponding to 95% confidence level = 1.96, p = estimated prevalence of the outcome of interest (transport injuries) = 0.041, d = margin of error = 0.025) [1]. Children who had congenital anomalies or an injury as a result of child abuse were excluded. A validated questionnaire (pilot-tested on a sample of n = 70 respondents) was employed as a data collection tool. It comprised of 16 items, encompassing five main domains: (1) Socioeconomic and demographic variables including age, gender, weight, height, parental education, area of residence, family income; (2) Type of Injury (e.g., fall, burn, road traffic accidents, animal bites, sport injuries, foreign body aspiration); (3) Injury setting and circumstances including location of injury, time of day, season of injury, time between injury and hospital presentation; (4) Primary caregiver; and (5) Clinical outcomes including the need for hospitalization, severity of injury and the treatment received). The resources used to design this questionnaire included WHO Injury Surveillance Guidelines (2001), previously published research, and discussions with senior consultant pediatricians and public health experts. International Classification of Diseases (ICD-10) codes, which range from S00 to Y34, and cover a broad spectrum of traumatic injuries, were used to categorize the injuries. The interviewer was a doctor on duty at the time of presentation of the patient, who filled out all the related details on the questionnaire based on the patient's or caregiver's described history. According to clinical presentation and the degree of medical intervention needed, Unintentional injuries in this study were categorized as minor, moderate, or severe. Cases recorded to have acquired minor injuries included those where functioning was not affected significantly and were managed in an outpatient department without the need for hospitalization or specialized care, including superficial bruises and cuts that didn't need suturing. Cases recorded with moderate injuries needed clinical attention, including suturing, short-term stay for observation, or emergency room visits, and included patients with brief loss of consciousness or foreign body removal without the need for extended hospitalization. Severe injuries comprised cases with prolonged unconsciousness, a Glasgow Coma Scale (GCS) score of less than 13, signs of neurological compromise, life-threatening emergencies, or significant trauma requiring hospitalization in the ICU or surgery. SPSS version 25.0 was employed to analyze the data. Quantitative data, including age, height, and weight, were presented as mean ± standard deviation (S.D). Qualitative data, including the type of injury, gender, parental education, area of residence, family income, location of injury, time of day, season of injury, Time between injury and hospital presentation, Primary caregiver, need for hospitalization, severity of injury, and treatment received, were presented as frequencies and percentages. Age and gender stratification of the data was done to account for potential effect modifiers. The chi-square test was applied

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to determine the significance of any associations, with a p-value of less than 0.05 considered significant.

RESULTS

A total of 242 patients were included in the study, with a mean age of 6.5 ± 3.2 years, ranging from 1 to 12 years. Male represented 133 (55%) of the sample, while female accounted for 109 (45%), showing a decreased number of injuries in growing girls. The mean weight and height of the children were 22.4 ± 7.1 kg and 110 ± 15 cm, respectively. A majority of the participants (60%) lived in urban areas, while 40% were from rural regions. Regarding the season of injury, 35% of injuries occurred in summer, 30% in spring, 25% in winter, and 10% in fall. 50% of children with unintentional injuries belonged to a group having a family income of less than 100000/month, 40% belonged to a group having a family income of less than 50000/month, while 10% children belonged to a group of families earning more than 100000/month (Table 1).

Table 1: Demographic Analysis

Category	Frequency (%), Mean ± SD
Age Group	
1 to 12 Years	6.5 ± 3.2
Gender	
Male	133 (55%)
Female	109 (45%)
Others	
Weight (kg)	22.4 ± 7.1 kg
Height (cm)	110 ± 15 cm
Residence	
Urban Areas	60%
Rural	49%
Season of Injury	
Summer	35%
Spring	30%
Winter	25%
Fall	19%
Family Income	
100000/Month	50%
50000/Month	40%
100000/Month	10%

The age distribution of injuries showed that most children, accounting up-to 40 %, were young (1-4 years), including toddlers and pre-schoolers. Among this group, 58% were females. In terms of injury classification, the Canadian Triage and Acuity Scale was applied; the majority of the injuries were minor, accounting up-to 40 % of all the reported injuries, with a higher proportion of males (55%) experiencing these injuries (Table 2).

Table 2: Age Group and Injury Severity: Gender-based Distribution

Category	Male, Frequency (%)	Female, Frequency (%)	Total, Frequency (%)
Age Group			
1–4 Years	40 (42%)	57 (58%)	97 (40%)
5–8 Years	49 (57%)	36 (43%)	85 (35%)
9–12 Years	30 (50%)	30 (50%)	60 (25%)
Injury Severity			
Minor Injuries	53 (55%)	44 (45%)	97 (40%)
Moderate Injuries	51 (60%)	34 (40%)	85 (35%)
Severe Injuries	30 (50%)	30 (50%)	60 (25%)

The distribution of mechanisms of injury revealed that transport-related injuries were the most common, accounting for 35% of the cases. Falls followed closely at 30%, while burns represented 15% of the injuries. The majority of injuries were reported to have occurred outside the home, with a peak observed during the evening hours. Among the affected children, 59% required surgical intervention, while the majority were discharged home safely following an appropriate management (Table 3).

Table 3: Mechanism, Environment, Clinical outcome of Injury, and Time between Injury and Hospital Presentation

Parameters	Frequency (%)
Type of Injury	
Transport Related	85 (35%)
Falls	73 (30%)
Burns	36 (15%)
Drowning	24 (10%)
Animal Bites	12 (5%)
Others (Poisoning Struck by Objects)	12 (5%)
Location of Injury	
Home	58 (24%)
Outside	183 (76%)
Time of Injury	
Morning	90 (37%)
Evening	118 (49%)
Night	34 (14%)
Primary Caregiver	
Both Parent	191 (79%)
Mother	27 (11%)
Father	17 (7%)
Other	7 (3%)
Clinical Outcome	
Discharged	94 (39%)
Admitted in Pediatric Dept.	32 (13%)
Referred to the Other Dept.	48 (20%)
Referred to Another Hospital	68 (28%)
Treatment Received	
Surgical Intervention	142 (59%)
Supportive Care	39 (16%)
Burn Care	22 (9%)

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Gastric Lavage	19 (8%)
Antidote	5 (2%)
CPR	15 (6%)
Time Between Injury and Hospital Presentation	
Within 1hr	109 (45%)
1h-3h	73 (30%)
More Than 3h	60 (25%)

Age showed a significant association with severe injuries (p=0.002), while gender was significantly associated with minor and moderate injuries (p=0.046 and p=0.032, respectively)(Table 4).

Table 4: Injury Severity by Age Group and Gender

Injury Severity	1–4	5–8	9–12	Male	Female	Total	χ^2 (Age)[a]; p-value[b]	χ^2 (Gender)[c]; p-value[d]
	Years, n (%)							
Minor	42 (43%)	29 (34%)	26 (43%)	53 (55%)	44 (45%)	97 (40%)	1.68[a]; 0.432[b]	4.01[c]; 0.046[d]
Moderate	30 (31%)	36 (42%)	19 (32%)	51 (60%)	34 (40%)	85 (35%)	3.04[a]; 0.219[b]	4.62[c]; 0.032[d]
Severe	25 (26%)	10 (12%)	25 (42%)	30 (50%)	30 (50%)	60 (25%)	12.34[a]; 0.002[b]	0.05[c]; 0.824[d]

(a: Chi-square (χ^2) test statistic for association between injury severity and age groups (1–4 yrs, 5–8 yrs, 9–12 yrs). b: Corresponding p-value for χ^2 (Age). c: Chi-square (χ^2) test statistic for association between injury severity and gender (Male, Female). d: Corresponding p-value for χ^2 (Gender))

DISCUSSION

This study reveals important findings that can lead to improved emergency care services and preventive strategies for children presenting with unintentional injuries. According to this study, young children such as toddlers and pre-school children were affected the most, accounting for 40% of unintentional injuries. 35% injuries occurred in the early to middle childhood age group, and 25% in the late childhood age group. Previous studies have also revealed the same that younger children are more susceptible to unintentional injuries due to lack of coordination and curiosity [7]. The gender distribution of injuries in this study showed that males were affected more, accounting for 55% of the cases. Worldwide data states the same. Male sustain more injuries due to their active and risk-taking behaviours. In this study, 35% of injuries were transport-related, making them the most common type of injury. Falls accounted for 30% of cases. However, according to previous research, falls were found to be the most common type of unintentional injury [8]. Transport-related injuries can be prevented by encouraging safe behaviors such as the use of helmets and child restraints [9, 10] and the regulation of school transportation. School curricula should include road safety education. Falls can be prevented by the use of stair gates and window guards at home and at school, and improved supervision. Maintenance of safe playgrounds is crucial to encourage a safe and healthy environment for the kids to grow. Health screening should be mandatory to identify predisposing conditions [11-13]. Simulation-based technologies that mimic real-life scenarios can enhance children's comprehension of safety procedures [14]. In terms of injury severity, 40% of the injuries were minor, including minor bruises and cuts, followed by 35% of moderate injuries. Severe injuries accounted for 25% of the cases, including head trauma and internal injuries. Similarly, in previous studies, a significant proportion of childhood unintentional injuries was contributed by fractures and head trauma [15]. Head injuries require urgent clinical attention in young children to prevent complications. The average time between injury and hospital presentation was 3.2 hours in this study. 45% of the children presented within 1st hour of the injury, resulting in effective management that minimized the risk of complications. 25% of children reached the hospital with a delay of 3 hours, which can result in worse outcomes. However, a study conducted in Northern Tanzania reported a median time of 10.2 hours when seen at local clinics, 8.0 hours via regional hospitals, and 1.4 hours when presented to the referral hospital [16]. Community awareness campaigns can emphasize the need for urgent clinical attention for unintentional injuries. Family circumstances may play a role in childhood unintentional injuries, as per this study. In 21% of the cases, one or both parents were not present at the time of injury. This implies that variations in the presence of a caregiver could impact children's risk exposure. Most families reported earnings below 50,000 PKR or between 50,000 and 100,000 PKR per month. It demonstrates that the financial constraints may increase the risk of harm. These findings are in line with earlier studies that linked the risk of childhood injuries to home circumstances and caregiving behaviors [17, 18]. The analysis of injury severity by gender in this study showed that the severity distribution was quite similar for both male and female. There was no significant difference between the two groups. This suggests that both genders are equally susceptible to moderate and severe injuries. However, the overall frequency of injury in males was higher. However, unintentional injury-related death rates were consistently higher in boys than girls, i.e, 27.0 vs. 22.9 per 100,000 among the 1–4 years age group and 16.4 vs. 12.2

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per 100,000 among the 5-14 years age group, according to the 2023 America's Children report. It indicates that both the frequency and severity of such injuries are greater among male children. [19]. Likewise, a study carried out in Karachi found that children between 2 and 4 years of age sustained the highest number of unintentional injuries, and boys accounted for about two-thirds (66%) of the cases [20].

There are several limitations to this study that should be considered. First, the use of a non-probability sampling technique means that the sample may not be representative of the larger population. Hence, the findings may not apply to different settings or regions. Second, the study is subject to potential recall bias, as details were recorded based on the narration of caregivers, which may be influenced by memory limitations. Additionally, since various clinicians assisted in filling out the questionnaires, observer bias may have been introduced.

CONCLUSIONS

Transport-related injuries and falls are the leading causes of unintentional injuries. These injuries are more common in boys and occur more frequently among young children. Most cases are minor, but a considerable proportion entail moderate to severe trauma, including head injuries. Preventive measures are warranted to reduce morbidity and mortality related to unintentional injuries, as they pose a major public health concern.

Authors' Contribution

Conceptualization: MN
Methodology: MN, HN, MKB, NH
Formal analysis: MN, HN, NH
Writing and Drafting: MN, MNH, HN, MKB, NH
Review and Editing: MN, MNH, HN, MKB, NH

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Determinants of Repeated Hospital Admission in Dialysis-Dependent Chronic Kidney Disease Patients

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ABSTRACT

Studies evaluating the factors leading to repeated hospital admissions in dialysis-dependent CKD patients are scarce in the context of local settings. Results of the study would benefit clinicians and patients in reducing hospitalization burden and health care costs by prompt management of potential factors leading to hospitalization. **Objective:** To determine the frequency of factors leading to repeated hospitalization in dialysis-dependent chronic kidney disease patients. **Methods:** The descriptive study was conducted at the Department of Nephrology, Khyber Teaching Hospital, Peshawar, during the period 11th May 2025 to 10th September 2025. A total of 176 male and female patients diagnosed with chronic kidney disease and receiving maintenance hemodialysis were enrolled. The patients were evaluated for factors leading to repeated hospitalization, including the presence of heart failure, anemia, mode of vascular access, and low serum albumin. **Results:** The mean age of patients was 58.68±6.73 years. 89 patients (50.6%) were female. Repeated hospitalization was recorded in 87 patients (49.0%). Factors of repeated hospitalization revealed heart failure in 82 patients (46.6%), anemia in 30 (17.0%), low albumin in 118 (67.0%), and AV fistula in 82 patients (46.6%) as a mode of vascular access. Female patients had more frequent repeated hospitalization (n = 45, 50.6%), p value 0.762. **Conclusions:** Heart failure, AV fistula usage, and low albumin were the most common variables associated with frequent hospitalization. A connection between hospitalization, duration, and cause of CKD was observed, but did not reach statistical significance.

INTRODUCTION

Through the preceding decade or so, persistent renal failure that requires dialysis has become a major global public health concern [1]. Because of its numerous medical concurrent conditions (such as hypertension, diabetes, low blood hemoglobin, cardiovascular conditions like cerebrovascular accidents, and peripheral vascular disease. Chronic kidney disease (CKD) leads to a relatively substantial medical care stress raised admission to the hospital and increased mortality. It additionally results in more extensive consumption of outpatient, emergency, and inpatient services [2]. Hospitalizations and rehospitalizations, particularly an increase in frequency and severity as the illness worsens, are the biggest strain on patients with advanced renal disease. ESRD patients have a significant load of multiple medical conditions, according to observational studies [3]. Hospitalization may be less likely in individuals with end-stage renal disease (ESRD) if the potential of readmission is identified early [4]. Research has shown that the frequency and reason of hospitalizations influence the prognosis for ESKD, and that there is a positive correlation between hospitalization rate and patient state in patients with ESRD.[5] Poorer quality of life, increased morbidity, and death are linked to hospitalization. When compared to patients without CKD, those who were diagnosed with the disease had a 1.4-fold increased risk of dying in the hospital and a 1.2-fold

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increased risk of being admitted again after being discharged [6]. Kidney failure patients were three times more likely to die in the hospital and 1.8 times more likely to be admitted. Most hospitalizations and fatalities among patients with CKD and renal failure are caused by circulating illnesses and infections [7]. In one study, 58 (37.7%) of the 154 participants receiving maintenance hemodialysis experienced a 30-day readmission to the hospital. Re-admission diagnoses for these patients included HD vascular access, such as fistula 26 (44.8%) or catheter 19 (36.5%), low serum albumin 36 (62.1%), anemia 12 (20.7%), and precipitation of heart failure 14 (24.1%) [1].

There were few studies examining the causes of recurrent hospitalizations in dialysis-dependent CKD patients in local contexts. Furthermore, it was not possible to generalize the findings of international studies. Therefore, the study was designed to fill the research void. The study findings would help patients and clinicians manage potential hospitalization risk factors promptly and lower hospitalization burden and health care costs. The study aimed to determine the frequency of factors leading to repeated hospitalization in dialysis-dependent chronic kidney disease patients.

METHODS

The descriptive study was conducted at the department of Nephrology, Khyber Teaching Hospital, Peshawar, during the period 11th May 2025 to 10th September 2025. Approval for the conduct of the study was granted vide no. 134/DME/KMC. A total of 176 male and female patients diagnosed with chronic kidney disease and receiving maintenance hemodialysis were enrolled. Patients taking immunosuppressive medications, post-renal transplant patients, concurrent medical conditions like chronic liver failure and endocrine disorders, and acute kidney injury patients were excluded. CKD was defined as mentioned in the 2024 KDIGO guidelines by imaging findings (shrunken kidneys on ultrasound, i.e., size less than 8cm) and eGFR <60ml/min/1.73m2 calculated on the Cockroft Gault Formula. Repeated hospital admission was defined as hospital admission for more than 24 hours within 30 days of prior hospitalization. The patients were assessed for factors of hospitalization in terms of 1) Heart failure was defined ESC 2021 guidelines as patients with ejection fraction <40% on ECHO and brain natriuretic peptide (BNP) >100pg/ml 2) Anemia: Blood hemoglobin level <12gm/dl for men and <11gm/dl for women 3) Low serum albumin: Serum albumin: Normal serum albumin ranges from 3.5 to 5.5gm/dl. Serum albumin level < 3.5 g/dl was called low serum albumin and 4). Mode of vascular access: through AV fistula or catheter, confirmed clinically and by medical record examination. Sample size was calculated using the WHO sample size formula (n = Z2. p (1-p)2/E2), where n = sample size, Z = 1.96 at 95% confidence interval, p = expected prevalence value, and E = margin of error = 6%. Sample size was 176, taking the anticipated frequency of anemia in patients with repeated hospitalization among CKD patients on maintenance hemodialysis (p) = 20.7%, 6% margin of error (E) [1]. Participants were enrolled using non probability consecutive sampling technique. Patients who met the recruitment parameters were admitted from the hospital's indoor department following permission from the CPSP and the hospital's research review board. All enrolled participants gave their informed consent after being fully informed about the study's goals, risks, and rewards. Demographic data such as age and gender were recorded from the patient's national identity card, while weight and height were measured using a weighing scale and a stadiometer, respectively. The duration of hemodialysis and etiology of CKD were confirmed from the medical record. Other parameters recorded were patient education, occupation, and SE status (classified using the Modified Kappaswamy scale, taking a score more than 10 as fair and 10 or below as poor). At the time of discharge from the index hospitalization, a thorough medical examination and history were taken. For the following 30 days, patients were monitored. According to operational criteria, hospitalization during the follow-up period was recorded, and patients were divided into those who had and did not experience repeated hospitalization. A 10-cc blood sample was taken from a main vein in the antecubital fossa of the patient's non-dominant arm after they had been comfortably seated on the chair. The sample was sent to the hospital lab after being evenly divided (05cc) in EDTA and gel tube. Anemia was assessed by measuring blood hemoglobin level using Nihon Kohden® Celltac G+ (MEK-9200) automated hematology analyzer, and serum albumin was measured with the dye-binding technique using Roche Cobas® 4000 biochemistry analyzer. Vascular access mode was observed. ECHO was done with Logiq E10, and the BNP level (measured using standardized chemiluminescent immunoassay Siemens Advia BNP Assay®) was used to diagnose heart failure.

Data were analyzed using the statistical analysis program IBM SPSS version 26. Means ± SD or median (IQR) was recorded for quantitative data like age, BMI, Hb, serum albumin and duration of hemodialysis after checking the normality of the data with Shapiro wilk test while frequencies and percentages were recorded for qualitative data like gender, residence, education, profession, SE status, cause of CKD, presence or absence of repeated hospitalization and factors leading to repeated hospitalization. Factors (anemia, heart failure, vascular access, and low serum albumin) were compared between those with and without repeated hospitalization using chi

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square of fisher exact test at 5% level of significance. Repeated hospitalization was stratified by age, gender, BMI, duration of hemodialysis, and cause of CKD to control effect modifiers. Post-stratification chi-square or fisher exact test was applied. p-value ≤0.05 was considered statistically significant.

RESULTS

The mean age of the participants was 58.68 ± 6.73 years, the mean BMI was 24.99 ± 1.054 kg/m^2, and the mean duration of CKD was 7.72 ± 0.24 years as reported in table 1.

Table 1: Descriptive Statistics of Study Participants (n=176)

Parameters	Mean ± SD
Age (Years)	58.68 ± 6.734
BMI (kg/m^2)	24.990 ± 1.054
Duration of CKD (Years)	7.72 ± 2.247

Participants aged more than 55 years were 119 (67.6%), while gender wise distribution was equivalent, with 89 female participants (50.6%). 113 patients (64.2%) had a BMI of 25.0 kg/m^2 or below. 107 patients (60.8%) belonged to rural areas. CKD duration more than 7 years was recorded in 94 participants (53.4%), while 96 participants (54.5%) had diabetes as the underlying cause of CKD, as shown in Table 2.

Table 2: Baseline Characteristics of Study Participants (n=176)

Parameters	Subgroups	n (%)
Age (Years)	55 or below	57 (32.4%)
	More Than 55	119 (67.6%)
Gender	Male	87 (49.4%)
	Female	89 (50.6%)
BMI (kg/m^2)	25.0 or below	113 (64.2%)
	More Than 25.0	63 (35.8%)
Residence	Rural	107 (60.8%)
	Urban	69 (39.2%)
Education	No Formal Schooling	42 (23.9%)
	Matric or below	66 (37.5%)
	Above Matric	68 (38.6%)
Profession	Salaried	85 (48.3%)
	Business	91 (51.7%)
SE Status	Fair	46 (26.1%)
	Poor	130 (73.9%)
CKD Duration (Years)	7 or below	82 (46.6%)
	More Than 7	94 (53.4%)
CKD Cause	Dm	96 (54.5%)
	Others	80 (45.5%)

Repeated hospitalization was recorded in 87 patients (49.0%), as shown in figure 1.

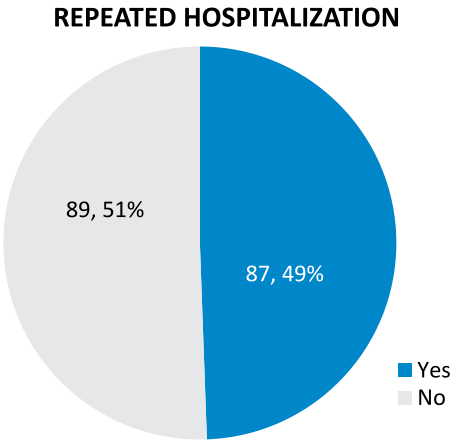

Figure 1: Distribution of Patients According to Repeated Hospitalization (n=176)

Analysis of factors of repeated hospitalization revealed heart failure in 82 patients (46.6%), anemia in 30 (17.0%), low albumin in 118 (67.0%), and AV fistula in 82 patients (46.6%) as a mode of vascular access, as reported in Table 3.

Table 3: Distribution of Factors of Repeated Hospitalization among Study Participants (n=176)

Factors of Repeated Hospitalization		n (%)
Heart Failure	Yes	82 (46.6%)
	No	94 (53.4%)
Anemia	Yes	30 (17.0%)
	No	146 (83.0%)
Low Albumin	Yes	118 (67.0%)
	No	58 (33.0%)
Vascular Access	AV fistula	82 (46.6%)
	Catheter	94 (53.4%)

Analysis of factors among patients with and without repeated hospitalization showed anemia in 18 patients (60.0%) with repeated hospitalization versus 12 (40.0%) without repeated hospitalization. The p-value for the difference in distribution was 0.204. Similarly, heart disease was more prevalent among patients with repeated hospitalization (n=45, 54.9%), p-value 0.177. 36 patients (43.9%) with AV fistula had repeated hospitalization compared to 51 (54.3%) with catheter access, p-value 0.171, as shown in table 4.

Table 4: Comparison of Factors of Repeated Hospitalization Among Patients with and without Repeated Hospitalization (n=176)

Factors of Repeated Hospitalization		Repeated Hospitalization		Total, n (%)	p-value
		Yes = 87, n (%)	No = 89, n (%)		
Anemia	Yes	18 (60.0%)	12 (40.0%)	30 (100.0%)	0.204
	No	69 (47.3%)	77 (52.7%)	146 (100.0%)	
Heart Failure	Yes	45 (54.9%)	37 (45.1%)	82 (100.0%)	0.177
	No	42 (44.7%)	52 (55.3%)	94 (100.0%)	

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Low Albumin	Yes	57 (48.3%)	61 (51.7%)	118 (100.0%)	0.670
	No	30 (51.7%)	28 (48.3%)	58 (100.0%)	
Vascular Access	AV fistula	36 (43.9%)	46 (56.1%)	82 (100.0%)	0.171
	Catheter	51 (54.3%)	43 (45.7%)	94 (100.0%)	

Repeated hospitalization was more common in patients aged more than 55 years (n=63, 52.9%), p-value 0.178. Female patients had more frequent repeated hospitalization (n=45, 50.6%) compared to males (n=42, 48.3%), p-value 0.762. The p-value for the difference in distribution of repeated hospitalization with respect to BMI was 0.559, while the respective p-values for distribution with respect to CKD duration and cause of CKD were 0.177 and 0.099, respectively, as reported in table 5.

Table 5: Stratification of Repeated Hospitalization with Various Parameters (n=176)

Baseline Parameters		Repeated Hospitalization		Total, n (%)	p-value
		Yes = 87, n (%)	No = 89, n (%)		
Age (Years)	55 or below	24 (42.1%)	33 (57.9%)	57 (100.0%)	0.178
	More Than 55	63 (52.9%)	56 (47.1%)	119 (100.0%)	
Gender	Male	42 (48.3%)	45 (51.7%)	87 (100.0%)	0.762
	Female	45 (50.6%)	44 (49.4%)	89 (100.0%)	
BMI (kg/m^2)	25.0 or below	54 (47.8%)	59 (52.2%)	113 (100.0%)	0.559
	More Than 25.0	33 (52.4%)	30 (47.6%)	63 (100.0%)	
CKD Duration (Years)	7 or below	45 (54.9%)	37 (45.1%)	82 (100.0%)	0.177
	More Than 7	42 (44.7%)	52 (55.3%)	94 (100.0%)	
Cause of CKD	DM	42 (43.8%)	54 (56.3%)	96 (100.0%)	0.099
	Others	45 (56.3%)	35 (43.8%)	80 (100.0%)	

DISCUSSION

The distinctive characteristics of repeated hospital admission across chronic kidney failure patients have never been examined before, as far as we are aware. Heart failure and low albumin constituted the most prevalent factors of repeated hospitalization among the studied variables in this study. Hospitalization occurred on multiple occasions a year. Risk factors for several hospitalizations annually, where the main kidney illness was diabetic renal disease, the comorbidity of coronary heart disease, or the catheter mode of vascular access. Mode of vascular access, cardiac conditions such as heart failure, and declining level of serum albumin and concurrent or sequelae of CKD, such as anemia, were prevalent in our study, but in a report, a significant proportion of hospitalizations occurred due to these reasons [8]. Access-related infections were the most common cause of hospitalization for PD patients according to Swedish research, while they were fewer in the HD group and rare in the dialysis population overall [9]. Neither Sweden nor the United States reported that the creation of dialysis access was the most common reason for hospitalization. Septicemia was the most prevalent clinical condition among the top ten most common reasons for hospitalizations in the United States. Regarding cardiovascular diseases, the United States had a significantly higher rate of admissions to hospitals for high blood pressure, coronary heart disease, and congestive heart failure (CHD) than China. In the USA, diabetes-related admissions were likewise extremely high [8]. Similarly, in Sweden, hospitalizations attributable to diabetes accounted for 6.4% and cardiovascular disorders for 19.8% [9]. The observed discrepancies may be the result of variations in the patient groups with respect to clinical practice, concomitant diseases, etiology of ESKD, and demographics (particularly age). First, the percentage of dialysis patients who were old varied by nation [10]. According to the reports, the largest percentage of dialysis patients in China belonged to the subgroup of people aged 45 to 64 years. The average age was higher in China and the USA compared to our findings [11, 12]. Similarly, our mean age was also lower than that reported in Sweden [9]. In comparison to children and adolescents, elderly individuals receiving dialysis might exhibit higher rates of age-associated concurrent medical conditions, such as insulin resistance and plaque buildup, as well as a greater likelihood of vulnerability and inadequate nutrition, and a greater probability of impaired mental behavior [13, 14]. These factors could lead to decreased physical wellness and clinical consequences [15, 16]. Second, the most prevalent cause of ESKD in China was glomerulonephritis, whereas in the United States, Europe, and certain other Asian countries had higher rates of high blood pressure and diabetes [17-19]. Prior research revealed that diabetic dialysis patients had a high incidence of cardiovascular and diabetic complications [20, 21]. From a reduction in kidney function to the need for renal replacement treatment, the circulatory system and heart may experience various structural and functional alterations [22, 23]. Dialysis patients may develop heart and vascular disease more quickly, particularly if they have cardiovascular risk factors like diabetes or high blood pressure. Patients receiving dialysis were at a greater risk, and almost half of the patients experienced numerous hospitalizations in this study. Prior research on hospital readmissions has mostly concentrated on thirty-day readmissions between patients receiving in-center hemodialysis and home-based peritoneal dialysis; however, dialysis is only provided in hospital settings in our country, hence no comparison can be drawn in this regard. A study reported that the 30-day unscheduled readmission rate was greater in the peritoneal dialysis population than in the hemodialysis population [8]. Peritoneal dialysis patients had a higher 30-day readmission rate than hemodialysis patients, according to a population-based study [24]. Nonetheless, some research produced contradictory findings,

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indicating that there were no or negligible variations in readmission risks among dialysis modalities [25]. The belief that readmissions after thirty days might reveal healthcare inadequacies throughout follow-up with patients from the hospital to the outpatient environment, however, remained constant. Clinical practice discrepancies between hemodialysis and peritoneal dialysis may contribute to variations in the performance of several hospitalizations.

The research has limitations in that it is a single-center and descriptive study design that does not allow generalizing the results and faces the causal limitation to make statements about the risk factors that lead to re-hospitalization. Moreover, the preoccupation with in-hospital dialysis in a particular country setting complicates the process of direct comparison of the national statistics about dialysis modalities and those found abroad. Future studies ought to be based on multicenter, longitudinal studies involving larger and more varied cohorts to further define the predictors of readmission to the hospital. Comparative analyses of various models of healthcare delivery and dialysis modalities and specific cost-effectiveness studies should also be conducted to guide ideal and patient-centered care trajectories to manage chronic kidney failure.

CONCLUSIONS

Although the connections were not statistically significant, the study found that recurrent hospitalization was prevalent among participants, especially among females and those over 55 years of age. Heart failure, AV fistula usage, and low albumin were the most common variables associated with frequent hospitalization. Although patterns indicated a potential correlation between hospitalization rates and the duration and cause of CKD, the findings did not reach statistical significance. To lower the frequency of hospitalizations in this population, our findings emphasize the necessity of focused care of modifiable risk factors, such as cardiovascular health and nutritional status. Larger sample sizes in future research might assist in shedding light on the tendencies that have been noticed.

Authors' Contribution

Conceptualization: SK
Methodology: SK, MFK
Formal analysis: SK, SS
Writing and Drafting: SK, MFK, SS, AA
Review and Editing: SK, MFK, SS, AA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Outcomes Following the Cutting Seton Procedure for High Anal Fistula

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ABSTRACT

Fistula in ano is a prevalent perianal condition caused by infection of the anal glands between the sphincter muscles, leading to substantial morbidity. It is reportedly more prevalent in males globally. Surgical management of high anal fistula remains challenging, and the cutting seton technique continues to be used as a treatment option. **Objective:** To evaluate the outcomes following the cutting seton procedure for high anal fistula. **Methods:** This cohort study was carried out at the Department of General Surgery, Hayatabad Medical Complex, Peshawar, and involved 171 patients who were diagnosed with high anal fistula, and the cutting seton procedure was performed on them. The demographic data, clinical characteristics, and surgical outcomes were documented. The pain was rated with the help of the Visual Analogue Scale (VAS), and recurrence and incontinence were recorded in the course of follow-up. The chi-square test was used, keeping p-value > 0.05 as statistically significant. **Results:** The mean age of patients was 42.3 ± 11.4 years, with 60.8% being male. Postoperative pain was reported in 55.0% of patients. Recurrence occurred in 12.9%, and incontinence was observed in 18.1%, primarily to flatus. Stratification showed no significant associations between outcomes and demographic or clinical variables (p>0.05 for all). **Conclusions:** Seton is a safe and efficient intervention in high anal fistula, and results are satisfactory regardless of the demographics of patients and are largely dependent on the surgical approach and fistula features.

INTRODUCTION

Fistula in ano is a prevalent perianal condition that is accompanied by severe discomfort and morbidity. It usually comes as a result of the nonspecific infection of the anal glands within the intersphincteric area [1]. Reportedly more prevalent among males globally. Anorectal infections are regarded as the cause of about 80% [2]. The prevalence is 18-34% in the United States and 25% in Western countries. Comparatively, it is also lower in the developing countries at about 12% [3, 4]. A survey of Quetta, Baluchistan, had determined a prevalence of 10% with a higher prevalence in males. Fistula in ano can also be linked to certain diseases like tuberculosis, Crohn's disease, malignancies, and HIV infection. Other risk factors are trauma, foreign bodies, radiation exposure, and long-term steroid use [5]. There are several classification systems of the anal fistula, which are the Parks, Standard, Milligan-Morgan, Goodsell, and the Mill and Thompson classification. Among these, Parks classification is the most popular, according to which fistulae can be divided into four different categories: intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric [6]. A fistula in ano is clinically characterized, in most cases, by pain around the anus, swelling, purulent discharge, bleeding, and excoriation of the skin. The

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diagnosis is done by a combination of physical examination (digital rectal examination), anal manometry, fistulography, CT scan, endoluminal ultrasonography, and MRI [7]. The low anal fistulae are normally treated surgically by fistulectomy or fistulotomy, and the recovery and functional results are generally favourable. Nevertheless, high anal fistulae are more difficult to treat, and are treated with more than 20 methods, such as fistulectomy with protective colostomy, staged fistulotomy, advancement flap repair, the use of fibrin glue or punches, and the placement of a seton. These methods are linked to a greater rate of failure and a high probability of functional disability [8, 9]. The sutures that are used in managing fistula are usually made of silk sutures, silicone, rubber, or elastic substances. Setons are either draining or cutting functionally. Seton draining is used to manage local sepsis, tract patency, and facilitate tract maturation [10]. It is particularly useful in complicated cases that assist in subsequent definitive treatment and reduce the size of external wounds. A cutting seton, on the other hand, is firmly clamped in the fistulous tract, exerting increasing pressure on the muscle fibers so as to push it through, augmenting fibrosis. The seton is commonly tightened with time (e.g., after every two weeks) until full fistulotomy and exteriorization of the tract [11]. According to a study by Shirah and Shirah out of a total number of 372 patients who were treated using cutting seton, 80.1% were men, and 19.9% were women. The symptoms lasted between 3 and 21 months. Full recovery was observed in 97.6% of the patients, and 15.6% had flatus but not feces incontinence. Only 2.4% reoccurred [12].

Despite the widespread use of the cutting seton technique for the management of high anal fistula, there remains limited evidence, particularly from developing countries, regarding its short-term postoperative outcomes, including pain, recurrence, and continence status. Moreover, it is unclear whether these outcomes are influenced by patient demographics and baseline clinical characteristics or are primarily determined by surgical and fistula-related factors. This study aims to evaluate the short-term outcomes following cutting seton placement in patients with high anal fistula and to assess their association with demographic and clinical variables.

METHODS

This cohort study was done in the Department of General Surgery, Hayatabad Medical Complex, Peshawar, between 1st April 2025 and 30th August 2025, after getting approval under Ref No. 2526. The sample size was 171 patients, according to the Open Epi sample size calculator. Based on the 2.4% recurrence rate after high anal fistula seton procedure [12], the confidence interval was calculated as 95%, and the margin of error is set to 2.3% [13]. The formula used for sample size calculation is n = DEFF × N × p(1-p)/d2/Z21-α/2 × (N-1) + p(1-p). The sampling method used was a non-probability consecutive sampling method. A high anal fistula was an aperture that occurred at a site above the dentate line and was diagnosed with magnetic resonance imaging (MRI). A seton was referred to as a substance composed of silk suture, silastic, Marceline rubber, or an elastic band to treat a fistula. Pain, recurrence, and incontinence were considered as the main outcomes of this study after three months of the cutting seton procedure. Pain intensity was assessed using the Visual Analogue Scale (VAS), scored from 0 (no pain) to 10 (worst pain imaginable). Patients marked a point on the scale corresponding to their perceived pain. For analysis, a score of >3 was considered as the presence of pain. The VAS is a validated and reliable tool for assessing pain intensity in clinical studies [14]. The recurrence was determined as the presence of the fistula at the same location within the three months of follow-up. Incontinence was defined as the involuntary loss of control over flatus or feces and was assessed at three months postoperatively using the Parks Incontinence Score. The Parks score classifies continence into four categories: Category 1: continent to solid stool, liquid stool, and flatus; Category 2: incontinent to flatus only; Category 3: incontinent to liquid stool (with or without flatus incontinence); and Category 4: incontinent to solid (formed) stool. The inclusion criteria were patients aged between 18-70 years of either sex or ethnicity who were diagnosed with high anal fistula according to the operational definition. Patients with comorbidities related to Crohn, tuberculosis, malignancy, HIV infection, or complex fistulae, with more than one external opening, or those patients with an internal opening high in the pelvis were excluded. Patients presenting on referral from other hospitals were also excluded to ensure a homogeneous study population, as referred cases often represent more complex disease or prior interventions that could influence postoperative outcomes. After receiving the approval of the Institutional Review Board (IRB), the patients in the General Surgery Ward diagnosed with high anal fistula were eligible after receiving informed written consent. An elaborate history of age, gender, body mass index (BMI (kg/m^2), socioeconomic status, profession and comorbidities like diabetes and hypertension were all noted. Perineal examination, including the digital rectal examination and proctoscopy, was done, and an MRI was performed to verify the diagnosis. Patients were hospitalized once diagnosed and made to take fluids and semi-solid food a day before surgery and kept nil after midnight. A consultant surgeon performed a cutting seton procedure by general or spinal anesthesia in the lithotomy

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position on the next day. Since there was no commercially available seton material in the area, Prolene I was used and probed through the fistulous tract. Both extremities were closely knotted at the rectum. Post-operative bleeding monitoring was done, and patients were discharged the next day with the instructions to revisit the outpatient department every two weeks to have the seton tightened until the tract was fully cut. A follow-up (3 months after surgery) was done on the patients. Data regarding pain, recurrence, and incontinence during the follow-up visits were recorded through a designed questionnaire.

Statistical analysis was performed using SPSS version 27.0. Mean ± standard deviation (SD) was calculated for continuous variables such as age, and BMI. Frequencies and percentages were computed for categorical variables including gender, socioeconomic status, profession, comorbidities, and fistula location (anterior or posterior) and pain score. Outcomes of pain, recurrence, and incontinence were stratified against age, gender, BMI, socioeconomic status, profession, and fistula location. Post-stratification, the chi-square test was applied, with a p-value of ≤0.05 considered statistically significant.

RESULTS

A total of 171 patients were included in the study which an average age of 43.1 ± 14.0 years. The majority of participants were aged between 31 and 40 years (26.3%), followed by 41 and 50 years (22.8%) and 18–30 years (18.7%). Most patients were male (60.8%), and a higher proportion belonged to the poor socioeconomic class (64.3%). Regarding occupation, housewives represented the largest group (35.1%), followed by individuals working in the private sector (16.4%) and laborers (12.9%), table 1.

Table 1: Demographic Characteristics (n=171)

Variable	Category	n (%)
Age (Years)	18–30	32 (18.7%)
	31–40	45 (26.3%)
	41–50	39 (22.8%)
	51–60	29 (17.0%)
	61–70	26 (15.2%)
Gender	Female	67 (39.2%)
	Male	104 (60.8%)
Socioeconomic Status	Middle Class	61 (35.7%)
	Poor	110 (64.3%)
Profession	Housewife	60 (35.1%)
	Laborer	22 (12.9%)
	Private Job	28 (16.4%)
	Government Employee	14 (8.2%)
	Businessman	11 (6.4%)
	Unemployed	18 (10.5%)
	Student	18 (10.5%)

Among clinical characteristics, 28.1% of the patients had diabetes, and 30.4% were hypertensive. In terms of body mass index (BMI), 41.5% had normal weight, 31.6% were overweight, 19.9% were obese, and 7.0% were underweight. Posterior fistulas were more commonly observed (65.5%) than anterior fistulas (34.5%), table 2.

