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Substance P and Its Role in Anxiety Disorders

OPEN ACCESS

Riffat Mehboob[1,2]

[1]Rotogen Biotech LLC, United States of America
[2]Lahore Medical Research Center[LLP], Lahore, Pakistan
riffat.pathol@gmail.com

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Anxiety disorders are the most prevalent mental illnesses in the world with an almost 19 percent prevalence among adults in the United States. Similar to major depressive disorder, they are associated with stress and pain and include disturbances in neurotransmitters like serotonin, dopamine, norepinephrine, and GABA and abnormalities in the activity of the amygdala and prefrontal cortex that leads to anxiety symptoms [1-3]. Exposure to stress results in increased endogenous Substance P (SP) in the central nervous system especially in the amygdala thus intensifying anxiety-related responses. This has led to a rising research interest on the role of SP in the development and control of anxiety disorders [4].

However, studies investigating psychiatric conditions often encounter methodological difficulties. Variables such as participant age, sex, and inclusion of subclinical populations can influence observed correlations and restrict the generalizability of findings. Moreover, findings of unexpected positive correlations between subclinical symptoms and gray matter volume challenge traditional interpretations, highlighting the importance of cautious analysis and interpretation of neuroimaging results [1,4].

Experimental evidence supports the involvement of SP in stress-induced anxiety. Animal studies have shown that emotional stress triggers SP release in the amygdala; for example, immobilization stress in rats leads to a prolonged elevation of SP in the medial amygdala (MeA), while mild stress causes only a short-lived increase. Notably, blocking neurokinin-1 receptors (NK-1R) in the MeA prevents the development of stress-induced anxiety-like behaviors, confirming the critical role of SP signaling in anxiety. Similarly, localized SP microinjections into specific brain regions have been shown to produce anxiogenic effects [4,5].

Moreover, SP triggers the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, leading to a high level of norepinephrine and cortisol, which accentuate the symptoms of anxiety even more. Simultaneously with the findings in MDD, NK-1R antagonists are shown to have anxiolytic effects thus supporting the primary place of the SP/NK-1R signaling in the pathophysiology of anxiety disorders [5].

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Original Article

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Severity of Coronary Artery Disease in Diabetic and Non-Diabetic Patients Presenting with Non-ST Elevation Myocardial Infarction

Ayesha Bibi[1], Matiullah Khan[1*], Bushra Anwer[2], Muhammad Qasim[1], Usama Irshad[1] and Mohsin Iqbal[1]

[1]Department of Cardiology, Ayub Teaching Hospital, Abbottabad, Pakistan
[2]Department of Medicine, Ayub Teaching Hospital, Abbottabad, Pakistan

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***Corresponding Author:**
Matiullah Khan
Department of Cardiology, Ayub Teaching Hospital, Abbottabad, Pakistan
drmati_79@yahoo.com

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ABSTRACT

Diabetes mellitus accelerates coronary artery disease (CAD) and may worsen outcomes in non–ST–elevation myocardial infarction (NSTEMI). However, data from South Asia comparing lesion complexity and left ventricular function in diabetic vs non-diabetic NSTEMI patients remain limited. **Objectives:** To compare angiographic complexity (SYNTAX score), lesion severity, and left ventricular ejection fraction (LVEF) between diabetic and non-diabetic NSTEMI patients. **Methods:** This analytical cross-sectional study was conducted over 2 months (June -August, 2025) and included 83 consecutive NSTEMI patients (41 diabetics, 42 non-diabetics). All underwent coronary angiography for SYNTAX scoring and echocardiography for LVEF. Continuous variables were compared using t-tests with 95% confidence intervals and Cohen's d, and categorical data were analyzed using Chi-square/Fisher's exact test with Cramér's V. **Results:** Diabetics had significantly higher SYNTAX scores (24.1 ± 5.9 vs 19.2 ± 5.0; mean difference 4.86, 95% CI 2.46–7.25, Cohen's d = 0.87) and more frequent severe stenosis (61.0% vs 33.3%; p=0.012, Cramér's V = 0.28). LVEF was significantly lower in diabetics (46.9 ± 7.6% vs 53.7 ± 6.2%; mean difference −6.84, 95% CI −9.87 to −3.81, Cohen's d = 0.97). Rates of heart failure, arrhythmia, and mortality did not differ significantly (p>0.05). **Conclusions:** Diabetic NSTEMI patients demonstrate greater anatomic complexity and impaired ventricular function compared to non-diabetics, yet short-term outcomes remain comparable when standardized guideline-directed therapy is applied. These findings underscore the importance of early risk stratification and consideration of adjunctive prognostic markers such as inflammatory indices in this high-risk group.

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide [1, 2], and its burden is amplified in patients with diabetes mellitus (DM). Non–ST–elevation myocardial infarction (NSTEMI) accounts for nearly two-thirds of acute coronary syndrome presentations and is associated with substantial risk of recurrent ischemic events and death [3]. Diabetes is a powerful risk modifier in this setting, as chronic hyperglycemia accelerates atherosclerosis, promotes multi-vessel disease, and contributes to worse left ventricular remodeling after infarction. Understanding the interplay between diabetes and angiographic complexity is crucial to guide optimal revascularization strategies and improve outcomes in this high-risk group [4]. The SYNTAX score, derived from coronary angiography, is an established tool for quantifying the anatomical complexity of CAD and informing revascularization decisions [5]. Comparative data evaluating SYNTAX scores specifically in diabetic vs. non-diabetic NSTEMI cohorts remain sparse in South Asia, despite the region's rising prevalence of both CAD and diabetes [6, 7]. This gap in evidence is notable given that South Asian populations develop CAD at younger ages, with more diffuse and severe lesions, yet region-specific angiographic data are limited. Similarly, left

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ventricular ejection fraction (LVEF) is a key prognostic marker in ACS but has been underreported in local comparative studies. Emerging inflammatory biomarkers such as the systemic immune-inflammation index (SII), calculated from platelet, neutrophil, and lymphocyte counts, have shown independent predictive value for major adverse cardiovascular events in ACS, including NSTEMI with diabetes [8, 9]. However, its application remains largely limited to research settings, and it has yet to be incorporated into routine risk stratification models or clinical guidelines. This represents an opportunity for future work to integrate systemic inflammatory status with angiographic risk scores to refine prognostic assessment. By addressing both anatomical and functional indices, this study aims to provide regionally relevant evidence that may inform decision-making and contribute to improved risk stratification in this high-burden population.

This study aims to compare angiographic complexity as measured by SYNTAX score and left ventricular function between diabetic and non-diabetic NSTEMI patients presenting to a tertiary care center in Pakistan.

METHODS

This analytical, comparative, cross-sectional, observational study was conducted in the Department of Cardiology, Ayub Teaching Hospital, Abbottabad. The study focused on patients presenting with Non-ST Elevation Myocardial Infarction (NSTEMI) and compared angiographic complexity and left ventricular function between diabetic and non-diabetic groups. Institutional ethical approval was obtained (Approval No. RMC-RC-EA/2025/149). The study was conducted over two months, from 4 June to 4 August, 2025. All consecutive eligible patients were enrolled to avoid selection bias. Sample size for comparing two independent means was calculated as: n (per group) = $[2 \times (Z1\text{-}\alpha/2 + Z1\text{-}\beta)^2 \times \sigma^2] \div \Delta^2$ with $Z1\text{-}\alpha/2 = 1.96$ (95% confidence) and $Z1\text{-}\beta = 0.84$ (80% power). Using a pooled standard deviation of $\sigma = 5.5$ (from prior regional data reporting SYNTAX-score variability around 5–6) [10] and an expected difference $\Delta = 4.0$–4.9 points between diabetics and non-diabetics, the required sample size was 30–36 per group (total 60–72). Written informed consent was taken. To ensure adequate precision, 41 diabetics and 42 non-diabetics were included. These assumptions were informed by studies showing greater angiographic complexity in patients with diabetes (SYNTAX framework) and higher angiographic severity in related cohorts [10, 11]. This yielded a minimum sample of 80 participants (40 per group). To strengthen statistical power, 83 patients were finally included (41 diabetics, 42 non-diabetics). Patients aged between 30 and 75 years who presented with Non-ST Elevation Myocardial Infarction (NSTEMI) were considered eligible. NSTEMI was defined based on typical chest pain, electrocardiographic changes (ST-segment depression or T-wave inversion), and elevated cardiac biomarkers. Diabetic status was confirmed either through a known diagnosis, current use of anti-diabetic medication, or an HbA1c value ≥6.5%. Patients were excluded if they had a history of prior coronary artery bypass graft surgery (CABG), severe valvular heart disease, non-ischemic cardiomyopathies, terminal illness, or incomplete angiographic or echocardiographic data that could compromise the analysis. The consecutive sampling technique was used to ensure representativeness of NSTEMI cases during the study period. Demographic and clinical data (age, sex, BMI, smoking, hypertension, dyslipidemia, family history of CAD, previous MI, prior PCI/CABG, CKD) were recorded. Laboratory tests included random blood sugar and HbA1c. Coronary angiography was performed, and the SYNTAX score was used to classify lesion complexity. LVEF was measured using Simpson's biplane method. Two senior interventional cardiologists independently performed SYNTAX scoring while blinded to patients' diabetic status. Disagreements were resolved by consensus. LVEF was measured by two echocardiographers and averaged to minimize inter-observer variation. An inter-class correlation coefficient (ICC = 0.91) from a pilot calibration confirmed high inter-rater reliability. Patients with incomplete angiographic data were excluded (complete-case analysis). For partially missing laboratory variables, pairwise deletion was used to maximize data retention. All data were analyzed using SPSS version 26. Continuous variables such as age, BMI, random blood sugar, HbA1c, SYNTAX score, left ventricular ejection fraction (LVEF), and hospital stay were expressed as mean ± standard deviation (SD). Categorical variables such as gender, smoking status, hypertension, dyslipidemia, family history, previous myocardial infarction (MI), previous PCI/CABG, chronic kidney disease (CKD), vessel involvement, severe stenosis, and in-hospital outcomes (heart failure, arrhythmia, mortality) were presented as frequencies and percentages. Before selecting the appropriate statistical tests, normality of continuous variables was examined using both the Kolmogorov–Smirnov test and the Shapiro–Wilk test, along with inspection of histograms, Q-Q plots, and skewness/kurtosis values. In this study, all key continuous variables (Age, BMI, Random Blood Sugar, HbA1c, SYNTAX Score, LVEF, and Hospital Stay) were found to be normally distributed (Shapiro–Wilk $p>0.05$ for both diabetic and non-diabetic groups). Since the assumptions of normality and homogeneity of variances (tested using Levene's test) were satisfied, comparisons of continuous variables between diabetic and non-diabetic groups were made using the Independent Samples t-test. This parametric test was

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selected because it provides a robust comparison of group means when normality is met. For categorical variables, Chi-square tests were applied; Fisher's exact test was used when expected cell counts were less than 5. Effect sizes were also calculated to enhance the interpretation of results. Cohen's d was reported for continuous variables, with values ≥ 0.8 considered large effects. For categorical variables, Cramér's V was calculated, with values between 0.2 and 0.3 indicating moderate associations. A p-value<0.05 was taken as statistically significant.

RESULTS

Before conducting group comparisons, the distribution of continuous variables was assessed. Normality testing using the Shapiro–Wilk test confirmed that age, BMI, random blood sugar, HbA1c, SYNTAX score, LVEF, and hospital stay were normally distributed (p>0.05 for both groups). Histograms and Q–Q plots confirmed symmetry, and Levene's test verified equality of variances (p>0.05). Therefore, the Independent Samples t-test was used for continuous variables and Chi-square (χ^2) or Fisher's exact test for categorical variables. Effect sizes were calculated (Cohen's d for continuous, Cramér's V for categorical) to quantify association strength. The mean age was higher in diabetics (58.2 ± 8.6) than in non-diabetics (55.9 ± 9.7), but this was not statistically significant (Mean diff = 2.32, 95% CI –1.66 to 6.31, t (81) = 1.16, Cohen's d=0.25, small). BMI and smoking were also similar (p=0.60 and p=0.746). Hypertension was significantly more frequent in diabetics (73.2% vs 47.6%, χ^2 (1) =5.655, p=0.017, Cramér's V=0.26, moderate)(Table 1).

Table 1: Baseline Demographic Characteristics of Diabetic and Non-Diabetic Patients Presenting with NSTEMI (n=83)

Variables	Diabetic (n=41)	Non-Diabetic (n=42)	Statistic (95% CI / Effect Size)	p-Value
Age (Years)	58.2 ± 8.6	55.9 ± 9.7	t(81)=1.16, MD=2.32 (–1.66 to 6.31), d=0.25	0.25
Male Gender (%)	20 (48.8%)	20 (47.6%)	χ^2 (1)=0.011, V=0.012	0.916
BMI (kg/m^2)	26.2 ± 2.9	26.5 ± 3.3	t(81)=–0.52, MD=–0.36 (–1.72 to 1.01), d=0.11	0.60
Smokers (%)	20 (48.8%)	19 (45.2%)	χ^2 (1)=0.105, V=0.035	0.746
Hypertension (%)	30 (73.2%)	20 (47.6%)	χ^2 (1)=5.655, Δ=25.6% (95% CI: 5.0–43.5), V=0.26	0.017
Dyslipidemia (%)	19 (46.3%)	17 (40.5%)	χ^2 (1)=0.291, V=0.059	0.590
Family History CAD (%)	13 (31.7%)	8 (19.0%)	χ^2 (1)=1.759, V=0.146	0.185

Diabetics had markedly higher glycemic indices (very large effect sizes). Previous MI was more frequent in non-diabetics (χ^2 (1)= 5.53, p=0.019)(Table 2).

Table 2: Biochemical Parameters and Clinical History of Diabetic vs. Non-Diabetic NSTEMI Patients

Variables	Diabetic	Non-Diabetic	Statistic / CI / Effect Size	p-Value
RBS (mg/dL)	194.8 ± 46.2	110.0 ± 22.5	t(81)=10.67, MD=84.8 (68.9–100.6), d=2.34	<0.001
HbA1c (%)	8.26 ± 1.85	5.58 ± 0.72	t(81)=8.70, MD=2.68 (2.06–3.29), d=1.91	<0.001
Previous MI (%)	7 (17.1%)	17 (40.5%)	χ^2 (1)=5.53, V=0.26	0.019
Previous PCI/CABG (%)	6 (14.6%)	6 (14.3%)	χ^2 (1)=0.002, V=0.005	0.964
CKD (%)	2 (4.9%)	3 (7.1%)	χ^2 (1)=0.188, V=0.048	0.665

Diabetics had significantly higher SYNTAX scores (t (81) = 4.04, MD=4.86, 95% CI 2.46–7.25, d=0.87, large). Severe stenosis was significantly more common in diabetics (χ^2 (1) = 6.36, p=0.012)(Table 3).

Table 3: Angiographic Severity, Vessel Involvement, and Lesion Characteristics in Diabetic vs. Non-Diabetic NSTEMI Patients

Variables	Diabetic	Non-Diabetic	Statistic / CI / Effect Size	p-Value
SYNTAX Score	24.1 ± 5.9	19.2 ± 5.0	t(81)=4.04, MD=4.86 (2.46–7.25), d=0.87	<0.001
Vessel Disease (Overall)	–	–	χ^2 (2)=3.70, V=0.21	0.157
Single-Vessel	19.5%	38.1%	-	–
Double-Vessel	29.3%	26.2%	OR=2.18 (0.73–6.49)	0.157
Triple-Vessel	51.2%	35.7%	OR=1.89 (0.78–4.56)	0.157
Left Main Disease	7.3%	9.5%	χ^2 (1)=0.13, V=0.04	0.718
Severe Stenosis	61.0%	33.3%	χ^2 (1)=6.36, V=0.28	0.012

LVEF was significantly lower in diabetics (t (81) = –4.49, MD=–6.84, 95% CI –9.87 to –3.81, d=0.97, large). The hospital stay difference was small and non-significant. Outcomes (HF, arrhythmia, mortality) showed weak, non-significant associations (Table 4).

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Table 4: Left Ventricular Function, Length of Hospital Stay, and In-Hospital Outcomes in Diabetic vs. Non-Diabetic NSTEMI Patients

Outcomes	Diabetic	Non-Diabetic	Statistic (95% CI / Effect Size)	p-Value
LVEF (%)	46.9 ± 7.6	53.7 ± 6.2	t(81)=−4.49, MD=−6.84 (−9.87 to −3.81), d=0.97	<0.001
Hospital Stay (days)	4.6 ± 2.1	5.1 ± 1.8	t(81)=−1.23, MD=−0.52 (−1.35 to 0.32), d=0.27	0.221
Heart Failure	4 (9.8%)	7 (16.7%)	χ^2 (1)=0.86, V=0.10	0.353
Arrhythmia	3 (7.3%)	6 (14.3%)	χ^2 (1)=1.04, V=0.11	0.307
Mortality	1 (2.4%)	1 (2.4%)	χ^2 (1)=0.00, V=0.002	0.986

Distribution of SYNTAX scores between groups, showing a rightward shift among diabetics (Cohen's d=0.87, large effect), was done. This study shows the mean ± 95% confidence intervals for random blood sugar, HbA1c, SYNTAX score, LVEF, and hospital stay in diabetic and non-diabetic groups. Diabetic patients had significantly higher random blood sugar, HbA1c, and SYNTAX scores, and significantly lower LVEF compared with non-diabetics (p<0.001 for all). Hospital stay was slightly shorter in diabetics, but this difference was not statistically significant (p=0.221)(Figure 1).