Table 2: Clinical Profile and Comorbidities (n=171)

Variable	Category	n (%)
Comorbidities	Diabetes	48 (28.1%)
	Hypertension (HTN)	52 (30.4%)
BMI (kg/m^2)	Underweight (<18.5)	12 (7.0%)
	Normal (18.5–24.9)	71 (41.5%)
	Overweight (25–29.9)	54 (31.6%)
	Obese (≥30)	34 (19.9%)
Location of Fistula	Anterior	59 (34.5%)
	Posterior	112 (65.5%)

A total of 55.0% of patients experienced pain (VAS>3), while recurrence of the condition was observed in 12.9%. Incontinence was reported in 18.1% of patients, out of which 12.3% had flatus incontinence and 5.8% had feces incontinence. However, no patient developed isolated liquid stool incontinence during follow-up, table 3.

Table 3: Outcomes at 3 Months Post-Procedure (n=171)

Variable	Category	n (%)
Pain Presence (VAS>3)	Yes	94 (55.0%)
	No	77 (45.0%)
Recurrence	Yes	22 (12.9%)
	No	149 (87.1%)
Incontinence	Positive	31 (18.1%)
	Negative	140 (81.9%)
If Incontinence Positive	Flatus incontinence	21 (12.3%)
	Feces incontinence	10 (5.8%)

On stratification of outcomes against various demographic and clinical variables, no statistically significant associations were found. Pain was more frequently reported among patients aged 31–40 years (62.2%) and 51–60 years (58.6%), but the association with age was not statistically significant (p=0.321). Gender-wise distribution showed similar rates of pain in males (53.7%) and females (55.8%) (p=0.605). Pain was most commonly reported among overweight individuals (57.4%), but again without statistical significance (p=0.777). Patients from poor socioeconomic backgrounds reported a slightly higher frequency of pain (58.2%) compared to those from good socioeconomic status (49.2%) (p=0.430). Pain prevalence across different professions varied minimally, with the highest percentage among students (66.7%), but with no significant association (p=0.982). Pain was slightly more frequent in patients with anterior fistulas (59.3%) compared to posterior (52.7%) (p=0.541). Similar trends were observed for recurrence and incontinence. Recurrence was slightly more frequent among students

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(22.2%) and obese patients (17.6%), but none of these associations reached statistical significance. Incontinence rates were highest among obese (26.5%) and underweight (25.0%) individuals. Patients with poor socioeconomic status had a higher rate of incontinence (20.9%) compared to those with good status (13.1%), although this was not statistically significant (p=0.321). No significant associations were observed between the location of fistula and pain (p=0.541), recurrence (p=0.543), or incontinence (p=0.998). Overall, postoperative pain, recurrence, and incontinence were independent of baseline demographic and clinical characteristics, table 4.

Table 4: Stratification of Outcomes by Demographic and Clinical Variables (n=171)

Variables	Category	Pain (Yes), n (%)	p-value	Recurrence (Yes), n (%)	p-value	Incontinence (Positive), n (%)	p-value
Age (Years)	18-30	15 (46.9%)	0.321	4 (12.5%)	0.821	5 (15.6%)	0.745
	31-40	28 (62.2%)		7 (15.6%)		6 (13.3%)	
	41-50	21 (53.8%)		3 (7.7%)		8 (20.5%)	
	51-60	17 (58.6%)		5 (17.2%)		7 (24.1%)	
	61-70	13 (50.0%)		3 (11.5%)		5 (19.2%)	
Gender	Male	36 (53.7%)	0.605	10 (14.9%)	0.792	12 (17.9%)	0.983
	Female	58 (55.8%)		12 (11.5%)		19 (18.3%)	
BMI (kg/m^2)	Under-weight	6 (50.0%)	0.777	1 (8.3%)	0.940	3 (25.0%)	0.616
	Normal	39 (54.9%)		8 (11.3%)		11 (15.5%)	
	Overweight	31 (57.4%)		7 (13.0%)		6 (11.1%)	
	Obese	18 (52.9%)		6 (17.6%)		9 (26.5%)	
Socioeconomic Status	Middle class	30 (49.2%)	0.430	7 (11.5%)	0.872	8 (13.1%)	0.321
	Poor	64 (58.2%)		15 (13.6%)		23 (20.9%)	
Profession	Housewife	33 (55.0%)	0.982	7 (11.7%)	0.914	12 (20.0%)	0.793
	Laborer	12 (54.5%)		3 (13.6%)		4 (18.2%)	
	Private Job	15 (53.6%)		3 (10.7%)		3 (10.7%)	
	Govt. Employee	8 (57.1%)		2 (14.3%)		2 (14.3%)	
	Businessman	5 (45.5%)		1 (9.1%)		2 (18.2%)	
	Unemployed	9 (50.0%)		2 (11.1%)		4 (22.2%)	
	Student	12 (66.7%)		4 (22.2%)		4 (22.2%)	
Fistula Location	Anterior	35 (59.3%)	0.541	9 (15.3%)	0.543	11 (18.6%)	0.998
	Posterior	59 (52.7%)		13 (11.6%)		20 (17.9%)	

* p-values ≤ 0.05 are statistically significant

DISCUSSION

In the current study, more than half of the patients (55.0%) reported postoperative pain with a mean Visual Analogue Scale (VAS) score of 4.8 ± 1.6. Pain was not significantly associated with age, gender, BMI, socioeconomic status, or fistula location. These findings are consistent with previous reports suggesting that postoperative pain is a common but highly variable experience. For instance, Khan et al. found comparable mean pain scores among patients undergoing anal fistula repair, and similarly reported no significant differences based on demographic characteristics [15]. Although there are some literature findings that younger age and lower socioeconomic status might have a higher perception of postoperative pain caused by the disparities in healthcare access, this study failed to establish any association, which may be because of the standard care of postoperative pain offered to the sample. Besides, the absence of correlation with the location of fistula is slightly different compared to the work published by Bayrak and Altintas, who have reported that high trans-sphincteric tracts were more painful after surgery [16]. This difference can indicate the variability in the procedure or be the difference in the complexity of fistulas that were not stratified in the present analysis. This study showed a recurrence rate of 12.9 that is similar to other international literature that reported the range of 10-25% based on technique and case selection. Recurrence was not significantly related to any stratified demographic or clinical variable. These results closely align with the findings of Taskin *et al.* who reported a 13% recurrence rate using hybrid seton and laser methods and also observed no significant difference across gender, BMI, or age groups [17]. In contrast, Bayrak and Altintas identified male gender, obesity, and previous fistula surgery as independent predictors of recurrence in their LIFT-procedure cohort [16]. One reason for the lack of association in the current study may be the exclusion of recurrent or complex fistulas in the original selection criteria, or limited sample size in certain subgroups, such

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as the underweight or business occupation category. The absence of a statistically significant association between recurrence and fistula location (anterior vs posterior) was also consistent with reports from studies using traditional and minimally invasive procedures, where anatomical location alone did not predict outcomes unless coupled with height or branching complexity of the tract [12]. Incontinence was reported in 18.1% of patients, of which 12.3% had incontinence to flatus and 5.8% to feces. This complication was not significantly associated with any of the stratified variables, including gender, BMI, age, or socioeconomic status. These findings are supported by a study by Khan et al. which found a similar incontinence rate of 16% after fistulotomy and fistulectomy procedures, with no clear associations with BMI or age [18]. Moreover, Amato et al. also noted that outcomes of continence after FILAC largely relied on the fistula height and sphincter complex maintenance as opposed to the demographics of patients [19]. This highlights an important aspect that operative technique is more significant to the continuation of continence than preoperative factors. It is also interesting that gender is not associated in this study because previous studies had sometimes suggested higher rates of incontinence in women, possibly because a weaker anal sphincter complex after childbirth caused it, although this is not a consistent finding in more recent controlled studies [20, 21].

Collectively, the lack of statistically significant correlations between the results of the postoperative period and demographic or clinical variables in this research indicates that additional factors, like the complexity of the fistula or the previous surgical procedures and technical peculiarities of the procedure, have a more significant effect on the outcomes than the baseline features. Whilst these findings have been encouraging in the aspects of equity of surgical gain among group of populations, there is still the need to focus future research to encompass the tract morphology, height, and MRI classification systems to enable prediction of exact outcomes in patients.

CONCLUSIONS

The cutting seton procedure is a viable and feasible alternative to the treatment of high anal fistula, with moderate pain, recurrence, and incontinence. Demographic factors and baseline clinical factors did not impact postoperative outcomes significantly, which means that the procedure delivers similar results to patients of various groups. These results confirm cutting seton as an effective treatment modality, especially where resources are few, and highlight the significance of surgical practice and fistula characteristics on outcomes.

Authors' Contribution

Conceptualization: HK
Methodology: FOS, AM, A
Formal analysis: AS
Writing and Drafting: FOS, TAR, NK
Review and Editing: HK, FOS, TAR, AM, NK, AS, A

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Prevalence of Gestational Diabetes Mellitus among Pregnant Females

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ABSTRACT

Gestational diabetes mellitus (GDM) is a prevalent pregnancy complication marked by glucose intolerance, which poses significant risks to both maternal and fetal health, including preeclampsia, cesarean delivery, macrosomia, and an increased susceptibility to type 2 diabetes later in life. **Objectives:** To determine the frequency and prevalence of GDM in pregnant women. **Methods:** A descriptive cross-sectional study was conducted with 160 pregnant women aged 18-45 years at the University of Lahore Teaching Hospital. Data were collected using a structured questionnaire and clinical measurements, including a 50-gram oral glucose challenge test (GCT), followed by a 100-gram oral glucose tolerance test (OGTT) for those with positive GCT results. **Results:** The mean age of participants was 27.08 ± 4.35 years, with a majority being well-educated (57.9% graduates, 35.2% with master's degrees, and 1.3% with an MBBS). Most women were housewives (50.3%), followed by office workers (27%) and teachers (20.1%). The mean BMI was 31.70 ± 6.18, indicating a high prevalence of overweight/obesity. Despite recognizing the seriousness of GDM and the importance of a healthy lifestyle, 27% of participants did not exercise regularly, and 23.8% met the criteria for GDM. **Conclusions:** The study revealed a high prevalence of GDM, primarily driven by overweight/obesity and physical inactivity.

INTRODUCTION

Diabetes mellitus refers to a group of metabolic disorders characterized by persistent hyperglycemia resulting from defects in insulin production, secretion, or action. Insulin, a hormone secreted by the pancreas, plays a critical role in regulating blood glucose levels by facilitating the transport of glucose into cells for energy or storage [1, 2]. When insulin fails or is insufficient, blood glucose levels rise, leading to both acute and chronic complications such as retinopathy, nephropathy, neuropathy, and cardiovascular diseases, significantly affecting quality of life and increasing mortality risks [3, 4]. Diabetes is categorized into Type 1 Diabetes (T1DM), Type 2 Diabetes (T2DM), gestational diabetes mellitus (GDM), and other special types [5]. Gestational diabetes develops during pregnancy, when the body is unable to produce sufficient insulin to meet the demands of pregnancy. The incidence of GDM is increasing globally due to various factors, including lifestyle, genetics, and sociodemographic influences [6].

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Women who are overweight, older, or belong to certain ethnic groups, such as South Asians, Hispanics, and African Americans, are at higher risk. Additionally, a personal history of diabetes further increases the likelihood of developing GDM, indicating a strong genetic predisposition [7]. In Pakistan, the prevalence of GDM is alarmingly high, with several studies indicating that the condition affects a significant portion of the pregnant population. For example, a study conducted in Karachi found that approximately 9-15% of pregnant women were diagnosed with GDM [8], while another study in Lahore highlighted a prevalence of 10.7% among pregnant women. This high prevalence is attributed to factors such as poor dietary habits, physical inactivity, increasing rates of obesity, and a high incidence of gestational diabetes in women with a family history of diabetes [9]. Pakistan, like many other low-resource countries, faces challenges in early diagnosis and proper management of GDM, which can lead to increased maternal and fetal complications, including preeclampsia, large-for-gestational-age babies, and increased risk of Type 2 diabetes in the years following delivery [10]. Globally, the burden of GDM is on the rise, and the World Health Organization (WHO) reports that the condition affects approximately 6-9% of pregnancies worldwide [11]. In high-income countries, more accurate diagnoses are possible due to standardized screening guidelines. However, in low-income settings, limited healthcare resources often result in underdiagnosis and an increased risk of long-term complications for both mothers and infants [12]. The increasing rates of GDM demand effective public health strategies to address prevention, early detection, and management. Screening methods such as the oral glucose tolerance test (OGTT) have been widely used to identify women at risk. International guidelines now recommend universal or selective screening based on risk factors. The consequences of GDM extend beyond pregnancy, affecting the long-term health of both mothers and their offspring, making it a critical public health concern [13].

There is limited recent data from a hospital in Lahore that combines GDM prevalence with basic demographic and lifestyle profiling. Most existing studies either focus solely on prevalence or lack structured screening using both GCT and OGTT. Therefore, this study aimed to update the regional prevalence data and to describe the lifestyle, physical activity, and dietary habits of pregnant women undergoing GDM screening, to inform local maternal health strategies.

METHODS

This descriptive cross-sectional study was carried out to establish the prevalence of gestational diabetes mellitus (GDM) and to measure its determinants. The research was conducted at the Department of Gynecology at the University of Lahore Teaching Hospital at Lahore, Pakistan, between January and June 2024. Pregnant women aged 18-45 years with singleton pregnancies and a gestational age between 24 and 28 weeks were included, as this is the recommended period for GDM screening. Women with multiple pregnancies or chronic conditions such as cardiovascular diseases or renal disorders were excluded from the study. The participants were selected using a convenience sampling technique, inviting pregnant women attending the University of Lahore Teaching Hospital during the study period. Ethical approval was obtained from the University of Lahore's Ethical Review Committee (ERC114/23/10), and informed consent was obtained from all participants, ensuring voluntary participation. Confidentiality of all personal data was maintained throughout the study. The sample size of 160 participants was determined using the Cochran formula for sample size estimation. The formula used for calculation was: n=Z2×p×(1−p)E2n=Z2×p×(1−p)E2 Where n is the sample size, ZZ is the Z-value (1.96 for a 95% confidence level), pp is the estimated prevalence of GDM (0.20, based on regional prevalence data), and EE is the margin of error (0.05). The estimated prevalence of GDM in the region was used as 20% [14]. The questionnaire used in this study was self-structured and designed to collect data on participants' demographics, lifestyle factors, and awareness of GDM. It included closed-ended questions about physical activity and diet. Responses were categorized into predefined groups, such as exercise frequency and dietary habits. Data interpretation was conducted using a proforma to ensure consistency in recording and analysis, enabling efficient statistical evaluation of the findings. For example, responses related to physical activity were classified based on the number of times participants exercised per week (e.g., no exercise, 1–2 times per week, 3+ times per week). However, the questionnaire did not collect detailed information regarding the duration or intensity of physical activity (e.g., number of minutes per session or exercise type). As such, individuals who engaged in brief low-intensity activity and those with more prolonged or vigorous exercise may have been grouped similarly. Similarly, dietary habits were categorized by the frequency of fruit and vegetable intake, and the awareness of GDM was analyzed as either "yes" or "no" responses. Participants underwent an initial 50-gram Oral Glucose Challenge Test (GCT) as a screening for GDM. According to the standard procedure for the GCT, participants fasted for at least 8 hours before ingesting a 50-gram glucose solution. After one hour, blood glucose levels were measured, and a level of ≥140 mg/dL was considered a positive result, indicating the need for further testing. Those with a positive GCT

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result proceeded to the 100-gram Oral Glucose Tolerance Test (OGTT). In the OGTT procedure, participants fasted overnight, and fasting blood glucose was measured before they ingested a 100-gram glucose solution. Blood glucose levels were measured at fasting, 1-hour, 2-hour, and 3-hour intervals following the ingestion of glucose. The diagnosis of GDM was made based on the Carpenter-Coustan criteria, which required at least two abnormal glucose readings: fasting glucose ≥95 mg/dL, 1-hour post-glucose ≥180 mg/dL, and 2-hour post-glucose ≥155 mg/dL [15]. Data were analyzed using SPSS version 25.0. Descriptive statistics such as means, frequencies, and percentages were calculated to describe the demographic and clinical characteristics of the participants.

RESULTS

The average age of participants was 27.08 ± 4.35 years, and the average height was 1.59 ± 0.11 meters. Participants had a mean weight of 79.64 ± 10.21 kg and a mean BMI of 31.5 ± 5.94, indicating that the majority were overweight or obese. The mean fasting glucose level was 85.16 ± 13.74 mg/dL, and the 1-hour and 2-hour post-glucose test values were 135.11 ± 24.12 mg/dL and 111.72 ± 20.16 mg/dL, respectively. Demographic information, including age, height, weight, BMI, and gestational diabetes measurements (Table 1).

Table 1: Demographic Variables

Variable	Mean ± SD	Maximum	Minimum
Age (Years)	27.08 ± 4.35	37	21
Height (m)	1.59 ± 0.11	1.80	1.50
Weight (kg)	79.64 ± 10.21	95	56
BMI (kg/m^2)	31.5 ± 5.94	47.78	19.54
Gestational Diabetes Levels			
Fasting Glucose (mg/dL)	85.16 ± 13.74	132	69
1-Hour Glucose (mg/dL)	135.11 ± 24.12	185	82
2-Hour Glucose (mg/dL)	111.72 ± 20.16	150	73
Pregnancy Week at GCT Test	24-40 weeks (range)	40	24

The majority of participants were well-educated, with 57.9% holding a graduate degree and 50.3% being housewives. All participants (100%) agreed that gestational diabetes is a serious condition and that regular exercise could help prevent it. Regarding family health history, none of the participants reported a family history of type 2 diabetes. Additionally, doctors were the main source of health information for most participants (94.3%). All questionnaire-related information, including education, occupation, previous pregnancies, birth complications, family history of type 2 diabetes, and sources of health information (Table 2).

Table 2: Questionnaire-Related Information

Categories	Frequency (%)
Education Level	
Graduate	92 (57.9%)
Intermediate	10 (5.7%)
Master's Degree	56 (35.2%)
MBBS	2 (1.3%)
Occupation	
Doctor	5 (2.5%)
Housewife	80 (50.3%)
Office Job	43 (27%)
Teacher	32 (20.1%)
Previous Pregnancies	
Yes	96 (59.7%)
No	64 (40.3%)
Birth Complications	
Yes	0 (0%)
No	160 (100%)
Family History of Type 2 Diabetes	
Yes	0 (0%)
No	160 (100%)
Source of Health Information	
Doctor	150 (94.3%)
Family	10 (5.7%)
Perception of Gestational Diabetes	
Yes	160 (100%)
No	0 (0%)
Exercise Prevents Gestational Diabetes	
Yes	160 (100%)
No	0 (0%)

A significant portion of participants (27%) reported no regular exercise, while 20.1% exercised three times per week. Regarding dietary habits, 99.4% of participants believed that a healthy diet helps prevent gestational diabetes, and a majority consumed 3 portions of fruits and vegetables daily. Additionally, most participants (99.4%) reported that they do not eat a lot of processed foods or foods high in sugar. The participants' exercise habits, fruit and vegetable consumption, and dietary habits, (Table 3).

Table 3: Exercise, Diet, and Lifestyle Habits

Categories	Frequency (%)
Exercise Frequency (Per Week)	
0	43 (27%)
1	16 (10.1%)
2	21 (13.2%)
3	32 (20.1%)
4	27 (17%)
5	15 (9.4%)
6	5 (3.1%)
Daily Fruit and Vegetable Intake	
0 portions	3 (1.9%)

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1 portion	29 (18.2%)
2 portions	36 (22.6%)
3 portions	38 (23.9%)
4 portions	34 (21.4%)
5 portions	16 (10.1%)
6 portions	4 (1.9%)
Consumption of Processed Foods or High Sugar	
Yes	0 (0%)
No	160 (100%)

DISCUSSION

The GDM is a significant metabolic disorder with wide-reaching implications for maternal and fetal health. The growing prevalence of GDM, especially in developing countries, is concerning as it poses substantial risks, including preeclampsia, cesarean delivery, macrosomia, and long-term susceptibility to type 2 diabetes. This study, conducted with pregnant women attending an antenatal clinic at the University of Lahore Teaching Hospital, provides important insights into the factors influencing GDM awareness, risk, and management. The participants in this study, primarily in their late 20s, reflect the common demographic seen in antenatal settings in developing countries, where younger women (aged 25-35) are more likely to be pregnant due to higher birth rates. The mean age of 27.08 ± 4.35 years aligns with similar cohorts across Southeast Asia and low- and middle-income countries [16]. The association between maternal age and increased GDM risk is well-documented, as advancing age is linked to reduced insulin sensitivity, which our findings support. Although our sample included mainly younger women, future studies should focus on older pregnant women, who are at an elevated risk for GDM. Regarding anthropometrics, the participants in this study displayed a BMI of 31.70 ± 6.18, placing many in the overweight to obese categories. This is consistent with global trends, where a high BMI is a well-established risk factor for GDM due to its relationship with insulin resistance and metabolic dysregulation. Obesity, both pre-pregnancy and during pregnancy, significantly increases the risk of developing GDM [17]. The high proportion of overweight and obese participants underscores the need for early and effective interventions focusing on weight management and lifestyle changes to mitigate the risk of GDM. Educational attainment in the cohort was high, with 93% of participants holding at least a graduate degree. This level of education has been associated with better health outcomes due to enhanced health literacy and a greater likelihood of seeking medical advice [18-20]. However, despite this, many participants were housewives, which may limit their exposure to healthcare education and resources, particularly in more traditional societies where health behaviors are influenced by occupation and social roles [21, 22]. Thus, it is important to consider the influence of occupation and socio-economic factors on health outcomes and to tailor health education programs accordingly. This study also revealed that 59.7% of participants had previous childbirth experience, which aligns with findings that multiparity increases the risk of GDM. Interestingly, no participant reported a history of birth complications, which may reflect either an underreporting due to recall bias or the absence of complications in the study sample. The lack of reported family history of type 2 diabetes among the participants was another intriguing result, as familial factors are strongly associated with an increased risk of GDM [23]. This may suggest that non-genetic factors such as lifestyle behaviors are more prominent in this cohort.

Although this study contains some key insights, it has some limitations. Since the study is a one-center study, with the study population mostly younger, the study results might not be entirely applicable, especially to older pregnant women who have a higher risk of gestational diabetes mellitus. Also, self-reported obstetric and family history could have resulted in recall bias. Multicenter investigations utilizing bigger and more varied populations in the future are justified to enhance the comprehension of the role of demographic, genetic, and lifestyle elements in GDM. Also, longitudinal studies of the effectiveness of preventive measures, including weight control and customized health education, would be beneficial and would contribute to better maternal and fetal health.

CONCLUSIONS

This study highlights the high prevalence of GDM among pregnant women, particularly influenced by factors such as obesity and lack of physical activity. Despite high educational levels, many women did not engage in regular exercise, emphasizing the need for targeted health interventions. Early screening, lifestyle changes, and improved awareness are essential to reduce GDM's impact on maternal and fetal health. Addressing these factors could lead to better long-term health outcomes for both mothers and their children. Future research should explore the role of psychosocial factors, such as stress, in gestational diabetes development.

Authors' Contribution

Conceptualization: KA
Methodology: HY, NY
Formal analysis: SZ, RS
Writing and Drafting: AH, AZ, TY, NY
Review and Editing: KA, AH, AZ, SZ, RS, HY, TY, NY

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

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Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Comparison of Treatment Outcomes Between Intravenous Immunoglobulin and Steroid Therapy in Pediatric ITP (Idiopathic Thrombocytopenic Purpura)

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ABSTRACT

Idiopathic Thrombocytopenic Purpura (ITP) is a common and significant bleeding disorder in children with variable underlying etiologies. **Objectives:** To compare the short-term effectiveness and safety of IVIg versus corticosteroids in children with newly diagnosed ITP. **Methods:** An observational, cross-sectional comparison was conducted at a tertiary pediatric care center over a period of one year. Using consecutive sampling, 210 children were assigned to initial therapy with IVIg (n=105) or corticosteroids (n=105). Primary endpoints were time to platelet recovery and complete response by day 7; secondary endpoints included hospital stay, relapse ≤3 months, and adverse events. Group comparisons used Mann–Whitney U or chi-square/Fisher's exact tests; multivariable logistic regression adjusted for age, gender, and baseline platelet count. **Results:** IVIg led to faster recovery (median 2 vs 4 days) and shorter hospital stay (3 vs 5 days), both p<0.001; higher complete response by day 7 (90.5% vs 71.4%, p<0.001); lower relapse (9.5% vs 21.0%, p=0.012) and fewer adverse events (11.4% vs 33.3%, p<0.001). IVIg independently predicted day-7 complete response (OR 4.5, 95% CI 1.9–10.8). **Conclusions:** In this non-randomized cohort, IVIg showed superior short-term effectiveness and safety versus corticosteroids.

INTRODUCTION

Idiopathic Thrombocytopenic Purpura (ITP) is an important cause of acquired thrombocytopenia in children, and is an important cause of significant morbidity both in developed and resource-limited countries. It is estimated to have a global incidence of 410 cases per 100,000 children per annum, with most happening during early childhood [1]. Precise national-level statistics are not available in Pakistan, though hospital records indicate a similar or even greater burden, which may be due to infections, late diagnosis, and restrictions on access to healthcare [2]. ITP often follows a viral infection or immunization, particularly in children aged 2–10 years [3]. Although many children recover spontaneously within six months, around 20–25% develop chronic ITP, leading to recurrent bleeding episodes and significantly affecting quality of life [4]. First-line treatments for newly diagnosed ITP include corticosteroids and intravenous immunoglobulin (IVIg), both of which aim to increase platelet counts and reduce bleeding risk. However, the choice of therapy is influenced by clinical presentation, urgency of platelet elevation, side effect profiles, and healthcare setting [5]. Corticosteroids, on the other hand, are more affordable and widely used but

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may be associated with slower response times and more side effects with prolonged use [6]. A number of recent studies have compared the efficacy of IVIg and corticosteroids. In a 2020 systematic review, IVIg demonstrated faster initial platelet response but similar long-term remission rates compared to steroids [7]. Another randomized trial showed that IVIg achieved platelet counts ≥30,000/mm^3 within 48 hours in 80% of children compared to 59% in the steroid group [8]. However, this result was not statistically significant in a 2021 Indian study that found no difference between long-term remission or bleeding scores in both groups [9]. The absence of contextual evidence makes clinical decision-making complex, and the physician is left with extrapolated information that may not be relevant to local issues, including delayed diagnosis, frequent infections, and IVIg shortage [10].

Pakistan does not have national ITP information and so international studies have to be extrapolated. There is no local comparative study of IVIg and steroids and long-term results, such as the development of chronic ITP, and side effects of steroids have not been evaluated. The non-randomized study is prone to selection bias, as the treatment is not based on standardized protocols but on IVIg availability. Limitation in generalizability: A single-center study can only generalize to individuals recruited in the same time frame, whereas short-term follow-up (three months) cannot measure long-term outcomes. This study aims to compare the short-term treatment response, relapse rate, and adverse events among pediatric ITP patients receiving either IVIg or corticosteroids. Secondary objectives included assessing the time to platelet count recovery and the need for second-line treatment within three months of follow-up.

METHODS

This cross-sectional comparative study was carried out in the Department of Pediatric Medicine and Hematology at The Children's Hospital and The Institute of Child Health, Multan. The study duration was from 5th October 2024 to 5th October 2025. Non-probability consecutive sampling was used. Ethical approval was obtained from the Institutional Review Board (1980/IRB/CHC/2024). Confidentiality was maintained. Children aged 1–15 years with newly diagnosed immune thrombocytopenic purpura (ITP) were included. Children already treated with steroids or intravenous immunoglobulin (IVIg), or those with inherited thrombocytopenia, malignancy, or active infection, were excluded. Written informed consent was taken from caregivers. Treatment was not randomized. The treating physician decided the treatment based on clinical judgement and the availability of IVIg. Parental preference did not influence treatment choice. No variables were missing, and all required data points were complete for all participants, so no imputation or additional handling of missing data was needed. The sample size was calculated using the WHO Sample Size Calculator with a 95% confidence level and 5% margin of error. An expected IVIg response rate of 60% resulted in a final sample of 210 children [11]. This assumed rate of 60% ensured adequate statistical power for comparison between treatment groups. All enrolled children completed the study. The sample size was divided into two groups of 105 each. The two groups were clinically comparable at baseline, with no significant differences in bleeding severity or presenting features before treatment, and logistic regression was used to adjust for remaining confounders. The primary treatment outcomes were time to platelet recovery and complete response at day 2, day 7, and day 30. Time to platelet recovery was defined as the number of days required to reach a platelet count ≥30 × 10^9/L after initiation of therapy. Complete response was defined as platelet count ≥100 × 10^9/L, and partial response as ≥30 × 10^9/L, according to International Working Group criteria. Secondary outcomes included hospital stay duration, relapse within 3 months, and adverse events. Relapse was defined as a decline in platelet count to <30 × 10^9/L after an initial response. All platelet counts at baseline, day 2, day 7, and day 30 were taken from hospital laboratory reports included in each patient's medical record. For this study, treatment efficacy was defined as the hematologic response achieved after receiving IVIg or corticosteroids. Efficacy included the following components: (1) time to platelet recovery, defined as the number of days needed to reach a platelet count ≥30 × 10^9/L; (2) complete response at day 2, day 7, and day 30, defined as platelet count ≥100 × 10^9/L; (3) partial response, defined as platelet count ≥30 × 10^9/L; and (4) sustained response without relapse during the 3-month follow-up period. These standardized definitions were used to assess and compare the short-term efficacy of both treatment groups. Platelet counts at baseline, day 2, day 7, and day 30 were measured using the hospital's standardized hematology protocol. A 2–3 mL venous blood sample was drawn into EDTA tubes by trained nursing staff. Samples were processed within 2 hours of collection in the hospital hematology laboratory. Platelet counts were obtained using an automated hematology analyzer (Sysmex XN-series), which is calibrated daily according to manufacturer and hospital quality-control procedures. Any abnormal or flagged readings were repeated, and the repeat value was used for analysis. The platelet count printed on the laboratory report was recorded in the study proforma. Data taken from medical records included baseline clinical presentation, bleeding severity, laboratory-confirmed platelet counts, treatment

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administered, hospital stay duration, and all documented adverse events. Adverse events were predefined as vomiting and hypertension. Vomiting was recorded if documented in physician notes or nursing flowcharts. Hypertension was extracted from routine nursing vital-sign charts based on age-adjusted pediatric blood pressure thresholds and was confirmed by the treating physician. In addition to reporting individual adverse events, a composite safety endpoint termed "any adverse event" was calculated. This composite included the occurrence of at least one predefined adverse event (vomiting, hypertension, or both) during hospitalization. The purpose of this composite measure was to summarize the overall safety profile of each treatment group. Follow-up compliance was ensured by scheduling clinic visits on day 7, day 30, and at 3 months post-treatment. Attendance was verified through clinic records. For patients who did not return for scheduled visits, a telephone call was made to obtain platelet counts performed at external laboratories or to encourage an in-person reassessment. Relapse data were obtained either during clinic visits or through verified laboratory reports shared by caregivers. All 210 enrolled children completed follow-up through 3 months. Statistical analysis was performed using IBM SPSS version 26.0. Normality of continuous variables was assessed using the Shapiro–Wilk test, and appropriate statistical tests were applied based on distribution. An independent t-test was used for normally distributed variables. The Mann–Whitney U test was used for non-normal variables. Chi-square or Fisher's exact test was used for categorical variables. Pearson correlation was applied to normally distributed variables, while Spearman correlation was used for non-normally distributed variables, including baseline platelet count and time to platelet recovery, which did not meet the normality assumptions. Logistic regression was adjusted for age, gender, and baseline platelet count to control for confounding, while bleeding severity was excluded as it did not differ significantly between groups. A p-value <0.05 was considered significant. Model adequacy was checked using the Hosmer–Lemeshow goodness-of-fit test, which confirmed an acceptable fit for the logistic regression model.

RESULTS

No dropouts, and 210 pediatric patients were enrolled and completed the study. Participants were divided into two groups: one receiving intravenous immunoglobulin (IVIg) and the other receiving steroid therapy (n=105, 50.0% each). Although the baseline sociodemographic factors (age, gender, parental education, and income) were similar across groups, both day 2 and day 7 treatment responses were significantly different. The IVIg group was noted to have a superior rate of complete response by day 2 (80.9% vs 57.1%, p<0.001), and by day 7 (90.5% vs 71.4%, p<0.001). Chi-square analyses were consistent with these differences, showing that the IVIg group achieved better early treatment efficacy. The relapse rate was significantly lower in the IVIg group (9.5%) compared to the steroid group (21.0%) (p=0.012). Also, the adverse events occurred more often in steroid-treated children (33.3 percent) compared to IVIg (11.4 percent, p<0.001). Hypertension was especially found in the steroid group (4.8%), and the level of vomiting was not significantly different between groups. The exact test of Fisher proved that there was a significant difference in the prevalence of hypertension (p=0.023). The efficacy of IVIg was further supported by logistic regression analysis that indicated that IVIg increased the probability of achieving a complete response at day 7 significantly with an odds ratio of 4.5 (95% CI: 1.910.8, p<0.001). Also, a higher baseline platelet count was independently related to a higher odd of response (OR = 1.04 per unit increase, p=0.002), despite age and gender. The study presents the descriptive statistics of the continuous variables of age, initial platelet count, platelet recovery time, and the duration of stay in the hospital in children undergoing IVIg (n = 105) or steroid therapy (n=105). The Shapiro-Wilk test ensured that age data were normal, but not platelet count, recovery time, and hospital stay. In this regard, an independent t-test or Mann-Whitney U test was adopted. This table shows that the age and the count of platelets across the groups were similar, but platelet recovery and hospitalization duration were shorter in the IVIg group. These results highlight the hastened recovery and decreased inpatient load with IVIg (Table 1).

Table 1: Descriptive Statistics of Continuous Variables in IVIg (n=105) and Steroid Therapy (n=105) Groups

Variables	IVIg Group	Steroid Group	p-value
Age (Years)*	7.4 ± 3.2	7.4 ± 3.2	0.900
Baseline Platelet Count ($\times 10^9$/L)	12 (IQR: 8–18)	14 (IQR: 10–20)	0.073
Time to Platelet Recovery (days)	2 (IQR: 1–3)	4 (IQR: 3–6)	<0.001
Hospital Stay Duration (days)	3 (IQR: 2–4)	5 (IQR: 4–7)	<0.001

*Mean ± SD, analyzed via independent t-test. Median (IQR), analyzed via Mann–Whitney U test Normality tested with Shapiro-Wilk; others non-normal (p<0.001)

The demographic and baseline clinical variables were obtained from two sources. Sociodemographic variables, including age, sex, parental education, income bracket, and residence (urban or rural), were extracted from the standardized admission form completed at the time of hospital registration. Clinical presentation features such as mucosal bleeding, severity of bleeding, fever, petechiae, and other presenting symptoms were taken from initial physician assessment notes documented in the medical record. All data were recorded in the study proforma at

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enrollment by the research team, ensuring consistency and avoiding missing information. This table demonstrates no statistically significant differences in gender, education, income, or presenting symptoms, indicating well-balanced groups at baseline with equivalent disease severity before treatment (Table 2).

Table 2: Frequency Distribution of Baseline Categorical Characteristics (n=210)

Variables	IVIg Group, n (%)	Steroid Group, n (%)	p-value
Female	60 (57.1%)	58 (55.2%)	0.840
Parental Education (≥ Intermediate)	72 (68.6%)	70 (66.7%)	0.640
Family Income (>PKR 30,000)	61 (58.1%)	59 (56.2%)	0.640
Urban Residence	62 (59.0%)	65 (61.9%)	0.680
Mucosal Bleeding	48 (45.7%)	50 (47.6%)	0.760
Severe Bleeding	35 (33.3%)	38 (36.2%)	0.660
Fever Present	67 (63.8%)	70 (66.7%)	0.580
Petechial Rash	53 (50.5%)	55 (52.4%)	0.810

*Chi-square test applied

The results of the treatments of the two groups (n=105 each) were reported as complete response at day 2 and day 7, and relapse within 3 months, and adverse events. The negative events were hypertension and vomiting. Chi-square and Fisher's exact test were used in the low-frequency outcomes to determine group differences (Table 3).

Table 3: Comparison of Treatment Outcomes and Adverse Events in IVIg vs Steroid Groups (n=105 Each)

Outcomes	IVIg Group, n (%)	Steroid Group, n (%)	p-value
Complete Response by Day 2	85 (80.9%)	60 (57.1%)	<0.001
Complete Response by Day 7	95 (90.5%)	75 (71.4%)	<0.001
Relapse within 3 months	10 (9.5%)	22 (21.0%)	0.012
Any Adverse Event	12 (11.4%)	35 (33.3%)	<0.001
Hypertension†	0 (0.0%)	5 (4.8%)	0.023
Vomiting	4 (3.8%)	8 (7.6%)	0.250

*Chi-square test; †Fisher's exact test

This study indicates correlations and predictive variables with treatment response and platelet recoveries. Pearson correlation evaluated the age in relation to the time to recover; Spearman correlation was used to evaluate the baseline platelet count in relation to recovery time. Binary logistic regression analyzed predictors of full response on Day 7 (Table 4).

Table 4: Correlations and Predictors of Complete Response at Day 7

Variables	Result	p-value
Analysis		
Pearson: Age vs Time to Recovery	r = 0.12	0.090
Spearman: Platelet Count vs Recovery	ρ = −0.42	<0.001
Logistic Regression Predictors of Day 7 Response		
Treatment: IVIg (vs Steroid)	OR = 4.5 (95% CI: 1.9–10.8)	<0.001
Platelet Count (per 1×10^9/L)	OR = 1.04 (95% CI: 1.02–1.06)	0.002
Age (years)	OR = 1.02 (95% CI: 0.96–1.08)	0.480
Gender (Female vs Male)	OR = 0.89 (95% CI: 0.45–1.75)	0.720

*Multivariate logistic regression adjusted for age, gender, and baseline platelet count. Pearson/Spearman correlations based on data normality (Shapiro-Wilk)

DISCUSSION

The sample population consisted of 210 pediatric patients, with half of them in IVIG and the other half in steroid therapy. These results are in line with more recent meta-analyses, which show higher early platelet responsiveness after IVIG compared to corticosteroids in childhood idiopathic thrombocytopenia [12-14]. The combined evidence also suggests that IVIG enables fast hemostatic platelet increments within 2448 hours, as compared to steroids, which acts slower, though they have identical long-term results [15]. The use of IVIG in the acute correction of platelet counts in moderate to severe ITP in children has received consensus-level support [16], although with short-term responses. An early platelet recovery followed by IVIG was retrospectively associated with long-term positive results at 6 and 12 months, and the percentage of responders with persistent or chronic disease was lower [17]. Those observations echo the reduced relapse rate in the present IVIG cohort (9.5%) compared with steroid-treated children (21.0%). According to generic hematologic studies, a quick platelet increment decreases the risk of bleeding and possible complications, which gives biological plausibility to the increased efficacy observed in this case [18]. Patient relevance is evidenced by the fact that IVIG has a better efficacy, durability, and safety profile over steroids in childhood thrombocytopenia [19]. Future studies are recommended to use multicenter designs and use larger cohorts and longer follow-up to determine chronic ITP evolution, economic outcome, and comparative side effects profile, including the cognitive and metabolic effects of steroids in children [20, 21].