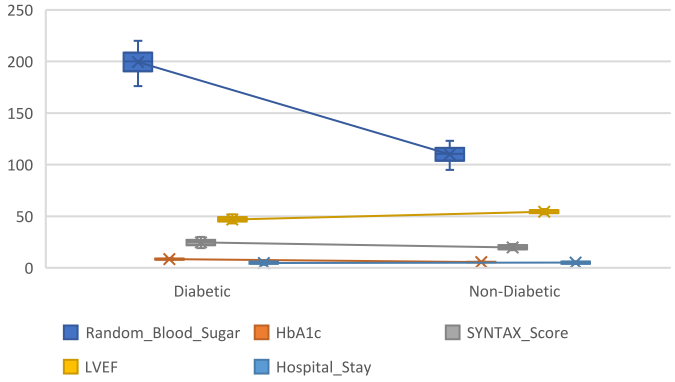

Figure 1: Comparison of Key Continuous Variables between Diabetic and Non-Diabetic NSTEMI Patients

DISCUSSIONS

In this cross-sectional study of NSTEMI patients, diabetes was associated with greater anatomic complexity as reflected by higher SYNTAX scores, a greater proportion of severe stenosis, and lower LVEF, whereas in-hospital complications, including heart failure, arrhythmia, and mortality, were not significantly different between groups. These findings were biologically consistent and in agreement with contemporary evidence from recent cohorts. Our results showed markedly higher random glucose and HbA1c levels in diabetic patients, which supports the strong link between chronic dysglycemia and diffuse, calcific atherosclerosis. Recent work by Ma et al. confirmed that time-in-range metrics are inversely related to coronary artery disease burden in type 2 diabetes [12]. Similarly, Koushki et al. reported that even non-diabetic STEMI patients with elevated HbA1c exhibit higher SYNTAX scores, emphasizing that hyperglycemia worsens lesion complexity across the clinical spectrum [13]. The nearly five-point higher mean SYNTAX score observed in the diabetic group, together with its moderate association with severe stenosis, was therefore both statistically and clinically meaningful. Several studies, including those by Yan et al. and Lawton et al. have demonstrated that SYNTAX and SYNTAX Score II retain strong prognostic value, particularly in diabetics with multi-vessel disease [14, 15]. Abdeldayem et al. reported that patients with high SYNTAX scores had substantially higher twelve-month mortality, underlining the clinical importance of anatomic complexity in diabetics [16]. The difference in mean SYNTAX score seen in our study, which showed a large Cohen's d effect size, was therefore not only statistically significant but also clinically relevant for risk stratification and treatment planning. The lower LVEF in diabetics found in our cohort was expected and consistent with the observations of Cole et al. who reported that diabetic patients presenting with NSTEMI more frequently have moderate-to-severe systolic dysfunction at baseline [17]. Our observed difference in LVEF, with a Cohen's d close to one, is in line with mechanistic studies linking diabetes to microvascular dysfunction, chronic inflammation, and myocardial fibrosis that contribute to depressed contractility. Moreover, LVEF strongly stratifies outcomes across ACS types, with lower LVEF portending higher early and late events [18]. Our study between-group LVEF gap (Cohen's d ≈ 1) was therefore consistent with mechanistic literature by Islam et al. linking diabetes to microvascular dysfunction, inflammation, and myocardial fibrosis that depresses contractility [19]. Both diabetic and non-diabetic patients were managed according to the same institutional NSTEMI protocol, which included dual antiplatelet therapy, anticoagulation, high-intensity statins, and early invasive revascularization. The application of standardized management pathways in both groups likely contributed to the absence of significant differences in short-term outcomes such as heart failure, arrhythmia, and in-hospital mortality, despite more complex coronary anatomy in diabetics. These findings are consistent with contemporary studies by Cole et al. and De-Miguel-Yanes et al. which reported that adherence to guideline-directed ACS management can mitigate early mortality differences between diabetic and non-diabetic patients, although long-term risk remains elevated in diabetics [17, 20]. Our study also demonstrated a trend toward more triple-vessel

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disease in diabetic patients, which did not achieve statistical significance, likely due to sample size limitations. However, the effect size measured by Cramér's V suggested a clinically relevant difference. Larger registries have consistently reported a higher prevalence of multi-vessel and diffuse CAD in diabetics, which influences revascularization strategy and often favors CABG when anatomical complexity is high. Beyond anatomical scores, emerging evidence highlights the value of inflammatory biomarkers such as systemic immune-inflammation index and high-sensitivity CRP, which independently predict major adverse cardiovascular events in diabetic patients with ACS. Incorporating these biomarkers into future studies could refine risk stratification and help target intensive secondary prevention and closer follow-up for the highest-risk patients. Taken together, these findings highlight that diabetes is a marker of higher anatomic complexity and worse left ventricular function, that comparable short-term outcomes can be achieved with standardized evidence-based care, and that future research should integrate angiographic assessment with inflammatory biomarkers to enhance risk prediction and guide tailored therapies.

CONCLUSIONS

Diabetic patients with NSTEMI exhibited higher SYNTAX scores, more severe stenosis, and lower LVEF, confirming greater anatomical and functional disease burden. Despite this, short-term outcomes were similar between groups, likely due to standardized guideline-based management. These results highlight the need for early risk identification, strict control of cardiovascular risk factors, and timely revascularization. Future studies should combine angiographic scores with inflammatory biomarkers to improve risk prediction and personalize care in diabetic NSTEMI patients.

Authors Contribution

Conceptualization: AB
Methodology: AB, MA, MQ, UI, MI
Formal analysis: MK, BA, UI
Writing review and editing: AB, MQ, UI, MI

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Epidemiology and Outcomes of Liquefied Petroleum Gas (LPG) Burns at a Regional Burn Center in Karachi: A One-Year Retrospective Review

Samia Tasleem[1], Sadaf Gulzar[1*], Saba Kiran[1], Minha Murtaza[1], Amber Bawa[1], and Jameeat Mal[1]

[1]Burns Center, Karachi, Pakistan

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***Corresponding Author:**
Sadaf Gulzar
Burns Center, Karachi, Pakistan
drofplastics@mail.com

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ABSTRACT

Liquefied petroleum gas (LPG) burns have increased significantly in recent years, posing substantial public health challenges, particularly in resource-constrained environments such as Pakistan. Understanding the epidemiology and clinical profile of LPG burns can guide effective preventive and management strategies. **Objectives:** To analyze demographic and clinical features of LPG-related burn injuries and assess patient outcomes following treatment. **Methods:** This retrospective cross-sectional study was conducted at Dr. Ruth K.M. Pfau Civil Hospital's burn center in Karachi. Records from January 1 to December 31, 2022, were reviewed using convenience sampling. Demographic details, injury mechanisms, accident location, delay before hospital admission, total body surface area (TBSA) burned, anatomical injury sites, treatment interventions, and patient outcomes were analyzed. **Results:** Among 159 LPG burn patients, 108 (67.9%) were male. Children accounted for 38 (23.9%), while young adults comprised 79 (49.7%). Most patients, 93 (58.5%), belonged to low socioeconomic backgrounds, and 97 (61.0%) worked as laborers. Gas leaks caused most injuries, with 135 (84.9%) patients suffering deep, full-thickness burns involving more than 25% TBSA. Skin grafting was performed in 55 patients (56.7%), tangential excision in 36 (37.1%), and amputation in 6 (6.1%). The overall mortality rate was 62 (38.9%). **Conclusions:** LPG-related burns at our center are characterized by extensive full-thickness injuries and high mortality. These findings underscore the urgent need for enhanced safety regulations, routine equipment inspection, and targeted community education to prevent LPG burn incidents.

INTRODUCTION

Burn injuries impose a major health burden globally, especially in low- and middle-income countries (LMICs) where more than 90% of burn cases occur. Worldwide estimates indicate roughly 9–11 million new burn injuries and 120,000–180,000 burn deaths each year, with flames and cooking-related burns predominating [1, 2]. South Asia carries a disproportionate share of this burden. In India alone, over one million people sustain moderate-to-severe burns annually, and in Pakistan, burns are a leading cause of injury-related disability (often cited as the second leading cause of disability) [3]. As in much of South Asia, the home kitchen is a common setting for burns in Pakistan, and women and children are at particularly high risk [3, 4]. Liquefied petroleum gas (LPG) is widely used for cooking and heating in Pakistan, often as an alternative to kerosene or wood [5]. However, poorly maintained or substandard LPG equipment can cause catastrophic burns. In our region, sudden cylinder explosions and gas leaks have resulted in very severe burn injuries. A recent survey of LPG-related accidents at the National Burn Centre found that most patients had extremely high burn surface area (>60% TBSA) and a very high mortality (~60%) [6]. In contrast, studies from other settings with increasing LPG use have shown lower average severity. A Chinese burn center saw a mean TBSA ~31% and only 4.1% mortality among LPG-burn patients, while a study in Rwanda

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reported a median TBSA of 25% and 16% mortality for LPG-related burns [7, 8]. Such comparisons highlight the exceptional severity of LPG cylinder explosions in our context. Given the scarce burn surveillance in Pakistan, facility-based studies are needed to fill gaps. By identifying predictors of morbidity and mortality specific to LPG burns, our findings will underpin targeted prevention campaigns, inform safety regulations, and optimize clinical protocols in resource-constrained contexts.

This study aims to characterize patient demographics, delineate injury mechanisms, anatomical patterns, TBSA involvement, and evaluate management strategies, including conservative care, grafting, excision, and amputation, and their outcomes.

METHODS

This retrospective, cross-sectional study was conducted at the Burn Center of Dr. Ruth K.M. Pfau Civil Hospital, Karachi. Using convenience sampling, all patient records from January 1 to December 31, 2022, of individuals admitted for burns related to LPG leakage or cylinder explosions were examined. Ethical approval was obtained from the Dow University of Health Sciences Institutional Review Board (Ref. No. IRB-3106/DUHS/EXEMPTION/2023/400). The study used convenience sampling in retrospective chart reviews. Patients admitted during the study period with burn injuries resulting from liquefied petroleum gas (LPG) leakage or cylinder explosion were eligible for inclusion. Sample size was calculated using the WHO sample size calculator for a single population proportion. Assuming a 95% confidence level, a margin of error of 5% and an expected prevalence of LPG burns among burn admissions of 11%, the calculation yielded ≈151 cases [6]. To compensate for an anticipated 20% rate of incomplete or missing data, the sample was inflated to 181. Twenty records lacking key documentation (e.g., burn depth, total body surface area) and two files about non-LPG burn causes were excluded. The final analytic cohort comprised 159 patients. Socioeconomic status was determined using the Modified Kuppuswamy Scale, updated for Pakistan's 2022 CPI (IW). This composite index scores the household head's occupation, educational attainment, and monthly family income to stratify patients into lower, middle, and upper socioeconomic classes [9]. Data extraction was performed independently by two trained reviewers using a standardized proforma; any discrepancies were resolved through discussion or adjudicated by a third reviewer. Collected variables included demographics (age group, sex, residence, occupation), clinical parameters (burn etiology, setting, degree, and total body surface area [TBSA]), timeliness of care (interval from injury to presentation, first-aid measures), presence of inhalation injury, interventions (conservative management, skin grafting, tangential excision, amputation), and outcomes (length of stay, discharge status: recovery, death, or leave-against-medical-advice). Outcome variables were defined as follows: mortality (in-hospital death), length of stay (days from admission to discharge, death, or LAMA), burn complications (wound infection per CDC criteria, sepsis by Sepsis-3 definitions, acute respiratory distress syndrome, acute kidney injury by KDIGO, and contractures), functional recovery (restoration of activities of daily living and joint range of motion at discharge), burn severity (first-degree/superficial to third-degree/full-thickness or mixed), and TBSA (estimated by Rule of Nines in adults or Lund and Browder chart in children). Statistical analyses were conducted in SPSS version 23.0 (IBM Corp., Armonk, NY), with categorical variables presented as counts and percentages and continuous variables as means ± standard deviations; associations were tested using chi-square analyses, with $p < 0.05$ indicating statistical significance.

RESULTS

A total of 159 patient records with complete data were analyzed. The cohort comprised 51 females (32.1%) and 108 males (67.9%). Age distribution was: 38 children under 18 years (23.9%), 79 young adults aged 18–40 (49.7%), 34 older adults aged 41–60 (21.4%), and 8 elderly patients over 60 (5.0%). Most patients (93; 58.5%) came from lower socioeconomic backgrounds; 75 (47.2%) had completed secondary education. Private-sector laborers constituted 97 cases (61.0%), while 43 were housewives (27.0%), 11 were unemployed (6.9%), and 8 were in business (5.0%) (Table 1).

Table 1: Characteristics of End Stage Renal Disease Patients on Maintenance Hemodialysis (N=144)

Characteristics	Category	Frequency (%)
Gender	Female	51 (32.1%)
	Male	108 (67.9%)
Age group	< 18	38 (23.9%)
	18–40	79 (49.7%)
	41–60	34 (21.4%)
	> 60	8 (5.0%)
Socioeconomic Status	Lower	93 (58.5%)
	Middle	44 (27.7%)
	Upper	22 (13.8%)
Education	Primary	45 (28.3%)
	Secondary	75 (47.2%)
	Matric	15 (9.4%)
	Intermediate	12 (7.5%)
	Graduate & above	12 (7.5%)
Occupation	Private job	97 (61.0%)
	Housewife	43 (27.0%)
	Unemployed	11 (6.9%)
	Business	8 (5.0%)

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Seventy-one percent (113) presented directly to the burn center; the remaining 28.9% were referrals after first aid elsewhere. LPG burns resulted from gas leaks in 97 cases (61.0%) and cylinder blasts in 62 (39.0%). Injuries occurred most often at workplaces (110; 69.2%), followed by vehicles (26; 16.4%), homes (19; 11.9%), and other sites (4; 2.5%). Regarding severity, 135 patients (84.9%) had full-thickness burns over >25% total body surface area (TBSA); 19 (11.9%) had partial-thickness burns. Inhalation injury was noted in 129 cases (81.1%). Time to presentation was under 6 hours in 108 patients (67.9%), 6–12 hours in 21 (13.2%), 12–24 hours in 17 (10.7%), and beyond 24 hours in 13 (8.2%). First-aid had been administered in 72 cases (45.3%). (Table 2).

Table 2: Clinical Variables of Burn Patients

Characteristics	Category	Frequency (%)
Cause of Injury	Gas leak	97 (61.0%)
	Cylinder blast	62 (39.0%)
Place of injury	Home	19 (11.9%)
	Workplace	110 (69.2%)
	Vehicle	26 (16.4%)
	Other	4 (2.5%)
Time from Burn Injury to Presentation	< 6 hours	108 (67.9%)
	6–12 hours	21 (13.2%)
	< 24 hours	17 (10.7%)
	> 24 hours	13 (8.2%)
First Aid	Received	72 (45.3%)
	Not received	87 (54.7%)
Inhalation Injury	Present	129 (81.1%)
	Absent	30 (18.9%)
TBSA Burned	< 15%	15 (9.4%)
	15–30%	53 (33.3%)
	31–45%	26 (16.4%)
	46–60%	22 (13.8%)
	61–75%	20 (12.6%)
	> 75%	23 (14.5%)
Degree of Burn	Full thickness	135 (84.9%)
	Partial thickness	19 (11.9%)
	Mixed	5 (3.1%)
Procedure Performed	Conservative management	62 (39.0%)
	Grafting	55 (34.6%)
	Amputation	6 (3.8%)
	Tangential excision	36 (22.6%)
Length of Hospital Stay	≤ 7 days	107 (67.3%)
	8–14 days	36 (22.6%)
	> 14 days	16 (10.1%)
Outcome	Discharge	80 (50.3%)
	Death	62 (39.0%)
	LAMA	17 (10.7%)

The burns involved various regions of the body, including the head, neck, upper and lower limbs, trunk, and genitalia. Surgical management was required in 97 patients: 55 (34.6%) underwent skin grafting, 36 (22.6%) had tangential excision, and 6 (3.8%) required amputation; the remaining 62 (39.0%) were managed conservatively (Figure 1).

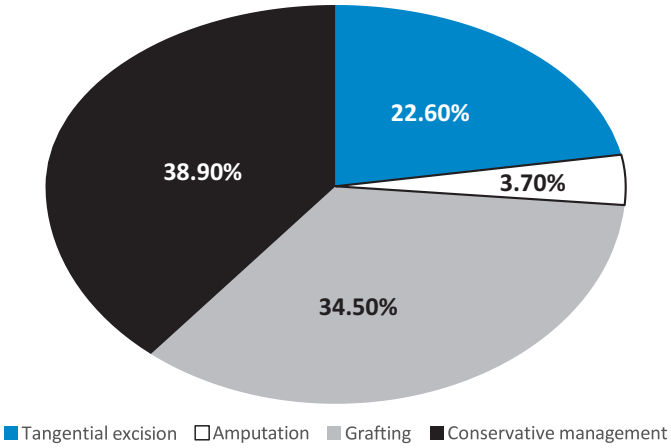

Figure 1: Percentages of Procedures Performed on Burn Patients

Hospital stays were ≤7 days for 107 patients (67.3%), 8–14 days for 36 (22.6%), and >14 days for 16 (10.1%). At study end, 80 patients (50.3%) were discharged after full recovery, 17 (10.7%) left against medical advice (LAMA), and 62 (39.0%) died (Figure 2).