Only vomiting and hypertension were considered adverse events, whereas steroid-specific effects such as growth suppression were not included. Additional restrictions to validity include no blinding or consecutive sampling. The outcomes of a single tertiary hospital in Multan are unlikely to be applicable in other areas. Add full monitoring of safety that incorporates growth and cognition. Create an evidence-based treatment algorithm in Pakistani healthcare environments.

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CONCLUSIONS

In this study, intravenous immunoglobulin resulted in faster platelet recovery, higher early treatment response, fewer adverse events, and lower relapse compared to corticosteroids in children with newly diagnosed ITP. These findings suggest that IVIg may be a more effective short-term treatment option in our local setting.

Authors' Contribution

Conceptualization: AZ
Methodology: SA, AH
Formal analysis: UF, AH
Writing and Drafting: ZA, MKA
Review and Editing: ZA, AZ, MKA, UF, SA, AH

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Effect of a Six-Month Certificate Course in Health Professions Education on the Adversity Quotient of Medical Teachers

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ABSTRACT

Medical teachers frequently face high-stakes, stressful situations that challenge their emotional and professional effectiveness. Adversity Quotient (AQ) reflects an individual's ability to withstand stress, and faculty development programs like CHPE may enhance both teaching competence and psychological resilience. **Objective:** To evaluate the effects of a six-month course in CHPE on the AQ of the medical teachers. **Methods:** The study was a pre-test post-test quasi-experimental quantitative study on 55 medical teachers who participated in the CHPE program at Fatima Jinnah Medical University, Lahore. The data were gathered on the Adversity Response Profile (ARP) questionnaire. The measurement of AQ scores was undertaken before the course and after the course. IBM SPSS Statistics version 28.0 was used to analyze the data. **Results:** The AQ of the participants improved significantly after the CHPE intervention (Median [IQR]: 106 [96 -118] vs. 142 [134-156]; Z = -5.943, p<0.001). Before the course, 69.1% had Low AQ and 30.9% had Moderately Low AQ. Once it was completed, 49.1% got Moderate AQ, 16.4% got Moderately High AQ, and 5.5% got High AQ. The subgroup analyses showed an increase in median AQ scores where gender and years of experience did not significantly affect the results (p>0.05). **Conclusions:** The six-month CHPE program had a statistically significant impact on the Adversity Quotient of the medical teachers and implied that a well-designed faculty development intervention could make academic healthcare professionals resilient and adaptive.

INTRODUCTION

Medical practitioners are exposed to stressful and emotionally demanding circumstances regularly when working in the hospital or when doing their studies. This exposure requires one to be strong to ensure good health and performance [1]. AQ is a construct that was created by Stoltz; it represents the ability of a person to survive and overcome challenges, and it affects their performance, motivation, and adaptability [2]. The concept explains the manner in which individuals react to the challenge in four quantifiable dimensions, namely control, origin and ownership, reach, and endurance (CO2RE), which are the cognitive and behavioral processes that allow them to maintain perseverance in response to pressure [3]. Unfortunately, the medical professionals often face unpleasant situations in the healthcare facilities, where the patient and family are the initial victims, and the healthcare professionals involved are the second victims. The second victim phenomenon significantly impacts clinical staff, fellow workers, colleagues, and, subsequently, patients, students, and personal contacts [4]. Low resilience can compromise teaching effectiveness, decision-making, and interpersonal relationships, ultimately affecting learning and patient care [5]. Individuals with high AQ exhibit stronger problem-

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solving abilities, greater emotional stability, and superior organizational behavior, including altruism and conscientiousness [6]. Health Professions Education (HPE) courses generally range from 6-month Certificate courses at various universities to 2-year Master's and Ph.D. programs. Health Professions Education (HPE) faculty development programs are aimed at improving the teaching effectiveness, leadership ability, and reflective practice of medical educators [7]. The Certificate in Health Professions Education (CHPE), as an example of a structured program, combines the most important elements. They cover multiple facets of the approach towards teaching and learning, professionalism, and leadership skills, requiring in-depth insight into human psychology, and have been observed to create a change in the personality traits, style, and behaviors of the teachers, all of which are conceptually in line with elements of the Adversity Quotient (AQ) [8, 9]. Although some previous studies focused on AQ in the medical student group and its relationship with academic performance have been conducted [10, 11], limited research has explored whether educational interventions can enhance AQ among medical teachers, particularly in developing countries. This study investigates the effect of a six-month Certificate Course in Health Professional Education (CHPE) on the AQ of medical teachers at a government medical university in Pakistan. Using the Adversity Response Profile (ARP) questionnaire, adapted from Stoltz's validated instrument [12], the study evaluates whether formal HPE training enhances resilience and adaptability.

There is scanty evidence on the causal effectiveness of faculty development interventions such as CHPE in promoting psychological resilience (Adversity Quotient) of medical teachers. Medical teachers work under a lot of pressure, and evidence-based interventions to construct resilience in their professional training are not intensively researched and implemented. The findings are expected to contribute evidence for integrating psychological resilience training into faculty development programs to strengthen educator performance and institutional well-being. This study aims to evaluate the effects of a six-month course in CHPE on the AQ of the medical teachers.

METHODS

This study employed a pre-test post-test quasi-experimental design without a control group at the Department of Medical Education, Fatima Jinnah Medical University (FJMU), Lahore, Pakistan, after taking the ethical approval (88/Research Proposal/Medicine/FJ/ERC). The duration of the study was October 2023 to May 2024. This design allows for the measurement of change over time but limits causal inference; therefore, results are interpreted as pre-post associations. The purposive sampling technique required participation from both genders, who are presently engaged in academic teaching and undergoing the six-month CHPE course at FJMU. Only those who could understand and were ready to fill out the study questionnaire were taken into consideration. Those who had either a history or current mental problem that might affect the study or confound the outcome were not considered. A total of 55 participants were included from consecutive CHPE batches. The sample size was determined using Cochran's formula for finite populations (n=52). The initial population frame (N) comprised all eligible medical teachers enrolled in the CHPE program during the study period (n=60), with a 95% confidence level, Z=1.96, margin of error of 0.05, and an estimated population proportion (p) of 0.5, with an additional 10% allowance for potential attrition. To account for potential non-response or attrition, this was increased by 10%, resulting in a target sample size of 57. The Adversity Response Profile (ARP) questionnaire was used to collect data based on the Adversity Quotient (AQ) framework adapted by Stoltz. The ARP is a psychometric instrument that was validated and whose development was done by Paul G. Stoltz to determine how well an individual will react positively to the unwanted or a challenging situation. It is highly construct valid and reliable (Cronbach alpha coefficients of between 0.76 and 0.90 in its four subscales, Control, Ownership, Reach, and Endurance (CORE)) to be highly internally consistent and stable across a variety of populations [11]. It consists of 20 scenarios or statements reflecting common professional and personal challenges. Each item is rated on a five-point Likert scale: strongly disagree/never (1), disagree/rarely (2), neutral/sometimes (3), agree/often (4), and strongly agree/always (5). The ARP evaluates four core dimensions collectively referred to as CO^2RE, which represent: Control (C): The extent to which individuals perceive control over adverse events. Origin/Ownership (O2): The degree of accountability individuals assumes for dealing with adversity. Reach (R): The perceived scope of the impact of adversity across different life domains. Endurance (E): The perceived duration of adversity's effects. Scores for each dimension were computed by summing item responses corresponding to that subscale. The subscale item responses were then added to obtain scores in each dimension. It was then calculated as the total Adversity Quotient $AQ = (C + O + R + E) \times 2$. A higher score means that one is more resilient and flexible to adapt to a negative situation. Mean AQ score in each participant was obtained by dividing the overall AQ score by the number of items answered, giving a standard measure of AQ to be compared with other respondents. Based on total scores, participants were categorized into five AQ levels as follows: Low AQ: 117 or below, Moderately Low AQ: 118–134, Moderate

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AQ: 135–160, Moderately High AQ: 161–177, and High AQ: 178 or above [12]. Data collection was carried out in two phases. In the pre-intervention phase, participants completed the Adversity Response Profile (ARP) before commencing the Certificate Course in Health Professions Education (CHPE). In the post-intervention phase, the same cohort completed the ARP again upon completion of the six-month program, immediately after their final assessment. In order to guarantee consistency in the course delivery process, the facilitator manual was elaborated to describe the aims of the courses, methods of instruction, and evaluation. Consistent checking was done by conducting different faculty observations, reviewing teaching sessions, and surveys of participant feedback, whereby the implementation of course objectives was the same in all batches. The study was voluntary, and informed consent was obtained through a written form after a briefing on the purpose and confidentiality of the study.

Data analysis was performed using IBM SPSS Statistics version 28.0. Normality of continuous variables was assessed using the Shapiro–Wilk test. As age, years of teaching experience, and Adversity Quotient (AQ) scores were non-normally distributed, they were summarized as median with interquartile range (IQR). Categorical variables, including gender, designation, and qualification, were expressed as frequencies and percentages. Pre- and post-intervention AQ scores were compared using the Wilcoxon signed-rank test. Differences in AQ scores by gender were analyzed using the Mann–Whitney U test, while comparisons across years of teaching experience were performed using the Kruskal–Walli's test. Demographic variables (age, gender, and designation) were stratified, and post-intervention AQ categories were compared using the Chi-square test. Subgroup analyses were also conducted, with median AQ scores compared across gender and years of experience. A p-value<0.05 was considered statistically significant.

RESULTS

Among the 55 medical teachers enrolled in the six-month Certificate Course in Health Professional Education (CHPE), the majority were females, most participants had extensive professional exposure holding various postgraduate degrees, the majority belonged to clinical sciences, and most were working in public sector institutions (Table 1).

Table 1: Demographic Characteristics of Study Participants (n=55)

Variables	Category	Frequency (n%)
Gender	Male	19 (34.5%)
	Female	36 (65.5%)
Years of Teaching Experience	< 1 Year	6 (10.9%)
	5–10 Years	14 (25.5%)
	11–15 Years	14 (25.5%)
	> 15 Years	21 (38.2%)
Specialty	Medicine and Allied (Medicine, Pediatrics, Dermatology, Psychiatry, Nephrology)	13 (23.6%)
	Surgery and Allied (General Surgery, Orthopedics, Neurosurgery, Plastic Surgery, Urology, ENT, Ophthalmology, Anesthesiology)	15 (27.3%)
	Obstetrics & Gynaecology	6 (10.9%)
	Basic Sciences (Anatomy, Physiology, Pharmacology, Community Medicine, Microbiology)	10 (18.2%)
	Diagnostic Specialties (Pathology, Radiology)	6 (10.9%)
	Medical Education	5 (9.1%)
Qualification	MBBS + MCPS	4 (7.3%)
	MBBS + MPhil	10 (18.2%)
	MBBS + FCPS	35 (63.6%)
	MBBS + MHPE / MRCP	6 (10.9%)
Job Sector	Public	40 (2.7%)
	Private	15 (27.3%)

A statistically significant increase was observed in the median AQ scores of participants following the six-month CHPE course ($Z = -5.943$, $p<0.001$). However, in the absence of a control group, this improvement represents a pre-post association and should not be interpreted as definitive evidence of a causal effect from the CHPE program. indicating a substantial improvement in their ability to cope with and respond to adversity (Table 2).

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Table 2: Comparison of Pre- and Post-Intervention Adversity Quotient(AQ)Scores(n=55)

Variables	Median (IQR)	Z-value	p-value	Effect size (r)	95% Confidence Interval
Pre-intervention AQ	106 (96–118)	−5.943	<0.001*	0.80	0.68 – 0.88
Post-intervention AQ	142 (134–156)				

*Wilcoxon Signed-Rank Test, p-value<0.05

Following completion of the six-month course, substantial improvement was observed, with 98.3% medical teachers achieving a marked positive shift in resilience levels after the intervention. Only 1.8% remained in the Low AQ category(Figure1).

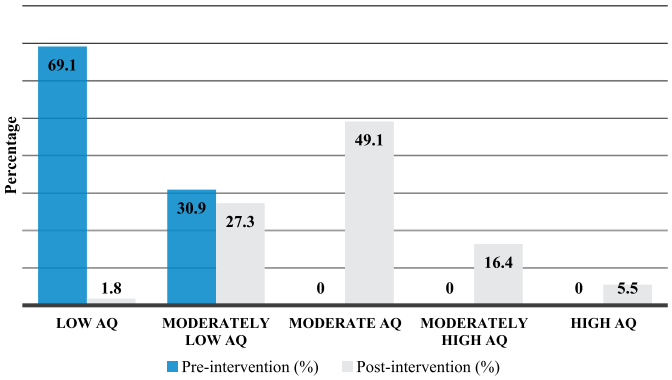

Figure 1: Comparison of Adversity Quotient (AQ) Categories of Medical Teachers Before and After the Certificate Course in Health Professional Education(CHPE)(n=55)

Before the CHPE intervention, male participants demonstrated slightly higher median AQ scores than females, and this difference was statistically significant (U = 228.000, Z = −2.023, p=0.043). After completion of the six-month course, the difference between male and female AQ scores was no longer significant (U = 291.500, Z = −0.895, p=0.371), suggesting comparable post-intervention resilience gains across genders. Analysis of Pre-intervention AQ scores revealed a significant difference across teaching experience groups (p=0.032). Median scores were highest among teachers with 11-15 years of experience and lowest among those with >15 years. Following the intervention, post-AQ scores no longer differed significantly by experience (p=0.542), suggesting the CHPE program was associated with a converging effect on resilience across career stages(Table 3).

Table 3: Association of Pre- and Post-Intervention Adversity Quotient(AQ)Scores with demographics(n=55)

Variables	Gender	Median (IQR)	Z-value	p-value
AQ Measure				
Pre-intervention AQ	Male	108 (98–120)	−2.023	0.043*
	Female	103 (94–115)		
Post-intervention AQ	Male	140 (130–154)	−0.895	0.371
	Female	143 (135–158)		
AQ Score				
Variables	**Gender**	**Median (IQR)**	**χ^2 (df)**	**p-value**
Pre-AQ	<1 Year	99.0 (90.0–110.0)	8.79 (3)	0.032[a]
	5–10 Years	110.0 (101.0–118.0)		
	11–15 Years	112.0 (100.0–124.0)		
	> 15 Years	96.0 (84.0–108.0)		
Post-AQ	<1 Year	154.0 (145.0–165.0)	2.15 (3)	0.542[a]
	5–10 Years	139.0 (122.0–158.0)		
	11–15 Years	137.0 (120.0–162.0)		
	>15 Years	146.0 (135.0–160.0)		

[a]Kruskal-Wallis H test

The gender and years of experience analysis of the AQ scores revealed that all subgroups had an increase in their median AQ scores after the educational intervention. Even though the median scores showed a positive change in all the groups, the results showed that AQ scores were not statistically influenced by gender or years of experience, and the interaction between Gender and Years of Experience was not significant(Table 4).

Table 4: Comparison of AQ Scores by Gender and Years of Experience

Gender	Years of Experience	Pre-intervention AQ Median (IQR)	Post-intervention AQ Median (IQR)	Gender Effect p-value	Experience Effect p-value	Gender × Experience Interaction p-value
Male	<1 Year	102 (94–112)	144.33 (144–145)	0.059	0.101	0.405
	5-10 Years	108 (100–120)	138.43 (120–160)			
	11-15 Years	117 (102–124)	116.80 (90–170)			
	>15 Years	103.5 (92–110)	141.75 (130–155)			
Female	<1 Year	87.33 (82–95)	163.33 (152–175)	0.079	0.315	0.368
	5-10 Years	110.57 (102–122)	138.57 (130–150)			
	11-15 Years	108.44 (104–126)	147.78 (140–160)			
	>15 Years	95.76 (94–112)	146.24 (130–160)			

DISCUSSION

Medical practitioners often encounter stressful experiences in clinical and academic practice, and patients and their families are often viewed as the initial victims, and their caregivers as the second victims in unfortunate occurrences. The research touches upon this essential point that has been previously ignored, i.e., the psychological health of medical teachers, thereby contributing to our knowledge on AQ and its possible

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impact on empowering teachers, thereby enhancing the quality of medical education [12, 13]. The current study has appropriately assessed the effects of a six-month-long Certificate Course in Health Professional Education (CHPE) on the AQ of medical teachers who had attended the course at a public-sector medical university in Pakistan. The findings revealed that there was a considerable increase in AQ scores after the CHPE program was undertaken. It was found that the median AQ rose to 142 (IQR 134-156) ($p<0.001$). These results align with the past research that has shown that professional education interventions, especially those that include reflective learning and self-regulation, may support psychological flexibility and coping strategies by educators and clinicians [14, 15]. Most of the participants (69.1%) recorded low AQ levels prior to intervention, but after the CHPE course, nearly half the participants (almost 50.4%) reported moderate AQ, and another 21.9% reported moderately high or high AQ. Adult learning principles, mentoring, and feedback integrated in the faculty development programs have proven to have positive effects on self-efficacy, motivation, and professional identity variables that are closely interconnected with AQ improvement [16]. The analysis of gender showed that the participants who are male presented with a slightly higher AQ when compared to women ($p=0.043$), which may be due to prior exposure to leadership or decision-making positions. The same patterns can be noted in other resilience training and emotional intelligence programs in which gender differences in coping styles and stress perception may be minimized with the help of structured learning environments [17, 18]. Interestingly, there was no significant difference in AQ improvement with teaching experience, with participants of all levels of experience showing similar post-intervention improvements. This fact can be interpreted to mean that the CHPE course is not only beneficial to senior faculty but also to early-career educators. As per previous research, resilience can be developed by means of specific training, irrespective of professional experience, which supports the idea that adaptability is something that can be taught and changed [19, 20]. This observation is not a new one since previous research has established that training programs that are well-planned usually have an equal impact on the learners regardless of their gender. As an example, a systematic review revealed that communication training in medical education had an equal positive effect on both male and female students [21]. Secondly, teacher training studies have indicated that there are no consistent gender or years-of-teaching differences in programs that can boost self-efficacy and well-being. Collectively, these results support the idea that designed educational interventions can generate similar effects in heterogeneous cohorts of participants, at least when very well designed, and are therefore especially useful in inclusive professional development [22].

A primary methodological limitation is the pre-test post-test design without a concurrent control group. Despite the fact that this study showed a substantial post-intervention change in AQ, its small sample and single-institution design have the potential to limit its generalizability. Also, the experiment used self-reported scores of AQ, which may be subject to the social desirability bias. Future studies need to involve multicenter longitudinal investigations involving bigger samples to determine the sustainability of AQ improvement. Lack of a control group and short-term follow-up was another limitation of this study.

CONCLUSIONS

The results indicate that faculty development programs like the CHPE program are crucial in enhancing the resilience and flexible nature of medical teachers. The inclusion of AQ-related modules in health professional education programs in the future would result in improved general well-being, instructional performance, and leadership potential of medical educators in the long run, benefiting learners and healthcare systems.

Authors' Contribution

Conceptualization: BS
Methodology: BS
Formal analysis: BS
Writing and Drafting: BS
Review and Editing: BS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Success of Endoscopic Dacryocystorhinostomy Using Flap Technique

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ABSTRACT

Acquired nasolacrimal duct obstruction is a frequent cause of epiphora and recurrent dacryocystitis, leading to substantial impairment in quality of life. Endoscopic dacryocystorhinostomy using mucosal flap techniques has been advocated to enhance ostium patency and reduce failure rates. **Objectives:** To evaluate the success rate, complications, and factors associated with outcomes of flap-based endoscopic dacryocystorhinostomy in patients with acquired nasolacrimal duct obstruction. **Methods:** This prospective single-arm interventional study was conducted in the Department of Otorhinolaryngology, Shaikh Zayed Hospital, Lahore, from January to June 2025. Seventy-two adults with syringing-confirmed acquired nasolacrimal duct obstruction were enrolled through non-probability consecutive sampling. All underwent standardized endoscopic dacryocystorhinostomy using a mucosal flap technique under general anaesthesia. **Results:** Seventy-two patients were enrolled, with a mean age of 42.03 ± 11.36 years and a mean disease duration of 7.97 ± 2.61 months. Most patients were female (63.9%). At 3 months, functional success was 66/72 (91.7%), anatomical success 68/72 (94.4%), and overall success 66/72 (91.7%; 95% CI 83.0–96.1), with no significant associations with baseline variables (all p>0.05). Complications declined over time; 3-month rates were infection 2.8%, granulation 5.6%, synechiae 2.8%, and restenosis 5.6%. At 1 week, infection 6.9% and granulation 11.1%. **Conclusions:** Endoscopic dacryocystorhinostomy using a mucosal flap technique provides a high success rate with low complication frequency in acquired nasolacrimal duct obstruction and appears largely independent of baseline clinical variables.

INTRODUCTION

Epiphora, the overflow of tears onto the face, is a common ophthalmic complaint that causes both social inconvenience and functional disturbance [1]. The most frequent underlying cause is acquired nasolacrimal duct obstruction (NLDO), which affects predominantly middle-aged and elderly individuals, with a higher incidence in women [2]. Chronic obstruction predisposes to recurrent dacryocystitis, mucoceles, and pyoceles, placing a significant burden on patients and healthcare systems [3]. The definitive treatment of NLDO is dacryocystorhinostomy (DCR), a surgical procedure designed to bypass the obstruction by creating a direct fistula between the lacrimal sac and the nasal cavity [4, 5]. First attempted by Caldwell in 1893 through an endonasal route and later popularized by Toti in 1904 through an external approach, DCR has since evolved into two major techniques: external and endonasal [6, 7]. With advances in endoscopic visualization and powered instrumentation, endoscopic endonasal DCR (EnDCR) now achieves outcomes comparable to external DCR while offering additional benefits, including the absence of external scars, shorter recovery, and simultaneous management of intranasal pathology [8]. The long-term outcome of endoscopic dacryocystorhinostomy (EnDCR) is often limited by restenosis of the osteotomy, most commonly caused by granulation tissue, synechiae, and cicatricial

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closure [9]. To reduce this risk, surgical refinements have focused on preserving and apposing mucosal flaps rather than sacrificing them. Conventional EnDCR removes the nasal mucosa overlying the sac, leaving bare bone that heals by secondary intention and predisposes to scarring [10]. Variants such as posteriorly based, inferiorly based, double-sided overlapping, lobulated pedicled, and combined nasal–lacrimal sac flaps have been introduced to create mucosa-to-mucosa anastomosis, encouraging primary healing and long-term patency [11]. Results in the literature remain inconsistent: Romanos *et al.* observed superior outcomes with flap preservation (98%) compared to conventional excision (84.8%, p=0.013) [12]. Meta-analysis by Vinciguerra *et al.* noted overall success rates above 89% in both flap and non-flap groups, with no significant statistical difference, though flap preservation was associated with lower granulation and restenosis [13]. Given these controversies, further evaluation of flap-based techniques in EnDCR is warranted. This study seeks to provide clarity on the role of flap preservation in sustaining long-term patency and reducing restenosis, thereby contributing to improved surgical standards for the management of nasolacrimal duct obstruction.

The study has gap in generalizability to other countries due to its multicenter design, the small sample size (n=72), which could fail to identify subpopulation differences, and short follow-up making it impossible to identify late failures, a non-probability sampling bias, and an uncontrolled control group to compare the techniques, and no validated patient-reported outcomes, which reduces its usefulness in assessing functional outcomes. This study aims to assess the success of endoscopic dacryocystorhinostomy using the flap technique, focusing on both anatomical and functional outcomes.

METHODS

This prospective single-arm interventional study was executed in the Department of Otorhinolaryngology, Shaikh Zayed Hospital, Lahore, from January 2025 to June 2025, following authorization from the Technical and Ethical Review Committee (02-TERC/NHRC-SZH/INT-SC/-497). A non-probability consecutive sampling was used to enroll patients. A sample size of 72 patients was calculated using a 95% confidence level, 5% margin of error, and an expected success rate of 95.1% for endoscopic dacryocystorhinostomy (EnDCR) using the flap technique [14]. Patients aged 18 to 70 years of either sex with symptomatic acquired nasolacrimal duct obstruction (NLDO) confirmed by probing and syringing, presenting with epiphora with or without recurrent dacryocystitis, and willing to provide informed consent with availability for follow-up, were included. Exclusion criteria comprised congenital NLDO, presaccal obstruction (punctal stenosis, canalicular or common canaliculus block), functional epiphora without anatomical obstruction, and secondary NLDO due to trauma, irradiation, granulomatous disease, nasal tumors, or lacrimal sac malignancy. Patients with prior lacrimal surgery, those undergoing major concurrent nasal surgery, and those with severe ocular comorbidities causing tearing (eyelid malposition, facial palsy, dry eye) were excluded. After taking informed written consent, baseline demographic and clinical information, including age, sex, side of involvement, duration of disease, and comorbidities such as diabetes mellitus, hypertension, allergic rhinitis/asthma, and smoking status, were recorded at enrolment. All procedures were performed under general anaesthesia using a 0-degree rigid endoscope. Nasal decongestion was achieved with adrenaline-soaked pledgets, followed by submucosal infiltration of lidocaine with adrenaline from the maxillary line to the anterior axilla of the middle turbinate. A mucosal incision was initiated at the upper border of the inferior turbinate with a No. 15 blade, extended ~10 mm anteriorly, and carried superiorly in a curvilinear fashion to 8–10 mm above the middle turbinate insertion, then completed posteriorly. The mucosal flap was elevated with a Freer elevator and reflected posteriorly. The lacrimal fossa was opened using a Kerrison punch. The lacrimal sac was tented with a probe, incised, and fashioned into anterior and posterior flaps. The nasal flap was divided into superior and inferior components to achieve circumferential mucosal coverage. A triamcinolone-impregnated absorbable gelatin sponge was placed to stabilise flaps. Postoperatively, saline irrigation, antibiotics, and anti-inflammatory therapy were prescribed. Postoperative visits were scheduled at 1 week, 1 month, and 3 months. Interim visits (1 week and 1 month) were conducted to assess healing, perform nasal endoscopic inspection and toilet where required, and document early adverse findings (infection, granulation tissue, synechiae, and early restenosis). The primary endpoint was assessed at 3 months, where functional success (complete resolution of epiphora) and anatomical success (endoscopic ostium patency with confirmed patency on irrigation) were formally determined. Overall success was defined as the concurrent presence of functional and anatomical success at 3 months. All data were entered and analyzed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were summarized as frequencies and percentages. Proportions were reported with 95% confidence intervals calculated using the Wilson score method for binomial data. Comparisons between categorical variables were performed using Chi-square or Fisher's exact test, as appropriate. All tests were two-

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tailed, and a p-value <0.05 was considered statistically significant. No patients were lost to follow-up, and complete data were available for all analyses.

RESULTS

The mean age of the patients was 42.03 ± 11.36 years, while the mean duration of disease was 7.97 ± 2.61 months. Out of 72 patients, 34 (47.2%) were aged ≤ 40 years, and 38 (52.8%) were > 40 years. There were 26 (36.1%) males and 46 (63.9%) females. Side involvement was almost equal, with 34 (47.2%) cases on the right and 38 (52.8%) on the left. Diabetes mellitus was present in 12 (16.7%) patients, while 60 (83.3%) had no diabetes. Hypertension was observed in 14 (19.4%) patients, whereas 58 (80.6%) were non-hypertensive. Allergic rhinitis was found in 10 (13.9%) patients and absent in 62 (86.1%). Asthma was noted in 8 (11.1%) patients, while 64 (88.9%) had no history of asthma. Regarding smoking status, 42 (58.3%) were non-smokers, 12 (16.7%) were ex-smokers, and 18 (25.0%) were current smokers (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Patients (n=72)

Variables	Categories	Frequency (%)
Age group	≤ 40 years	34 (47.2%)
	> 40 years	38 (52.8%)
Sex	Male	26 (36.1%)
	Female	46 (63.9%)
Side involved	Right	34 (47.2%)
	Left	38 (52.8%)
Diabetes mellitus	Yes	12 (16.7%)
	No	60 (83.3%)
Hypertension	Yes	14 (19.4%)
	No	58 (80.6%)
Allergic rhinitis	Yes	10 (13.9%)
	No	62 (86.1%)
Asthma	Yes	8 (11.1%)
	No	64 (88.9%)
Smoking status	Non-smoker	42 (58.3%)
	Ex-smoker	12 (16.7%)
	Current-smoker	18 (25.0%)

The three-month follow-up functional success was achieved in 66 (91.7%) patients, while anatomical success was achieved in 68 (94.4%) patients. Overall success was observed in 66 (91.7%, 95% CI 83.0% to 96.1%) patients (Figure 1).

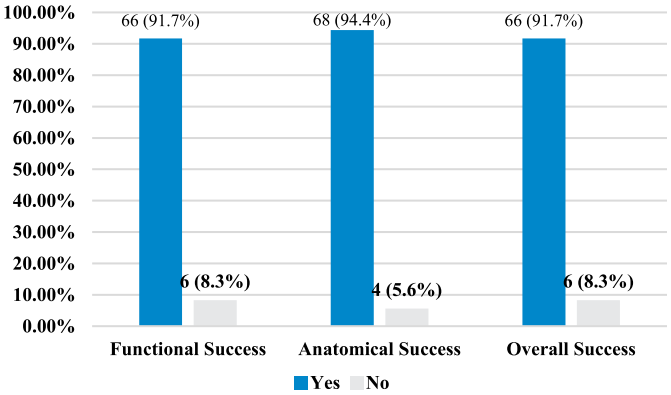

Figure 1: Functional, Anatomical, and Overall Success of Endoscopic Dacryocystorhinostomy Using Flap Technique at Three Months

At 3 months, overall surgical success showed no significant association with baseline factors. Success was comparable in patients ≤40 years and >40 years (p=0.887), and between males and females (p=0.459). Outcomes were similar for right and left side procedures (p=0.117). Hypertension (p=0.369), allergic rhinitis (p=0.150), asthma (p=0.070), and smoking status (p=0.073) also showed no significant impact on surgical success (Table 2).

Table 2: Association of Baseline Characteristics with Overall Surgical Success at 3 Months (n=72)

Variables	Categories	Overall, Success Yes, n (%)	Overall, Success No, n (%)	p-value
Age group	≤ 40 years	31 (47.0%)	3 (50.0%)	0.887
	> 40 years	35 (53.0%)	3 (50.0%)	
Sex	Male	23 (34.8%)	3 (50.0%)	0.459
	Female	43 (65.2%)	3 (50.0%)	
Side of involvement	Right	33 (50.0%)	1 (16.7%)	0.117
	Left	33 (50.0%)	5 (83.3%)	
Diabetes mellitus	Yes	12 (18.2%)	0 (0.0%)	0.253
Hypertension	Yes	12 (18.2%)	2 (33.3%)	0.369
Allergic rhinitis	Yes	8 (12.1%)	2 (33.3%)	0.150
Asthma	Yes	6 (9.1%)	2 (33.3%)	0.070
Smoking status	Non-smoker	40 (60.6%)	2 (33.3%)	0.073
	Ex-smoker	9 (13.6%)	3 (50.0%)	
	Current-smoker	17 (25.8%)	1 (16.7%)	

Postoperative complications were infrequent. At 1 week, infection was observed in 5 patients (6.9%), granulation tissue in 8 (11.1%), and synechiae in 6 (8.3%). By 1 month, the frequency of infection decreased to 3 patients (4.2%), granulation to 6 (8.3%), and synechiae to 4 (5.6%); ostium restenosis was documented in 2 patients (2.8%). At 3 months, infection further declined to 2 patients (2.8%), granulation to 4 (5.6%), and synechiae to 2 (2.8%), whereas ostium restenosis increased to 4 patients (5.6%) (Table 3).

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Table 3: Postoperative Complications at Different Follow-Up Intervals(n=72)

Complications	1 Week, n (%)	1 Month, n (%)	3 Months, n (%)
Infection	5 (6.9)	3 (4.2)	2 (2.8)
Granulation	8 (11.1)	6 (8.3)	4 (5.6)
Synechiae	6 (8.3)	4 (5.6)	2 (2.8)
Ostium restenosis	0 (0.0)	2 (2.8)	4 (5.6)

DISCUSSION

The present study evaluated the outcomes of endoscopic dacryocystorhinostomy (EnDCR) using a mucosal flap technique in patients with acquired nasolacrimal duct obstruction (NLDO). At three months, the overall surgical success rate was 91.7%, with low complication rates and no significant influence of baseline demographic or clinical variables on outcome. The mean age of our study population was 42.03 ± 11.36 years, which is comparable to findings by Bani-Ata *et al.* who reported a mean age of 41.6 years in their series of 77 patients undergoing single- or double-flap EnDCR [15]. Shahid *et al.* also described a similar mean age of 51.1 years in 100 patients with chronic dacryocystitis [16]. In contrast, Jeong and Kim noted a higher mean age of 66.5 years in their large retrospective series of 509 eyes [17]. The broad age range across studies suggests that EnDCR is effective across diverse age groups, consistent with our finding that success rates did not differ significantly between patients ≤40 years and those >40 years (p=0.887). Female predominance was evident in our study (63.9%), aligning with prior reports. Bani-Ata *et al.* reported 67.5% females, Wang *et al.* 85.7%, and Jeong and Kim 84.3% [17, 18]. This consistent female preponderance reflects the recognized epidemiology of acquired NLDO, which is more common among women due to narrower bony nasolacrimal canals. However, in our series, gender was not associated with surgical outcome (p=0.459). Laterality in present study was balanced (47.2% right, 52.8% left), which mirrors the distribution observed by Bani-Ata *et al.* (46.8% right, 53.2% left) and Wang *et al.* (50.8% left, 42.9% right) [15, 18]. As in these prior reports, we found no difference in outcomes between right- and left-sided procedures (p=0.117), suggesting that anatomical laterality does not alter prognosis when surgical technique is standardized. Comorbidities were infrequent in our cohort: diabetes mellitus in 16.7%, hypertension in 19.4%, allergic rhinitis in 13.9%, and asthma in 11.1%. These rates are broadly consistent with those reported by Romanos *et al.* who documented diabetes in 13%, hypertension in 17.4%, and allergic conditions in 21.7% of their series of 188 patients [12]. In our study, none of these comorbidities significantly affected outcome (all p >0.05). This finding is in agreement with Zloto *et al.* and Rezaeian *et al.* all of whom demonstrated no significant association between comorbidities and EnDCR success [19, 20]. Smoking was recorded in 41.7% of our patients (16.7% ex-smokers, 25% current smokers), similar to the 39.9% prevalence reported in the conventional flap group of Romanos *et al.* Our results showed no significant effect of smoking status on outcome (p=0.073), paralleling Romanos *et al.* who found no adverse impact of smoking on long-term success [12]. The overall success rate of 91.7% at three months in our study is consistent with the literature, which generally reports success between 88% and 96%. Wanumkarng *et al.* in a multicenter Thai series of 729 procedures, observed 92% overall success, with improvement to 100% after refinement of bone removal and flap suturing techniques [21]. Shahid *et al.* documented anatomical success in 94% of cases, while Bani-Ata *et al.* achieved 84.4% overall, with significantly higher rates in the double-flap (96.8%) compared to the single-flap (76.1%) group [15, 16]. Jeong and Kim reported six-month anatomical success of 95.6% with combined flaps, 92.9% with nasal flap alone, and 88.2% with no flap, confirming that flap preservation improves long-term patency [17]. Hamdy *et al.* compared posteriorly versus inferiorly based flaps and reported overall success of 93.3% at six months, with no significant intergroup difference [22]. Rezaeian *et al.* in a randomized trial of 60 patients, found success rates approaching 99% for both double-sided overlapping flap and conventional approaches, with no statistical difference [20]. Similarly, Patel *et al.* reported complete resolution in 100% with flap preservation and 97.05% with flap excision, again without a significant difference [23]. The meta-analysis by Vinciguerra *et al.* including 3059 procedures, confirmed a pooled success of ~90% irrespective of powered versus mechanical techniques and found no significant difference between flap and non-flap strategies [13]. Minor variations in reported rates across studies likely reflect differences in flap design, use of stenting, follow-up duration, and surgeon experience. Importantly, all agree that success rates are consistently high when meticulous technique ensures wide, mucosalized ostium creation. Complications in our series were infrequent and minor. Granulation occurred in 5.6%, synechiae in 2.8%, restenosis in 5.6%, and infection in 2.8%. These findings mirror other reports, where complication rates were generally below 10% and most commonly involved granulation or synechiae. For example, Hamdy *et al.* reported overall complications in 33.3% of patients, largely minor issues such as adhesions and granuloma, while Wang *et al.* noted only a single case of granulation (1.5%) among 67 eyes over two years [18, 22]. Patel *et al.* found granulation in 8.8% of flap-excised cases, while none occurred in the flap-preservation group [23]. Jeong and Kim demonstrated significantly reduced

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granulation rates in combined flap techniques (2–3%) compared with no flap (6–8%) ($p<0.05$) [17]. These findings collectively support the view that flap preservation techniques minimize granulation and restenosis by providing mucosa-to-mucosa anastomosis, which is consistent with the relatively low complication profile observed in our study. This study's strengths lie in its prospective design, standardized flap-based EnDCR technique, and structured follow-up, which provide reliable outcome assessment. A specifically designed proforma minimized data loss and ensured consistency.

Limitations include the single-center setting, modest sample size, and relatively short follow-up of three months, which may not capture late failures or restenosis. Future research should involve larger, multicenter cohorts with extended follow-up to confirm durability, explore patient-reported functional outcomes, and compare flap techniques with adjunctive measures such as stenting or mitomycin C, thereby refining surgical standards and optimizing long-term results for patients with NLDO.

CONCLUSIONS

This study demonstrated that endoscopic dacryocystorhinostomy (EnDCR) using a flap technique achieved an overall success rate of 91.7% at three months, with minimal postoperative complications. Outcomes were not significantly influenced by baseline variables, including age, sex, laterality, diabetes, hypertension, allergic rhinitis, asthma, or smoking status. Infection, synechiae, granulation, and restenosis occurred infrequently and were managed conservatively. These findings support flap-based EnDCR as a safe, effective, and broadly applicable approach for the management of acquired nasolacrimal duct obstruction.

Authors' Contribution

Conceptualization: RA, MAS
Methodology: RA, MI, SL, MZA
Formal analysis: HAI,
Writing and Drafting: RA, MI, SL, MZA, MAS
Review and Editing: RA, MI, SL, MZA, HAI, MAS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Patient Satisfaction Levels and Determinants among Inpatients in Tertiary Hospitals in Hayatabad, Peshawar

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ABSTRACT

Quality of healthcare is assessed by patient satisfaction, which is a very important factor. There has been very little research on the reasons for inpatient satisfaction referring to tertiary healthcare centers in Peshawar, Pakistan. **Objectives:** To find out the factors and levels of inpatient satisfaction in tertiary healthcare setups in Hayatabad, Peshawar. **Methods**: A cross-sectional comparative study was done in Hayatabad, Peshawar, from March to August 2025. Three public hospitals and three private hospitals were selected for this purpose. A convenience sample of 664 adults was collected through the proportionate method of sampling. Data analysis was performed with SPSS. **Results:** Overall, patient satisfaction was low – only approximately 13.9% of patients reported being satisfied. Patients who received services in private hospitals had a higher satisfaction level (16.9%) compared to patients who were treated in public hospitals (12.0%) (p=0.050). Patient satisfaction also had a positive relationship with socioeconomic status, with a higher number of middle-class patients being satisfied (30.4%) (p=0.001). Patients' ratings for cleanliness in private hospitals were higher (p=0.045). Education, occupation, and place of residence were significant indicators of patients' ratings of quality, efficiency, and cost (p<0.050). **Conclusions:** Patient satisfaction levels among tertiary hospitals in Hayatabad, Peshawar is low; therefore, these centers need to improve affordability, cleanliness, and the efficiency of service delivery for patient satisfaction and patient-centered services.