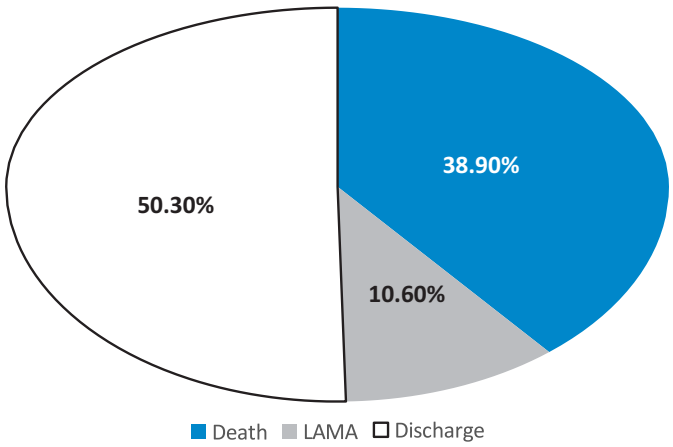

Figure 2: Outcomes of Burn Patients

Patients with full degree burn, only 39.3% of patients were discharged after completing treatment, while 45.2% died in hospital, and 15.6% LAMA. Two-thirds (68.9%) of survivors stayed one week or less; 22.2% remained for one to two weeks, and 8.9% for more than two weeks. The majority (67.3%) had short stays (≤1 week), with 22.6% admitted for 1–2 weeks and 10.1% exceeding two weeks. A Pearson chi-square test showed a significant association between burn depth and patient outcome (χ^2=16.734; p=0.002), whereas no significant relationship was found between burn degree and length of stay (χ^2=1.774; p=0.777) (Table 3).

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Table 3: Degree of Burn by Clinical Outcomes, Length of Stay, and Inhalational Injury (N=159)

Degree of Burn	Outcomes			Length of Stay		
	Discharge N (%)	Death N (%)	LAMA N (%)	≤1 Week N (%)	1–2 Weeks N (%)	>2 Weeks N (%)
Full-Thickness (N=135)	53 (39.3)	61 (45.2)	21 (15.6)	93 (68.9)	30 (22.2)	12 (8.9)
Partial- Thickness (N=19)	15 (78.9)	1 (5.3)	3 (15.8)	11 (57.9)	5 (26.3)	3 (15.8)
Mixed (N=5)	3 (60.0)	0 (0.0)	2 (40.0)	3 (60.0)	1 (20.0)	1 (20.0)
Total (N=159)	71 (44.7)	62 (39.0)	26 (16.4)	107 (67.3)	36 (22.6)	16 (10.1)
p-Value	0.002*			0.777		

DISCUSSION

In this study of LPG-related burns, we found very severe injuries with unusually high mortality. Most of our patients suffered large flame burns, reflecting the high-energy nature of cylinder explosions. Compared to the global burn registry data, our cohort had much larger burns. The WHO registry analysis shows that cookstove burns often average ~30% TBSA with mortality around 41% [2], but our patients' TBSA values exceeded this (the majority >60%). Similarly, in China, the mean TBSA for LPG burns was only ~31% [7]. In current study mortality (nearly 50%) was also dramatically higher than reported elsewhere: the Chinese series had 4.1% mortality, and the Rwandan cohort 16% [7, 8]. These differences likely reflect the predominance of high-pressure cylinder blasts in our population, whereas in other settings, gas burns more often result from slow leaks or cooking accidents. Prior studies in nearby countries reinforce these patterns. In India, LPG burns have been rising in recent decades as LPG usage has increased. Previous studies found that LPG incidents accounted for about 11% of all burns in one year, with 80% due to leakage, mainly from cylinders or pipes. In our series, most LPG burns also arose from gas leaks or cylinder failures; in fact, the majority were caused by cylinder blasts, consistent with the "kitchen bomb" effect described in the literature [6, 10-13]. These comparisons suggest that while LPG is often safer than open fire or kerosene, its misuse or equipment failure can produce far more devastating injuries than typical cooking burns. Current outcomes align with overall burn trends in Pakistan but highlight the particular danger of LPG blasts. A recent Pakistani burn registry review (all causes) reported an overall in-hospital mortality of ~23%, whereas our LPG-specific cohort had substantially higher deaths. Likewise, the national burn center found that burns >50% TBSA predicted high mortality, a finding evident in our LPG patients, most of whom exceeded that threshold [14]. Inhalation injuries and delayed presentation (common in rural LPG accidents) likely compound mortality. The alarming impact of LPG burns in developing countries calls for urgent preventive action. Experience from other LMICs illustrates effective approaches. For example, the WHO advocates multi-pronged burn prevention strategies: education campaigns, improved stove design, and stringent safety regulations [15, 16]. In Brazil and Japan, for instance, regulatory agencies mandate rigorous cylinder manufacturing standards, regular inspections, and recertification, greatly reducing accidents [17-19]. Public awareness is also crucial. Community-based education in high-burn regions has improved safe cooking practices [20]. In Rwanda, researchers noted that increased LPG adoption (for clean fuel goals) was accompanied by targeted safety initiatives to mitigate burn risk [8]. In Indonesia, simple interventions such as replacing old hoses and promoting periodic equipment checks were recommended after studies showed that most LPG burns stemmed from worn stove parts [7]. Similarly, community outreach programs and "safe stove" distribution in Bangladesh and Nepal have demonstrated modest reductions in home burn incidence. Given our findings, Pakistan could adopt similar policies: enforce quality standards for cylinders and valves, mandate regular cylinder testing or exchange programs, and run public campaigns on LPG safety (e.g., checking for leaks, keeping stoves outdoors). Clinics and burn centers should also educate patients and the public. Environmental interventions, such as designing pressure-relief valves or flame arrestors on cylinders, could further reduce explosions. Importantly, collaborative efforts are needed: government regulation must be paired with community education and industry cooperation to ensure both the supply of safe equipment and informed users [16]. This study has several limitations. It is retrospective and based at a single tertiary care center, so referral bias may over-represent severe cases and limit generalizability. Hospital records may omit some details (e.g., precise leak source or pre-hospital care), and data abstraction relies on chart accuracy. Assessment of burn size (TBSA) and inhalation injury may vary between clinicians, introducing inter-observer variability. The lack of a control group and the absence of long-term follow-up data are additional constraints. Like other registry-based analyses, we could not capture injuries treated outside our center or long-term quality-of-life outcomes. Despite these limitations, our large cohort provides valuable insight into a relatively understudied injury type in Pakistan.

CONCLUSIONS

This study highlights the extreme severity of LPG cylinder accidents in Pakistan. In our series of patients, the majority sustained large flame burns (often >60% TBSA) and had very high mortality rates, far exceeding those reported in most other countries. These findings underscore the

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critical need for prevention: enforcing safety regulations on LPG equipment, educating users, and implementing technology fixes. The burden of LPG burns must be urgently addressed through combined policy, educational, and engineering strategies to protect vulnerable households and reduce avoidable burn deaths.

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Authors Contribution

Conceptualization: ST, SG
Methodology: SG, JM
Formal analysis: ST, MM, AB
Writing review and editing: ST, SG, MT, AB, JM

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Adjunctive Use of Chlorhexidine and Metronidazole Gels in Periodontal Disease: An Observational Study

Sitwat Sagheer[1], Talea Hoor[1], Farzeen Tanwir[2], Izrum Shafi Rajput[3*], Syeda Javeria Ikram[3] and Urooj Zafar[4]

[1]Department of Pharmacology, Bahria University Health Science Campus, Karachi, Pakistan
[2]Department of Periodontology, Bahria University Health Science Campus, Karachi, Pakistan
[3]Department of Pharmacology and Therapeutics, Baqai Medical College, Baqai Medical University, Karachi, Pakistan
[4]Department of Pharmacology and Therapeutics, Baqai Dental College, Baqai Medical University Karachi, Pakistan

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***Corresponding Author:**
Izrum Shafi Rajput
Department of Pharmacology and Therapeutics, Baqai Medical College, Baqai Medical University, Karachi, Pakistan
izrumnafees@gmail.com

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ABSTRACT

Periodontal inflammation is characterized by gingival bleeding, pocket formation, and compromised oral health. **Objectives:** To evaluate the periodontal effects of Chlorhexidine (CHX) gel and Metronidazole (MET) gel in individuals with periodontal inflammation. **Methods:** This observational longitudinal study included a total of 48 participants who were enrolled at the Dental OPD and divided into two groups. Group A received 0.2% CHX gel, and Group B received 0.8% MET gel. Both gels were applied twice daily for 14 days following scaling and root planing. Oral hygiene maintenance and adherence to gel application were monitored through patient diaries and follow-up visits. Clinical parameters, including bleeding on probing (BOP), probing depth (PD), periodontal index score, and oral hygiene index (OHI), were recorded at baseline and after 14 days using a standardized periodontal probe. **Results:** In the CHX group, BOP significantly reduced from 26.13 ± 8.14 to 15.38 ± 6.36 ($p = 0.001$), while OHI improved from 22.67 ± 5.55 to 5.71 ± 2.90 ($p < 0.001$). Similarly, the MET group demonstrated a significant reduction in BOP from 24.67 ± 3.25 to 8.58 ± 3.78 ($p < 0.001$) and OHI from 24.58 ± 5.11 to 6.71 ± 3.22 ($p < 0.001$). However, no significant change was observed in probing depth for either group (CHX: $p = 0.705$; MET: $p = 0.705$). **Conclusions:** The use of CHX and MET gels significantly decreases BOP and improves OHI, but no significant change was on probing depth, demonstrating their effectiveness in reducing periodontal inflammation without affecting pocket depth.