INTRODUCTION

Patient satisfaction is universally accepted as an indicator of quality in healthcare, as it encompasses the patient's experiences with communication, care, environment, responsiveness, and clinical outcomes [1]. Patient satisfaction also correlates most highly with compliance, hospital utilization, etc., and as a result, has become an important metric for evaluating health systems [2]. In a dual health system context such as Pakistan, there are private facilities and public tertiary hospitals that serve a large population. Patient experiences vary between the two sectors, given differences in costs, staffing, infrastructure, and governance [3]. International research lends support to the finding that the private facility is ranked better on staff courtesy, promptness, and ward environment, whereas public facilities are valued more regarding accessibility and affordability [4, 5]. International studies consistently demonstrate that inpatient satisfaction differs between public and private healthcare systems and is influenced by factors such as service quality, cleanliness, staff responsiveness, affordability, and efficiency. Evidence shows that patients admitted to private hospitals generally report higher

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satisfaction levels due to better infrastructure, shorter waiting times, cleaner environments, and improved interpersonal care, while public hospitals are more frequently preferred for affordability and accessibility [6, 7]. Socioeconomic status, education level, and place of residence have also been identified as significant determinants of patient satisfaction across diverse settings, with urban and educated patients reporting higher satisfaction compared to rural and less-educated populations [8, 9]. Several studies conducted in Pakistan have investigated the satisfaction of patients in both sectors, producing mixed findings. Khattak *et al.* from Peshawar found that overall satisfaction was much higher in private hospitals than public hospitals, but both groups still reported being dissatisfied with the amount of time spent with the doctor during the visit [10]. In another comparative study from Peshawar, the authors similarly reported higher satisfaction levels in private hospitals across several domains; however, affordability was an important predictor for patients' preference [11]. A multicenter study from Karachi indicated that access and affordability were the greatest contributors to patient satisfaction in public hospitals, while private hospitals performed significantly better across the interpersonal and environmental domains [12]. In Pakistan, Hussain and others determined that there was less overall satisfaction than at private hospitals, which was explained by issues of overcrowding, waiting time, and cleanliness [13]. Another research in Ghana found that in hospitals, private hospitals outperformed public facilities' environmental factors and attitude of staff, and that public facilities were preferred based on cost [14]. Evidence from other South Asian countries adds to the contrast of better satisfaction and care in the private hospital sector. For example, a study from Bangladesh revealed that significantly more patients in private hospitals were satisfied with inpatient care (75%) compared to patients at public hospitals (51%). The primary factors influencing patient satisfaction were affordability, length of stay, and ward environment [15]. Looking at Cyprus, Talias *et al.* found that private hospital patients were also significantly more satisfied than public hospital patients regarding the hospital environment and staff responsiveness, although public hospitals were preferred for time-sensitive medical care [4]. Despite these studies, the evidence base regarding comparative inpatient satisfaction in Khyber Pakhtunkhwa and specifically at the city of Peshawar is thin. Tertiary hospitals in Peshawar offer care to the large metropolitan community, as well as the surrounding tribal districts and border-crossing patients from Afghanistan. Past patient satisfaction studies conducted in Peshawar were limited to single hospitals (or only evaluated outpatients) and are lacking in comparative evidence that captures inpatient satisfaction across both public and private hospital sectors [10, 11]. Patient satisfaction is a key indicator of healthcare quality and an essential measure for identifying gaps in service delivery. It reflects patients' perceptions of the care they receive and guides efforts to improve quality, efficiency, and equity in healthcare systems.

In Peshawar, a major tertiary care hub for Khyber Pakhtunkhwa and neighboring regions, there is limited evidence on inpatient satisfaction, as most studies in Pakistan have focused on outpatient settings. Understanding the levels of inpatient satisfaction and the factors that influence it is critical for enhancing patient-centered care and informing policy decisions. This study aims to evaluate whether these determinants can provide valuable insights for healthcare providers and administrators to improve service delivery, resource allocation, and overall patient experience in tertiary hospitals of Hayatabad, Peshawar.

METHODS

A cross-sectional study took place from 1st March 2025 to 30th August 2025. Data were collected from six tertiary care hospitals situated in Hayatabad, Peshawar, Khyber Pakhtunkhwa, Pakistan — 3 representing the public sector and the other 3 the private sector. Ethical approval for the study was granted by the Institutional Review Board of the Northwest School of Medicine before the study began (Approval Number: IRB&EC/2025-GH/0306). Verbal informed consent was obtained from all participants, and they were assured that their anonymity, confidentiality, and voluntary participation would be protected. The study population included adult inpatients who were admitted to the medicine and allied, as well as surgical and allied wards of the selected hospitals. The sample size was calculated using Open Epi software with a total population size (N) of 1,000,000, hypothesized frequency of the outcome factor (p) of 50% ± 5, and fixed confidence limit (d) of 5% with a 99% confidence interval including the finite population correction factor (FPC). The sample size was determined using the following standard formula: n = [DEFF*Np(1-p)]/[(d2/Z21-α/2*(N-1)+p*(1-p)]. A total of 664 participants were recruited for the study using a convenience sampling technique. Adult patients admitted more than 24 hours and who were able to understand and respond to the survey instrument met the inclusion criteria. Exclusion criteria were for critically ill patients, impaired cognition, and refusal to participate. Data collection took place systematically in hospital wards. Four members of the research team were involved in data collection. After the study purpose was explained to the patients and they agreed to participate, the researchers gave them the survey instrument to complete. The study tool was

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developed following a comprehensive literature review [13-15]. Relevant variables identified from the literature were incorporated into the design of the tool. It was then reviewed and refined by subject specialists to ensure content validity. Subsequently, the tool was pilot tested on a sample group to assess its clarity and to identify any difficult or missing variables. The data collection tool comprised several domains, including demographic information and study-specific variables. These variables covered two main areas: satisfaction with physical facilities (such as cleanliness, toilets, food, lighting, cooling, diagnostic services, medicine availability, and affordability) and satisfaction with staff behavior (including doctors, nurses, paramedical staff, ward attendants, security, and administrative personnel). Responses were recorded on a three-point scale: Yes, No, and I Don't Know. The data collection tool underwent a pilot study on 30 patients before the main study, to assess clarity and reliability, and minor modifications were made. Data were entered and analyzed using IBM SPSS Statistics (Version 25), and descriptive statistics were used to calculate frequencies and percentages. Chi-square test statistical analysis was conducted for the comparison between public and private hospitals, with statistical significance established at $p<0.050$.

RESULTS

A total of 664 patients participated in the study. Of these, 62.7% were admitted in public hospitals and 37.3% in private hospitals. Male participants constituted 60.1%, while female made up 39.9%. More than half of the participants were from urban areas (55.9%), while 44.1% were from rural regions. Regarding education, one-third were illiterate (33.3%), while 15.5% were graduates and 3.5% postgraduates. The largest occupational group was skilled workers (28.5%), followed by housewives (18.7%). Socioeconomically, 13% belonged to the upper class (Monthly income>200,000 PKR), 59.5% belonged to the middle class (Monthly income from 100,000-200,000 PKR), and 27.6% belonged to the lower class (Monthly income <100,000 PKR) (Table 1).

Table 1: Socio-Demographic Characteristics of Study Participants (n=664/100%)

Variables	Categories	Frequency (%)
Health Setup	Public	416 (62.7%)
	Private	248 (37.3%)
Gender	Male	399 (60.1%)
	Female	265 (39.9%)
Place of Residence	Urban	371 (55.9%)
	Rural	293 (44.1%)
Education	Illiterate	221 (33.3%)
	Primary Education	133 (20.0%)
	High School	109 (16.4%)
	Secondary Education	75 (11.3%)
	Graduate	103 (15.5%)
	Post-Graduate	23 (3.5%)
Occupation	Unskilled	79 (11.9%)
	Skilled	189 (28.5%)
	Employed	137 (20.6%)
	Unemployed	64 (9.6%)
	Housewife	124 (18.7%)
	Student	71 (10.7%)
Socio-economic Status	Upper Class	86 (13.0%)
	Middle Class	395 (59.5%)
	Lower Class	183 (27.6%)
Department	Medicine	330 (50.7%)
	Surgery	334 (50.3%)

Overall, only 13.9% of patients reported being satisfied, while 86.1% expressed dissatisfaction with their hospital care experience. Satisfaction was slightly higher in private hospitals (16.9%) than public hospitals (12.0%), although this difference was borderline significant ($p=0.050$), indicating generally low satisfaction across tertiary hospitals, suggesting systemic challenges affecting inpatient care across both healthcare sectors in Hayatabad, Peshawar (Table 2).

Table 2: Association between Level of Satisfaction and Type of Health Setup

Satisfied	Health-Setup		Total	p-value
	Public	Private		
Type of Health Setup				
No	366	206	572	0.050
Yes	50	42	92	
Total	416	248	664	

Patient satisfaction differed significantly according to socioeconomic status ($p=0.001$). Among middle-class patients, 30.4% reported satisfaction — notably higher than the upper class (11.6%) and lower class (9.8%) (Table 3).

Table 3: Association Between Level of Satisfaction and Socio-Economic Status of Participants

Satisfied	Socio-economic Status			Total	p-value
	Upper Class	Middle Class	Lower Class		
Type of Health Setup					
No	76	275	165	572	0.001
Yes	10	120	18	92	
Total	86	395	183	664	

Patient satisfaction was assessed through five key domains: Availability of Resources, Cost of Services, Cleanliness, Quality of Services, and Efficiency of Services. Each domain was analyzed in relation to hospital type and socio-demographic factors to identify differences between public and private healthcare centers. A significant association was found between the availability of resources and both education level ($p=0.004$) and

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department (p=0.022). Graduates and high school–educated patients perceived better resource availability compared to illiterate participants. Patients admitted to medicine departments (89.1%) reported greater resource availability than those in surgery (68.3%). Cost perception differed significantly by education (p<0.001), occupation (p=0.001), and socioeconomic status (p=0.002). Cleanliness showed a significant association with both residence (p-value<0.001) and hospital type (p=0.045). Urban patients (78.7%) rated facilities as cleaner than rural patients (65.9%). Private hospitals were perceived to maintain higher cleanliness standards (77.0%) compared to public hospitals (70.7%). Private hospitals outperformed public hospitals in cleanliness (Table 4).

Table 4: Association between Availability of Resources, Education, Department, Cost, Sociodemographic Factors, Cleanliness, and Setup/ Residence Factors

Variables		No	Yes	Total	p-value
Availability of Resources					
Education	Illiterate	25	196	221	0.004
	Primary	16	117	133	
	High School	6	103	109	
	Secondary	13	62	75	
	Graduate	14	89	103	
	Post-Graduate	8	15	23	
Department	Medicine	36	294	330	0.022
	Surgery	46	228	334	
Cost and Sociodemographic Factors					
Cost		**Low Cost**	**High Cost**	**Total**	**p-value**
Education	Illiterate	52	169	221	<0.001
	Primary	16	117	133	
	High School	15	94	109	
	Secondary	28	47	75	
	Graduate	25	78	103	
	Post-Graduate	5	18	23	
Occupation	Unskilled	15	64	79	0.001
	Skilled	36	153	189	
	Employed	26	111	137	
	Unemployed	26	38	64	
	Housewife	18	106	124	
	Student	20	51	71	
Socioeconomic Status	Upper Class	7	79	86	0.002
	Middle Class	98	297	395	
	Lower Class	36	147	183	
Cleanliness and Setup / Residence Factors					
Cleanliness		**Unclean**	**Clean**	**Total**	**p-value**
Residence	Urban	79	292	371	<0.001
	Rural	100	193	293	
Health Setup	Public	122	294	416	0.045
	Private	57	191	248	

Perceived quality of services was significantly higher among urban, educated, and skilled patients (p<0.050). Urban residents, highly educated individuals, and skilled participants perceived quality services as more educated compared to rural, less-educated, and unskilled groups. The efficiency of services showed significant associations with place of residence (p-value = 0.001), education (p-value=0.012), and occupation (p-value=0.028), but not with departments (p-value=0.490) (Table 5).

Table 5: Association between Quality of Services and Sociodemographic Factors, Services and Sociodemographic/ Department Factors

Variables		Poor	Good	Total	p-value
Services and Sociodemographic Factors					
Residence	Urban	40	331	371	0.007
	Rural	52	241	293	
Education	Illiterate	34	187	221	0.014
	Primary	18	115	133	
	High School	11	98	109	
	Secondary	19	56	75	
	Graduate	7	96	103	
	Post-Graduate	3	20	23	
Occupation	Unskilled	17	62	79	0.042
	Skilled	24	165	189	
	Employed	13	124	137	
	Unemployed	14	50	64	
	Housewife	18	106	124	
	Student	6	65	71	
Services and Sociodemographic / Department Factors					
Factor Category		**Inefficient**	**Efficient**	**Total**	**p-value**
Residence	Urban	70	301	371	0.001
	Rural	110	183	293	
Education	Illiterate	46	175	221	0.012
	Primary	42	91	133	
	High School	31	78	109	
	Secondary	28	47	75	
	Graduate	18	85	103	
	Post-Graduate	7	16	23	
Occupation	Unskilled	18	61	79	0.028
	Skilled	51	138	189	
	Employed	38	99	137	
	Unemployed	18	46	64	
	Housewife	20	104	124	
	Student	27	44	71	
Department	Medicine	74	256	330	0.490
	Surgery	98	236	334	

DISCUSSION

The current study showed low overall inpatient satisfaction, with just 13.9% of patients being satisfied with the inpatient hospital stay, and the rest dissatisfied (86.1%). While satisfaction was somewhat higher in private hospitals (16.9%) versus public hospitals (12.0%), it was not statistically significant. In contrast, Begum *et al.* in Bangladesh reported 75% satisfaction in private hospitals,

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compared to 51% in public hospitals [15], and Shaikh *et al.* in India found that the majority of participants (60%) in private hospitals rated high service quality practices in hospitals [16]. However, Ozam *et al.* in Saudi Arabia reported 84% satisfaction in private hospitals, and 69% in public hospitals [17]. The consistently higher satisfaction levels than those of the current study are a potential indication of systemic limitations on care delivery in Pakistan's tertiary care system, including congestion, workforce shortage, and inconsistent service quality in overall care, which lowers satisfaction levels in both sectors. Satisfaction in our current study was found to be statistically significantly influenced by socioeconomic status (p=0.001), with middle-class patients reporting the highest satisfaction (30.4%), and upper (11.6%) and lower classes (9.8%) reporting less satisfaction. The study sees the same associations in Bangladesh and India, where middle-income patients were the most satisfied, due to affordability and realistic expectations [15, 16]. Differences indicate that satisfaction determinants are likely different along the healthcare financing mechanism; for instance, in out-of-pocket models (Pakistan and Bangladesh), cost may be a significant moderating factor. Education level was found to be an additional predictor, and there was elevated satisfaction expressed by graduates and those with high school education related to resource availability (p=0.004) and service quality (p=0.014), which is similar to the results captured by Dinsa *et al.* in Ethiopia that patients with education reported higher satisfaction levels associated with communication and coordination of care [18]. Shaikh *et al.* similarly identified that education improved a person's perception of technical quality and interaction with the provider [16]. Therefore, this reinforces that educated patients who are informed expect and value a systematic/effective pathway for their access to service delivery. Occupation had a meaningful impact on overall satisfaction related to cost, quality and efficiency (p<0.050) and satisfaction with skilled employed illustrated greater experiences compared to unskilled unemployed, with similar differences being found in India and China where individuals employed in the formal-sector reported significantly higher levels of satisfaction as a consequence of greater health literacy and financial resources available to them [16, 19]. This lends itself to the conclusion that socioeconomic empowerment distilled a better patient experience through improved communication and/or decreased clinically biased cost. In terms of residence, urban participants had significantly greater satisfaction with cleanliness (p-value<0.001), quality (p=0.007), and efficiency (p=0.001) as compared to rural inhabitants. This is consistent with studies from Saudi Arabia and Tanzania, where urban participants reported higher satisfaction due to familiarity with the hospital system and more access to information [17, 20]. The dissatisfaction found in rural areas in this study may suggest limited exposure to tertiary facilities and heightened expectations of services based on unequal access to healthcare previously. Cleanliness ranked higher than the majority of the themes in the services area, with private hospitals and urban patients reporting significantly higher levels of satisfaction (p=0.045). Begum *et al.* and Ozam *et al.* similarly identified the role of environmental hygiene in patient satisfaction as one of the strongest predictors of overall satisfaction [15, 17]. The relatively low levels of cleanliness perceived in public hospitals in Peshawar demonstrate structural limitations and overcrowding in facilities; this finding is similar to some of the findings regarding public facilities in India and Bangladesh. Cost perception has significant correlations for education (p-value<0.001), occupation (p=0.001), and socioeconomic class (p=0.002), where middle-class patients perceived lower costs for care. Studies from Bangladesh, China, and Tanzania have likewise suggested that affordability is the driver of some satisfaction, regardless of the quality of service witnessed [19, 20]. Despite general satisfaction levels reaching over 80%, the Chinese cohort's perception of cost remained the most significant predictor of dissatisfaction [15]. This parallels the Pakistani context, where private hospital users reported strain on their finances, despite an improved care experience. Perceived resources were viewed more positively relating to medicine departments and educated patients, as previously found in studies similar to Ethiopia and India, where resource adequacy (medication, diagnostic access, and availability of staff) positively related to patient satisfaction [18, 16]. In this study, reported surgical patients experienced some dissatisfaction in this regard, perhaps because of waiting for procedures to occur, along with a shortage of supply, in the public tertiary setting. Finally, service quality and efficiency- significantly influenced by prerequisite education and occupational work related to the education-expect responsiveness of the healthcare system. These similar relationships were also seen in the Laishram *et al.* study within Manipur, or Shekhawat *et al.* study in the hospital, with patient satisfaction questionnaires mentioned, in private hospitals with trained clinicians who could conduct the service delivery process more efficiently, patients' level of satisfaction was 70% or greater [21, 22]. The Peshawar participants who experienced an overall satisfaction degree of just 13.9% were nearly one quarter of the findings, suggesting that structural inefficiency of the healthcare system, rather than the experience or that specific interpersonal relationship with the healthcare system, remains a barrier

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for a patient-centered health system approach in Pakistan. Low patient satisfaction in similar contexts is often attributed to broader structural inefficiencies within the healthcare system rather than individual provider interactions[23, 24].

This study has many limitations. This one city investigation in Hayatabad, Peshawar, cannot be used to represent all the tertiary hospitals in Pakistan. Convenience sampling creates selection bias, whereas the cross-sectional design records satisfaction at a single time points only. There is no clinical outcome that is correlated with clinical outcomes, and the responses of the currently admitted patients are subject to the risk of social desirability bias. The fact that the private hospitals are underrepresented (37.3% in the hospital) might not be quite representative of the experiences of the private sector. The next directions should measure the satisfaction and clinical outcomes and implement the targeted interventions (cleanliness protocols, staff training, reduction of waiting time) with the help of pre-post designs. Research on health equity ought to focus on the reasons behind the low level of satisfaction reported by rural, less-educated, and lower-class patients.

CONCLUSIONS

This study concluded that among the tertiary level hospitals situated in the city of Peshawar, there was considerably low reported patient satisfaction overall, in both public and private hospitals. Patient characteristics (e.g., socioeconomic, educational, occupational, residential, etc.) were found to have different influences on patient experiences in terms of cost, cleanliness, quality, and efficiency. Middle-class, urban, and educated patients reported the most satisfaction, while the less educated or rural patients reported the most dissatisfaction. Overall, the results of the study indicate the need for system change and support overarching recommendations for improving cost, quality, and equity in inpatient hospital care.

Authors' Contribution

Conceptualization: ZU, SZ[1], SZ[2]
Methodology: ZU, MAB, MWA, HUK, AK, SZ[1], SZ[2]
Formal analysis: ZU, MAB, MWA, HUK, AK, SZ[1], SZ[2]
Writing and Drafting: ZU, SZ[1], SZ[2]
Review and Editing: ZU, MAB, MWA, HUK, AK, SZ[1], SZ[2]

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Faculty Perceptions of Feedback in Objective Structured Clinical Examinations (OSCEs)

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ABSTRACT

Objective Structured Clinical Examinations (OSCEs) are widely used to assess clinical competence in health professions education. Although OSCEs are considered reliable and objective, their educational impact largely depends on the quality of feedback provided. **Objective:** To evaluate the faculty perceptions regarding OSCE feedback practices in local institutional settings. **Methods:** This descriptive cross-sectional study was conducted at Bashir Institute of Health Sciences, Islamabad, from January 2025 to June 2025. A total of 110 faculty members involved in OSCE conduction and evaluation were recruited using non-probability consecutive sampling. Data were collected using a structured, self-administered questionnaire developed using expert opinion and feedback from the literature, addressing demographic characteristics, perceptions of OSCE feedback, preferred feedback practices, and perceived barriers. Data were analyzed using SPSS version 26.0 with descriptive statistics and the Pearson Chi-square test. **Results:** The mean age of participants was 43.37 ± 8.17 years, with females comprising 52.7% of the sample. Most faculty agreed that feedback is essential for student learning (60.0%) and improves clinical competence (84.5%). Immediate feedback was preferred by 52.7% of participants, while written (33.6%) and one-to-one (31.8%) methods were most favored. Lack of formal training (57.3%), large student numbers (43.6%), and stressful OSCE environments (42.7%) were identified as key barriers. No significant associations were observed between overall perception of feedback and faculty characteristics. **Conclusions:** Faculty members value feedback in OSCEs but face practical challenges that limit its effective delivery. Focused faculty development and institutional support are needed to enhance feedback quality.

INTRODUCTION

Assessment is a key feature of health professions education, not only as a method of measuring competence but also as a strong influence on learning behaviors [1]. The Objective Structured Clinical Examination (OSCE) has become widely used for evaluating clinical skills because of its structured format, objectivity, and ability to assess multiple domains of clinical competence. Over time, OSCEs have become an integral part of undergraduate and postgraduate training in medicine and dentistry [2, 3]. Although the reliability and standardization of OSCEs are well recognized, the educational impact of assessment extends beyond scoring and grading [4]. Feedback during and after OSCEs is a crucial tool that enables learners to reflect on their performance, identify areas of weakness, and develop strategies for improvement. It has been demonstrated that effective feedback contributes to improvements in clinical reasoning, reinforcement of appropriate practices, and promotion of self-directed

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learning. In contrast, delayed, vague, or inconsistent feedback can diminish the formative value of OSCEs and limit their contribution to learner development [5, 6]. Faculty members play a central role in determining the quality of feedback provided during OSCEs. Their perceptions, training, and workload influence not only how feedback is delivered but also how it is received by students [7].

Although the importance of feedback is widely acknowledged, several studies have identified practical barriers faced by faculty, including time constraints, large student groups, and a lack of formal training in feedback delivery. Such challenges can undermine the consistency and effectiveness of feedback practices, particularly in resource-constrained educational institutions. In Pakistan, research on OSCEs has largely focused on student perceptions and assessment outcomes, with comparatively little attention given to faculty perspectives on feedback practices. Understanding faculty viewpoints is essential for developing targeted interventions to enhance feedback quality and optimize the educational impact of OSCEs. The findings of this study may inform faculty development initiatives and contribute to the optimization of OSCE-based assessment in health professions education. This study aimed to explore faculty perceptions regarding feedback in OSCEs, identify preferred feedback practices, and examine perceived barriers to effective feedback delivery within an institutional context.

METHODS

This descriptive cross-sectional study was conducted at Bashir Institute of Health Sciences, Islamabad, and its affiliated Dr. Bashir General and Dental Teaching Hospital from January 2025 to June 2025 to explore faculty perceptions regarding feedback in Objective Structured Clinical Examinations (OSCEs). Ethical approval was obtained from the Ethical Review Committee of Bashir Institute of Health Sciences, Islamabad (Ref: BIHS/ERC/2025-01). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Confidentiality was maintained through coded identifiers and restricted access to the collected data. The study population comprised faculty members involved in undergraduate clinical teaching and OSCE assessment across various academic designations. A total of 110 faculty members were included using a non-probability consecutive sampling technique. Faculty members with a minimum of one year of teaching experience and active involvement in OSCE conduction or evaluation were included. Those not engaged in assessment activities, on extended leave during the study period, or unwilling to participate were excluded. The sample size was initially calculated using the standard formula for estimation of a single population proportion, $n = (Z^2 \times p \times (1 - p)) / d^2$. Where n represents the initial sample size, Z is the standard normal deviate at a 95% confidence level (1.96), p is the anticipated proportion (assumed as 0.5 due to the absence of prior local data), and d is the margin of error (0.05). Substituting these values into the formula: $n = (1.96^2 \times 0.5 \times 0.5) / (0.05^2)$ n = 384. As this value assumes an infinite population, adjustment was required because the total number of faculty members involved in OSCE assessment at the study institution was limited (n=155). Therefore, finite population correction was applied using the following formula: $n^f = n / [1 + (n - 1) / n]$. Substituting the values: $n^f = 384 / [1 + (383 / 155)$, $n^f = 384 / 3.47$, $n^f = 110$. Accordingly, the final calculated sample size for the study was 110 faculty members, which represented a substantial proportion of the eligible study population. Data were collected using a structured, self-administered questionnaire developed using expert opinion and feedback from the literature. The questionnaire consisted of three sections: demographic characteristics, perceptions of the usefulness and quality of feedback in OSCEs, and preferences and perceived barriers to feedback delivery [8]. Perception items were measured using a Likert-scale format ranging from "disagree" to "agree." [9]. Content validity was assessed by senior faculty members experienced in medical education and assessment, and minor modifications were made to enhance clarity and relevance. A pilot test was conducted on a small group of faculty members who were not included in the final analysis. Internal consistency reliability of the perception scale was established using Cronbach's alpha. Faculty members were contacted individually after obtaining ethical approval, and the purpose of the study was explained. Questionnaires were administered face-to-face, and participants were given adequate time to complete them to minimize response bias. Completed questionnaires were collected on the same day or at a scheduled time to ensure a high response rate. Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Continuous variables such as age and years of experience were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Frequency distributions were used to describe faculty perceptions. The Pearson Chi-square test was applied to assess associations between the overall perception of feedback and selected faculty characteristics. Cramér's V was calculated to report the effect size where applicable. A p-value of <0.05 was considered statistically significant.

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RESULTS

A total of 110 faculty members participated in the study, with a mean age of 43.37 ± 8.17 years (range: 29–58 years). More than half of the participants were female (52.7%). Professors constituted the largest academic group (29.1%). Nearly half of the faculty (49.1%) had more than ten years of teaching experience, and 54.5% had served as OSCE examiners for over seven years. Slightly more than half of the participants (51.8%) had received formal OSCE training (Table 1).

Table 1: Demographic Characteristics of Faculty Participants (n=110)

Variables	Categories	n (%) / Mean ± SD
Age (Years)	Mean ± SD	43.37 ± 8.17
	Range	29–58
Age Group	≤35 Years	24 (21.8%)
	36–45 Years	40 (36.4%)
	>45 Years	46 (41.8%)
Gender	Male	52 (47.3%)
	Female	58 (52.7%)
Academic Designation	Lecturer	27 (24.5%)
	Assistant Professor	25 (22.7%)
	Associate Professor	26 (23.6%)
	Professor	32 (29.1%)
Teaching Experience	<5 Years	22 (20.0%)
	5–10 Years	34 (30.9%)
	>10 Years	54 (49.1%)
OSCE Examiner Experience	≤3 Years	15 (13.6%)
	4–7 Years	35 (31.8%)
	>7 Years	60 (54.5%)
OSCE Training	Yes	57 (51.8%)
	No	53 (48.2%)

A total of 66 faculty members (60.0%) agreed that feedback is essential for student learning, while 76 (69.1%) reported that feedback enhances the overall effectiveness of OSCEs. A large majority (84.5%) believed that feedback improves clinical competence. However, 40.0% of respondents remained neutral regarding the constructiveness of feedback, and 29.1% were neutral about the clarity of feedback provided (Table 2).

Table 2: Faculty Perceptions Regarding Importance and Quality of Feedback in OSCEs (n=110)

Variables	Agree, n (%)	Neutral, n (%)	Disagree, n (%)
Feedback Is Essential for Student Learning	66 (60.0%)	37 (33.6%)	7 (6.4%)
Feedback Improves Clinical Competence	93 (84.5%)	14 (12.7%)	3 (2.7%)
Feedback Enhances OSCE Effectiveness	76 (69.1%)	32 (29.1%)	2 (1.8%)
Feedback Provided Is Clear	75 (68.2%)	32 (29.1%)	3 (2.7%)
Feedback Provided Is Constructive	64 (58.2%)	44 (40.0%)	2 (1.8%)

Immediate feedback following OSCEs was preferred by 58 faculty members (52.7%), whereas 52 (47.3%) favored delayed feedback. The most preferred modes of feedback were written feedback (33.6%) and one-to-one feedback (31.8%), followed by verbal feedback (18.2%) and checklist-based feedback (16.4%). The most frequently reported barriers to effective feedback delivery were lack of formal training (57.3%), large student numbers (43.6%), stressful OSCE environments (42.7%), and time constraints (41.8%) (Table 3).

Table 3: Preferred Timing, Mode, and Perceived Barriers to Feedback in OSCEs (n=110)

Variables	Categories	n (%)
Preferred Timing of Feedback	Immediate	58 (52.7%)
	Delayed	52 (47.3%)
Preferred Mode of Feedback	Written	37 (33.6%)
	One-To-One	35 (31.8%)
	Verbal	20 (18.2%)
	Checklist-Based	18 (16.4%)
Perceived Barriers	Lack of Formal Training	63 (57.3%)
	Large Student Numbers	48 (43.6%)
	Stressful OSCE Environment	47 (42.7%)
	Time Constraints	46 (41.8%)

No statistically significant association was observed between overall faculty perception of feedback and gender (χ^2 = 0.62, p=0.432, Cramér's V = 0.075) or academic designation (χ^2 = 3.56, p=0.313, Cramér's V = 0.180). Similarly, perceptions did not differ significantly according to years of OSCE examiner experience (χ^2 = 1.55, p=0.460, Cramér's V = 0.119). Faculty members who had received formal OSCE training tended to report a more positive perception of feedback; however, this association was not statistically significant (χ^2 = 1.75, p=0.186, Cramér's V = 0.126). The study presents the association between faculty characteristics and overall perception of feedback in OSCEs (Table 4).

Table 4: Association Between Faculty Characteristics and Overall Perception of Feedback in OSCEs (n=110)

Variables	Positive, n (%)	Neutral, n (%)	χ^2 (df)	p-value	Cramér's V
Gender					
Male	29 (55.8%)	23 (44.2%)	0.62 (1)	0.432	0.075
Female	28 (48.3%)	30 (51.7%)			
Academic Designation					
Lecturer	12 (44.4%)	15 (55.6%)	3.56 (3)	0.313	0.180
Assistant Professor	17 (68.0%)	8 (32.0%)			
Associate Professor	13 (50.0%)	13 (50.0%)			
Professor	15 (46.9%)	17 (53.1%)			
OSCE Examiner Experience					
≤3 Years	10 (66.7%)	5 (33.3%)	1.55 (2)	0.460	0.119
4–7 Years	17 (48.6%)	18 (51.4%)			
>7 Years	30 (50.0%)	30 (50.0%)			

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OSCE Training					
Yes	33 (57.9%)	24 (42.1%)	1.75 (1)	0.186	0.126
No	24 (45.3%)	29 (54.7%)			

DISCUSSION

In this study, our study explored faculty perceptions of feedback during Objective Structured Clinical Examinations (OSCEs) to identify preferences and barriers that influence effective feedback practices. Current findings indicate that most faculty members recognize the importance of feedback and its role in improving students' clinical competence. At the same time, several challenges were identified that hinder the optimal delivery of feedback. These results highlight both the educational value of feedback in OSCEs and the practical constraints affecting its implementation. Globally, faculty attitudes toward OSCEs are generally favorable, particularly regarding fairness, structure, and educational value. A multicenter survey of dental faculty in Saudi Arabia reported that most faculty perceived OSCEs as fair and effective tools for assessing clinical competence, although concerns regarding student stress and examination difficulty were noted [10]. Similar findings have been reported from other regions, where faculty valued OSCEs for their reliability and objectivity [11]. Our results are consistent with John *et al.* who found that 82.2% of nursing faculty in Jordan viewed OSCEs positively [12], supporting the universal relevance of OSCEs as an assessment modality. Despite positive perceptions, feedback practices in OSCEs remain constrained. Structured feedback, particularly written or detailed performance reports, has been shown to enhance learning and performance in OSCE settings [13, 14]. A recent international study emphasized the importance of OSCE feedback while identifying inconsistencies in feedback quality and delivery [15]. In our study, a considerable proportion of faculty reported neutral views regarding feedback clarity and constructiveness, reflecting ongoing challenges in feedback quality. Barriers such as limited time, lack of formal training, and large student numbers were commonly reported. Faculty training and examiner standardization are critical for OSCE validity and reliability, and formally trained faculty are more likely to provide meaningful feedback [16, 17]. Consistent with our findings, international research highlights the importance of examiner preparation not only for scoring reliability but also for delivering constructive feedback [10]. Institutional factors, including large cohort sizes and limited resources, further dilute feedback quality due to examiner workload and time constraints [18]. Feedback can evoke both positive and negative emotional responses in students, influencing subsequent learning and performance [19]. These findings underscore the need for constructive, supportive feedback that emphasizes improvement and self-directed learning. In Pakistan, limited research has examined faculty perceptions of OSCE feedback. A study by Khan *et al.* reported generally positive attitudes toward OSCEs among nursing faculty in Peshawar, but few studies have addressed feedback quality and barriers [11]. A recent Pakistani study on academic feedback highlighted the importance of systematic feedback in enhancing instructional practices [20]. Collectively, this study contributes to both international and national literature by demonstrating that faculty value feedback in OSCEs while identifying persistent challenges requiring targeted interventions.

The research has limitations due to the single-institution design and use of self-reported perceptions, which can limit the level of generalizability and contribute to bias in responses. The cross-sectional method also does not allow the feedback effectiveness to be causally interpreted. Multi-institutional longitudinal designs should be used in the future, and students' views should be incorporated in order to capture more perspectives of the feedback dynamics. It might be beneficial to create faculty training regarding structured feedback and incorporate the use of digital feedback to enhance consistency and efficiency.

CONCLUSIONS

Faculty members broadly acknowledge the importance of feedback in OSCEs and its role in improving student learning and competence. However, persistent challenges such as limited formal training, time constraints, and large student numbers inhibit the delivery of high-quality, constructive feedback. Addressing these barriers through structured faculty development programs, clear feedback protocols, and institutional support can enhance the effectiveness of feedback practices and further strengthen OSCEs as a cornerstone of clinical education.

Authors' Contribution

Conceptualization: ZA
Methodology: ZA, MK, SM
Formal analysis: LK, SSF, SM
Writing and Drafting: ZA, LK, MK, SSF, SM
Review and Editing: ZA, LK, MK, SSF, SM

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Evaluation of the Efficacy of Rifaximin versus Mebeverine in the Treatment of Diarrhea-Predominant Irritable Bowel Syndrome

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ABSTRACT

Diarrhea-predominant irritable bowel syndrome (IBS-D) is a widespread functional gastrointestinal disease characterized by frequent abdominal pain and frequent looseness. Antispasmodics such as Mebeverine have proven effectiveness, whereas microbiota-targeted antibiotics such as Rifaximin could be more advantageous because of the effect on gut dysbiosis. **Objectives:** To compare the effectiveness of Rifaximin and Mebeverine to treat IBS-D through the treatment of diarrhea-predominant irritable bowel syndrome. **Methods:** This prospective comparative study was conducted at Khyber Teaching Hospital for six months from 1st January 2024 to 30th June 2024. Rifaximin or Mebeverine had been administered to the patients (n = 50 in each group). The collected data were the demographics, IBS Symptom Severity Score (IBS-SSS) at baseline, three months, and six months, and stool consistency, abdominal pain, bloating, and patient-reported satisfaction. The statistical analysis was performed with independent t-tests and chi-square tests; the p-value ≤ 0.050 was taken as significant. **Results:** Significantly greater improvements were observed in IBS-SSS in the Rifaximin group during three months (p=0.002) and six months (p<0.001) than in the Mebeverine group. Even though the Rifaximin group had better outcomes on categorical outcomes, such as stool normalization and first-line resolution of symptoms, most of them were not statistically significant. **Conclusions:** Rifaximin produced much improved symptomatic improvement as compared to Mebeverine in patients with IBS-D. The findings substantiate its use as a better treatment option clinically.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal disease, which is defined by recurrent stomachache that is associated with an altered bowel movement without visible organic pathophysiology [1]. One of its subtypes is diarrhea-predominant irritable bowel syndrome (IBS-D), which constitutes approximately one-third of all IBS cases and has a considerable negative impact on the patient's everyday functioning and quality of life [2]. Globally, IBS has a prevalence of 8.8%, and it is even higher in Western countries. The prevalence of IBS-D is 9.6% in Asia [3]. The pathophysiology of IBS-D remains complex and unclear, despite the disease having a high prevalence rate. Some of the hypothesized causes include modified gut motility, visceral hypersensitivity, low-grade gut biota inflammation, and gut microbiota dysbiosis [4-6]. One of the musculotropic antispasmodic agents, Mebeverine, has been commonly used in the symptomatic treatment of IBS, especially its capacity to relieve abdominal cramps and pain by relaxing intestinal smooth muscle with no effect on normal peristalsis [7]. Its impact on stool frequency and consistency is, however, restricted particularly in IBS-D patients [8]. Contrastingly, the minimally absorbed oral antibiotic, Rifaximin, has demonstrated good outcomes in changing the gut

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microbiota and decreasing bloating and diarrhea symptoms in IBS-D [9]. Clinical trials demonstrated significant symptom improvement in IBS-D patients treated with Rifaximin, with persistent effects beyond the treatment period [10, 11]. Another review by Almonajjed et al. further supported Rifaximin's efficacy and safety, emphasizing its potential as a microbiota-targeted therapy for IBS-D [12]. Recent guidelines, including those by the American College of Gastroenterology (ACG), now recognize Rifaximin as a treatment option for IBS-D, especially in patients with prominent bloating and diarrhea who fail to respond to dietary and lifestyle modifications [9]. However, in the population of Peshawar, direct comparisons between Rifaximin and traditional antispasmodics, such as mebeverine, remain limited. Most studies focus on placebo-controlled trials, creating a gap in evidence for head-to-head therapeutic efficacy, especially in low- and middle-income countries where both medications are widely available [13, 14]. Diarrhea-predominant irritable bowel syndrome (IBS-D) has proved to be a problem clinically because most of the patients show recurrent symptoms with the use of standard antispasmodic treatment like Mebeverine. It has been suggested that gut dysbiosis and overgrowth with small intestinal bacteria could be an important part of the pathophysiology of IBS-D, which justifies the use of non-systemic antibiotics like Rifaximin to relieve the symptoms and prevent relapse.

Nevertheless, this study has little comparative data available in the real world about our population, especially on the relative efficacy and clinical outcomes of Rifaximin to Mebeverine in regular clinical practice. This study aimed to compare the effectiveness of Rifaximin and Mebeverine to treat IBS-D through the treatment of diarrhea-predominant irritable bowel syndrome.