INTRODUCTION

Periodontal diseases, including gingivitis and periodontitis, are among the most prevalent oral health concerns worldwide. These conditions primarily result from the accumulation of dental plaque, a key etiological factor [1]. Plaque buildup triggers an inflammatory response that can lead to the loss of gingival tissue, bone, and periodontal ligament, ultimately forming periodontal pockets and increasing the risk of tooth loss [2]. Dental plaque consists of bacterial colonies embedded within a matrix of salivary glycoproteins and extracellular components [3]. Research shows that chronic periodontitis develops due to a variety of microorganisms, which both initiate and advance the disease condition [4]. The bacterial biofilm is mainly disturbed through mechanical methods like scaling and root planing. However, studies indicate that mechanical debridement by itself may occasionally be inadequate in eliminating the microorganisms responsible for periodontal diseases. For this reason, chemical agents for plaque removal have become increasingly favored as supplementary treatments alongside mechanical therapy [5, 6]. The primary objective in managing gingivitis is the elimination

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of disease-causing bacterial pathogens, which has led to the use of multiple treatment approaches, including systemic and topical antimicrobial therapies. However, prolonged use of systemic antibiotics can result in the development of resistance and may also cause adverse effects such as nausea and diarrhea. Consequently, topical antimicrobial agents such as Chlorhexidine and Metronidazole have gained increasing attention for their ability to directly target periodontal pathogens. When combined with mechanical plaque removal, these agents not only improve treatment outcomes but also help to more effectively slow the progression of the disease [6, 7]. Chlorhexidine is widely regarded as the gold standard among antiseptic mouth rinses due to its broad-spectrum antimicrobial activity and strong substantivity. Its mechanism of action involves disruption of bacterial cell walls, which causes cytoplasmic leakage and ultimately leads to cell death. Recent clinical studies and meta-analyses have demonstrated modest but significant improvements with its use. Sustained-release delivery systems, such as chlorhexidine chips, have shown greater clinical efficacy with probing depth reductions of about 0.5–0.6 mm and improvements in gingival indices at one to three months, while gels demonstrated less consistent benefits [8, 9]. Chlorhexidine demonstrates potent antibacterial action in periodontal pockets through the rapid binding of its positively charged molecules to negatively charged bacterial cell surfaces. It is considered safe, with limited issues of patient tolerance and low potential for microbial resistance. Nonetheless, its fast elimination from the periodontal pocket quickly reduces the local concentration to below therapeutic levels following subgingival application, resulting in diminished treatment efficacy [10]. Although it is effective, its long-term use is often discouraged based on the side effects experienced: an unpleasant taste, possible taste alteration, and undesirable tooth staining, which may pose a compliance problem with the patients [11]. Metronidazole is a well-established antimicrobial agent with selective activity against obligate anaerobes, particularly Gram-negative rods and spirochetes commonly implicated in periodontal infections. Local delivery of metronidazole gel has been shown to significantly reduce bacterial load in gingival crevicular fluid, thereby aiding in infection control [12]. Research has shown that Metronidazole gel is effective in bringing down the total number of bacteria in the gingival crevicular fluid, helping in controlling periodontal infection [13]. While Metronidazole gel has shown promising antibacterial effects, its additional benefits beyond mechanical debridement remain controversial [14]. Several studies have evaluated the systemic use of metronidazole alone or in combination with scaling and root planing (SRP) for the management of gingivitis. These investigations have demonstrated notable improvements in both microbiological and clinical parameters [15]. Such favorable outcomes have also contributed to a reduced need for surgical interventions targeting the gingiva and supporting periodontal structures. Furthermore, the local application of metronidazole in gel form, delivered directly to pathogen-specific sites, has been shown to achieve higher drug concentrations at the targeted area [16]. Chlorhexidine, while regarded as the gold standard, is limited by rapid clearance from periodontal pockets and adverse effects such as staining and altered taste, which affect compliance. Metronidazole, on the other hand, demonstrates selective antimicrobial activity against anaerobic pathogens, but evidence regarding its long-term benefits as a locally delivered gel remains inconsistent.

This study aims to evaluate the efficacy of chlorhexidine (CHX) and metronidazole (MET) gels as adjunctive therapies to mechanical debridement in reducing periodontal inflammation and improving oral hygiene parameters.

METHODS

This observational longitudinal study was conducted at Bahria University Medical Sciences, Karachi, with ethical approval from its Ethical Review Committee (Ref. No. ERC 71/2022). The study took place at the Dental Periodontal OPD from November 2022 to April 2023, and institutional consent was obtained before commencement. A total of 48 participants aged 25–50 years diagnosed with periodontitis were recruited based on specific eligibility criteria. The sample size was calculated using the OpenEpi sample size calculator with a 95% confidence interval, 80% study power, and a 5% margin of error, which required a minimum of 42 participants; however, 48 were enrolled using a convenience sampling method to account for potential dropouts. Inclusion criteria required patients to have more than 20 teeth, a probing depth of 4–6 mm in at least two teeth per quadrant, and confirmed periodontitis, along with adherence to proper oral hygiene practices. Patients were excluded if they were pregnant or lactating, had dental prostheses, had undergone periodontal therapy in the last six months, or had a history of smoking, smokeless tobacco use, or allergy to metronidazole or chlorhexidine. Those with craniofacial syndromes, medications affecting gingival conditions (e.g., nifedipine, cyclosporine, phenytoin), or systemic diseases such as diabetes mellitus, cardiovascular disease, hematologic disorders, or immunodeficiency were also excluded. Informed consent was obtained in both Urdu and English from all participants. Participants were categorized into two groups based on the treatment they were already receiving at the Dental OPD. Group A included patients

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using 0.2% Chlorhexidine (CHX) gel, while Group B comprised those using 0.8% Metronidazole (MET) gel. Both gels were applied twice daily for three minutes, in the morning and evening, following scaling and root planing, for a period of 14 days. Oral hygiene practices and adherence to antiseptic gel application were observed as part of routine periodontal care. Participants were observed over 14 days, with two follow-up visits: one at day 7 to monitor adherence and oral hygiene practices, and a final assessment at day 14, at which endpoint periodontal parameters (OHI, BOP, PD) were recorded. Compliance was monitored using patient-maintained logs, periodic follow-up visits, and reminders by the research team. Data were collected by two trained investigators who conducted comprehensive periodontal assessments, including probing depth (PD), bleeding on probing (BOP), and Oral Hygiene Index (OHI). Baseline examinations were performed after scaling, root planing, and polishing to ensure uniform starting conditions. Clinical examinations were performed using a standard dental examination set, which included a mouth mirror, periodontal probe, and tweezers. Clinical parameters were recorded at baseline and at the 14-day follow-up, including the Oral Hygiene Index-Simplified (OHI-S), bleeding on probing (BOP), and probing depth (PD). The OHI-S, developed by Greene and Vermillion in 1964, evaluates oral hygiene status based on the presence of debris and calculus, using six representative tooth surfaces to provide a practical and reliable assessment [17]. Additionally, a CPITN (Community Periodontal Index of Treatment Needs) probe was used for assessing periodontal status. All instruments were sterilized according to standard infection control protocols prior to use, and measurements were conducted by trained investigators to ensure accuracy and consistency [18]. Data were analyzed using SPSS version 23.0. Descriptive statistics were presented as mean ± standard deviation for quantitative variables, while qualitative data were expressed as frequencies and percentages. Kolmogorov–Smirnov test assessed data normality. Independent sample t-tests were used for normally distributed variables, while Mann-Whitney U tests analyzed non-normally distributed variables. Chi-square tests compared categorical variables, and paired t-tests assessed within-group pre- and post-treatment differences. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 55 individuals were initially assessed for eligibility. After screening, a total of 48 participants meeting the inclusion criteria were included in the study, and all completed the study without any dropouts. Among the participants, 16 were female (33.3%) and 32 were male (66.7%). Marital status distribution showed that 3 individuals (6.3%) had never married, 41 (85.4%) were married, and 4 (8.3%) were previously married. In terms of educational background, 6 participants (12.5%) had no formal qualifications, 22 (45.8%) had qualifications below a degree level, and 20 (41.7%) held a degree or higher. Occupationally, 6 individuals (12.5%) were professionals, 20 (41.7%) were in intermediate-level jobs, 14 (29.2%) were manual workers, and 8 (16.7%) were unemployed. Regarding medical history, 18 participants (37.5%) had documented health conditions, while 30 (62.5%) reported no prior medical issues. This demographic data provides a comprehensive overview of the study population, aiding further analysis of potential health-related associations (Table 1).