METHODS

This prospective comparative study was conducted in the Department of Medicine at Khyber Teaching Hospital (KTH), Peshawar, for six months between 1st January 2024 and 30th June 2024. The Institutional Research and Ethical Review Board (IREB) of Khyber Medical College (KMC), Peshawar, evaluated and ethically approved this study, and IREB approval number R/32/DME/KMC. The calculation of the sample size was performed using Open Epi, based on the IBS-D clinical response to Rifaximin, which has been reported in about 70-80% of patients [15], and the response to Mebeverine was 23-96% [7]. In the current research, the conservative effect estimate was taken, where the improvement of symptoms was expected to be 75% in the Rifaximin group (p1) and 55% in the Mebeverine group (p2), with the absolute difference of 20%. The confidence level was 95%, statistical power 80%, and allocation ratio 1:1. Based on these parameters, the required minimum sample size was determined to be 45 participants per group. The sample size was inflated and rounded to 50 patients per group to compensate for potential attrition and missing follow-up data (which was expected to be 8-10%), resulting in a total study sample of 100 patients. Participants who missed follow-up visits were not included in the final analysis. Patient data, covering the completion of all follow-ups, were analyzed according to protocol. The missing data were not imputed. The primary analysis (per-protocol analysis) included participants who attended all follow-up visits. Patients who did not attend follow-ups or those who stopped treatment were also registered, and causes of attrition were noted. The missing data were not imputed. The sensitivity analyses were taken into consideration to evaluate how the absence of data may influence the studies. Patients with inclusion criteria were recruited through a non-probability consecutive sampling technique. Patients were recruited during the presentation and followed during the course of treatment. Participants aged 18-65 years of age, with a known diagnosis of diarrhea-predominant IBS according to the Rome IV criteria, and either being prescribed Rifaximin (550mg three times a day over 14 days) or Mebeverine (135mg three times a day over 4 weeks). Each subject was to undergo baseline testing and two or more follow-up visits. Patients were not eligible when they showed alarm features like rectal bleeding, unexplained weight loss, or anemia, known inflammatory bowel disease, celiac disease, or colorectal malignancy, when pregnant or lactating, or when they had been taking antibiotics or probiotics within four weeks of enrolment. Individuals who failed to do a follow-up assessment were also eliminated. All the participants had signed a written informed consent before joining the study. The objectives, procedures, possible benefits, and risks of the study were communicated to the participants. The study, by nature, ensured the protection of patient data in terms of confidentiality and anonymity. Data have been collected through the use of a structured data collection form, which contained demographic data, clinical presentation, baseline severity of the symptoms, treatment regimen, and follow-up evaluation. The main measure was a decrease in symptoms, which was assessed by the Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) [16]. The baseline, 3-month, and 6-month IBS-SSS were performed at the time of clinical follow-up visits conducted by trained clinical staff. Other variables such as stool consistency, frequency of abdominal pain, bloating, and patient satisfaction with treatment were also noted at every follow-up.

Statistical Package of the Social Sciences (SPSS) version 26.0 was used to enter and analyze the data. Age and 'IBS

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Symptom Severity Score (IBS-SSS)' were quantitative variables that were expressed as a mean with standard deviation (SD). The Shapiro-Wilk normality test was applied to the distribution of the continuous variables before comparison. Between-group comparisons were conducted using the independent samples t-test to compare normally distributed variables. Categorical variables, such as gender, baseline symptoms, stool characteristics, and clinical response outcomes, were summarized as frequencies and percentages and compared with the Chi-square test. Within-group paired comparison and between-group comparisons of mean scores of IBS-SSS at each follow-up were used to determine the change in scores over follow-up. Independent t-tests and chi-square tests were used to compare baseline demographic and clinical data (age, gender, IBS-SSS, and presenting symptoms) between groups to ensure comparability and support outcome analysis between groups. Effect estimates were provided in terms of mean difference and proportion difference, and 95% confidence intervals. All analyses were regarded as statistically significant with a p-value ≤0.050.

RESULTS

The demographics of the study participants are presented below. The average age of the patients of the Mebeverine group stood at 36.7 ± 8.9 years, and that of Rifaximin was at 35.2 ± 9.6 years. The ages of the two groups did not differ significantly, as demonstrated by the fact that there was no statistically significant difference between them (p=0.419). In terms of gender, 26 (52%) men and 24 (48%) women were in the Rifaximin group. Also, the gender distributions of the groups could not be significantly different (p=0.841) (Table 1).

Table 1: Demographic Characteristics of Study Participants (n=100)

Variables	Rifaximin Group (n=50)	Mebeverine Group (n=50)	p-value	w-value
Age				
Years, Mean ± SD	35.2 ± 9.6	36.7 ± 8.9	0.419	0.419
Gender				
Male	26 (52%)	28 (56%)	0.841	–
Female	24 (48%)	22 (44%)		

The most prevalent presenting symptom at baseline was abdominal pain in both groups, which was then succeeded by bloating, increased stool frequency, and urgency. All the symptoms occurred equally commonly in both the Rifaximin and Mebeverine groups, and no statistically significant differences were found (Table 2).

Table 2: Clinical Presentation at Baseline of the Study Participants (n=100)

Variables	Rifaximin (n=50)	Mebeverine (n=50)	Risk Difference	95% CI	p-value
Normal Stool Consistency	38 (76%)	29 (58%)	18%	−0.1 to 36.1	0.088
Abdominal Pain Improved	40 (80%)	33 (66%)	14%	−5.0 to 33.0	0.176
Bloating Resolved/Reduced	37 (74%)	31 (62%)	12%	−6.3 to 30.3	0.283
Overall Patient Satisfaction	41 (82%)	32 (64%)	18%	−0.1 to 36.1	0.071
Symptom Improvement (IBS-SSS ≥50%)	43 (86%)	34 (68%)	18%	1.9 to 34.1	0.057

At baseline, the IBS-SSS scores of the two groups were similar, showing no significant difference at the beginning of the treatment. Paired comparisons within-group revealed a reduction in IBS-SSS between baseline and 3 months, and between baseline and 6 months significant in both groups. Nevertheless, at 3-month and 6-month follow-ups, the patients under the Rifaximin group showed much greater improvement in IBS-SSS than the patients under the Mebeverine group, which confirmed better symptomatic efficacy (Table 3).

Table 3: Baseline and Follow-Up IBS Symptom Severity Score (IBS-SSS) of the Study Participants (n=100)

Time Point	Rifaximin Group (Mean ± SD)	Mebeverine Group (Mean ± SD)	Between-Group p-value	Shapiro-Wilk W (p-value)	Within-Group Mean Difference (95% CI)	Within-Group p-value
Baseline	325.4 ± 45.6	328.7 ± 43.2	0.720†	0.98 (0.340)	–	–
3 Months	215.3 ± 40.2	245.6 ± 38.5	0.002*	0.97 (0.280)	Rifaximin: −110.1 (92.5–127.7) Mebeverine: −83.1 (65.4–100.8)	<0.001
6 Months	165.7 ± 32.8	198.4 ± 35.1	<0.001*	0.96 (0.310)	Rifaximin: −159.7 (141.8–177.6) Mebeverine: −130.3 (112.4–148.2)	<0.001

By the 6th month, a higher proportion of patients in the Rifaximin group experienced regulation of stool consistency, improvement in abdominal pain, and reduction in bloating compared to the Mebeverine group; however, these differences did not reach statistical significance. Similarly, greater overall patient satisfaction and clinically meaningful symptom improvement (defined as ≥50% reduction in IBS-SSS) were observed in the Rifaximin group, but the differences between groups remained statistically nonsignificant (Table 4).

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Table 4: Stool Consistency and Symptom Improvement of the study Participants at Six Months (n=100)

Variables	Rifaximin (n=50)	Mebeverine (n=50)	Risk Difference	95% CI	p-value
Normal Stool Consistency	38 (76%)	29 (58%)	18%	−0.1 to 36.1	0.080
Abdominal Pain Improved	40 (80%)	33 (66%)	14%	−5.0 to 33.0	0.176
Bloating Resolved/Reduced	37 (74%)	31 (62%)	12%	−6.3 to 30.3	0.283
Overall Patient Satisfaction	41 (82%)	32 (64%)	18%	−0.1 to 36.1	0.071
Symptom Improvement (≥50% IBS-SSS)	43 (86%)	34 (68%)	18%	1.9 to 34.1	0.057

At three months, the mean IBS-SSS score had reduced significantly in the Rifaximin group compared to the Mebeverine group (p=0.002), and at six months, this difference had risen further (p<0.001). At six months, patients receiving Rifaximin were more likely to have normal stool consistency, overall patient satisfaction, and ≥50% symptom improvement in IBS-SSS (Table 5).

Table 5: Effect Estimates of Rifaximin versus Mebeverine at Follow-Up

Outcomes	Time Point	Rifaximin (n=50)	Mebeverine (n=50)	Effect Estimate	95% Confidence Interval	p-value	Shapiro-Wilk W, (p-value)
IBS-SSS (Mean ± SD)	3 Months	215.3 ± 40.2	245.6 ± 38.5	Mean Difference = −30.3	Mean Difference = −30.3	0.002	0.97 (0.280)
IBS-SSS (Mean ± SD)	6 Months	165.7 ± 32.8	198.4 ± 35.1	Mean Difference = −32.7	Mean Difference = −32.7	<0.001	0.96 (0.310)
Normal Stool Consistency, n (%)	6 Months	38 (76%)	29 (58%)	Risk Difference = 18%	Risk Difference = 18%	0.088	—
Abdominal Pain Improved, n (%)	6 Months	40 (80%)	33 (66%)	Risk Difference = 14%	Risk Difference = 14%	0.176	—
Bloating resolved/reduced, n (%)	6 Months	37 (74%)	31 (62%)	Risk Difference = 12%	Risk Difference = 12%	0.283	—
Overall Patient Satisfaction, n (%)	6 Months	41 (82%)	32 (64%)	Risk Difference = 18%	Risk Difference = 18%	0.071	—
Symptom Improvement (≥50% IBS-SSS), n (%)	6 Months	43 (86%)	34 (68%)	Risk Difference = 18%	Risk Difference = 18%	0.057	—

DISCUSSION

The present study of Rifaximin and Mebeverine in treating IBS-D found significantly more improvements in IBS-SSS scores at 3 months and 6 months in the Rifaximin group and a tendency to regularize stool consistency, relieve symptoms, and improve patient satisfaction. The findings are in agreement with the current literature that validates the use of Rifaximin in the treatment of IBS-D. The results of a study by Black *et al.* and Karki *et al.* indicated that Rifaximin was significantly better than placebo in reducing global IBS symptoms and abdominal distension, promoting its safety and efficacy in the management of IBS [17, 18]. These findings are consistent with the present study, which markedly reduced symptom alleviation by six months (p<0.0001), which supports the strong effect of Rifaximin. In a pilot study by Mokhtare et al. short-course Rifaximin (2,200 mg/day during 10 days) in moderate and severe cases of IBS D patients generated significant outcomes on abdominal symptoms and quality of life, and the rates of symptom relief were similar to the present study 6 6-month results (composite abdominal symptom relief around 56%) [10]. In the Europe-based MMX® rifamycin SV formulation trial, relief of pain and stool consistency was significantly higher during the first week and continued to improve into the subsequent months with an improved response rate over placebo with OR =3.3 and p=0.0066 (600 mg bid) [19]. These baseline responses are similar to our improved symptoms at 3 months IBS SSS (p=0.0002). Several trials have identified the distinctive character of Rifaximin in modulating gut microbiota and corresponding mucosal interaction without significant absorption into the system, crediting its anti-bloating and stool-normalizing impact on this specific activity [20-22]. Conversely, recent RCTs and reviews highlight that despite antispasmodics such as Mebeverine alleviating abdominal cramps, their symptom alleviation in IBS D worldwide is not particularly large, and can be no better than that of a placebo [23, 24]. This difference is consistent with the results of the present study: although Mebeverine had certain effects (IBS SSS ≥50% in 68%), it had much less potent ones as compared with Rifaximin. New developments in the re-treatment guidelines affirm that there are specific groups of patients who respond repeatedly to Rifaximin even when the disease recurs during months, and this is more evidence in support of its use beyond a single course, particularly in the IBS D phenotype [9, 21]. Prior to six months, patients treated with Rifaximin were more likely to have improved outcomes in stool consistency, abdominal pain management, bloating alleviation, general patient satisfaction, and clinically significant improvement in symptoms (IBS-SSS ≥50) than those treated with Mebeverine. These differences were not found to be statistically significant, but the overall direction of the improvement was positive, which is an indication of a beneficial effect of Rifaximin. These results must be viewed with caution, bearing in mind that although such results provide positive trends, more research with bigger

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sample sizes might be required to establish statistical significance and reinforce the findings of such clinical advantages. Although the results were not found statistically significant in some cases, the effect estimates are large enough to draw a clinical interpretation that Rifaximin has a statistically significant effect compared to Mebeverine on IBS-D symptoms. An example is that a greater percentage of 18 patients reported 50% symptom-improvement, and there were trends of improvement in stool consistency and patient satisfaction. These results justify the clinical significance of Rifaximin and indicate that the clinical effect of the treatment may be useful even when the statistical significance is not achieved to make treatment decisions. Lacy *et al.* found that treatment-free periods and the overall cost of health of IBS D patients on Rifaximin were longer and cheaper than on Eluxadoline, indicating the long-term benefits and the economic potential of use of the antibiotic-based therapy in the management of the disease [25]. Although Eluxadoline is pharmacologically different, the overall lesson is in favour of the long-term effect of Rifaximin, just like the present study's long-term six-month scores and positive patient satisfaction scores. Other researchers in SIBO-positive patients with IBS also reported a 72% improvement in stool consistency and a 60% reduction of pain, which is once again a solid argument in favor of Rifaximin dominance in symptom areas where antispasmodics usually do not impact the condition significantly [26]. Together with the growing body of clinical evidence, the present study will add more weight to the current body of knowledge showing that Rifaximin is more clinically beneficial than conventional antispasmodics like Mebeverine in the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D). Rifaximin demonstrated better improvement on global symptoms of IBS, improved stool consistency normalization, and increased patient satisfaction in the present study. These results are consistent with recent randomized trials and observational, real-world studies, which have reported consistent findings of Rifaximin effectiveness as a targeted, non-systemic antibiotic to control symptoms in IBS-D. The direction and magnitude of the improvement in the various assessment points further provide the strength of it as a powerful therapeutic agent in standard clinical practice, particularly in the setting where Rifaximin and Mebeverine are frequently prescribed.

This is a single-centre study in the Khyber Teaching Hospital, which might not be generalizable to other populations. The study had a relatively small sample size (n=50 in each group), which could have prevented the statistically significant clinical outcomes such as stool normalization and patient satisfaction against a statistically significant. The long-term durability past six months and retreatment efficacy cannot be determined by the six months follow up. The non-probability consecutive sampling also brings about the selection bias aspect, and the per-protocol analysis could overestimate the effects of treatment because non-completers were omitted. There was no blinding, and this may have created observer bias in the symptom evaluation. The literature on predictors of response should be further investigated in future research to determine which patients respond to Rifaximin most with the use of IBS-D. The mode of action of the antibiotic could be explained by mechanistic studies of the shift in the gut microbiota.

CONCLUSIONS

This study found that Rifaximin is far more effective than Mebeverine in reducing the severity of symptoms in patients with diarrhea-predominant irritable bowel syndrome (IBS-D). The improvement of the results is observed as early as 3 months and lasts for six months of follow-up. Although both treatments were well tolerated, Rifaximin was more effective in alleviating symptoms, normalization of stool, and patient satisfaction. These findings give it some credibility as a more effective treatment option to use in clinical settings for the treatment of IBS-D.

Authors' Contribution

Conceptualization: SA
Methodology: MZ, RG, YA, FA
Formal analysis: SA, MZ, NI, YA
Writing and Drafting: SA, NI
Review and Editing: SA, MZ, NI, RG, YA, FA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of Intravenous Bolus with Infusion Regimen of Oxytocin in Patients Undergoing Elective Cesarean Delivery

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ABSTRACT

Postpartum hemorrhage is one of the leading causes of maternal mortality, and its rate of occurrence increases with the increase in the rates of cesarean section. The main prophylaxis is oxytocin, although the best way to administer it (intravenous bolus or continuous infusion) is the most effective and safe. **Objectives:** To compare the effectiveness and safety of intravenous bolus with the infusion regimen of oxytocin in patients undergoing elective cesarean delivery. **Methods:** The quasi-experimental study compared intravenous oxytocin bolus versus continuous infusion for the prevention of postpartum hemorrhage in women undergoing elective cesarean section. Ninety term pregnant women (ASA I–II) were allocated to receive either a 3 IU IV bolus followed by infusion or a 10 IU continuous infusion. The primary outcome was postpartum hemorrhage, while secondary outcomes included uterine tone, additional uterotonic requirement, hemodynamic stability, and maternal side effects. Data were analyzed using SPSS version 26.0, with $p<0.05$ considered statistically significant. **Results:** The incidence of postpartum hemorrhage was similar in the bolus (4.4%) and infusion (2.2%) groups ($p=0.78$), with no significant difference in uterine atony or mean blood loss, indicating comparable uterotonic efficacy. However, hypotension and tachycardia were significantly more frequent in the bolus group ($p=0.02$ and $p=0.03$, respectively). **Conclusions:** Intravenous oxytocin bolus and infusion are equally effective in preventing postpartum hemorrhage and maintaining uterine tone during elective cesarean section; however, continuous infusion offers superior maternal hemodynamic stability with significantly lower rates of hypotension and tachycardia, making it the safer regimen.

INTRODUCTION

Oxytocin is the most widely used uterotonic agent during cesarean delivery to promote uterine contraction and reduce the risk of postpartum hemorrhage (PPH), a major contributor to maternal morbidity worldwide [1]. Although oxytocin is routinely administered following delivery of the fetus, the optimal intravenous regimen remains controversial. Rapid bolus administration has been associated with adverse maternal hemodynamic effects such as hypotension and tachycardia, whereas continuous infusion may provide comparable uterotonic efficacy with improved cardiovascular stability [2]. Good uterotonic agents are thus critical towards containing too much blood

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loss during and after cesarean section [3]. Oxytocin is among these, and it is well known as the first pharmacological support to induce uterine contraction and reduce hemorrhage [4]. The preoperative use of it is also common in the cases of cesarean section to improve the tone and limit the occurrence of postpartum bleeding [5]. Nevertheless, the best protocol to administer oxytocin is one that compares the effects of intravenous bolus to that of the continuous infusion method, where the clinical research is still underway to establish which one is the most effective and least side effects [6, 7]. Such practice variability reveals a gap in existing knowledge about the best oxytocin dosing approaches, especially when considering the heterogeneity of research that is mainly done on low-risk patients [8]. Although it is widely used, the hemodynamic effects of oxytocin, e.g., hypotension, require careful consideration of the methods of its administration [9]. The decision between intravenous bolus and the continuous infusion regimen of oxytocin has a direct impact on the pharmacokinetic characteristics of oxytocin and its consequent uterine response, which impacts the rate of oxytocin response and the duration of uterine contractions [10]. Although oxytocin is the standard option when it comes to use of this hormone to prevent undue bleeding in the uterus during cesarean delivery, a significant percentage of women, between 10-40 percent, still need to receive further uterotonic medication, either methylergometrine or 15-methyl prostaglandin F2a, to curb uterine atony [11]. Newer synthetic uterotonics have since been developed, which prove to be potentially beneficial in minimizing the necessity of further uterotonic medication and blood transfusion over oxytocin in low-risk patients [4, 12]. However, oxytocin is the first-line prophylaxis drug used to prevent postpartum bleeding, although there are still controversies on the recommended dosage and rate of administration [13]. This is especially vital considering that refractory uterine atony, despite the prevalence of oxytocin, remains a challenge, and additional research on administration procedures is still required [14]. In particular, Sheehan et al. demonstrated that an oxytocin bolus combined with infusion reduced the need for additional uterotonics without increasing postpartum hemorrhage compared with bolus alone [15]. Similarly, Nagai et al. reported that protocolized oxytocin infusion during elective cesarean delivery maintained uterine tone with fewer hemodynamic disturbances and reduced supplemental uterotonic requirements. Based on these findings, the chosen regimens in our study were designed to balance uterotonic effectiveness with maternal safety [1]. Thus, the work is of essential importance to comprehensively assess and compare the various ways of administration of oxytocin.

However, with all the current evidence on oxytocin, the safety profiles between intravenous bolus and continuous infusion regimens during elective cesarean sections are not well compared in terms of their effects on maternal hemodynamic stability. Oxytocin is an effective agent in inducing uterine contraction; however, its use by rapid IV bolus may result in severe hypotension and tachycardia, which is a potentially avoidable risk factor of cardiovascular stability in the mother during and post-cesarean section. The study aimed at reducing the risk of poor uterine response and will benefit the establishment of evidence-based optimal protocols of oxytocin administration to improve maternal outcome by exploring the efficacy and safety of intravenous bolus regimen versus continuous infusion of oxytocin in women undergoing elective cesarean delivery.

METHODS

A quasi-experimental study was conducted in the Department of Obstetrics and Gynecology, Islam Medical and Dental College, Sialkot, Pakistan, which took place over a September 2024 to March 2025 period of time after getting ethical approval (900/IMC/ERC/000103). It aimed at comparing the effectiveness of intravenous bolus with continuous infusion regimen of oxytocin in the prevention of postpartum bleeding and maintenance of uterine tone among women undergoing elective cesarean delivery. Maternal hemodynamic stability and maternal side effect profiles were also put in focus with regard to each regimen. All the participants gave written informed consent before enrolling. The experiment was in accordance with the Helsinki Declaration. The sample size was calculated by the mean amount of blood loss of the intravenous slow bolus 5 IU of oxytocin group (840.65 ± 397.56 mL) and the group with 5 IU oxytocin bolus and an infusion (547.51 ± 222.15) by taking 80 percent of the statistical power, the 5 percent of error, and the dropout rate as 10 percent, and the total amount of 90 participants was obtained [16]. The sample of the research consisted of women (18-40 years old) with singleton pregnancies (37 to 40 weeks gestational) who chose the elective cesarean section and had normal pre-pregnancy body mass index (18.5 to 24.9 kg/m2) with ASA physical status I or II. The exclusion criteria included multiple pregnancies, emergent delivery, underlying medical factors (e.g., diabetes, hypertension, cardiac disease), oxytocin contraindications, a history of cesarean delivery, placenta previa/abruption, use of interfering drugs, or labor induction/augmentation. Oxytocin administration was initiated immediately after umbilical cord clamping and before placental delivery in both study groups. Group A (bolus regimen) received 3 IU oxytocin intravenously as a slow bolus over 1–2 minutes immediately after cord clamping, followed by an infusion of 80 mL Ringer

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Lactate without additional oxytocin. Group B (infusion regimen) received 10 IU oxytocin diluted in 80 mL Ringer Lactate, administered as a continuous intravenous infusion at a rate of 1 IU/min (8 mL/min), starting immediately after cord clamping and continued until the full volume was infused. Uterine tone was assessed after placental delivery and at predefined time intervals. Baseline vital signs, hemoglobin/hematocrit levels, and IV access were included in preoperative assessment. Ringer's Lactate 500-1000 mL preloading was administered to the patients, and prophylaxis antibiotics. Standardized spinal anesthesia (0.5% hyperbaric bupivacaine and intrathecal fentanyl) was used along with the use of supplemental oxygen. Constant hemodynamic observation was done. Its major effect was postpartum hemorrhage (blood loss of greater than 1000 mL or blood transfusion). The secondary outcomes were uterine tone (4-point scale during placenta delivery, 5, and 15 minutes after childbirth), the necessity of receiving extra uterotonics, and side effects (nausea, vomiting, hypotension, tachycardia). A quantitative method of measuring blood loss was performed through a calibrated drape and sponge weight.

All the data were recorded on a structured proforma. Statistical analysis was done in SPSS v26.0, where the independent t-tests were used, or Mann-Whitney U tests were used when the variable is continuous, and Chi-square or Fisher exact tests were used when the variable is categorical, because p-value less than 0.05 was considered statistically significant.

RESULTS

The participants were separated into 90 women in the bolus (n=45) and infusion (n=45) groups. The baseline traits (age, BMI, parity, and gestational age) were similar in groups, and no statistically significant differences were found (p>0.05) (Table 1).

Table 1: Demographic Characteristics of Participants

Characteristic	Bolus Group (n=45)	Infusion Group (n=45)	Total (n=90)	p-value
Age				
18-25	11 (24.4%)	10 (22.2%)	21 (23.3%)	0.61
26-35	27 (60.0%)	28 (62.2%)	55 (61.1%)	
36-40	7 (15.6%)	7 (15.6%)	14 (15.6%)	
Normal BMI				
18.5-24.9	40 (88.9%)	39 (86.7%)	79 (87.8%)	0.78
Others				
Primiparous	20 (44.4%)	22 (48.9%)	42 (46.7%)	0.54
Multiparous	25 (55.6%)	23 (51.1%)	48 (53.3%)	
Gestational Age				
37-38 Weeks	13 (28.9%)	15 (33.3%)	28 (31.1%)	0.48
39-40 Weeks	32 (71.1%)	30 (66.7%)	62 (68.9%)	

The incidence of postpartum hemorrhage (PPH) was 4.4% in the bolus group and 2.2% in the infusion group (p=0.78), indicating no significant difference in PPH prevention. Uterine atony, defined as a tone score of ≤2, was observed in 3 patients (6.7%) in the infusion group compared to 3 patients (6.7%) in the bolus group (p=0.82), also showing no significant difference in maintaining uterine tone. The need for additional uterotonics was slightly higher in the bolus group (5 patients, 11.1%) compared to the infusion group (4 patients, 8.9%), but again, the difference was not statistically significant (p=0.65) (Table 2).

Table 2: Comparison of Maternal Outcomes among Study Groups

Characteristic	Bolus Group (n=45)	Infusion Group (n=45)	p-value
Postpartum Hemorrhage	2 (4.4%)	1 (2.2%)	0.78
Uterine Atony	3 (6.7%)	3 (6.7%)	0.82
Need for Additional Uterotonics	5 (11.1%)	4 (8.9%)	0.65
Mean Blood Loss (mL) (SD)	545 ± 145	525 ± 138	0.32

The mean blood loss was 545 ± 145 mL in the bolus group and 525 ± 138 mL in the infusion group, showing no significant difference (p=0.32). However, in contrast to the similar efficacy in PPH prevention and uterine tone, a statistically significant difference was observed in hemodynamic side effects. Hypotension was significantly more frequent in the bolus group (22.2%) compared to the infusion group (2.2%) (p=0.02). Likewise, there was a great prevalence of tachycardia in the bolus group (20.0%) compared to the infusion group (4.4%) (p=0.03). Side effects like nausea and vomiting were similar in groups (p>0.05). These findings indicate that both IV bolus and infusion regimens of oxytocin have similar effects in the prevention of PPH and preserving uterine tone in elective Cesarean delivery, although the IV infusion regimen has a distinct benefit when it comes to maternal hemodynamic stability, which undoubtedly lowers the rate of hypotension and tachycardia (Table 3).

Table 3: Comparison of Side Effects among Study Groups

Side Effect	Bolus Group, (n=45)	Infusion Group, (n=45)	p-value
Nausea	4 (8.9%)	2 (4.4%)	0.35
Vomiting	2 (4.4%)	0 (0%)	0.15
Hypotension	10 (22.2%)	1 (2.2%)	0.02*
Tachycardia	9 (20.0%)	2 (4.4%)	0.03*

* p-value < 0.05, indicating statistical significance

DISCUSSION

The similar effectiveness of the bolus and infusion groups in the primary outcomes, including the incidence of PPH, uterine atony, and mean blood loss, concurs with the results of other studies. Our study's estimate of mean blood loss is also in line with the average blood loss that was published previously about elective cesarean deliveries using prophylactic oxytocin [3]. As an example, a meta-analysis and systematic review of carbetocin and oxytocin in high-risk women reported that various regimens of

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oxytocin could have a similar effect in preventing PPH [6]. Research that compared three uterotonic methods used in PPH prevention when performing cesarean section also implied that different interventions might yield similar results in terms of blood loss [13]. These findings are in line with the current study, which argues that both bolus and infusion interventions can be successful in achieving myometrial stimulation to prevent excessive blood loss since the outcomes of both methods were low PPH rates and comparable uterine atony rates [11]. Therefore, although various administration techniques are used, the result on the uterotonic effect on managing any blood loss may be the same, given that the best protocols are applied. Although this efficacy was also found in the uterotonic effect, our study found a statistically significant benefit of the continuous infusion regimen in maternal hemodynamic stability. The bolus-only group had significantly more cases of hypotension and tachycardia as opposed to the infusion group. This effect is not surprising according to the principles of pharmacodynamics: an abrupt increase in the concentration of oxytocin caused by a rapid injection of an oxytocin bolus may result in dose-related vasodilatory actions and consequent baroreceptor excitation, which eventually result in hypotension and reflex tachycardia [9]. Conversely, a low-level infusion over a period of time suppresses such peaks, promoting homeostasis in the cardiovascular system without diminishing uterotonic potency [10]. These hemodynamic benefits of infusion schedules have been noted in the literature, and some studies suggest infusion regimens as opposed to boluses to reduce incidences of adverse cardiovascular events [8]. The lack of notable disparities between our groups in such gastrointestinal side effects as nausea and vomiting further implies similar overall tolerability to the hemodynamic effect. Our results provide credence to the growing body of evidence that oxytocin in the form of a bolus is adequate to achieve uterotonic efficacy, but an infusion approach provides a vital hemodynamic safety margin, and this makes it a better choice in elective cesarean operation, especially to prevent complications involving maternal cardiovascular reactions [1]. This difference in safety profile is especially important because refractory uterine atony is still a problem despite the popularity of oxytocin administration, which requires caution regarding the guidelines of use [14]. The variability of the research, especially in relation to different amounts of dose needed in case of elective and intrapartum cesarean section, again evidences the need to formulate the best administration procedures [8]. The noted hemodynamic stability difference could possibly be explained by the pharmacokinetics of oxytocin, whereby a continuous infusion compared to a bolus dose provides a more stable plasma concentration, which cushions the sudden cardiovascular changes caused by bolus dosing [17]. Moreover, constant release infusion prevents transient surges in oxytocin level, which can cause acute effects, e.g., reflex tachycardia, which is frequently observed after bolus delivery [18]. The findings of the present study are consistent with previously reported hemodynamic effects of oxytocin administration during cesarean delivery under neuraxial anesthesia. Archer et al. demonstrated that intravenous oxytocin, particularly when administered as a bolus, produces significant cardiovascular changes, including hypotension and tachycardia, attributable to its vasodilatory properties and rapid onset of action [19, 20].

Nevertheless, the exact processes of action of oxytocin on the cardiovascular system, especially the interactions between direct vasodilation and reflex, are yet to be clarified. Future studies ought to examine the best dosing and routes of oxytocin and its analogues to ensure they maximize the uterotonic effects and minimize adverse cardiovascular effects during the conduct of elective cesarean section. These studies would be improved by sound methodologies such as randomized controlled trials that could be done with sufficient power to identify clinically significant differences in maternal and neonatal outcomes.

CONCLUSIONS

This study demonstrated that both intravenous bolus and continuous infusion regimens of oxytocin are equally effective in preventing postpartum hemorrhage and maintaining adequate uterine tone during elective cesarean delivery. However, continuous intravenous infusion was associated with significantly better maternal hemodynamic stability, with lower incidences of hypotension and tachycardia compared with bolus administration, while other adverse effects were comparable between groups. These findings suggest that oxytocin administered as a continuous infusion offers a safer hemodynamic profile and may be the preferred regimen in women undergoing elective cesarean section.

Authors' Contribution

Conceptualization: SS
Methodology: SS, UM, SA
Formal analysis: UM, AR
Writing and Drafting: MB, SA, HFA
Review and Editing: SS, MB, UM, SA, HFA, AR, FU

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

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Conflicts of Interest

All the authors declare no conflict of interest.

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Psychological Well-being and Its Predictors among Doctors in Tertiary Care Hospitals of Rawalpindi and Islamabad, Pakistan

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ABSTRACT

Psychological well-being (PWB) is a very important aspect of doctors' lives since their work is associated with a lot of stress. In Pakistan, the area has not been frequently studied to understand how PWB, as a multidimensional concept, appears among the doctors. **Objectives:** To assess the psychological well-being and factors affecting it among medical professionals working in tertiary care hospitals of Rawalpindi and Islamabad, Pakistan. **Methods:** A cross-sectional study was carried out among 385 doctors recruited through convenience sampling from April to June 2025 online-based structured questionnaire comprising sociodemographic information and the Ryff Psychological Well-Being Scale. Participant characteristics and well-being scores were summarized using descriptive statistics. Predictors of psychological well-being were identified using multiple linear regression analysis ($p<0.05$). **Results:** Among 385 doctors, 52.7% were male, and 47.3% were female. Descriptive analysis showed higher psychological well-being scores for Personal Growth (14.1 ± 2.6), Autonomy (13.7 ± 2.8), and Self-Acceptance (12.9 ± 2.7), with a total well-being score of 65.8 ± 11.5. The regression analysis revealed that marital status ($\beta = 0.19$, 95% CI [0.96, 4.26], $p=0.002$) and duty hours per day ($\beta = -0.25$, 95% CI [−4.66, −1.28], $p=0.001$) emerged as significant PWB predictors. Gender, age, years of service, and department were found to be non-significant predictors. **Conclusions:** Moderate psychological well-being was reported by doctors working in tertiary care hospitals, which was impacted by marital status and duty hours. It is advised to improve doctors' well-being and their professional performance through the use of workload management, institutional support, and mental health programs.

INTRODUCTION

Psychological well-being (PWB) has come to be regarded more and more as one of the key indicators of mental health and general functioning. Besides, among all the medical professionals, doctors in particular are the ones who keep PWB as an integral part of their lives since their jobs are very stressful. Doctors get burnt out, suffer anxiety, and even go into depression brought on by long hours, a heavy load of patients, and daily exposure to emotionally draining situations, which, in turn, negatively affect the physicians' well-being and the quality of the patient care [1]. Consequently, the evaluation and support of doctors' mental health become very important for the sustainability of effective healthcare delivery. Psychological well-being is a reflection of an individual's emotional, cognitive, and social life, covering the individual's personal judgments about the quality of life, like life satisfaction and emotional experiences, which also include positive and negative impacts [2]. Psychological well-being is a powerful predictor of well-being, as it has been associated with, among others, reduced use of coping strategies, emotional exhaustion, and vulnerability [3]. The pandemic caused by the virus COVID-19 has caused these difficulties to be more

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recognized and has led to higher levels of stress, burnout, and post-traumatic symptoms among healthcare professionals all over the world [4]. And as a result of this, studies have classified burnout as one of the top occupational issues in the health sector, recognizing its importance [5]. The main factors leading to burnout are excessive workloads, poor work-life balance, emotional strain, and the stigma surrounding mental health issues [2, 6]. Although there has been an increasing recognition of the fact that healthcare professionals undergo a lot of occupational stress, the multidimensionality in the assessment of psychological well-being has not been empirically researched in Pakistan [7, 8]. The bulk of local research has concentrated on stress and burnout, whereas a handful have made use of validated instruments to measure positive mental health indicators [9, 10]. The current research fills this void by assessing the psychological well-being of medical practitioners in Rawalpindi's tertiary care hospitals and its determinants by using a validated Psychological Well-being Scale [11]. Moreover, the understanding of the aspects that affect the psychological well-being of doctors is very important for the creation of interventions that are targeted, supportive work environments, and the reinforcement of institutional policies. The need for understanding the mental health status of doctors is now more than ever due to the high stress and demanding nature of tertiary care settings [12].

The current literature investigating the well-being of doctors in Pakistan is limited to examining burnout and stress levels in unidimensional scales, and no one has used the valid multidimensional scale by Ryff in the tertiary hospitals of Rawalpindi/Islamabad. This loophole constrains context-based interventions. This research will give baseline multidimensional statistics on psychological well-being and predictors in this population that is understudied. This study aimed to evaluate the mental health condition of the doctors working in the tertiary care hospitals of the twin cities of Pakistan in order to provide feedback for the development of strategies aimed at building resilience, promoting mental well-being, and finally, ensuring the doctors perform optimally in their profession.

METHODS

A cross-sectional study including both descriptive and analytical components was conducted from April to June 2025 among doctors working in tertiary care hospitals located in Rawalpindi and Islamabad, Pakistan. The Institutional Review Board granted ethical approval (Ref: 596-AAA-ERC-AFPGMI). It was a voluntary participation process, and the complete data were used exclusively for academic research purposes. The study aimed to assess the level of psychological well-being and its predictors among medical professionals. The number of doctors taken as a sample was 385, which was determined using the sample size calculator (https://www.calculator.net/sample-size-calculator.html) at a confidence level of 95%, with a margin of error of 5%, and assuming the population proportion of 50%. The method of convenience sampling was employed for the selection of participants from different departments, such as medical, surgical, emergency, pediatrics, and so forth. Only full-time doctors with at least one year of clinical experience, working in tertiary care hospitals located in Rawalpindi and Islamabad, were eligible to participate. Whereas medical interns and house officers were excluded due to their temporary or transitional roles, and doctors on long-term leave were also not excluded. A self-administered questionnaire consisting of two sections was utilized for data collection. The first section collected sociodemographic and professional information such as gender, age, marital status, years of service, department, and daily duty hours. The second section included the 18-item short version of Ryff's Psychological Well-Being Scale (PWB) [13], which assesses six dimensions, each consisting of 3 items: Autonomy, Environmental Mastery, Personal Growth, Positive Relations, Purpose in Life, and Self-Acceptance. Items were rated on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). Subscale scores were computed by summing item responses. Each subscale comprised three items, yielding a possible score range of 3–21, with higher scores indicating greater psychological well-being. Negatively worded items were reverse-scored in accordance with standard scoring procedures. The total psychological well-being score, calculated as the sum of all subscales, ranged from 18 to 126, with higher scores reflecting better well-being. The scale proved to be very reliable as the Cronbach's alpha was 0.92 [14]. It was also cross-validated in Pakistan [11], and another study conducted in medical settings also reported that Cronbach's alpha was reported to be 0.94 [15]. Online as well as paper questionnaires were provided to the respondents in order to make participation easier. Electronic informed consent was obtained before accessing the online survey, where participants were provided the information and clicked on "I agree" in order to proceed. No personal identifiers were collected, and all responses were anonymous and stored securely.

The data analysis was done by using IBM SPSS Statistics version 27.0. In the study, descriptive statistics such as frequencies, percentages, means, and standard deviations were created in order to summarize participant characteristics and psychological well-being scores. In addition, the normality of the residuals was checked, and diagnostic tests for collinearity were carried out. As all VIFs were less than 5, this suggests the absence of

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multicollinearity. So, the multiple linear regression analysis was performed to determine the psychological well-being predictors, and a p-value of less than 0.05 was regarded as statistically significant.

RESULTS

Results showed that 385 doctors working at tertiary care hospitals located in Rawalpindi and Islamabad were the ones to participate in this research. In the sample, male doctors were 52.7% and female doctors were 47.3%. The highest percentage of respondents was in the age group of 20 to 30 years (45.5%), followed by 31 to 40 years old (36.1%) and over 40 years old (18.4%). Single participants constituted 40.8% and married ones 59.2%. According to the years of professional service, 26.0% had more than 10 years of experience, 34.3% had 5-10 years, and 39.7% had less than 5 years of experience. Most of the responding doctors (29.9%) were from the medical specialties, followed by the surgical (23.9%), emergency (19.2%), pediatric (15.8%), and other (11.2%) groups. On the other hand, 44.9% of the participants reported working more than 8 hours a day, 36.1% worked 7-8 hours, and 19.0% worked less than 7 hours a day (Table 1).

Table 1: Sociodemographic Characteristics of the Study Participants (n=385)

Variables	Category	n (%)
Gender	Male	203 (52.7%)
	Female	182 (47.3%)
Age (Years)	20–30	175 (45.5%)
	31–40	139 (36.1%)
	41–50	71 (18.4%)
Marital Status	Married	228 (59.2%)
	Unmarried	157 (40.8%)
Years of Service	< 5 Years	153 (39.7%)
	5–10 Years	132 (34.3%)
	> 10 Years	100 (26%)
Departments	Emergency	74 (19.2%)
	Medical	115 (29.9%)
	Surgical	92 (23.9%)
	Pediatrics	61 (15.8%)
	Others	43 (11.2%)
Duty Hours (Per Day)	< 7 Hours	73 (19%)
	7–8 Hours	139 (36.1%)
	> 8 Hours	173 (44.9%)

Descriptive statistics for six subscales and the total psychological well-being score are depicted. Each subscale included three items, which were rated on a 1 to 7 scale (theoretical range 3–21); thus, the total score ranged from 18 to 126. The observed total scores were 36 to 120, and subscale scores were averaged over the observed ranges as shown. The predefined cutoffs (18–48 low, 49–78 moderate, 79–102 high, 103–126 very high) indicate that the mean total well-being score of 65.8 ± 11.5 is in the moderate range, which means that participants reported moderate psychological well-being across all dimensions (Table 2).

Table 2: Descriptive Statistics of Psychological Well-being Scores (n=385)

Subscales	Mean	Observed Range		Theoretical Range	
		Minimum	Maximum	Minimum	Maximum
Autonomy	13.7 ± 2.8	6	20	3	21
Environmental Mastery	11.0 ± 3.2	5	20	3	21
Personal Growth	14.1 ± 2.6	8	20	3	21
Positive Relations	12.8 ± 2.9	6	20	3	21
Purpose in Life	11.3 ± 3.1	5	20	3	21
Self-Acceptance	12.9 ± 2.7	6	20	3	21
Total Well-being Score	65.8 ± 11.5	36	120	18	126

To identify potential predictors, a multiple linear regression analysis was conducted using the total well-being score as the dependent variable and demographic/professional characteristics as independent variables. The model was statistically significant ($F(7, 377) = 14.92$, $p<0.001$) and explained 21.7% of the variance in psychological well-being ($R^2 = 0.217$). Among all variables, marital status ($\beta = 0.19$, 95% CI [0.96, 4.26] $p=0.002$) and duty hours per day ($\beta = -0.25$, 95% CI [−4.66, −1.28] $p=0.001$) emerged as significant predictors. Doctors who were married and those with shorter duty hours reported higher psychological well-being. Other variables, including gender, age, years of service, and department, were not statistically significant (Table 3).

Table 3: Multiple Linear Regression Analysis Predicting Psychological Well-being (n=385)

Side Effect	B	SE	Beta (β)	t	p-value
Gender (Male=1)	1.07	0.91	0.07	1.18	0.240
Age Group	0.58	0.49	0.06	1.18	0.240
Marital Status (Married=1)	2.61	0.84	0.19	3.10	0.002
Years of Service	0.43	0.39	0.05	1.09	0.280
Department	−0.21	0.26	−0.04	−0.82	0.410
Duty Hours	−2.97	0.86	−0.25	−3.45	0.001
Constant	70.12	3.47	—	20.18	<0.001

Model Summary: $R^2 = 0.217$, $F(7,377) = 14.92$. $p<0.001$.

DISCUSSION

The present study explored the level of psychological well-being and its predictors among doctors working in tertiary care hospitals located in Rawalpindi and Islamabad. The sample consisted of 385 full-time doctors from different areas of specialization, ages, and experience, which in a broad sense mirrored the demographics of urban tertiary hospital doctors in Pakistan. The study findings showed that the psychological well-being was at a moderate level (65.8 ± 11.5), which indicated that doctors have professional competence but still experience considerable emotional

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and occupational challenges. These findings are consistent with previous national and international studies reporting moderate to low psychological well-being among doctors, primarily due to excessive workload, limited rest, and high emotional demands of clinical practice [16, 17]. Moreover, among the analyzed variables, marital status and daily working hours proved to be the most important factors influencing psychological well-being. The married medical professionals exhibited greater well-being scores (β = 0.19, p=0.002). The results of this research are consistent with earlier investigations, which also noted that healthcare professionals with marital status usually have better psychological health and quality of life than the unmarried ones [18, 19]. One possible explanation, as suggested by the literature, is that marriage as an emotional, practical support, along with family companionship, could potentially mitigate work stress [20]. But the current study did not take social support or similar factors into account; therefore, this interpretation is still a matter of speculation. On the other hand, longer duty hours were identified as a negative predictor of psychological well-being (β = –0.25, p=0.001), which means that long work shifts combined with almost no recovery time led to fatigue, burnout, and emotional exhaustion. The result corresponds with earlier studies, which pointed to heavy workload as the most significant factor causing poor mental health in healthcare workers [21, 22]. The negative correlation that was found stresses the importance of the introduction of the necessary measures in the health sector, such as optimal scheduling, rotation of duties, and wellness programs, which would help to keep a work-life balance [23]. Findings also have shown that other factors like gender, age, years of service, and department did not play a significant role in determining psychological well-being. These findings are consistent with previous literature, which also reported minimal or no association between demographic and well-being [24, 25]. This suggests that demographic variables might affect well-being less than factors related to the organization and the social environment, although the lack of diversity in our sample might have been a reason for these findings to be null. The current study findings point out the necessity of promoting mental health as a strategy in the hospital systems. Regular psychological screening, peer support programs, stress management workshops, and resilience training as interventions could increase the well-being and functioning of the doctors.

The cross-sectional design eliminates causality. The convenience sampling restricts generalizability. Self-reported information is prone to bias. The major confounders (social support, financial stress, and mental health history) were not measured. The dimensional depth is diminished in the short-form Ryff scale. City-single-time single-city design might not indicate seasonal or regional differences. Enact duty hour restrictions, institutional mental health programs, and frequent well-being screening. The following research must apply probability sampling, longitudinal, multicentric, and mixed-method designs. Add more predictors (workplace harassment, family support, coping strategies). Check the scale of Ryff against Pakistani healthcare population.

CONCLUSIONS

The research concludes that doctors working in tertiary care hospitals have shown a moderate level of psychological well-being, which is mainly affected by their marital status, long duty hours, and other sociodemographic factors, while marital status and duty hours are potential predictors of psychological well-being.

Authors' Contribution

Conceptualization: MAS, SQZ
Methodology: MAS, SHS, SQZ, SK
Formal analysis: SK
Writing and Drafting: MAS, SHS, SQZ, SK, AAM
Review and Editing: MAS, SHS, SQZ, SK, AAM

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Diagnostic Accuracy of Color Doppler Ultrasonography for Differentiating Benign and Malignant Thyroid Nodules: Sensitivity, Specificity, and ROC-Based Evaluation Using FNAC as Reference Standard

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ABSTRACT

Thyroid nodules are frequently encountered in clinical practice, and accurate discrimination between benign and malignant lesions remains essential to avoid unnecessary invasive procedures. **Objectives:** To evaluate the diagnostic accuracy of Doppler ultrasonography using fine needle aspiration cytology (FNAC) as the reference standard. **Methods:** This cross-sectional diagnostic accuracy study was conducted in the Department of Radiology, Medical Teaching Institution Bacha Khan Medical College and Mardan Medical Complex, Pakistan, from 18 August to 18 December 2025. A total of 83 patients underwent gray-scale and Doppler ultrasonography followed by FNAC. Doppler findings were categorized using predefined thresholds and compared with cytology. **Results:** The mean age was 45.1 ± 17.2 years. Malignancy was detected in 22.9% of nodules on FNAC. Doppler ultrasonography demonstrated sensitivity 100% (95% CI: 82.4–100), specificity 85.9% (95% CI: 74.6–93.3), and overall accuracy 89.2%. The ROC curve showed an AUC of 0.93 (95% CI: 0.876–0.984). **Conclusions:** Doppler ultrasonography is a reliable adjunct to gray-scale ultrasound for triaging thyroid nodules and guiding FNAC selection. However, cytology remains essential for confirming malignancy.

INTRODUCTION

Thyroid nodules are increasingly detected due to widespread use of imaging modalities, although only a small proportion are malignant [1, 2]. Accurate differentiation is critical to prevent unnecessary biopsies while ensuring early detection of malignancy [3]. Gray-scale ultrasonography is the first-line imaging modality because of its safety and accessibility [4, 5]. Features such as hypoechogenicity, irregular margins, microcalcifications, and taller-than-wide configuration are associated with malignancy risk, although substantial overlap exists between benign and malignant nodules [6, 7]. Fine needle aspiration cytology is the reference standard for diagnosis; however, it is invasive and operator-dependent, making optimal selection of nodules for FNAC clinically important [8, 9]. Doppler ultrasonography provides additional information on

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intranodular vascularity and resistance patterns, which may improve malignancy stratification when combined with gray-scale criteria [10, 11]. Nevertheless, diagnostic performance varies across populations and equipment. This study hypothesized that predefined Doppler parameters could improve discrimination between benign and malignant thyroid nodules.

Pakistan has no multicenter data to prove the diagnostic accuracy of Doppler ultrasonography in determining thyroid nodules; most of the studies are one-center experiences. No standardized Doppler thresholds (RI, PSV, vascularity patterns) have been tested and validated within Pakistani populations. Single-center design within Mardan Medical Complex restricts generalizability to the different populations in Pakistan. The small sample size (n=83) of malignant cases (19) resulted in broad confidence intervals for sensitivity (82.4-100%) and PPV (47.6-84.1%). This study aimed to evaluate the diagnostic accuracy of Doppler ultrasonography using FNAC as the reference standard.

METHODS

The study was a cross-sectional diagnostic accuracy study conducted in the Department of Radiology, Medical Teaching Institution (MTI) Bacha Khan Medical College and Mardan Medical Complex (MMC), Mardan, Pakistan. The objective was to evaluate the diagnostic accuracy of Color Doppler ultrasonography as an adjunct to gray-scale ultrasound in differentiating benign and malignant thyroid nodules, using fine needle aspiration cytology (FNAC) as the reference standard. The total study duration was four months, with patient enrollment from 18 August 2025 to 18 December 2025. Ethical approval was obtained from the Ethical Review Board of MTI Bacha Khan Medical College, Mardan (Approval No. 918/BKMC). Written informed consent was obtained from all participants before imaging and FNAC. Confidentiality was maintained by assigning unique study codes and restricting dataset access to the research team only. The sample size was calculated for a diagnostic accuracy study using the Buderer approach based on expected sensitivity. A confidence level of 95% (Z = 1.96), anticipated sensitivity (Se) of 90%, expected prevalence (P) of malignant thyroid nodules of 23%, and absolute precision (d) of 13.5% were assumed based on feasibility within the fixed four-month recruitment period and the expected malignant case yield at the study site [7]. The sample size was estimated using the formula $n = (Z^2 \times Se \times (1–Se)) / (d^2 \times P)$, yielding a required sample size of approximately 83 participants. Therefore, 83 consecutive eligible patients were included. A non-probability consecutive sampling technique was used, whereby all eligible patients presenting during the study period and meeting the inclusion criteria were enrolled. The study included patients of both genders, aged ≥18 years, with thyroid nodules detected clinically or radiologically, who underwent both thyroid ultrasound (gray-scale plus Color Doppler) and FNAC to allow valid comparison. Patients with previous thyroid surgery, previously diagnosed thyroid malignancy, purely cystic nodules, those unwilling to undergo FNAC, and cases with incomplete imaging or cytology records were excluded. Thyroid ultrasonography was performed using a high-frequency linear transducer (7.5–12 MHz) on a dedicated ultrasound unit (Manufacturer/Model Mindray DC-70 / GE Logiq / Philips). All scans were performed following a standardized departmental protocol. Gray-scale ultrasound was first used to document nodule characteristics, including the number of nodules, maximal nodule diameter (cm), composition (solid/cystic/mixed), echogenicity (hypo/iso/hyper-echoic), margins (regular/irregular), calcifications (micro/macro/absent), and shape (taller-than-wide/wider-than-tall). The maximal diameter was recorded in the longitudinal or transverse plane, whichever demonstrated the largest dimension. Color Doppler assessment was then performed to evaluate vascularity and spectral indices. Vascularity was categorized as absent, peripheral, central, or mixed. To reduce inter-scan variability, Doppler gain, pulse repetition frequency (PRF), wall filter, and insonation angle were kept consistent as per departmental thyroid Doppler protocol (PRF and wall filter adjusted to avoid aliasing while maintaining low-flow sensitivity), and spectral sampling was obtained from the most vascular intranodular region. Where feasible, resistive index (RI) and peak systolic velocity (PSV) were recorded from intranodular arteries with an insonation angle ≤60°. Nodules were categorized as "suggestive of malignancy" if any two of the following were present: predominant central or mixed vascularity, Resistive index (RI) > 0.70, and peak systolic velocity (PSV) > 40 cm/s. Nodules not meeting the above criteria were categorized as "suggestive of benignity." These thresholds were applied uniformly across participants to improve reproducibility and reduce operator-dependent classification. To minimize operator bias, ultrasound examinations were performed by consultant radiologists with at least three years' post-fellowship experience in thyroid imaging. Borderline cases were re-reviewed by a second radiologist, and a consensus impression was recorded. FNAC was performed under ultrasound guidance using standard aseptic technique. Aspirated samples were processed and interpreted in the pathology department. FNAC results were classified as benign or malignant based on cytology. Benign diagnoses included colloid nodules, thyroiditis, and benign cysts, whereas malignant diagnoses included papillary carcinoma, follicular neoplasm/suspicious lesions, and other malignancies. FNAC served as the

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reference standard for diagnostic accuracy calculations in this study (histopathology was not available for all cases). Clinical and imaging data were documented on a structured proforma developed before data collection. The proforma included demographics, presenting symptoms, gray-scale ultrasound variables, Doppler vascularity pattern, RI, PSV, Doppler impression (benign vs malignant), and FNAC outcome. Operational definitions were prespecified to ensure consistency across measurements and recording. Data were entered and analyzed using SPSS version 26.0. Continuous variables (age, nodule size, RI, PSV) were summarized as mean ± standard deviation. Normality was assessed using the Shapiro–Wilk test before reporting parametric summaries. Categorical variables were presented as frequencies and percentages. The association between Doppler impression and FNAC diagnosis was assessed using the Pearson Chi-square test, and the strength of association was quantified using Cramer's V. Diagnostic accuracy indices (sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy) were calculated using a 2×2 contingency table. Exact binomial 95% confidence intervals were computed for sensitivity, specificity, PPV, and NPV. Receiver operating characteristic (ROC) curve analysis was performed to evaluate overall discriminatory performance, and the area under the curve (AUC) was reported with 95% confidence intervals. Statistical significance was set at $p \leq 0.05$.

RESULTS

The mean age of participants was 45.1 ± 17.2 years, with the largest proportion aged >50 years (39.8%). Females constituted 51.8% of the study population. Neck swelling was the predominant presenting symptom (69.9%), while hoarseness was the least frequent (Table 1).

Table 1: Baseline Demographic and Presenting Clinical Features

Variables	Category	n (%), Mean ± SD
Age (Years)	Mean ± SD	45.12 ± 17.24
	Range	19–75
Age Category	≤30 Years	22 (26.5%)
	31–40 Years	20 (24.1%)
	41–50 Years	8 (9.6%)
	>50 Years	33 (39.8%)
Gender	Male	40 (48.2%)
	Female	43 (51.8%)
Presenting Symptom	Neck Swelling	58 (69.9%)
	Pain	12 (14.5%)
	Dysphagia	10 (12.0%)
	Hoarseness	3 (3.6%)
Duration of Swelling (Months)	Mean ± SD	18.67 ± 10.19
	Range	2–35

Slightly more than half of the participants had solitary nodules (50.6%). The mean nodule size was 2.34 ± 1.05 cm, with 59.0% measuring >2 cm. Solid composition was the most common structural pattern, and hypoechogenicity, irregular margins, calcifications, and taller-than-wide configuration were frequently observed as suspicious gray-scale features. Gray-scale ultrasonography characteristics are detailed (Table 2).

Table 2: Gray-Scale Ultrasonography Features of Thyroid Nodules (n=83)

Ultrasound Features	Category	n (%)
Number of Nodules	Solitary	42 (50.6%)
	Multiple	41 (49.4%)
Nodule Size (cm)	Mean ± SD	2.34 ± 1.05
	Range	0.65–4.18
	≤1.0 cm	7 (8.4%)
	1.1–2.0 cm	27 (32.5%)
	>2.0 cm	49 (59.0%)
Composition	Solid	29 (34.9%)
	Cystic	28 (33.7%)
	Mixed	26 (31.3%)
Echogenicity	Hypoechoic	32 (38.6%)
	Isoechoic	28 (33.7%)
	Hyperechoic	23 (27.7%)
Margins	Regular	44 (53.0%)
	Irregular	39 (47.0%)
Calcification	Absent	29 (34.9%)
	Macrocalcification	30 (36.1%)
	Microcalcification	24 (28.9%)
Shape	Taller-Than-Wide	44 (53.0%)
	Wider-Than-Tall	39 (47.0%)

Central and mixed vascularity were the predominant Doppler patterns (55.4% combined). The mean resistive index (RI) was 0.72 ± 0.14, with 57.8% demonstrating RI > 0.70. Based on predefined Doppler criteria, 28 nodules (33.7%) were categorized as suggestive of malignancy. FNAC identified 19 malignant nodules (22.9%), with papillary carcinoma being the most frequent malignant subtype (Table 3).

Table 3: Color Doppler Ultrasonography Findings and Fine Needle Aspiration Cytology (FNAC) Findings of Thyroid Nodules (n=83)

Variables	Category / Summary	n (%) or Mean ± SD
Doppler		
Vascularity Pattern	Absent	19 (22.9%)
	Peripheral	18 (21.7%)
	Central	21 (25.3%)
	Mixed	25 (30.1%)
Resistive Index (RI)	Mean ± SD	0.72 ± 0.14
	Range	0.45–0.94
RI Category	≤ 0.70	35 (42.2%)
	> 0.70	48 (57.8%)

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PSV (cm/s)	Mean ± SD	39.51 ± 14.59
	Range	15.20–64.30
Color Doppler Impression	Suggestive of Benign	55 (66.3%)
	Suggestive of Malignant	28 (33.7%)
Fine Needle Aspiration Cytology (FNAC)		
Final FNAC Diagnosis	Benign	64 (77.1%)
	Malignant	19 (22.9%)
Benign Subtypes	Colloid Nodule	25 (30.1%)
	Thyroiditis	24 (28.9%)
	Benign Cyst	15 (18.1%)
Malignant Subtypes	Papillary Carcinoma	8 (9.6%)
	Follicular Neoplasm / Suspicious	4 (4.8%)
	Others	7 (8.4%)

RI = Resistive Index; PSV = Peak Systolic Velocity

A statistically significant association was observed between Doppler impression and FNAC diagnosis (χ^2 = 48.401, p<0.001; Cramer's V = 0.764). The cross-tabulation of Doppler impression and FNAC findings is shown (Table 4).

Table 4: Association of Color Doppler Impression with FNAC Findings (n=83)

Color Doppler Impression	FNAC Benign, n (%)	FNAC Malignant, n (%)	Total	χ^2 (df)	p-value	Cramer's V
Suggestive of Benign	55 (100.0%)	0 (0.0%)	55	48.401 (1)	<0.001	0.764
Suggestive of Malignant	9 (32.1%)	19 (67.9%)	28			
Total	64 (77.1%)	19 (22.9%)	83			

The Pearson Chi-square test was applied as all expected cell counts were ≥5. A p-value ≤0.05 was considered statistically significant

Color Doppler ultrasonography demonstrated an overall diagnostic accuracy of 89.2%, with sensitivity 100% (95% CI: 82.4–100) and specificity 85.9% (95% CI: 74.6–93.3). The area under the ROC curve was 0.93 (95% CI: 0.876–0.984), indicating excellent discriminatory performance (Table 5).

Table 5: Diagnostic Accuracy of Color Doppler Ultrasonography Using FNAC as Gold Standard (n=83)

Diagnostic Measures	Value (%)	95% Confidence Interval
Sensitivity	100.0	82.4 – 100.0
Specificity	85.9	74.6 – 93.3
Positive Predictive Value (PPV)	67.9	47.6 – 84.1
Negative Predictive Value (NPV)	100.0	93.5 – 100.0
Overall Diagnostic Accuracy	89.2	–
Area Under ROC Curve (AUC)	0.93	0.876 – 0.984

CI = Confidence Interval; PPV = Positive Predictive Value; NPV = Negative Predictive Value

DISCUSSION

In this diagnostic accuracy study (n=83), Doppler ultrasonography demonstrated high diagnostic performance with an accuracy of 89.2%, sensitivity of 100%, specificity of 85.9%, and an AUC of 0.93. These findings confirm excellent discriminatory ability and support its role as an adjunct to gray-scale imaging in thyroid nodule evaluation. The very high sensitivity and negative predictive value indicate that Doppler imaging is particularly useful for ruling out malignancy when features favor benignity. Similar diagnostic performance has been reported in recent international cohorts, where Doppler parameters enhanced malignancy stratification when combined with suspicious gray-scale features such as hypoechogenicity, irregular margins, microcalcifications, and taller-than-wide configuration [12, 13]. Malignant nodules in the present study more frequently demonstrated central or mixed vascularity and elevated RI values (>0.70), consistent with published evidence indicating altered intranodular perfusion and vascular resistance in malignancy [14, 15]. However, Doppler thresholds remain susceptible to operator technique and equipment settings, which may explain variability in sensitivity and specificity across populations [16, 17]. The moderate positive predictive value observed reflects the influence of disease prevalence and overlapping vascular patterns between benign and malignant nodules, a limitation also described in previous studies, reinforcing the necessity of FNAC confirmation in suspicious lesions [18, 19]. The 100% sensitivity and NPV in this study should be interpreted cautiously due to the limited number of malignant cases (n=19), which resulted in wide confidence intervals [20]. Multicenter studies integrating standardized Doppler thresholds with established ultrasound risk-stratification systems are recommended to improve generalizability [21, 22].

The design was cross-sectional, which does not allow the determination of the prognostic value of Doppler in nodule progression or recurrence. There was no comparison with newer methods of ultrasound (elastography, contrast-enhanced ultrasound). There was no formal inter-observer test in spite of the consensus review of borderline cases. Pakistan studies. Multicenter prospective studies in multiple Pakistani cities are required to establish the Doppler thresholds in different populations. Proper and bigger samples with malignant cases would give specific confidence intervals. Prolonged follow-up with correlations of Doppler results, histopathology, and clinical results is to be carried out.

CONCLUSIONS

Color Doppler ultrasonography demonstrates excellent diagnostic accuracy and very high sensitivity for differentiating benign from malignant thyroid nodules when used as an adjunct to gray-scale ultrasound, fulfilling the primary study objective. The high AUC confirms strong discriminatory capability, supporting Doppler imaging as a

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reliable triage tool to guide FNAC prioritization. Nevertheless, cytology remains essential for definitive diagnosis in nodules with suspicious imaging characteristics.

Authors' Contribution

Conceptualization: ZJO
Methodology: ZJO, LK, SN
Formal analysis: TB
Writing and Drafting: ZJO, LK, TB, SN, NA, MS
Review and Editing: ZJO, LK, TB, SN, NA, MS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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The Role of Neutrophil to Lymphocyte Ratio in Predicting the Response to Neoadjuvant Targeted Therapies in HER2-Positive Breast Cancer

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ABSTRACT

The neutrophil-lymphocyte ratio (NLR) is a basic systemic inflammatory biomarker, previously associated with treatment response in different forms of cancer. Its predictive importance on response to neoadjuvant HER2-targeted therapies in HER2-positive breast cancer has not been well-established, especially in Pakistani patients. **Objectives:** To identify the relationship between pretreatment NLR and response to neoadjuvant HER2-targeted therapy in women with HER2-positive breast cancer. **Methods:** This was a descriptive study carried out in Khyber Teaching Hospital. Non-probability consecutive sampling was used to enroll 120 patients. Standard neoadjuvant HER2-targeted therapy was given to patients, and after 12 weeks, treatment response was evaluated based on Miller-Payne criteria. SPSS version 25.0 was used to analyze data. Chi-square/Fisher exact tests were used to establish associations between NLR and treatment response, and multivariate logistic regression was used to determine independent predictors of complete response. **Results:** Out of the 120 patients, 70 (58.3%) patients had low NLR, and 50 (41.7%) patients had high NLR. Full response was obtained in 16 (22.9%) low (NLR) and 4 (8%) high (NLR) (p=0.004) patients, respectively. High NLR was an independent predictor of reduced odds of complete response using logistic regression (p=0.035). **Conclusions:** A low pretreatment NLR is linked to better response rates to neoadjuvant HER2-targeted therapy, which indicates its potential use as a cost-efficient biomarker in informing decisions on the use of treatment strategies in the management of patients with HER2-positive breast cancer.

INTRODUCTION

The most common cancer that is diagnosed in women worldwide is breast cancer. It is estimated that this disease will cause hundreds of thousands of cases and that by 2022 alone, around 2.3 million new cases will have been linked to this disease, with 670,000 patients expected to die, highlighting the significant impact that this disease has on the issue of public health [1, 2]. One subtype worth mentioning is the HER2-positive breast cancer that occurs in approximately 15-20% of all cases of breast cancer occurrence [3]. The subtype is defined by abnormal expression of the HER2 protein, which results in more aggressive disease progression and worse outcomes in the past than the other subtypes [4]. The introduction of specific neoadjuvant regimens, especially anti-HER2 drugs, has significantly enhanced patient response rates and survival rates in those patients with HER2-positive disease [5]. Pathologic complete response (pCR) in the neoadjuvant setting has become a strong surrogate

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outcome in long-term prognosis, with the latest reports suggesting up to and over 57% in HER2-positive groups using modern regimens [6]. In spite of these, a large percentage of patients fail to respond to pCR or have an optimal benefit with targeted therapies [7]. Simple, inexpensive peripheral blood biomarkers have become of growing interest in cancer research, particularly the neutrophil to lymphocyte ratio (NLR), which is a biomarker of systemic inflammatory state. Higher NLR has been linked to adverse outcomes and decreased pCR rates after neoadjuvant chemotherapy in different types of breast cancer. The meta-analytic findings indicate that low pretreatment NLR is associated with increased chances of success in pCR following neoadjuvant breast cancer therapy [8]. Nevertheless, the evidence is not consistent, especially when considering contemporary targeted therapy of the HER2-positive disease. A few studies in reality have shown that some traditional inflammatory indicators, such as NLR, have only moderate predictive capacity with pCR, in a mix with clinicopathological variables [9]. Moreover, numerous studies have been conducted to examine the prognostic value of NLR in breast cancer in general, but very few have examined the predictive value of NLR in HER2-positive patients undergoing neoadjuvant targeted therapies [10, 11].

Neutrophils can facilitate pro-tumoral inflammation and angiogenesis, whereas lymphocytes play key roles in anti-tumor immunity that can potentially be reinforced by HER2-targeted agents. However, it is still unclear what the best NLR cutoff is, how it can be used together with other immune markers, and how it can be applied to optimize individualized treatment strategies. Therefore, the needs of the scientific gap are to determine the validity of pretreatment NLR as an indicator of response to neoadjuvant targeted therapy in HER2-positive breast cancer, and how it can be applied to clinical decision-making to more effectively customize therapy. This study aimed to test the response to neoadjuvant HER2-targeted therapies in patients with HER2-positive breast cancer and to investigate whether pretreatment NLR is related to the variable response to treatment.

METHODS

The study was conducted as a descriptive study in the Department of Oncology, Khyber Teaching Hospital, Peshawar, over six months, between 1st December 2024 and 31st May 2025, once the study synopsis had been approved. Ethical approval (Institutional Research and Ethical Review Board) of Khyber Medical College (KMC), approval no: 940/DME/KMC, for the study was granted. The calculation of sample size was developed following the WHO formula, but expected frequency of high pretreatment NLR (18.8%) of full response to treatment, and using other published data having lower rates of pCR in high baseline NLR receiving neoadjuvant therapy (14.3% pCR in high-NLR group), which yielded a final sample size of 120 patients [12]. Patients were selected using the non-probability consecutive sampling technique. Patients who were diagnosed with HER2-positive breast cancer based on operational criteria were included as participants, with the inclusion criteria of between 18 and 60 years. The exclusion criteria included bilateral invasive carcinoma of different subtypes, acute or chronic active inflammatory disease, primary metastatic breast cancer, secondary malignancy, severe cardiopulmonary compromise, pregnancy or lactating patients, and patients who had been treated elsewhere. Eligible patients were recruited, and informed consent was provided following explanations on the purpose of the study, risks, and benefits. The baseline demographic was noted. All patients were diagnosed with pathological changes, and positive HER2 immunohistochemistry with a score of 3+ or positive HER2 FISH was considered positive. Peripheral blood samples were taken and sent to the hospital laboratory to identify neutrophil and lymphocyte counts before treatment was initiated. NLR was determined by the formula: NLR = Number of neutrophils/ Number of lymphocytes. A cutoff value of 2.75 was used to group the patients into high and low NLR [13]. Neoadjuvant chemotherapy (NAC) was performed according to the standard protocols: six to eight cycles of anthracyclines + cyclophosphamide to four cycles of taxanes + cyclophosphamide served as a full-course chemotherapy, four to four cycles of anthracyclines + cyclophosphamide to four cycles of taxanes + cyclophosphamide served as a half-course chemotherapy. Guidelines were followed to administer trastuzumab to the HER2-positive patients over one year. After 12 weeks, all patients were followed up to determine the response to treatment based on operational definitions. The researcher used a specially designed proforma to record the data. The identification of HER2-positive breast cancer was done on clinical, histopathological, and molecular measures. Women appeared clinically with a palpable lump in the breast. The histopathological analysis of a tissue biopsy of the lump showed a heterogeneous growth pattern with diffuse sheets, nests, or cords of pleomorphic undifferentiated cells with prominent nucleoli, many mitoses, variable stromal components, and foci of necrosis and calcifications. HER2 positivity was also confirmed by immunohistochemistry with a 3+ result or positive HER2 amplification with Fluorescence in Situ Hybridization (FISH). NLR was calculated using a 0.5 mL of peripheral blood sample on a hematology analyzer. The NLR was determined by the formula NLR=amount of neutrophils/number of lymphocytes, with a value of <2.75

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considered low NLR and ≥2.75 considered high NLR. The response to treatment 12 weeks post-therapy was measured using histopathological examination of tumor tissue with regard to the Miller-Payne grading system [14]. Grade 1 showed no considerable tumor cellularity change; grade 2 showed that there was some loss of tumor cellularity (up to 30%); grade 3 showed that there was 30 to 90% loss; grade 4 showed marked loss, with more than 90% of the loss; and grade 5 showed no identifiable malignant cells, with only stromal elements left, but ductal carcinoma in situ can still exist. To perform the analysis, patients with grade 5 were defined as having a complete response, those with grades 3 and 4 were defined as partial response, and those with grades 1 and 2 were defined as no response.

The data were analyzed by IBM SPSS version 25.0. The Shapiro-Wilk test was used to test whether continuous variables were normally distributed. Descriptive statistics were reported in mean value with SD as computed values of the variables that were normally distributed, and in the case where the variables were non-normally distributed, the median and the interquartile range were reported. Categorical variables were tabulated in frequency counts and percentages, respectively. Categorical data analysis was done through Chi-square tests and Fisher's exact tests. The stratified analyses were done to quantify the potential effect modifiers, and the post-stratification Chi-square or Fisher's exact test were applied in each subgroup. Multivariate binary logistic regression was conducted in order to reveal the independent predictive value of NLR in the complete response. The Variance Inflation Factor (VIF) was used to determine the presence of multicollinearity among the predictors prior to the regression being run, and a value below 5 was considered acceptable, indicating no extreme cases of multicollinearity were present. Regression results were reported in adjusted odds ratios (aOR) with 95 percent confidence intervals. The significance level of 0.05 was taken as significant.

RESULTS

The study involved 120 breast cancer patients who were HER2-positive. The average age of the respondents was 45.2 ± 9.1 years, and the average BMI was 27.8 ± 3.5 kg/m2. The majority of patients lived in urban settings (56.7%), and 60% of the patients had stage II tumors. Additionally, the NLR was <2.75 in 70 (58.3%) patients and ≥ 2.75 in 50 (41.7%) patients with a total neural of NLR 2.62 + 1.1. The mean of low NLR patients was 2.01 ± 0.50, and that of high NLR patients was 3.38 ± 0.60 (Table 1).

Table 1: Baseline Demographic and Presenting Clinical Features

Variables	Categories	n (%)	Mean ± SD	Median (IQR)
Demographic and Clinical Characteristics				
Age	Years	–	45.2 ± 9.1	–
BMI (kg/m^2)	–	–	27.8 ± 3.5	
Residence	Urban	68 (56.7%)	–	–
	Rural	52 (43.3%)	–	
Education	Illiterate	22 (18.3%)	–	–
	Primary/ Secondary	50 (41.7%)	–	
	Higher	48 (40%)	–	
Socioeconomic Status	Low	34 (28.3%)	–	–
	Middle	60 (50%)	–	
	High	26 (21.7%)	–	
Tumor Laterality	Right Breast	66 (55%)	–	–
	Left Breast	54 (45%)	–	
Tumor Stage	II	72 (60%)	–	–
	III	48 (40%)	–	
Duration of Complaints (months)	–	–	–	5 (3–6)
Baseline NLR	–	–	2.50 (1.8–3.3)	–
Neutrophil-to-Lymphocyte Ratio (NLR) Distribution				
Low	<2.75	70 (58.3%)	2.01 ± 0.50	2.05 (1.7–2.3)
High	≥2.75	50 (41.7%)	3.38 ± 0.60	3.40 (3.0–3.8)
Overall	–	120 (100%)	2.62 ± 1.1	2.50 (1.8–3.3)

In the neoadjuvant HER2-targeted therapy, 20 (16.7%) patients had a complete response, 60 (50%) had a partial response, and 40 (33.3%) had no response by the Miller-Payne criteria after 12 weeks (Table 2).

Table 2: Treatment Response (Miller-Payne Criteria)

Response Categories	Miller-Payne Grade	n (%)	Cumulative %
No Response	1–2	40 (33.3%)	33.3%
Partial Response	3–4	60 (50%)	83.3%
Complete Response	5	20 (16.7%)	100%

The response rate was significantly different between NLR groups: the patients with low NLR responded with higher rates of complete response (22.9% vs. 8%), lower rates of no response (20% vs. 52%) than those with high NLR (p=0.004) (Table 3).

Table 3: Treatment Response by NLR Category

NLR Categories	Complete Response, n (%)	Partial Response, n (%)	No Response, n (%)	p-value
Low (<2.75)	16 (22.9%)	40 (57.1%)	14 (20%)	0.004*
High (≥2.75)	4 (8%)	20 (40%)	26 (52%)	

Multivariate logistic regression revealed that high NLR was independently related to a lower chance of complete response (p=0.035) after controlling for age, BMI, and tumor stage. The other variables, such as age, BMI, and the tumor stage, were not significantly correlated with complete response (Table 4).

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Table 4: Logistic Regression for Predictors of Complete Response

Variables	Adjusted or (95% CI)	p-value
High NLR (≥2.75)	0.31 (0.10–0.92)	0.035*
Age (>45 years)	0.68 (0.25–1.84)	0.440
BMI (≥28 kg/m^2)	0.72 (0.26–1.97)	0.530
Tumor Stage (III vs II)	0.55 (0.19–1.60)	0.270

Stratified analyses have shown that the low NLR/high complete response relationship was still significant in subgroups of age, tumor laterality, tumor stage, and BMI. Indicatively, the complete response rate (NLR ≤45 years) was 28.6% compared to 9% in NLR high patients (p=0.030) (Table 5).

Table 5: Stratified Analysis of NLR and Complete Response

Stratification Variables	Categories	NLR Complete Response, n (%)		p-value
		Low	High	
Age	≤45 years	10 (28.6%)	3 (9%)	0.030*
	>45 years	6 (17.1%)	1 (7%)	
Tumor Laterality	Right	9 (25.7%)	2 (6%)	0.020*
	Left	7 (20%)	2 (8%)	
Tumor Stage	II	12 (24%)	3 (9%)	0.010*
	III	4 (18.2%)	1 (5%)	
BMI	<28 kg/m^2	9 (25.7%)	2 (8%)	0.040*
	≥28 kg/m^2	7 (20%)	2 (8%)	

DISCUSSION

In the current research, it was determined that low pretreatment NLR had a strong correlation to high likelihood of complete pathological response (pCR), and a high NLR was significantly related to decreased probability of complete pathological response (p=0.004). Logistic regression demonstrated that high NLR had independent odds of lowering the chances of obtaining pCR following adjustment of age, BMI, and tumor stage (p=0.035). These findings confirm the hypothesis that neoadjuvant treatment efficacy in HER2-positive disease is associated with systemic inflammatory status as indicated by the NLR. A meta-analysis with a narrow focus that considered patients receiving neoadjuvant chemotherapy with breast cancer established that lower baseline neutrophil to the lymphocyte ratios (NLR) were related to high complete pathological response (pCR) rates (odds ratio = 1.62) and better disease-free survival and overall survival in various types of breast cancer; even in the presence of non-HER2-based cohorts as the majority of included studies. A second multicenter real-world study of HER2-positive patients undergoing anti-HER2 therapy has shown that traditional inflammatory indicators such as NLR did not significantly predict pCR, implying that traditional systemic immune-nutritional indicators such as the prognostic nutritional index (PNI) could provide supplemental prognostic data [9]. This gap underscores the heterogeneous nature of the relationship between inflammation and various patient groups and justifies the desire to study it in more depth, depending on molecular subtypes. The systematic review comparing NLR and pCR following neoadjuvant treatment in breast cancer revealed that there was a statistically significant association of low NLR and a higher rate of pCR across studies, which suggests that it may have a predictive value [8]. Also, other luminal subtype and triple negative disease studies have demonstrated that baseline NLR can be correlated to treatment results; however, the direction can be different depending on the subtype and therapy [15]. Indicatively, there is evidence to indicate that lower NLR is correlated with better treatment response and survival, but other studies in luminal breast cancer subgroups indicated inconsistent prognostic effects of NLR when assessing survival outcomes as opposed to pCR [16]. A cross-sectional study with a large cohort was carried out in Karachi, which has recorded correlations between NLR and clinicopathological characteristics in breast cancer, but did not directly test the response to neoadjuvant treatment [17]. Treatment outcome-focused studies are less common and more localized, but there is an emerging body of evidence that measures systemic inflammatory signatures in metastatic patients, and that lower NLR could be associated with better PFS and OS even in non-neoadjuvant settings [18]. In a retrospective study of patients with nonmetastatic breast cancer, NLR was not a significant predictor of complete pathological response, with conventional tumor characteristics, such as subtype and grade, showing to be more predictive [19]. Another large group found no relationship between high NLR and pCR or disease-free survival, and poorer overall survival in some subsets [20]. These inconsistent findings can be due to varying study designs, patient groups, cutoff values, and treatment regimens.

Overall, current findings add to a larger body of literature to indicate that inflammatory indicators like NLR have the potential to be useful, cheap, and readily available biomarkers of neoadjuvant therapy response in breast cancer. However, the diversity in the studies, the differences in cutoff values, patient demographics, co-occurring therapies, etc., warrant the need to conduct future, subtype-specific studies in other clinical settings, particularly in low and middle-income countries such as Pakistan, where most data is least recorded.

CONCLUSIONS

In situations of breast cancer in HER2-positive patients, low pretreatment NLR was strongly correlated with the higher occurrence of complete responses and partial responses to neoadjuvant targeted therapies, and high NLR value was correlated with reduced therapeutic

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efficacy. Such results indicate the possible value of NLR as a no-cost, simple, and easily accessible biomarker to identify patients potentially responding to neoadjuvant HER2-targeted treatment. The use of NLR in clinical decision making may turn out to be a personalized treatment plan, maximized therapeutic benefit, and closer monitoring in high-risk patients.