Table 1: Frequency Distribution of Socio-Demographic Data

Demographic Data	Category	n (%)	Within Groups (CHX)	Within Groups (MET)	p-Value
Gender	Female	16 (33.3%)	33.3%	33.3%	0.620
	Male	32 (66.7%)	66.7%	66.7%	
Marital Status	Never married	3 (6.3%)	4.2%	8.3%	0.836
	Married	41 (85.4%)	87.5%	83.3%	
	Divorced/Widowed	4 (8.3%)	8.3%	8.3%	
Educational Level	No qualification	6 (12.5%)	12.5%	12.5%	0.179
	Degree	20 (41.7%)	54.2%	29.2%	
Occupation	Professional	6 (12.5%)	20.8%	4.2%	0.325
	Intermediate	20 (41.7%)	33.3%	50.0%	
	Manual	14 (29.2%)	29.2%	29.2%	
	Unemployed	8 (16.7%)	16.7%	16.7%	
Medical History	Present	18 (37.5%)	33.3%	41.7%	0.766
	Absent	30 (62.5%)	66.7%	58.3%	

CHX: Chlorhexidine gel, MET: Metronidazole gel
*p < 0.05 indicates statistical significance

The number of teeth remained unchanged, with a mean of 25.54 ± 2.23 in the CHX group and 24.33 ± 1.88 in the MET group. Both Bleeding on Probing (BOP) and Oral Hygiene Index (OHI) showed significant reductions in both groups (BOP: CHX 26.13 ± 8.14 to 15.38 ± 6.36, MET 24.67 ± 3.25 to 8.58 ± 3.78, p<0.001; OHI: CHX 22.67 ± 5.55 to 5.71 ± 2.90, MET 24.58 ± 5.11 to 6.71 ± 3.22, p < 0.001). Probing Depth (PD) decreased in both groups (CHX 2.11 ± 0.65 to 1.25 ± 0.43; MET 2.35 ± 0.73 to 1.31 ± 0.57), but the change was not statistically significant (p=0.705) (Table 2).

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Table 2: Pre-Post Comparison of Periodontal Parameters Between CHX and MET Groups

Parameter	Group	Baseline Mean ± SD	Endpoint Mean ± SD	% Change	Cohen's d	t-Value	p-Value
Bleeding on Probing (BOP)	CHX	26.13 ± 8.14	15.38 ± 6.36	-41.1%	1.47	-4.496	0.001*
	MET	24.67 ± 3.25	8.58 ± 3.78	-65.2%	4.56	-4.496	0.000*
Probing Depth (PD)	CHX	2.11 ± 0.65	1.25 ± 0.43	-40.8%	1.56	-0.381	0.705
	MET	2.35 ± 0.73	1.31 ± 0.57	-44.3%	1.59	-0.381	0.705
Oral Hygiene Index (OHI)	CHX	22.67 ± 5.55	5.71 ± 2.90	-74.8%	3.83	-3.845	0.000*
	MET	24.58 ± 5.11	6.71 ± 3.22	-72.7%	4.61	-3.845	0.000*

In both CHX and MET groups, Bleeding on Probing (BOP) showed a significant reduction from baseline to endpoint (CHX: 26.13 ± 8.14 to 15.38 ± 6.36, t=-4.496, p=0.001; MET: 24.67 ± 3.25 to 8.58 ± 3.78, t=-4.496, p<0.001). Oral Hygiene Index (OHI) also improved significantly in both groups (CHX: 22.67 ± 5.55 to 5.71 ± 2.90, t=-3.845, p < 0.001; MET: 24.58 ± 5.11 to 6.71 ± 3.22, t = -3.845, p < 0.001). Probing Depth (PD) decreased in both groups (CHX: 2.11 ± 0.65 to 1.25 ± 0.43; MET: 2.35 ± 0.73 to 1.31 ± 0.57), but the changes were not statistically significant (t=-0.381, p=0.705). These results indicate that both CHX and MET gels were effective in reducing gingival bleeding and improving oral hygiene, while reductions in PD were modest and not statistically significant (Table 3).

Table 3: Pre- and Post-Treatment Comparison of Periodontal Parameters in CHX and MET Groups

Parameter	Group	N	Baseline Mean ± SD	Endpoint Mean ± SD	t-Value	p-Value
Bleeding on Probing (BOP)	CHX	24	26.13 ± 8.14	15.38 ± 6.36	-4.496	0.001*
	MET	24	24.67 ± 3.25	8.58 ± 3.78	-4.496	0.000*
Probing Depth (PD)	CHX	24	2.11 ± 0.65	1.25 ± 0.43	-0.381	0.705
	MET	24	2.35 ± 0.73	1.31 ± 0.57	-0.381	0.705
Oral Hygiene Index (OHI)	CHX	24	22.67 ± 5.55	5.71 ± 2.90	-3.845	0.000*
	MET	24	24.58 ± 5.11	6.71 ± 3.22	-3.845	0.000*

CHX: Chlorhexidine gel, MET: Metronidazole gel
*p < 0.05 indicates statistical significance

DISCUSSIONS

Scaling and root planing (SRP) remains the standard non-surgical treatment for periodontitis, effectively removing supra- and subgingival deposits. However, in moderate to severe cases, mechanical debridement alone may not fully eliminate pathogenic microorganisms. Adjunctive therapies, such as locally applied antimicrobial agents, have therefore been explored to enhance periodontal outcomes [14]. In this study, both locally delivered chlorhexidine (CHX) and metronidazole (MET) gels, used alongside SRP, significantly reduced bleeding on probing (BOP) over 14 days, with MET demonstrating a greater proportional reduction. These findings are consistent with previous reports indicating that both CHX and MET gels effectively improve gingival inflammation when used as adjuncts to mechanical therapy. MET may offer stronger suppression of gingival inflammation due to its targeted antimicrobial activity, although clinical superiority cannot be definitively claimed, as outcomes can be influenced by gel concentration, delivery method, patient compliance, and baseline inflammation [16, 19]. While BOP and oral hygiene improved markedly, probing depth reductions were not statistically significant. This is consistent with short-duration studies, where tissue remodeling and reattachment typically lag behind reductions in bleeding and plaque burden [20]. Innovations in local drug delivery, including sustained-release CHX and MET formulations, have shown promise in maintaining effective therapeutic concentrations over time [21]. Additionally, in vitro studies suggest a potential synergistic effect between CHX and MET against periodontal pathogens [22, 23]. The study's follow-up was limited to 14 days, which may not capture the full trajectory of periodontal healing or potential relapse. Also, while MET showed a stronger BOP reduction, we cannot conclusively claim superiority in all contexts. Variation in gel concentration, delivery formulation, compliance, and baseline inflammation can modulate outcomes. Nevertheless, our results support the efficacy of locally delivered CHX and MET gels in reducing gingival bleeding in periodontitis patients over a short period, and they somewhat favor MET for bleeding suppression in our cohort. Future studies with longer observation, microbiological assays, and possibly split-mouth randomized designs would solidify comparative advantages.

CONCLUSIONS

In conclusion, both CHX and MET gels significantly reduced bleeding on probing; however, the MET group demonstrated a greater reduction, achieving a notably lower BOP value at the 14-day follow-up. Probing depth remained unchanged in both groups, and while improvements were observed in the oral hygiene index, these changes did not reach statistical significance. These findings suggest that both treatments are effective in reducing periodontal inflammation, as evidenced by the decrease in BOP, but they do not significantly impact probing depth or overall oral hygiene within the study period.

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Authors Contribution

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

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Correlation Between Spinopelvic Sagittal Alignment Parameters and Low Back Pain

Muhammad Bilal[1*], Faizan Ali Janjua[1], Abdullah Jan[1], Asif Ali Jatoi[1], Muhammad Asad Qureshi[1], and Ejaz Aslam[1]

[1]Department of Spine Surgery, Bahria International Hospital, Bahria Town, Islamabad, Pakistan

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***Corresponding Author:**
Muhammad Bilal
Department of Spine Surgery, Bahria International Hospital, Bahria Town, Islamabad, Pakistan
lalibkhn@gmail.com

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ABSTRACT

Low back pain is a common musculoskeletal disorder with a major socioeconomic impact. Understanding its association with spinopelvic alignment may enhance diagnosis and treatment by identifying key biomechanical factors linked to symptom severity. **Objectives:** To assess the relationship among spinopelvic parameters and low back pain severity. **Methods:** This retrospective study was conducted at Bahria International Hospital, Rawalpindi, Pakistan, including 150 patients. Full-spine standing X-rays were used to assess sagittal vertical axis, sacral slope, pelvic tilt, pelvic incidence, and lumbar lordosis using Surgimap® software. A visual analog scale was used to measure the severity of the pain, and Pearson correlation analysis was performed to determine associations between spinopelvic parameters and LBP severity. **Results:** Pelvic tilt showed a positive correlation with lumbar pain, which is significant ($r=0.52$, $p<0.001$) and radicular pain ($r=0.33$, $p=0.002$). Sagittal vertical axis was also positively correlated with lumbar ($r=0.47$, $p<0.001$) and radicular pain ($r=0.38$, $p=0.001$). A significant negative correlation of lumber lordosis was exhibited with both lumbar ($r=-0.49$, $p<0.001$) and radicular pain ($r=-0.41$, $p<0.001$). No significant correlation was found for PI or SS. **Conclusions:** Pelvic tilt and sagittal vertical axis positively correlate with low back pain severity, whereas lumbar lordosis exhibits a protective role. These findings emphasize the importance of spinopelvic alignment in low back pain pathophysiology.