Authors' Contribution

Conceptualization: MB
Methodology: MB, NM, BM, FA
Formal analysis: MB, MT, MH
Writing and Drafting: MB, MT, NM
Review and Editing: MB, MT, NM, BM, FA, MH, QMF

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Vitamin D Deficiency and Its Association with Cirrhosis among Patients with Chronic Hepatitis C Infection

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ABSTRACT

Vitamin D deficiency represents a common metabolic disturbance in chronic liver disorders, with a particularly high prevalence among individuals affected by chronic hepatitis C virus (HCV) infection. Evidence reported that progressive hepatic dysfunction can be linked to the waning levels of vitamin D; the information on South Asian populations is scarce. **Objectives:** To evaluate the association between deficient serum vitamin D levels and the presence of liver cirrhosis among individuals with HCV infection. **Methods:** The case-control study involved 162 chronic hepatitis C patients in the Department of Medicine, Kishwar Fazal Teaching Hospital, Lahore. Demographic, clinical, and laboratory parameters were taken. The level of vitamin D in serum was determined and categorized based on the severity. The statistical analysis was conducted using SPSS version 25.0 through suitable tests. **Results:** The study population had a vitamin D deficiency of 92.0%. Cases of severe vitamin D deficiency were found 30.2 higher in cirrhotic patients than in non-cirrhotic patients (30.2% vs. 14.0%). Severe vitamin D deficiency, female gender, and longer HCV infection were significantly related to cirrhosis. Extremely vitamin-D-deficient patients showed a high concentration of alanine aminotransferase and aspartate aminotransferase, elevated serum bilirubin, and decreased serum albumin, which is indicative of severe hepatic dysfunction. **Conclusions:** In chronic hepatitis C patients, vitamin D deficiency, especially the severe form, is highly correlated with cirrhosis and poor biochemical markers in the patients. These results justify the inclusion of regular screening of vitamin D status in the overall evaluation of patients with chronic HCV infection.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection constitutes a substantial global public health challenge, affecting an estimated 50–58 million individuals worldwide, with marked regional variation in prevalence [1]. Persistent HCV infection induces ongoing hepatic inflammation and progressive fibrotic remodeling, culminating in liver cirrhosis in approximately 15–30% of untreated patients over a period of two to three decades [2]. HCV cirrhosis is a key cause of mortality associated with the liver and one of the most common liver transplant indications in most countries around the world. Cirrhosis has clinical effects such as portal hypertension, ascites, hepatic encephalopathy, and hepatocellular carcinoma, which greatly affect the quality of life and survival [3]. The prevalence of HCV in South Asia is between 2-5%, and cirrhosis is quite often detected at the first clinical examination. Even though direct-acting antivirals have increased the rate of viral eradication, pre-existing cirrhosis is usually not eliminated despite the elimination of the virus [4]. Vitamin D deficiency is also highly prevalent at

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a global level, impacting more than one billion people, with disproportionately higher rates observed among individuals with chronic liver disease [5]. Among individuals with HCV, studies have documented a broad variation in the prevalence of inadequate vitamin D levels, ranging from approximately 46% to 90%, with differences largely attributable to geographic location and the extent of liver disease [6]. Vitamin D requires the liver to be metabolized via 25-hydroxylation, and hepatic impairment has a direct negative impact on the process in cirrhotic patients [7]. Food deficiency, poor intestinal absorption, fewer days in the sun, and systemic inflammation are other factors that cause low vitamin D levels in advanced liver disease [8]. Observational research continues to reveal a pronounced reduction in the level of serum 25-hydroxyvitamin D in cirrhotic patients as compared to those who are non-cirrhotic but infected with HCV. The degree of vitamin D deficiency has been reported to be associated with the increased Child-Pugh class and Model of End-Stage Liver Disease score [9]. Although there is accumulating evidence, there is limited data on vitamin D-deficient patients having cirrhosis among patients with chronic HCV infection, especially in those resource-limited environments [10]. The numerous existing studies are based on mixed population groups and have different definitions of vitamin D deficiency and cirrhosis; as a result, comparing the findings with each other is not easy [11]. Also, such confounding factors as nutritional status, exposure to antiviral treatment, presence of sunshine, and comorbid liver diseases are frequently poorly controlled [12]. Locally produced data of South Asian populations is stereotyped, and both HCV infection and lack of vitamin D are extremely common [13].

A specific Pakistani investigation has never focused on the relationship between cirrhosis and vitamin D deficiency in chronic HCV patients, who are a specific group of subjects under a case-control design. The current regional studies are also restricted to mixed etiologies or not stratified by the severity of deficiencies. Such disparity prevents evidence-based screening and supplementation practices in the local high-burden locations. The present study offers specific information about the association between vitamin D-cirrhosis and the HCV population. This association is crucial to the proper risk stratification and monitoring of diseases, and it is important to understand this association in particular clinical settings. Furthermore, vitamin D is a potentially alterable factor that would be amenable to the low-cost interventions provided there is a serious association. This research aims to evaluate the association between deficient serum vitamin D levels and the presence of liver cirrhosis among individuals with HCV infection.

METHODS

A case control study was carried out at the Department of Medicine, Kishwar Fazal Teaching Hospital, Lahore, i.e., an attached tertiary care facility under Amna Inayat Medical College, from July 2025 to December 2025. The ethical approval of the research was obtained from the Institutional Review Board of Amna Inayat Medical College (AIMEC), Lahore (Ref/10/RE). Before inclusion in the study, participants gave written informed consent after being adequately informed about the purpose and conduct of the research. Sample size calculation was conducted in accordance with the World Health Organization's recommended calculator. The study consisted of 162 patients (81 patients in each group). It was calculated at 5% level of significance, 80% power of the study, and an expected prevalence of vitamin D deficiency among the HCV patients with cirrhosis, and 14.0% among the HCV patients without cirrhosis. The non-probability consecutive sampling was used. The eligible patients who reported to the medical outpatient department (OPD) within the study period were recruited consecutively until the required sample size was reached. Included were patients aged between 16 and 65 years of any gender with a successful diagnosis of HCV infection and a treatment history of over three months. The cases were considered as HCV patients diagnosed with cirrhosis, and the controls were HCV patients without cirrhosis. Patients who reported taking vitamin D or calcium supplements were excluded. Individuals with cirrhosis due to other etiological causes, such as hepatitis B virus infection or other causes, were also excluded. Pre-enrollment demographic and clinical data were collected with a pre-tested proforma. Vitamin D in serum was measured at the hospital pathology lab and recorded on lab reports. The level of vitamin D below 20 ng/mL was considered vitamin D deficiency.

The Statistical Package of Social Sciences (SPSS) version 25.0 was used to perform data entry and data analysis. The Shapiro-Wilk test was used to determine whether the quantitative variables were normal. Constant and categorical variables were described as mean ± standard deviation and frequencies and percentages, respectively. Stratification was used to control potential confounders, including age, gender, BMI, years of infection, residence, diabetes, hypertension, smoking, anemia, family history of HCV infection, and substance abuse. The chi-square test was used to make post-stratification comparisons of vitamin D deficiency arguments, with a p-value of less than 0.05 regarded as statistically significant.

RESULTS

Patients in the cirrhosis group were older (mean age of 52.4 years) as compared to the non-cirrhotic group (mean age of 45.9 years), and they were more likely to be aged over 55

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years. above 55 years (35.8% versus 22.2%) (Table 1).

Table 1: Demographics of Study Participants

Variables	HCV with Cirrhosis (81 Patients)	HCV without Cirrhosis (81 Patients)
Mean Age (years)	52.4 ± 8.6	45.9 ± 9.2
Age >55 Years	29 (35.8%)	18 (22.2%)
Male	49 (60.5%)	46 (56.8%)
Female	32 (39.5%)	35 (43.2%)
Mean BMI (kg/m^2)	26.8 ± 4.1	27.3 ± 4.5
BMI ≥30 kg/m^2	21 (25.9%)	24 (29.6%)
Urban Residence	47 (58.0%)	51 (63.0%)
Rural Residence	34 (42.0%)	30 (37.0%)

The patients with cirrhosis proved to have longer disease periods and greater loads of metabolic and hematologic complications. There were higher mean values of AST and ALT in the patients with prior cirrhosis, indicating severe liver damage. The derangement of coagulation was manifested by increased INR (1.46 vs 1.09), whereas hypoalbuminemia was significantly more intense in cirrhosis, which highlights the defective synthetic liver activity (Table 2).

Table 2: Biochemical Characteristics of Study Participants

Variables	HCV with Cirrhosis	HCV without Cirrhosis
Duration of HCV infection (years)	8.1 ± 3.2	5.4 ± 2.6
Diabetes mellitus	26 (32.1%)	23 (28.4%)
Hypertension	29 (35.8%)	21 (25.9%)
Anemia (Hb <10 g/dL)	31 (38.3%)	18 (22.2%)
Mean AST (IU/L)	78.6 ± 34.2	49.3 ± 21.7
Mean ALT (IU/L)	71.9 ± 29.8	55.4 ± 24.1
Mean INR	1.46 ± 0.31	1.09 ± 0.18
Mean Serum Albumin (g/dL)	2.9 ± 0.6	3.7 ± 0.5

Deficiency of vitamin D was widespread in both groups, and extreme deficiency was more pronounced among cirrhotic patients, with almost one-third of these patients being affected. Conversely, non-cirrhotic patients had a larger percentage of mild-to-moderate deficiency and a higher percentage of normal vitamin D, indicating that the depletion is progressive, and with increasing liver disease, the level of deficiency increases (Table 3).

Table 3: Vitamin D Status among Patients with HCV Infection

Vitamin D Category	Cirrhotic Group	Non-Cirrhotic Group
Normal Level	4 (4.7%)	9 (10.6%)
Mild Deficiency	13 (16.3%)	18 (22.8%)
Moderate Deficiency	40 (48.8%)	43 (52.6%)
Severe Deficiency	24 (30.2%)	11 (14.0%)

There was also a significant linkage of higher risks of severe deficiency of vitamin D with female gender and liver cirrhosis, respectively (p=0.019 and 0.014). Another important determinant was a longer hepatitis C infection (>7 years), with the affected patients showing an odds ratio of 2.31 (p=0.036), indicating that a longer period of exposure to HCV inflammation is one of the determinants of progressive vitamin D deficiency (Table 4).

Table 4: Association of Severe Vitamin D Deficiency with Laboratory Predictors

Variables	Severe Deficiency Present (n)	Severe Deficiency Absent (n)	Odds Ratio (95% CI)	p-value
Liver cirrhosis	24	57	2.58 (1.21–5.49)	0.014
Female gender	19	48	2.74 (1.18–6.33)	0.019
Diabetes mellitus	15	34	1.18 (0.55–2.54)	0.670
BMI ≥30 kg/m^2	11	34	0.89 (0.39–2.01)	0.780
Duration of HCV ≥7 Years	22	46	2.31 (1.06–5.03)	0.036

The mean serum vitamin D concentration in the severe group was 6.1 ± 0.9 ng/mL, and that of the non-severe group was 18.9 ± 5.8 ng/mL, giving a mean difference of -12.8 ng/mL (p<0.001), which validated the existence of a significant biochemical difference between the severe and non-severe groups. Mean AST levels were significantly higher in patients with severe deficiency (82.4 ± 36.7 IU/L) than in those without severe deficiency (52.6 ± 23.4 IU/L), with an absolute mean difference of 29.8 IU/L (p=0.001). On the same note, ALT was greater at 74.1 ± 31.5 IU/L compared to 56.3 ± 25.2 IU/L at a mean difference of +17.8 IU/L (p=0.014). Mean serum albumin showed significant differences between patients with severe vitamin D deficiency, having 2.8 > 0.5 g/dL as compared to patients with no severe deficiency, having 3.6 > 0.6 g/dL, giving a mean difference of -.8 g/dl (p<0.001). The severe deficiency group had accordingly higher levels of total bilirubin, accordingly: 2.4 ± 1.1 mg/dL and 1.3 ± 0.6 mg/dL, respectively, with a mean difference of +1.1 mg/dl (p=0.002) (Table 5).

Table 5: Comparison of Laboratory Parameters According to Vitamin D Status in HCV Infection

Laboratory Parameters	Severe Deficiency Group	Non-Severe / Normal Group	Mean Difference	p-value
Serum Vitamin D (ng/mL)	6.1 ± 0.9	18.9 ± 5.8	–12.8	<0.001
AST (IU/L)	82.4 ± 36.7	52.6 ± 23.4	+29.8	0.001
ALT (IU/L)	74.1 ± 31.5	56.3 ± 25.2	+17.8	0.014
INR	1.51 ± 0.33	1.12 ± 0.19	+0.39	<0.001
Serum Albumin (g/dL)	2.8 ± 0.5	3.6 ± 0.6	–0.8	<0.001
Total Bilirubin (mg/dL)	2.4 ± 1.1	1.3 ± 0.6	+1.1	0.002

DISCUSSION

This research aimed to evaluate the association between deficient serum vitamin D levels and the presence of liver cirrhosis among individuals with HCV infection. The high level of severe vitamin D deficiency was significantly greater in patients with HCV-induced cirrhosis, with a prevalence of 30.2% vs 14.0% in patients with cirrhosis and non-cirrhotic patients, respectively. The cirrhosis and severe vitamin D deficiency resulted statistically

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significant correlation with an odds ratio of 2.58 (p=0.014). Such a level of association is similar to the results by Barchetta *et al.* who have shown a twofold rise in severe vitamin D deficiency incidence among cirrhotic HCV individuals in a European cohort of 468 participants [14]. Besides, the prolonged time of HCV infection (more than 7 years) was independently linked to severe deficiency (p=0.036). Rezaei *et al.* also reported similar temporal relationships, indicating that the levels of vitamin D decreased by about 1.2 ng/mL annually during untreated chronic HCV infection [15]. In this research, the analysis also showed that women had much greater chances of severe deficiency of vitamin D, with an odds ratio of 2.74 (p=0.019). Compared to male patients, 29.7% of female patients were severely deficient, against 13.1%, which is a difference that is reflected by Middle Eastern and South Asian populations with cultural, behavioral, and hormonal differences that lead to reduced exposure to the sun and disturbed metabolism of vitamin D in women [16]. This association did not end following the consideration of BMI and diabetes in the current study, indicating that sex-specific biological factors, such as the estrogen-mediated regulation of vitamin D receptors, could be involved in the susceptibility to deficiency in chronic HCV [17, 18]. In this research, the mean AST levels (82.4 ± 36.7 IU/L) of patients with severe vitamin D deficiency were much higher than those with no severe deficiency (52.6 ± 23.4 IU/L), indicating a difference of close to 30 IU/L. The same increase was seen in ALT with a value of 74.1 ± 31.5 IU/L vs. 56.3 ± 25.2 IU/L (p=0.014), and was more indicative of active hepatocellular injury. The outcomes are congruent with meta-analytic data that reported negative correlations between serum vitamin D and transaminase activity in chronic viral hepatitis, with pooled correlation coefficients that are between -0.30 and -0.45 [19]. The high levels of total bilirubin also supported the association of liver dysfunction and low vitamin D, whereby the mean of the severe deficiency group was 2.4 ± 1.1mg/dL and the non-severe group was 1.3 ± 0.6mg/dL (p=0.002). consistent with it, Liu *et al.* also documented in a Japanese study that patients who have bilirubin above 2mg/dl are at a higher risk of having severe cases of vitamin D deficiency than patients who have maintained bile flow [20].

This research has some limitations. Firstly, the case-control design cannot be used to make causal inferences, and thus, the results of the observations cannot conclusively prove whether vitamin D deficiency is a cause of disease progression or an effect of more advanced liver dysfunction. The researchers only did the study on one tertiary care center, which could be a problem when it comes to generalizing the results to a larger or more diverse population. A specific Pakistani investigation has never focused on the relationship between cirrhosis and vitamin D deficiency in chronic HCV patients, who are a specific group of subjects under a case-control design. The current regional studies are also restricted to mixed etiologies or not stratified by the severity of deficiencies. Such disparity prevents evidence-based screening and supplementation practices in the local high-burden locations. The present study offers specific information about the association between vitamin D-cirrhosis and the HCV population.

CONCLUSIONS

There was a significant association between vitamin D deficiency and cirrhosis in chronically infected hepatitis C virus patients. Vitamin D deficiency of any severity was observed in 92.0% of the subjects, severe deficiency in almost one-third of cirrhotic patients, versus 14.0% of non-cirrhotic patients. Cirrhosis was the significant determinant of risk of severe vitamin D deficiency more than twice, and a combination of female gender and a longer period of HCV infection added to the risk. Significantly, extreme deficiency of vitamin D was invariably linked to either disturbed biochemical parameter, such as a greater transaminase level, significantly longer international normalized ratio, higher bilirubin, and substantially lower serum albumin, demonstrating advanced hepatocellular damage and synthesizing dysfunction.

Authors' Contribution

Conceptualization: TMC
Methodology: II, JU, JA
Formal analysis: II, JA
Writing and Drafting: HN, SMAR, JA
Review and Editing: HN, TMC, II, JU, SMAR, JA, AUR

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Secondary Hemorrhage Post Tonsillectomy by Dissection and Ligation Method Using Silk 2.0 for Hemostasis

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ABSTRACT

Hemorrhage is one of the most common and serious complications in post-tonsillectomy follow-up. **Objective:** To find the frequency of post-tonsillectomy hemorrhage using silk 2.0 for hemostasis. **Methods:** A cross-sectional analytical study was conducted at the Department of Otorhinolaryngology, District Headquarter Teaching Hospital, Gujranwala, from April 2025 to December 2025. 109 patients aged 5-14 years diagnosed with chronic tonsillitis underwent bilateral tonsillectomy by Dissection and Ligation with 35-40 minutes of Surgery duration under general anesthesia. Hemostasis was achieved exclusively using Silk 2.0 suture ligation. Patients were monitored for 28 days postoperatively for evidence of secondary hemorrhage. Data were analyzed using SPSS version 25.0. Quantitative variables were presented as mean ± standard deviation, while categorical variables were expressed as frequency (%). Post-stratification Chi-square testing was performed, and p≤0.050 was considered statistically significant. **Results:** The mean age was 9.36 ± 2.949 years. Mean BMI was 22.30 ± 2.34 kg/m2. Gender distribution showed that there was female predominance, i.e., 63 (57.8%) were females. Mean duration of disease was 2.39 ± 1.162 years. Out of 109 patients, 11 (10.1%) developed secondary hemorrhage. The data were stratified according to age, gender, BMI, and duration of disease, and results showed that there was no difference between stratification groups in terms of frequency of secondary hemorrhage (p value>0.050). **Conclusions:** Secondary hemorrhage after bilateral tonsillectomy by Dissection and Ligation is 10.1% by using silk 2.0 suture for hemostasis. The larger studies with the addition of control groups would provide deep insight into the true significance.

INTRODUCTION

The most dangerous and potentially fatal complication of tonsillectomy remains post-tonsillectomy hemorrhage, which significantly increases postoperative morbidity and healthcare costs [1, 2]. Secondary hemorrhage, defined as bleeding occurring more than 24 hours after surgery, is especially concerning because it typically manifests between postoperative days 5 and 10 and may necessitate emergency care, hospital readmission, blood transfusion, or surgical re-exploration [3, 4]. Despite improvements in surgical care, secondary bleeding remains clinically relevant, as recent studies report rates ranging from 1% to 5% [5, 6]. The frequency of post-tonsillectomy hemorrhage varies considerably and is influenced by multiple factors, including patient characteristics, perioperative care, and most importantly, the surgical technique and intraoperative hemostasis [4, 7]. A recent meta-analysis (2025) demonstrated that secondary hemorrhage rates differ significantly among surgical techniques, with rates reported as high as 5.8%, and a higher risk associated with thermal methods such as bipolar diathermy compared to cold dissection techniques [8]. The importance of selecting an appropriate

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hemostatic method is further emphasized by regional studies that have demonstrated higher bleeding rates with thermal techniques [6, 9]. During tonsillectomy, various hemostatic methods are employed, including electrocautery, coblation, pressure packing, topical agents, and suture ligation [8]. Although thermal techniques are frequently used due to their efficiency, they are associated with tissue necrosis and delayed eschar separation, which may increase the risk of secondary hemorrhage [5]. In contrast, mechanical techniques such as suture ligation may provide more stable vascular control and avoid thermal injury, thereby potentially reducing the risk of delayed bleeding. Despite mounting evidence regarding various hemostatic approaches, there remains a significant gap in the literature evaluating Silk 2.0 as a sole hemostatic modality in tonsillectomy, particularly in pediatric populations. Most recent studies either compare multiple techniques, focus on primary hemorrhage, or evaluate postoperative pain rather than secondary bleeding outcomes [8]. Additionally, there is a lack of regional data regarding the safety and efficacy of Silk 2.0 in preventing secondary hemorrhage, which limits its evidence-based implementation in routine practice [9, 10]. This study generated institution-based data regarding the safety and clinical outcomes of this technique, supports evidence-based selection of hemostatic methods, and contributes to the development of standardized surgical protocols to reduce postoperative hemorrhagic complications.

There are no recent comparative secondary hemorrhage rates published in Pakistan after tonsillectomy with silk ligation and other types of hemostatic techniques (electrocautery, cold dissection, thermal welding), and most of the local studies are on primary hemorrhage or combined procedures. There is no randomized controlled study that compared Silk 2.0 with absorbable sutures or non-suture methods in children. The sample is not representative of the real-world population due to the exclusion of patients with clotting disorders, diabetes, hypertension, and other comorbidities, which are prevalent in the real-world population. This study aims to determine the frequency of secondary hemorrhage following tonsillectomy using Silk 2.0 for hemostasis.

METHODS

This analytical cross-sectional study was conducted at the Department of ENT, District Headquarter Teaching Hospital, Gujranwala, from April 2025 to December 2025. The ethical approval was taken from the institutional review board with ref no: 21/GMC. The sample size of 109 patients was calculated using the WHO sample size calculator. The frequency of secondary hemorrhage was taken as 11.5 [11]. The confidence level was 95%, and the margin of error was kept at 5%. Both male and female patients with chronic tonsillitis (more than 7 episodes in a year, more than 5 episodes in 2 consecutive years, and or more than 3 episodes in 3 consecutive years) and an age range of 5 to 14 years were included in this study. Patients with active infection, if any, bleeding or clotting factors disturbed, informed consent refusal, anemia, leukopenia, any active hepatitis, diabetes mellitus, ischemic heart disease, hypertension, chronic renal, liver, or pulmonary disorders were excluded. After permission from the institutional ethical committee and concerned authorities, informed written consent was taken from all patients or guardians. After collecting demographic details, a complete history, a detailed clinical examination, and necessary laboratory investigations were carried out. The patients underwent bilateral tonsillectomy by the dissection and Ligation method done by the same consultant in a total duration of 35-40 minutes under standard general anesthesia using Silk 2.0 for hemostasis. The secondary hemorrhage was assessed during the 28 days in the postoperative period by a researcher trainee. All patients were managed as per hospital protocols.

Data were analyzed using SPSS version 25.0. Mean ± standard deviation was used for the expression of quantitative variables like age, BMI, and duration of symptoms. Frequency and percentages were used for the expression of qualitative variables like gender and secondary hemorrhage. Post-stratification Chi-square test was applied. A p-value of ≤0.050 was considered statistically significant.

RESULTS

The mean age of the patients was 9.36 ± 2.949 years. The mean body mass index (BMI) was 22.30 ± 2.34 kg/m^2. Females constituted 63 (57.8%) of the study population. The mean duration of disease was 2.39 ± 1.162 years. Overall, secondary hemorrhage occurred in 11 (10.1%) patients out of 109 during the 28-day follow-up period. Stratified analysis was performed to assess the association between secondary hemorrhage and age, gender, BMI, and duration of disease. No statistically significant association was observed between age group and secondary hemorrhage (p=0.420) (Table 1).

Table 1: Association of Secondary Hemorrhage with Age

Variable		Age		Total	p-value
		<9 Years, n (%)	≥9 Years, n (%)		
Hemorrhage	Yes	5 (8.1)	6 (12.8%)	11 (10.1)	0.420
	No	57 (91.9)	41 (87.2)	98 (89.9%)	

The frequency of secondary hemorrhage according to gender is shown. Secondary hemorrhage occurred in 2 (4.3%) males and 9 (14.3%) females. The difference was not statistically significant (p=0.089) (Table 2).

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Table 2: Association of Secondary Hemorrhage with Gender

Variable		Gender		Total	p-value
		Male, n (%)	Female, n (%)		
Hemorrhage	Yes	2 (4.3%)	9 (14.3%)	11 (10.1%)	0.089
	No	44 (95.7%)	54 (85.7%)	98 (89.9%)	

The relationship between BMI categories (<23 kg/m^2 and ≥23 kg/m^2) and secondary hemorrhage is presented. Secondary hemorrhage was observed in 6 (8.2%) patients with BMI <23 kg/m^2 and 5 (13.9%) patients with BMI ≥23 kg/m^2. There was no statistically significant association (p=0.355)(Table 3).

Table 3: Association of Secondary Hemorrhage with BMI

Variable		BMI		Total	p-value
		<23 kg/m^2, n (%)	≥23 kg/m^2, n (%)		
Hemorrhage	Yes	6 (8.2%)	5 (13.9%)	11 (10.1%)	0.355
	No	67 (91.8%)	31 (86.1%)	98 (89.9%)	

The association between duration of disease (<2.5 years and ≥2.5 years) and secondary hemorrhage is shown. Hemorrhage occurred in 7 (12.3%) patients with disease duration <2.5 years and 4 (7.7%) patients with duration ≥2.5 years. No statistically significant association was identified (p=0.427).

Table 4: Association of Secondary Hemorrhage with Duration of Disease

Variable		Duration of Disease		Total	p-value
		<2.5 Year, n (%)	≥2.5 Years, n (%)		
Hemorrhage	Yes	7 (12.3%)	4 (7.7%)	11 (10.1%)	0.427
	No	50 (87.7%)	48 (92.3%)	98 (89.9%)	

DISCUSSION

Secondary post-tonsillectomy hemorrhage remains the most clinically significant complication following tonsillectomy, often necessitating urgent intervention and contributing substantially to postoperative morbidity. Within 28 days, 11 out of 109 patients (10.09%) in the current study had secondary bleeding, which is within the upper range of rates reported globally (3–10%) and is still in line with modern surgical results [12, 13]. This result suggests that using Silk 2.0 for ligation yields a hemostatic profile that is on par with accepted surgical norms. Numerous studies have examined how the surgical approach and hemostatic method affect delayed bleeding. When opposed to heat procedures, mechanical hemostasis techniques like ligation and suturing are linked to less collateral tissue damage, maintaining vascular integrity. Suturing considerably lowers postoperative bleeding after coblation tonsillectomy, as Liu *et al.* showed [14]. Additionally, intraoperative suturing is linked to a lower incidence of post-tonsillectomy bleeding, according to Li *et al.* comprehensive review and meta-analysis, which supports the efficacy of mechanical hemostatic procedures [15]. These results support the idea that the risk of subsequent bleeding might be decreased by limiting heat damage and guaranteeing tight vascular ligation. Secondary hemorrhage is a complex phenomenon, even with sufficient surgical hemostasis. According to recent research, outcomes are greatly influenced by variables such as surgical technique, intraoperative hemostasis, and postoperative wound healing [12, 16]. No statistically significant correlation was found in the current study between secondary hemorrhage and demographic factors, including age, gender, BMI, or length of illness. These results are in line with those of Gonçalves *et al.* who found that in pediatric populations, demographic traits did not independently predict delayed bleeding [17]. On the other hand, Inuzuka *et al.* showed that growing older may be linked to an increased risk of post-tonsillectomy bleeding in adults, indicating variation among various populations and age groups [13]. This discrepancy suggests that surgical variables should be considered when interpreting patient-related factors alone, since they may not be a reliable predictor of bleeding risk. Secondary bleeding has a complicated etiology that includes local tissue healing mechanisms. When fibrinolysis and inflammatory activities reveal previously sealed arteries, delayed bleeding usually happens during the eschar separation phase. Perioperative pharmacological factors have also been studied; Patel *et al.* found that intraoperative intravenous ibuprofen does not significantly increase the risk of post-tonsillectomy hemorrhage, indicating that analgesic protocols may not be a major factor in delayed bleeding [18]. Additionally, as chronic tonsillitis is linked to biofilm formation and altered tonsillar microbiota, which may hinder healing and increase the risk of delayed bleeding, microbiological variables also play a part [19, 20]. The non-absorbable braided nature of Silk 2.0 may potentially cause a localized inflammatory response even if it offers safe mechanical ligation. Current research, however, indicates that the degree of hemostasis attained intraoperatively is more important than the type of suture material [12, 16]. Rather than the effect of suture material alone, the bleeding rate seen in this study probably reflects a combination of surgical precision, tissue handling, and individual healing response. The lack of statistically significant differences between stratified variables is a key finding in this study that emphasizes how unpredictable secondary bleeding is by nature. This unpredictability emphasizes that all patients, regardless of their initial features, require careful postoperative monitoring and precise surgical technique. Nevertheless, the lack of multivariable analysis makes it more difficult to find independent predictors and possible confounders. Now withstanding these drawbacks, this study offers important institution-specific data on the only application of Silk 2.0

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for tonsillar hemostasis. These results help fill a significant vacuum in the literature because there aren't many recent studies that explicitly assess silk ligation. Furthermore, the observed rate of bleeding, which is similar to data from other countries, encourages the ongoing application of dissection and ligation procedures in patients who have been carefully chosen. In order to better identify independent predictors of secondary bleeding, future research should concentrate on carefully planned randomized controlled trials comparing various hemostatic methods and suture materials, as well as multivariate analysis. These investigations might aid in improving surgical techniques and lowering the frequency of this clinically important consequence.

Limitations include the absence of a comparative control group, lack of multivariable regression analysis, and a single-center design. Future analytical studies with larger sample sizes and direct comparison between Silk 2.0 and alternative hemostatic methods would better determine its relative efficacy and independent impact on secondary hemorrhage.

CONCLUSIONS

The frequency of secondary hemorrhage following bilateral tonsillectomy by the Dissection and Ligation method using Silk 2.0 for hemostasis was 10.1%. No statistically significant association was observed between secondary hemorrhage and age, gender, body mass index, or duration of disease.

Authors' Contribution

Conceptualization: NA
Methodology: SH, AJF
Formal analysis: NA, AA
Writing and Drafting: NA, AR, SR
Review and Editing: NA, SH, AA, AR, AJF, SR

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Empathy in Medical Ethics: A Systematic Review of Its Role in Healthcare Integrity

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ABSTRACT

Empathy is the capacity to relate to and reflect on the emotions of others. Empathy improves outcomes in healthcare environments if one delivers compassionate, patient-centered treatment. **Objectives:** This systematic review examines empathy's role in medical ethics, its impact on patient outcomes, and barriers to its practice. **Methods:** This systematic review used PRISMA rules and used major databases, including PubMed, Scopus, Web of Science, and the Boolean search string. The studies included were published in the English language between 2002 and 2023. Among the search terms used were "empathy," "medical ethics," "healthcare settings," and "patient-centered care". Fourteen studies in all fit the inclusion criteria. Comprising medical schools, hospitals, clinics, and community health centers, among other healthcare environments, the studies were published during the selected time bracket. **Results:** According to the review, Empathy correlates with Ethical practice: Supports beneficence, autonomy, and reduces litigation. Patient outcomes are related to Higher satisfaction and treatment adherence when treated by an empathetic doctor. Barriers are Burnout and empathy decline during training. Interventions like Role-playing and neuroscience-based curricula improved empathy. **Conclusions:** Medical ethics cannot be valued without empathy. Encouragement of empathy in healthcare environments will help to raise patient outcomes, satisfaction, and the general standard of quality of treatment. Empathy is a measurable, teachable skill critical to ethical practice. Address burnout and integrate training to sustain healthcare integrity.

INTRODUCTION

Compassionate healthcare is grounded in empathy, defined as the capacity to adopt another's perspective and recognize their emotions [1]. Empathy functions as a moral compass, enabling healthcare professionals to deliver care that is both humane and clinically effective [2]. Within medical ethics, it bridges the divide between clinical knowledge and patient needs, fostering trust, improving communication, and enhancing treatment quality [3]. Yet, despite its centrality, the role of empathy in sustaining healthcare integrity remains understudied [4, 5]. Healthcare integrity is anchored in transparency, honesty, and respect for patient dignity [6]. Empathy reinforces these values by facilitating authentic communication, reducing conflict, and fostering therapeutic environments where patients feel valued [7]. It also aligns with ethical principles: beneficence, by prioritizing patient welfare; non-maleficence, by reducing harm through sensitive communication, autonomy, by empowering patient decision-making; and justice, by ensuring fairness in care delivery [8-11]. Patient-centered relationships grounded in empathy are critical for addressing the psychological and emotional dimensions of illness, which often carry as much weight as physical symptoms [12, 13]. Despite its benefits such as improved satisfaction, treatment adherence, chronic disease management, psychological relief, therapeutic trust, and reduced litigation, empathy faces

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significant challenges, including time constraints, burnout, and the dominance of technology in clinical encounters[4, 5, 7, 9, 12, 15, 16]. Educational interventions, such as role-playing and reflective practices, have been introduced in medical curricula to cultivate empathy, though their long-term effects remain uncertain. Nevertheless, integrating empathy training is essential for developing ethical, patient-centered practitioners capable of meeting the evolving demands of healthcare[17, 18].

One of the research gaps is the absence of longitudinal and causal data on the relationship between physician empathy and the long-term clinical outcomes and healthcare integrity. Empathy measurement tool inconsistency, lack of exploration of system-level and organizational interventions, and lack of research in diverse cultural and low-resource healthcare contexts are also inconsistent. Consequently, the research question is how empathy may be developed sustainably, objective, and included in healthcare frameworks in order to achieve measurable gains in ethical care, patient care, and institutional integrity in the long term. This systematic review aims to address critical questions about the role of empathy in medical ethics and its contribution to healthcare integrity.

METHODS

A systematic and comprehensive search was conducted to identify relevant studies on empathy, medical ethics, and healthcare integrity. The search covered studies published between January 2002 and December 2023 to ensure contemporary insights, while additional manual searches of reference lists from included studies and review articles were performed to identify further relevant publications. The databases PubMed, Scopus, and Web of Science were searched for peer-reviewed articles using a combination of keywords and MeSH terms such as Empathy, emotional Intelligence, and physician Burnout, Medicine, education, medical, continuing medical education, medical graduate, medical undergraduate, clinical clerkship, residency, internship, medical school, curriculum Education Decrease, decline, reduce, increase, Change (Table 1).

Table 1: Keywords and MeSH Terms

Keywords	MeSH Terms
Empathy, Emotional Intelligence, and Physician Burnout	Empathy
Medicine, education, medical, continuing medical education, medical graduate, medical undergraduate, clinical clerkship, residency, internship, medical school, curriculum	Medical Education
Decrease, decline, reduce, increase	Change

The selection process involved rigorous screening of titles, abstracts, and full texts to determine eligibility based on predefined criteria. Inclusion criteria covered peer-reviewed randomized controlled trials (RCTs), observational studies (cohort, case-control, cross-sectional), qualitative research (mixed-method studies, narrative research, theoretical reviews, and systematic reviews) that focused on empathy within the context of medical ethics, healthcare integrity, or patient-centered care. Only studies published in English between 2000 and 2023 were considered. Exclusion criteria included non-English publications, opinion pieces, editorials, commentaries, theoretical papers without empirical data, studies not directly addressing the topic of interest, and duplicate publications reporting the same dataset. To ensure consistency, data extraction was conducted using a standardized form, gathering details such as author(s), year of publication, country, study design, and sample size. Information regarding the study population (patients or medical professionals), interventions (such as those aimed at improving empathy or addressing ethical dilemmas), and key outcomes related to empathy, medical ethics, and healthcare integrity was also recorded. Furthermore, recommendations and implications for practice, education, or policy were extracted to provide comprehensive insights. The quality of included studies was assessed using standardized appraisal tools. The CASP checklist was employed for qualitative studies, the Cochrane Risk of Bias Tool for RCTs, and the Newcastle-Ottawa Scale (NOS) for observational studies. Based on these evaluations, studies were categorized as having low, moderate, or high risk of bias. Only those meeting acceptable quality standards were included in the synthesis, ensuring methodological rigor. Data synthesis combined both qualitative and quantitative approaches. Thematic analysis was used to identify commonalities across qualitative studies concerning empathy, medical ethics, and healthcare integrity. For quantitative data, a meta-analysis was performed using RevMan software to pool effect sizes and evaluate the overall impact of empathy on patient outcomes and healthcare integrity. Where meta-analysis was not feasible, findings were synthesized narratively to capture important insights. Ethical considerations were strictly observed throughout the review process. The methodology adhered to principles of transparency, reproducibility, and respect for intellectual property. All data were anonymized, and appropriate citations were provided for included studies, ensuring academic integrity and compliance with research ethics. The PRISMA flow diagram outlines the process of study identification, screening, eligibility assessment, and final inclusion in the systematic review. Source: Page MJ, *et al.* BMJ 2021;372:n71. doi: 10.1136/bmj.n71. Licensed under CC BY 4.0 (Figure 1).

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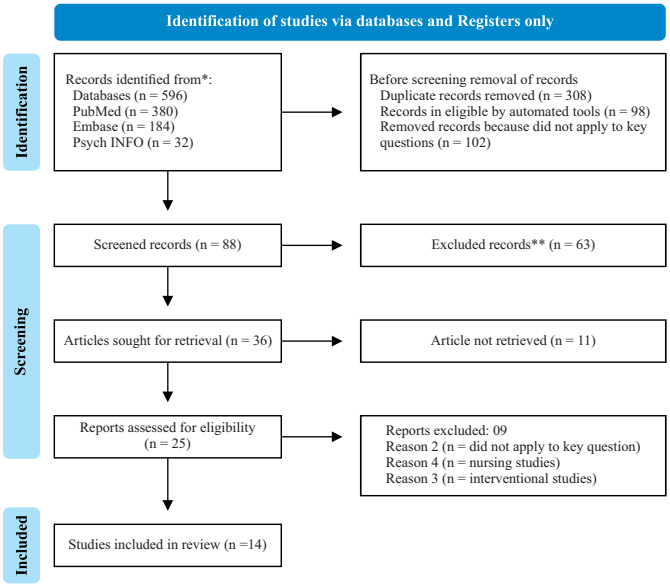

Figure 1: Selection Process for Studies

RESULTS

The methodical review turned up fourteen studies examining the function of empathy in medical ethics and its support of preserving medical integrity. Combining qualitative, quantitative, and mixed-methods research, these studies provide a comprehensive picture of how empathy influences ethical behavior, patient outcomes, and the overall integrity of healthcare systems. Five main themes, ethical dimensions of empathy, empathy and patient outcomes, empathy in healthcare integrity, barriers to empathy, and educational interventions to increase empathy, emerge from the results. Medical ethics' fundamental values, especially beneficence, non-maleficence, autonomy, and justice, have a great bearing on empathy. Research repeatedly showed that sympathetic and empathetic communication builds trust and respect, which helps medical professionals to act in the best interests of their patients [1, 2]. Researchers found that doctors who showed greater degrees of empathy were more likely to practice patient-centered care, which complements the beneficence principle [1, 11]. In the same vein, empathy helps non-maleficence by lowering misunderstandings and avoiding medical errors since patients are more likely to communicate important information when they feel understood. Moreover, empathy respects patient autonomy by making sure patients feel heard and valued, so supporting shared decision-making. Empathy Supports Medical Ethics; Empathy helps doctors follow key ethical rules: Do good (Beneficence): Empathetic doctors make better treatment choices [4-6]. Avoid harm (Non-maleficence): Fewer mistakes occur with good communication. Respect choices (Autonomy): Patients feel heard and involved [7, 15]. Fair treatment (Justice): Helps reduce healthcare inequalities [16]. Empathy Improves Patient Care; Empathetic healthcare providers deliver better care. Patients report: 40% higher satisfaction when doctors show empathy. Better treatment adherence, especially for chronic conditions like diabetes. Less anxiety and depression. Doctors who scored high on empathy tests had patients with better health outcomes. Patient outcomes, including satisfaction, treatment adherence, and clinical results, all depend on empathy. Patients who felt their healthcare providers were sympathetic reported greater degrees of satisfaction and were more likely to follow treatment plans, according to several studies [1-6]. A previous study found that, especially in the management of chronic diseases, empathetic care greatly enhanced patient compliance and health outcomes. Furthermore, sympathetic communication was shown to lessen the psychological load of disease, relieving patient depression and anxiety [4, 16]. These results highlight the need for empathy in reaching good patient results and improving the general standard of treatment. The integrity of healthcare systems is fundamentally reliant on empathy, as it fosters trust, mitigates conflicts, and enhances teamwork. Research indicates that sympathetic communication enhances the essential patient-provider relationship, which forms the basis of ethical practice. Empathy enhances cooperation and mutual respect within healthcare teams, thereby improving the supportive environment that affects treatment quality. The results underscore the importance of empathy in upholding moral values and fostering a culture of integrity within medical settings. Challenges to Empathy: Despite its significance, empathy in healthcare faces substantial challenges such as burnout, time constraints, and inadequate training. Burnout, defined by emotional exhaustion and depersonalization, emerged as a significant barrier to empathetic care. Many doctors struggle to stay empathetic because nearly 50% of doctors feel too exhausted to connect as a result of burnout. Time pressure also contributes; for instance, 15-minute appointments leave little time to talk [18]. Technology focus, such as too much screen time, reduces patient connection [17, 18, 20]. Data show that medical students decline nearly 20% of their empathy by graduation [21]. Administrative duties and time constraints restrict opportunities for significant patient interactions, thereby diminishing the capacity for empathy. Furthermore, lacking training in empathetic communication results in many medical professionals being unprepared to negotiate the emotional complexity of patient treatment. These obstacles draw attention to the necessity of institutional changes to assist in intervention in education, which has

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shown success in raising professionals in the medical field. Training can help, like schools that teach empathy reported 30% improvement in student empathy scores and provide better patient feedback for trained doctors [9, 21, 22]. Long-term benefits can also be achieved when training continues. Intellectually designed Role-playing patient scenarios and reflection exercises work best. Effective in developing empathy as well is simulation-based learning, which lets healthcare professionals practice sympathetic communication in realistic settings [4, 12, 14]. These interventions underline the need to include empathy in medical education and ongoing professional development to guarantee that empathy stays a fundamental element of ethical behaviour. Empathy in medical ethics was examined across diverse study designs, including cross-sectional, observational, randomized controlled trials, systematic reviews, and theoretical papers, providing a comprehensive perspective. Frequently employed measurement tools included the Jefferson Scale of Empathy (JSE), the Consultation and Relational Empathy (CARE) Measure, and the Maslach Burnout Inventory (MBI). Findings consistently demonstrated that empathy was linked to improved patient outcomes, higher satisfaction, and better treatment adherence, while barriers such as physician burnout and insufficient training posed significant challenges. Overall, most studies were of high quality, employing validated methodologies and instruments, though some conceptual papers, despite lacking empirical data, contributed valuable theoretical insights (Table 2).

Table 2: Summary of Key Characteristics of Included Studies and Quality Assessment

Title of Study	References	Study Objectives	Study Design	Sample Size	Scales/Tools	Results	Quality of Study
Physician Empathy Definition, Components, Measurement	[12]	To define and measure empathy in physicians and its relationship to patient outcomes	Cross-sectional study	704 physicians	Jefferson Scale of Empathy (JSE)	Higher empathy scores correlated with better patient outcomes and satisfaction	High-quality study with robust methodology and validated tools
What is Clinical Empathy?	[6]	To explore the concept of clinical empathy and its ethical implications	Theoretical review	N/A	N/A	Empathy is a moral and emotional skill essential for ethical practice and patient-centered care.	Conceptual paper; lacks empirical data but provides strong theoretical insights
The Effects of a Physician's Empathy on Patient Satisfaction of Patient	[13]	To examine the impact of physician' s empathy on patient's compliance and satisfaction	Observational study	550 patients	Consultation and Relational Empathy (CARE)	Empathetic physicians had higher patient satisfaction and treatment adherence rates.	Moderate quality; limited by self-reported data from patients.
Empathy and Quality of Care	[3]	To estimate the relationship between empathy and quality of care in general practice	Mixed-methods study	40 physicians	CARE Measure	Empathy was strongly associated with improved patient outcomes and trust in healthcare providers	High-quality study with a balanced approach to qualitative and quantitative data.
Empathy Decline and Its Reasons	[1]	To investigate the fall-off in empathy among students of medical schools and residents working in hospitals	Systematic review	18 studies	Various empathy scales	Empathy declines during medical training due to burnout, workload, and lack of emphasis on humanistic care.	High-quality review with comprehensive analysis of multiple studies.
Teaching Empathy to Medical Students	[2]	Evaluate the effectiveness of empathy training programs for medical students	Randomized controlled trial	125 students	Jefferson Scale of Empathy (JSE)	Empathy training significantly improved empathy scores among medical students.	High-quality RCT with clear methodology and validated tools.
Burnout and Its Association with Work-Life Balance	[4]	To assess burnout levels among physicians and their impact on empathy	Cross-sectional study	7,288 physicians	Maslach Burnout Inventory (MBI)	High burn out levels were associated with lower empathy levels and job satisfaction.	High-quality study with a large sample size and validated tools.
The Science of Empathy	[14]	To explore the neuroscience of empathy and its application in clinical practice	Narrative review	N/A	N/A	Empathy is a neurologically based skill that can be enhanced through training and mindfulness practices	Conceptual paper; lacks empirical data but gives valuable insights about science of empathy.
Effectiveness of Empathy in General Practice	[8]	To evaluate the effectiveness of empathy and its role in settings of general practice	Systematic review	10 studies	Various empathy scales	Empathy enhanced patients' satisfaction, prescription adherence, and clinical outcomes in general practice.	High-quality review highlights diverse healthcare settings.

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Empathy Training for Resident Physicians	[5]	To assess the impact on the residents, physicians' training	Randomized controlled trial	100 residents	Jefferson Scale of Empathy (JSE)	Empathy training led to significant improvements in empathy scores and patient satisfaction.	High-quality RCT with clear methodology and validated tools.
Impact of Empathy on Medical Students: Integrative Review	[18]	To summarize the impact of empathy on medical students from perspectives of Mental health, Academic performance, Competence, and preference	Interview review	2295	Jefferson Scale of Empathy (JSE)	All four perspectives highly depend on medical students' empathy	High-quality RCT with clear methodology and validated tools.
Empathy and Big Five Personality Model in Medical Students and Its Relationship to Gender and Specialty Preference: A Cross-Sectional Study	[9]	To assess the relationship between personality and empathy in addition take into account of gender, preference of specialty	Cross-sectional study	110	IRI, NEO-FFI, EQ, JSPE	Higher scores on empathy have been found among students who preferred majors with people-focused specialties	High-quality RCT with clear methodology and validated tools.
Characterizing Change in Students' Empathy Throughout their Career in the School of Medicine	[10]	To examine the trends of empathy by longitudinal study, determine the differences in empathy between males and females, and the preference for medical specialties.	Longitudinal study	1162	JSPE-S	Students with a preference for technology-oriented specialties had a lower score of empathy	High-quality RCT with clear methodology and validated tools.
Level of Empathy Among Medical Students at Kuwait University, Kuwait	[11]	To evaluate the level among medical students along with its association with sociodemographic details, level of stress, and its impact on their personality.	Cross-sectional study	264	PSS, JSPE-S, ZKPQ	Empathy could not affect the specialty preferences of students in medical school	High-quality RCT with clear methodology and validated tools.

DISCUSSION

Empathy directly supports the four key principles of medical ethics. Beneficence: it helps physicians select the best treatments [1,6]. Non-maleficence: it reduces medical errors through improved communication. Autonomy: it ensures patients feel heard and involved in decisions [7, 13, 15]. Justice: it promotes fairness and equal care. For example, when physicians show empathy, patients trust them more and feel less anxious [2]. This is critical because emotional distress often weighs as heavily as physical pain [3, 17]. Researchers describe empathy as a moral habit, cultivated as part of a physician's character. A resident who actively listens to a grieving family exemplifies this virtuous practice. Similarly, *Care Ethics* prioritizes relational dynamics over rigid rules; a physician spending extra time with an elderly patient to build trust illustrates this approach [11, 12]. Empathy integrates seamlessly with the principles of beneficence, non-maleficence, autonomy, and justice. It ensures that care is not only clinically effective but also compassionate and respectful. Compassionate communication fosters trust and lowers patient anxiety, both of which are essential for a strong therapeutic alliance. Given that psychological and emotional burdens often parallel physical symptoms, such alliances are vital [1-3, 13]. Respecting autonomy and promoting fairness also demonstrate how empathy strengthens justice in healthcare delivery. Empathy involves emotional resonance, the ability to recognize and share a patient's feelings. For instance, when a physician acknowledges a patient's fear of surgery and responds with reassurance, they demonstrate empathy. Compassion, however, extends beyond understanding to actively addressing suffering. For example, a nurse tailoring a diabetic patient's meal plan to their cultural preferences shows compassion by translating empathy into action [4, 17]. Evidence confirms that empathetic care improves measurable outcomes. Studies show up to a 30% improvement in treatment adherence among patients treated by empathetic physicians. Hypertensive patients, for example, demonstrated higher compliance rates, while clinics using CARE scores reported improved patient satisfaction. In chronic diseases such as diabetes, heart disease, and depression, empathetic physicians achieved better outcomes; for instance, diabetic patients showed lower HbA1c levels. Cancer patients also reported reduced

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distress when physicians acknowledged emotional struggles. These findings affirm that empathy is not merely a "soft skill" but a clinical necessity. Patients consistently report better adherence, greater satisfaction, and improved outcomes when their providers are empathetic [4-7, 18, 20, 21]. Moreover, empathetic communication reduces patient anxiety and depression, easing the psychological burden of illness. Beyond patient outcomes, empathy strengthens healthcare integrity. It fosters trust, lowers conflict, and promotes teamwork within healthcare teams. The patient–provider relationship is grounded in trust, and empathy builds this by showing genuine concern for patients' well-being. Teams with empathetic members experience fewer conflicts, collaborate more effectively, and face lower risks of litigation. Patients are approximately 40% less likely to sue physicians they perceive as empathetic. Hospitals that encourage empathetic practice foster environments where both patients and staff feel valued [4, 8]. Solutions to strengthen empathy include curricular integration, institutional support, and systemic reforms. Medical schools and hospitals should mandate empathy training through role-playing, patient narratives, and reflective practices. For instance, the UK's General Medical Council now requires empathy assessments in residency programs. Reducing administrative tasks, such as streamlining electronic health records, frees time for patient interaction, leading to higher empathy scores. Institutional measures, such as workload regulation and mental health support, are also essential for reducing burnout. Training interventions have proven effective. Role-playing patient scenarios increased empathy scores by 28%. Reflective writing and sharing experiences improved empathy among medical trainees. Patient feedback systems raised empathy scores by 35%, with benefits sustained for up to three years. Simulation-based learning has also been shown to enhance empathetic communication in realistic clinical settings. These findings underscore the importance of embedding empathy development into both medical education and professional training [21-26]. Recent evidence underscores the pivotal role of empathy in shaping both clinical outcomes and patient experiences. Higher levels of physician empathy have been shown to improve chronic pain management and patient-reported outcomes. Systematic reviews further confirm empathy's positive influence on patient satisfaction, trust, and adherence, though heterogeneity in measurement approaches remains a challenge. Educational interventions aimed at cultivating empathy, including structured training and Balint groups, have demonstrated significant effectiveness in enhancing empathy among medical and nursing trainees, thereby strengthening professional development [27, 28, 29]. Moreover, physician empathy continues to emerge as a central component of effective doctor–patient communication, fostering improved understanding and relational quality. These insights complement earlier foundational contributions that defined and conceptualized empathy in medical practice, demonstrated its association with patient satisfaction and compliance, and emphasized its role in improving clinical outcomes and quality of care [21, 30-36]. Collectively, the convergence of older and more recent evidence highlights empathy as both a clinical competency and an educational priority in contemporary healthcare.

Despite its clear benefits, empathy faces significant barriers in healthcare. Three major challenges are burnout, rushed consultations, and inadequate training. Burnout, affecting nearly one in two physicians, drains emotional energy and limits their ability to connect with patients. Short appointments averaging only 15 minutes restrict meaningful communication. In addition, many medical schools lack robust training in empathetic communication, leaving physicians unprepared to address patients' emotional needs. Administrative burdens further reduce time for patient interactions, exacerbating depersonalization and lowering the capacity for empathy. These barriers highlight the urgent need for structural reforms to sustain empathetic practice. Future directions emphasize the need for longitudinal research and systemic change. Empathy should be consistently integrated into medical curricula and tracked alongside other healthcare quality indicators. Key questions remain: How does empathy affect long-term health outcomes? What are the most effective methods for teaching empathy to experienced practitioners? Can empathy help reduce healthcare disparities? Addressing these questions requires longitudinal studies and rigorous evaluations of empathy-focused reforms across diverse healthcare settings. Strengthening empathy will not only improve patient care but also promote justice, fairness, and integrity within healthcare systems.

CONCLUSIONS

Medical ethics can't exist without empathy, which is also the main engine of healthcare integrity. Promoting sympathetic treatment can improve patient outcomes, boost confidence, and uphold ethical standards. However, to make sure that empathy stays a top priority in clinical practice, problems like burnout and time limits need to be addressed. Keeping healthcare systems honest and giving not only efficient but also kind and respectful care depends on teaching and practicing empathy.

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Authors' Contribution

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

Conflicts of Interest

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Systematic Review

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Impact of Intermittent Fasting on Human Endocrine and Metabolic Physiology: A Systematic Review

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ABSTRACT

Intermittent fasting (IF) is increasingly recognized as a dietary approach that may improve endocrine and cardiometabolic health by aligning eating patterns with circadian rhythms. **Objectives:** To systematically evaluate recent human studies (2018–2024) investigating the effects of intermittent fasting on endocrine and metabolic physiology, with emphasis on insulin sensitivity, hormonal balance, and cardiometabolic outcomes. **Methods:** PubMed, Scopus, and the Cochrane Library were searched according to PRISMA 2020 guidelines. Randomized controlled, crossover, cohort, and observational studies reporting endocrine (insulin, leptin, ghrelin, cortisol) and metabolic (glucose, lipids, body composition) outcomes associated with intermittent fasting were included. Study quality was assessed using the Joanna Briggs Institute tools. **Results:** Eighteen studies (~1,250 participants) were included. Early time-restricted eating and alternate-day fasting were consistently associated with improved insulin sensitivity, glycemic control, lipid profiles, and blood pressure. Several trials reported endocrine benefits independent of major weight loss. Most randomized studies showed low risk of bias. **Conclusions:** Low-risk randomized evidence supports early time-restricted eating and alternate-day fasting as effective strategies for improving insulin sensitivity and glycemic control. Other hormonal outcomes remain associative and require further trials. Intermittent fasting is a promising, culturally adaptable approach for metabolic risk reduction.

INTRODUCTION

Disorders of metabolism and the endocrine system, including obesity, type 2 diabetes mellitus, and metabolic syndrome, are rapidly increasing worldwide and represent a major public health burden. Conventional management strategies emphasize sustained caloric restriction; however, long-term adherence to continuous dieting remains poor, and metabolic benefits often diminish over time [1]. Consequently, alternative dietary strategies that are both effective and sustainable are increasingly being explored [2]. Intermittent fasting (IF) has emerged as a promising dietary approach that alternates defined periods of eating and fasting. Common IF patterns include time-restricted eating (TRE), alternate-day fasting (ADF), and periodic fasting regimens such as the 5:2 diet [3, 4]. Unlike traditional calorie-restricted diets, IF focuses primarily on meal timing rather than continuous energy reduction. Aligning food intake with circadian rhythms may favorably modulate key metabolic hormones, including

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insulin, cortisol, leptin, and ghrelin—thereby improving glucose and lipid homeostasis [5, 6]. At the cellular level, IF has been associated with activation of AMP-activated protein kinase (AMPK) and autophagy pathways, which support mitochondrial function, cellular repair, and oxidative stress reduction [7]. Clinical studies have reported improvements in insulin sensitivity, fasting glucose, lipid profiles, and inflammatory markers across diverse populations, with several trials demonstrating metabolic benefits even in the absence of substantial weight loss [8-10]. These findings suggest that IF may exert partially weight-independent metabolic effects mediated by metabolic switching from glucose to fatty acid and ketone utilization [11-13].

Despite growing interest, the endocrine and metabolic effects of IF remain heterogeneous across fasting protocols, study designs, and populations, resulting in inconsistent conclusions. Evidence is particularly limited in South Asian settings, where unique dietary practices, fasting customs, and high metabolic disease burden warrant region-specific evaluation. This study aimed to synthesize human studies published between 2018 and 2024 to assess the effects of intermittent fasting on endocrine and metabolic physiology, with particular focus on insulin sensitivity, hormonal regulation, and cardiometabolic outcomes.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was not prospectively registered in PROSPERO, which has been explicitly acknowledged as a methodological limitation due to the potential risk of selective outcome reporting. A comprehensive literature search was conducted in PubMed, Scopus, and the Cochrane Library to identify relevant studies published between January 1, 2018, and December 15, 2024. The final database search was completed on December 15, 2024. The electronic search strategy incorporated both Medical Subject Headings (MeSH) and free-text keywords. Database-specific reproducible Boolean search strings were applied. In PubMed, the following strategy was used: ("Intermittent Fasting" [MeSH] OR "Time-Restricted Eating" [MeSH] OR "Alternate Day Fasting" [MeSH] OR Ramadan fasting OR "5:2 diet") AND ("Insulin Sensitivity" [MeSH] OR "Endocrine System" [MeSH] OR cortisol OR leptin OR ghrelin OR "Glucose Metabolism" [MeSH]) with filters for humans, English language, and publication years 2018–2024. Comparable keyword-based strategies were applied in Scopus and the Cochrane Library using Title/Abstract/Keyword fields. In addition, reference lists of all eligible studies were manually screened to identify potentially missed publications. The initial search yielded 535 records. Eligible studies were selected based on predefined inclusion and exclusion criteria. Included studies were human research articles published in English that employed randomized controlled, crossover, cohort, or observational designs and evaluated any intermittent fasting protocol, including time-restricted eating, alternate-day fasting, the 5:2 diet, or Ramadan fasting. Primary outcomes were explicitly defined as endocrine parameters, including insulin sensitivity, fasting insulin, leptin, ghrelin, and cortisol, while secondary outcomes included metabolic variables such as fasting glucose, lipid profile, body composition, and body mass index. Reviews, meta-analyses, conference abstracts, pilot studies, case reports, animal or laboratory studies, and studies lacking quantifiable endocrine or metabolic outcomes or accessible full texts were excluded. All records were imported into EndNote to remove duplicates. Two independent reviewers screened titles and abstracts, followed by a full-text review of potentially eligible studies. Inter-reviewer screening reliability demonstrated 92% agreement ($\kappa = 0.86$), and disagreements were resolved through consensus or third-reviewer arbitration. Data were extracted using structured extraction forms. These forms were pilot-tested on three randomly selected studies before full extraction to enhance consistency and minimize extraction bias. Extracted information included authorship, publication year, study design, sample size, population characteristics, fasting protocol type and duration, primary endocrine outcomes, secondary metabolic outcomes, and key findings. Methodological quality and risk of bias were evaluated using the Joanna Briggs Institute (JBI) critical appraisal tools appropriate for each study design. Studies were classified as low risk of bias if ≥80% of checklist items were scored as "Yes," moderate risk if 60–79%, and high risk if <60%. Risk of bias grading was incorporated into the interpretation of findings to strengthen evidence appraisal because of substantial clinical heterogeneity (different fasting protocols and populations), methodological heterogeneity (varying study designs), and outcome heterogeneity (variable endocrine and metabolic measures). Meta-analysis was not performed, and narrative synthesis was adopted. Findings were stratified according to fasting protocol and study design, and weight-dependent and weight-independent endocrine effects were interpreted separately to minimize confounding by weight loss. Formal funnel plot analysis for publication bias was not feasible due to heterogeneity and limited comparable outcomes; therefore, potential publication bias has been acknowledged as a limitation. Additionally, several included trials had small sample sizes (n<20), and limited

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statistical power has been acknowledged when interpreting hormonal effects. Causal inferences have been restricted to randomized controlled trials, while observational findings have been interpreted as associative. PRISMA 2020 flow diagram summarizing the selection process for studies evaluating the endocrine and metabolic effects of intermittent fasting. A total of 535 records were identified, and 18 studies met the final inclusion criteria (Figure 1).

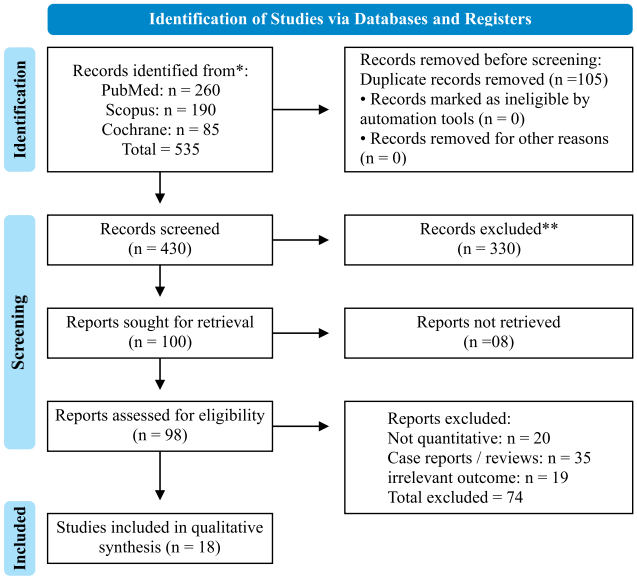

Figure 1: Selection Process for Studies

RESULTS

The study summarizes the characteristics of the 18 human studies included in this review. The majority of included investigations were randomized or controlled clinical trials conducted in the United States, Europe, and Asia, reflecting a broad geographic representation. Of the 18 included studies, 16 were randomized or controlled clinical trials, whereas two were observational Ramadan fasting studies, and results are therefore stratified by study design. Early time-restricted eating (TRE) and alternate-day fasting (ADF) were the most frequently evaluated intermittent fasting protocols. Most studies involved participants with obesity, metabolic syndrome, or non-alcoholic fatty liver disease, highlighting the application of intermittent fasting in high-risk metabolic populations. Across trials, early TRE demonstrated the strongest endocrine and cardiometabolic effects, particularly on insulin sensitivity, adipokine balance, and circadian hormone rhythms. Several trials reported minimal or no weight change, yet still demonstrated improvements in insulin sensitivity, indicating partially weight-independent endocrine benefits. In contrast, some late TRE and 5:2 fasting protocols produced metabolic outcomes comparable to continuous calorie restriction, suggesting that not all intermittent fasting regimens confer superior benefits, (Table 1).

Table 1: Characteristics of Included Human Studies on Intermittent Fasting and Endocrine–Metabolic Physiology (2018–2024)

Sr. No.	References	Country	Study Design	Sample Size	Population	Intermittent Fasting Protocol	Duration	Main Endocrine Outcomes	Main Metabolic Outcomes
1	[14]	USA	Controlled feeding trial	8	Men with prediabetes	Early time-restricted feeding (6-h window, early day)	5 weeks	↑ Insulin sensitivity, changes in ghrelin and other circadian hormones	Improved cardiometabolic profile without major weight loss
2	[15]	USA	Controlled crossover study	11	Overweight adults	Early TRE vs usual late eating	4 weeks	Improved 24-h insulin and cortisol rhythmicity	Better 24-h glucose control and lipid handling
3	[16]	USA	Randomized clinical trial	90	Adults with obesity	Early TRE (eating 7:00–15:00) vs ≥12-h eating window	14 weeks	↑ Insulin sensitivity, favourable hormonal profile	Greater weight and fat loss, ↓ diastolic BP
4	[17]	USA	Randomized trial	58	Adults with obesity	4-h vs 6-h TRF vs control	8–10 weeks	↓ Fasting insulin, improved adipokine pattern	~3–4% weight loss, ↓ BP and oxidative stress
5	[18]	USA	Single-arm paired trial	19	Adults with metabolic syndrome	10-h TRE (self-selected window)	12 weeks	Better insulin regulation, improved hormonal milieu	↓ Weight, ↓ HbA1c, ↓ BP, improved lipids
6	[19]	USA	Randomized clinical trial	116	Adults with overweight / obesity	16:8 TRE vs 3 structured meals	12 weeks	No major endocrine advantage vs control	Modest weight change, no clear cardiometabolic benefit
7	[20]	China	Randomized clinical trial	139	Adults with obesity	Calorie restriction ± 8:00–16:00 TRE	12 months	Hormonal effects mainly mediated by weight change	Similar weight loss with or without TRE; no extra metabolic gain
8	[21]	China	Randomized trial	90	Healthy adults without obesity	6-h early TRE vs 6-h late TRE vs control	5 weeks	Differences in insulin and circadian hormone responses between early vs late TRE	Improved metabolic health with early TRE vs late TRE/control

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9	[22]	Italy	Randomized trial	82	Resistance-trained adults	TRE combined with resistance training	12 months	↓ Inflammatory markers, favourable endocrine risk profile	↓ Cardiometabolic risk factors, preserved muscle mass
10	[23]	China	Randomized controlled trial	80	NAFLD patients	Alternate-day fasting vs usual diet	12 weeks	Improved insulin resistance indices	↓ Weight, ↓ dyslipidaemia, improved liver-related markers
11	[24]	Iran	Randomized clinical trial	70	Adults with metabolic syndrome	Modified ADF vs daily calorie restriction	8 weeks	Improved insulin sensitivity vs control	Greater ↓ weight, waist circumference, BP and TG
12	[25]	USA	Randomized controlled trial	80	NAFLD patients	Alternate-day fasting + aerobic exercise vs control	8 weeks	Favourable changes in insulin resistance and inflammatory markers	↓ Liver fat, ↓ weight, improved lipid profile
13	[26]	UK	Randomized parallel study	27	Overweight / obese adults	5:2 intermittent energy restriction vs continuous restriction	16 weeks (incl. follow-up)	No clear superiority of IER for post-prandial insulin vs CER	Similar weight loss; mixed effects on lipids and glucose
14	[27]	UK	Randomized trial	36	Normal-weight young adults	5:2 IER vs continuous restriction	Several weeks	Comparable effects on basal/post-prandial insulin and hormones	Similar metabolic responses between 5:2 and continuous restriction
15	[28]	Netherlands	Randomized crossover trial	37	Adults with overweight / obesity	Intermittent restricted eating vs continuous restriction	2 × 4-week periods	Changes in fasting insulin and appetite hormones	Similar or slightly improved metabolic flexibility with IER
16	[29]	USA	Randomized controlled trial	213	Adults with metabolic syndrome	Personalized 8–10-h TRE vs usual care	12 months	Improved insulin regulation and endocrine cardiometabolic profile	Better glycaemic control and composite MetS score
17	[30]	UAE	Prospective observational study	57	Overweight and obese adults	Diurnal Ramadan fasting (dawn–sunset)	1 month	Changes in ghrelin, leptin, melatonin, and cortisol	Modest ↓ weight and waist; lifestyle-linked changes
18	[31]	France	Quasi-experimental trial	20	Obese men	Ramadan IF with training	Ramadan month + follow-up	Altered leptin, GLP-1, PYY, CCK; no change in ghrelin	↓ BMI, ↓ body fat %, improved body composition indices

Presents the endocrine outcomes reported across included studies. Insulin sensitivity outcomes were reported in 12 studies, leptin in 6 studies, ghrelin in 7 studies, and cortisol in 5 studies. Most randomized controlled trials evaluating early TRE and ADF demonstrated consistent improvements in insulin sensitivity, fasting insulin concentrations, and adipokine profiles. Endocrine improvements in insulin sensitivity were predominantly supported by low-risk randomized controlled trials, allowing cautious causal interpretation, whereas outcomes related to ghrelin and cortisol were largely derived from moderate-risk observational or small-sample trials and should therefore be interpreted as associative. Studies evaluating late TRE and 5:2 fasting showed mixed endocrine responses, often comparable to continuous calorie restriction, suggesting that feeding window timing plays a critical role in hormonal regulation (Table 2).

Table 2: Summary of Endocrine Outcomes Reported Across Included Studies (2018–2024)

Sr. No.	References	Key Hormonal Outcomes	Overall Endocrine Effect
1	[14]	↑ Insulin sensitivity; changes in ghrelin and circadian hormones	Early TRE improved insulin action and hormonal rhythms
2	[15]	Improved 24-h insulin and cortisol rhythmicity	Better alignment of circadian endocrine markers
3	[16]	↑ Insulin sensitivity; favourable adipokine profile	Endocrine benefits more pronounced with early TRE
4	[17]	↓ Fasting insulin; ↑ adiponectin patterns	Short feeding windows improved hormonal markers
5	[18]	Better insulin regulation; improved metabolic hormones	TRE enhanced insulin control in metabolic syndrome
6	[19]	No significant endocrine advantages vs control	Hormonal outcomes largely unchanged
7	[20]	Endocrine changes mainly mediated by weight loss	TRE did not add major hormonal benefit beyond calorie restriction
8	[21]	Distinct insulin and circadian hormone shifts between early vs late TRE	Early TRE produced more favourable endocrine timing
9	[22]	↓ Inflammatory markers; modest endocrine improvements	TRE + resistance training improved inflammatory–endocrine profile
10	[23]	Improved insulin resistance indices	ADF enhanced insulin sensitivity in NAFLD
11	[24]	↑ Insulin sensitivity vs control	Modified ADF produced stronger hormonal improvement
12	[25]	↓ Insulin resistance; ↓ inflammatory markers	ADF + exercise improved metabolic hormones
13	[26]	No superiority of 5:2 over continuous restriction for post-prandial insulin	Hormonal changes modest and similar between groups

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14	[27]	Comparable basal/post-prandial insulin changes between groups	IF and continuous restriction produced similar endocrine responses
15	[28]	Altered fasting insulin; minor appetite-hormone shifts	Small endocrine effects, largely comparable to CER
16	[29]	Improved insulin regulation; favourable cardiometabolic hormones	TRE enhanced metabolic–endocrine status in MetS
17	[30]	Changes in ghrelin, leptin, melatonin, cortisol	Ramadan fasting altered appetite and circadian hormones
18	[31]	Changes in leptin, GLP-1, PYY, CCK; stable ghrelin	Ramadan IF modified gut hormones and appetite regulation

The study summarizes the metabolic outcomes reported across the included studies. Most randomized trials demonstrated significant reductions in body weight, fasting glucose, HbA1c, lipid levels, and blood pressure, particularly in early TRE and ADF protocols. These metabolic improvements were most pronounced in participants with obesity and metabolic syndrome. Across trials, improvements in insulin sensitivity and glycaemic control were observed even in studies reporting minimal weight change, indicating partially weight-independent endocrine effects, whereas lipid and adiposity outcomes were largely weight-dependent. Protocols such as late TRE and 5:2 intermittent energy restriction generally showed metabolic effects similar to continuous calorie restriction, highlighting heterogeneity in metabolic responsiveness among fasting regimens. Ramadan Fasting (Observational Evidence) Observational Ramadan fasting studies Al-Rawi *et al.* and Zouhal *et al.* demonstrated modest hormonal and metabolic changes; however, these findings represent associative evidence and were therefore interpreted separately from randomized controlled trials [30, 31] (Table 3).

Table 3: Summary of Metabolic Outcomes Reported Across Included Studies (2018–2024)

Sr. No.	References	Key Hormonal Outcomes	Overall Endocrine Effect
1	[14]	Improved glucose tolerance; reduced oxidative stress	Early TRE enhanced cardiometabolic profile
2	[15]	Better 24-h glucose control; improved lipid handling	Improved metabolic rhythm and glycemic stability
3	[16]	Greater weight and fat loss; ↓ diastolic BP	Early TRE is superior for metabolic improvement
4	[17]	~3–4% weight loss; ↓ BP; ↓ oxidative stress	Both 4-h and 6-h TRF improved metabolic health
5	[18]	↓ Weight, ↓ HbA1c, ↓ BP; improved lipid markers	Notable metabolic benefits in metabolic syndrome
6	[19]	Modest weight change; no major lipid/glucose improvements	TRE not superior to structured meals
7	[20]	Weight loss similar across groups; no additional TRE advantage	Calorie restriction drove most metabolic changes
8	[21]	Improved metabolic health with early TRE vs late TRE	Early eating window enhanced metabolic regulation
9	[22]	↓ Cardiometabolic risk factors; maintained muscle mass	TRE + training improved metabolic risk
10	[23]	↓ Weight; ↓ dyslipidaemia; improved liver markers	ADF effective in NAFLD metabolic improvement
11	[24]	Greater ↓ weight, waist circumference, TG, BP	Modified ADF metabolically superior to CER
12	[25]	↓ Liver fat; ↓ weight; improved lipid profile	ADF + exercise produced strong metabolic gains
13	[26]	Similar weight loss; mixed lipid/glucose effects	No metabolic advantage for 5:2 pattern
14	[27]	Comparable metabolic responses across groups	IF and CER had similar metabolic outcomes
15	[28]	Slight improvements in metabolic flexibility	Differences modest; IF ≈ CER
16	[29]	Improved glycaemic control; better composite metabolic score	TRE beneficial in metabolic syndrome
Observational Ramadan Fasting Studies			
17	[30]	↓ Weight & waist circumference	Ramadan IF produced modest metabolic improvements
18	[31]	↓ BMI and body fat percentage	Ramadan IF + training improved body composition

Presents the methodological quality assessment of included studies using the Joanna Briggs Institute criteria. Most randomized controlled trials demonstrated a low overall risk of bias, particularly in outcome measurement and reporting domains. Moderate risk of bias was primarily observed in confounding control and participant selection, especially in observational Ramadan fasting studies. Endocrine and metabolic improvements in insulin sensitivity, fasting glucose, and lipid profile were predominantly supported by low-risk randomized trials, whereas hormonal outcomes such as ghrelin and cortisol were largely supported by moderate-risk observational studies and therefore should be interpreted as associative. Additionally, several studies reporting hormonal outcomes included small sample sizes ($n < 20$), and these findings should be interpreted cautiously due to limited statistical power (Table 4).

Table 3: Summary of Metabolic Outcomes Reported Across Included Studies (2018–2024)

Sr. No.	References	Selection Bias	Measurement Bias	Confounding Control	Outcome Reporting	Overall Risk
1	[14]	Low	Low	Moderate	Low	Moderate
2	[15]	Low	Low	Moderate	Low	Moderate
3	[16]	Low	Low	Low	Low	Low
4	[17]	Low	Low	Moderate	Low	Moderate

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5	[18]	Moderate	Low	Moderate	Low	Moderate
6	[19]	Low	Low	Low	Low	Low
7	[20]	Low	Low	Low	Low	Low
8	[21]	Low	Low	Low	Low	Low
9	[22]	Low	Low	Moderate	Low	Moderate
10	[23]	Low	Low	Low	Low	Low
11	[24]	Low	Low	Moderate	Low	Moderate
12	[25]	Low	Low	Low	Low	Low
13	[26]	Low	Low	Moderate	Low	Moderate
14	[27]	Low	Low	Moderate	Low	Moderate
15	[28]	Low	Low	Moderate	Low	Moderate
16	[29]	Low	Low	Low	Low	Low
17	[30]	Moderate	Moderate	Moderate	Low	Moderate
18	[31]	Moderate	Moderate	Moderate	Low	Moderate

DISCUSSION

This systematic review included 18 human studies (2018–2024) and examined the endocrine and metabolic impacts of different forms of intermittent fasting (IF), including time-restricted eating (TRE), alternate-day fasting (ADF), and Ramadan fasting. Findings derived from low-risk randomized controlled trials provide causal evidence that early TRE and ADF improve insulin sensitivity and glycemic control. The body of evidence further indicates that intermittent fasting is associated with improvements in lipid metabolism and hormonal balance through both weight-dependent and partially weight-independent mechanisms. The majority of included studies reported changes in endocrine function, particularly insulin sensitivity and circadian hormones such as leptin, ghrelin, and cortisol. Hormonal outcomes related to leptin, ghrelin, and cortisol were primarily derived from moderate-risk or small-sample studies and should therefore be interpreted as associative rather than causal. These findings are in accordance with Kim *et al.* who reported fasting-related modulation of cortisol and insulin rhythm [5], and with early TRE trials demonstrating consistent endocrine benefits [32, 33]. Intermittent fasting has been linked to activation of AMP-activated protein kinase (AMPK) and autophagy pathways that enhance mitochondrial efficiency and cellular repair. These mechanistic associations are supported mainly by experimental and translational evidence and should be interpreted as biologically plausible explanations rather than direct clinical proof. Molecular evidence from Arif supports improved insulin resistance and lipid metabolism mediated by AMPK activation [7]. Several randomized trials demonstrated endocrine improvements even in the absence of major weight loss, indicating partially weight-independent metabolic effects. Consistent metabolic benefits were observed across randomized trials, including improvements in body weight, fasting glucose, HbA1c, triglycerides, and blood pressure, particularly in early TRE and ADF protocols. These findings are congruent with large meta-analyses documenting favorable effects of intermittent fasting on glycemic and lipid profiles [6, 8]. Lipid and adiposity outcomes were largely weight-dependent, whereas improvements in insulin sensitivity and glycemic control were partially weight-independent. Fasting has also been associated with favorable inflammatory and cardiovascular biomarker changes. Trials included in this review demonstrated reductions in cardiometabolic risk factors and inflammatory cytokines, particularly among patients with metabolic syndrome [34, 35]. These findings are in accordance with Horne *et al.* who reported cardioprotective galectin-3 modulation following fasting [10]. Ramadan fasting studies included in this review were observational and culturally specific; therefore, their findings represent associative evidence only and were interpreted separately from randomized controlled trials. While these studies reported favorable endocrine and metabolic changes consistent with Al-Rawi *et al.* [30], their inference level differs from randomized evidence and should not be generalized as causal physiological effects.

Unregistered protocol, no meta-analysis was done because it was heterogeneous, no assessment of publication bias, small sample sizes in some studies, observational Ramadan studies have only associative evidence, South Asian-based studies are limited, hormonal outcomes are available only in moderate-risk studies, weight-independent effects might be confounded, English-only limitation, and shortening of search to 20182024. P PROSPERO Prospectively record systematic review protocols. Perform extensive, prolonged, randomized controlled trials in South Asians with a uniform fasting regimen. Add extensive hormone test and weight-stratified analysis to decontaminate weight-independent endocrine effects. Conduct meta-analyses as enough homogeneous data is collected. Consider culturally

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modified fasting programs such as Ramadan.

CONCLUSIONS

Low-risk randomized controlled trials provide causal evidence that early time-restricted eating and alternate-day fasting improve insulin sensitivity and glycemic control. Other hormonal outcomes, including leptin, ghrelin, and cortisol, are associated with intermittent fasting but require further adequately powered randomized trials for causal confirmation. Observational Ramadan fasting studies provide culturally specific associative evidence and should be interpreted separately from randomized trials. Intermittent fasting, therefore, represents a promising dietary strategy for metabolic risk reduction, particularly in South Asian populations; however, causal conclusions should be restricted to outcomes supported by randomized evidence. Further high-quality long-term trials are warranted to refine fasting protocols and clarify endocrine mechanisms.

Authors' Contribution

Conceptualization: SSAT
Methodology: SSAT, MA
Formal analysis: AA, AR, MA
Writing and Drafting: SSAT, MK, AS, AA, AR, MA
Review and Editing: SSAT, MK, AS, AA, AR, MA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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