INTRODUCTION

One of the most prevalent musculoskeletal ailments is low back pain (LBP). LBP affects approximately 65% to 80% of individuals during their lifetime. Globally, an estimated 568 million people are affected by LBP, making it the foremost cause of years lived with disability [1]. Despite its high prevalence, identifying a precise nociceptive source for LBP remains challenging in most cases. A small proportion of cases are attributed to identifiable pathological conditions such as spinal fractures, malignancies, or infections. The majority result from a complex interplay of factors, including disc degeneration, facet joint osteoarthritis, paraspinal muscle dysfunction, and psychosocial influences [2]. Among the known causes, degenerative disc disease (DDD) is the most frequently recognized factor in LBP. Magnetic resonance imaging (MRI) findings, including Modic changes and the Pfirrmann grading system, are commonly employed to classify DDD in clinical settings. Additionally, the zygapophyseal (facet) joints have been identified as a significant source of back pain. Percutaneous interventions targeting these joints have shown effectiveness in alleviating discomfort [3]. Dysfunction of the paraspinal muscles is another critical contributor. Its evidence linking increased disability in LBP patients to muscular impairment. Psychological aspects such as depression, anxiety, catastrophizing, and self-efficacy further compound the complexity of LBP, predisposing affected individuals to chronic disability [1]. The concept of spinopelvic alignment has emerged as a crucial factor in understanding LBP pathogenesis. Dubousset's "cone of economy" describes how the axial

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skeleton works in concert to maintain an efficient standing posture. This includes the functioning of feet, lower limbs, pelvis, spine, and cranium. Any imbalance in these structures leads to increased muscular activity and energy expenditure, resulting in back pain and fatigue [4]. Thus, assessing spinopelvic parameters is essential in evaluating sagittal alignment and its correlation with LBP. The key parameters defining sagittal spinopelvic alignment include sacral slope (SS), pelvic tilt (PT), pelvic incidence (PI), and lumbar lordosis (LL). A fixed anatomical parameter is PI, which represents the angle between a line created from the sacral endplate's center to the femoral head's midpoint. Additionally, another perpendicular line is drawn to the sacral endplate as well. SS is the angle between the upper sacral endplate and a horizontal reference line. PT measures pelvic alignment in the sagittal plane and LL reflects the curvature of the lumbar spine, which plays a crucial role in maintaining balance [2]. Abnormal sagittal alignment may contribute to mechanical stress, compensatory muscle activity, and pain generation.

This study aims to determine the correlation between parameters of spinopelvic sagittal alignment and LBP in individuals without prior spinal surgery or deformities.

METHODS

This retrospective study was conducted from February 2025 to July 2025 at Bahria International Hospital, Rawalpindi, Pakistan. The study was carried out after ethical approval from the ethical review board of Bahria International Hospital, Rawalpindi, Pakistan (Ref. No. BARMT-BIH-8-RWP-HR-F-37). Participants' informed consent was not taken. A total of 150 patient records were eligible for inclusion in the study. The sample size was calculated using the flowing formula [5], with a confidence level of 95%, a margin of error of 8%, and an assumed correlation coefficient of 0.3 between spinopelvic parameters and VAS scores, based on previous literature.

$$\frac{(Z\frac{\alpha}{2}+Z_{\beta})^2}{(0.5\times 1n\frac{1+r}{1-r})^2}+3$$

Using this formula, the minimum sample size was estimated to be 85 patients; however, 150 eligible records were included to enhance statistical power and account for incomplete data. Patients included were those aged 25 to 65 years who presented with mechanical low back pain of more than six weeks duration (chronic), with or without radiculopathy, and were diagnosed with single-level lumbar disc herniation (LDH) on MRI. The age range of 25 to 65 years was chosen to focus on the working-age population most commonly affected by mechanical low back pain, while excluding pediatric and elderly individuals, who typically have different pathophysiological mechanisms. Patients with radiculopathy were not separately analyzed but were included only if MRI confirmed LDH without central or foraminal stenosis. All included cases had undergone complete clinical examination, including assessment of deep tendon reflexes, sensory testing, straight leg raise (SLR), and motor strength grading. MRI confirmed disc herniation at L4-L5 or L5-S1 levels, with no signs of spinal canal stenosis or cord compression. MRI findings were limited to single-level herniation at L4-L5 or L5-S1 levels without spinal canal stenosis, foraminal narrowing, or cord compression. The data were gathered from electronic medical histories and imaging archives. Patients with acute LBP (less than 6 weeks), history of recent trauma, or red flag signs such as unexplained weight loss or neurological deficits suggesting cauda equina were excluded. The patients who were excluded also had uncontrolled hypertension, malignancies, osteoporosis, prior spinal trauma or fractures, diabetes mellitus, and metabolic disorders. These disorders included metabolic bone diseases and hypo- or hyperthyroidism. Patients with even controlled diabetes were excluded to eliminate confounding effects on spinal pathology. Additionally, individuals with a history of lumbar surgery, spondylolisthesis, spinal canal narrowing, or any other structural spinal abnormality were excluded. Patients with a BMI greater than 30.0 kg/m^2 were also excluded to reduce confounding due to obesity-related biomechanical alterations. To ensure the specific assessment of spinopelvic parameters, only patients without coronal plane deformities were included. Patients who had previously undergone thoracic, abdominal, or spinal surgery or had a history of spinal malignancies, vertebral fractures, or infections were excluded. Routine inflammatory markers (ESR and CRP) were available in records for most patients and were within normal range, ruling out infectious causes like TB or brucellosis. None of the patients in the study underwent surgical intervention. All were managed conservatively with analgesics, muscle relaxants, physiotherapy (including core strengthening and postural training), and ergonomic counseling. Surgical management was not indicated based on absence of red flag symptoms, lack of progressive neurological deficits, and good response to conservative treatment as per clinical notes. Spinopelvic parameters were assessed using full-spine standing X-rays. All X-rays were performed in the same standardized standing position with patients instructed to keep knees extended and arms flexed with hands resting on the clavicles. The Surgimap® program, Version 2.3.0.1(NY, USA), was employed to measure sagittal spinopelvic alignment parameters, including sagittal vertical axis (SVA), sacral slope (SS), pelvic tilt (PT), pelvic incidence (PI), and lumbar lordosis (LL). PI was determined as the angle created by a line drawn from femoral head's

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center to sacral plate's midpoint. A vertical line to the sacral plate is also a part of it. It is thought to be an immovable anatomical parameter that does not change with the change of posture. Cobb method was used to measure lumbar lordosis, assessing the angle between the L1's superior endplate and the S1's superior endplate. Sacral slope was determined as the angle between the upper sacral endplate and a horizontal reference line, whereas a lower SS specifies an extra vertical sacrum, and an elevated SS suggests a more horizontal sacrum. The angle between the vertical axis and a line connecting the sacral plate's midpoint to the bi-coxo-femoral axis is determined as Pelvic tilt. The relationship between these parameters follows the formula PI = SS + PT. Severity of the pain was calculated by using a visual analog scale (VAS), where patients were presented with a 10-cm horizontal line reaching from one side of "no pain" to other side of "worst pain imaginable". Pain scores were extracted from previous medical records, ensuring consistency in assessment across patients. Outcome measure included VAS scores recorded at initial presentation. No follow-up pain scores or functional outcome data (such as Oswestry Disability Index) were available due to retrospective design limitations. Due to the retrospective nature, no follow-up data were available regarding recurrence, disease course, or transition to surgical management. Measurements of radiographic parameters were all performed by a single trained investigator. To minimize variability and enhance consistency, each measurement was repeated twice at different time points, and the average value was used. SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA) was used to carry out statistical analyses. The relationship between spinopelvic parameters and LBP severity was examined using Pearson correlation coefficients. Data normality was confirmed using the Shapiro-Wilk test. A statistically significant p-value is considered as ≤0.05. Correlation strength was considered weak for the ranges from 0.2 to 0.39, moderate for 0.4 to 0.59, strong for 0.6 to 0.79, and very strong for the ranges between 0.8 to 1. This study builds upon prior local research conducted by Chughtai (2023), which also investigated correlations between spinopelvic parameters and chronic low back pain; however, the present study incorporates a larger sample size, more stringent exclusion criteria, and standardized radiographic measurements using dedicated software tools [6].

RESULTS

The study comprised a total of 150 patients with low back pain. The mean age of the participants was 47.21±10.32 years, with males 78(52%) and females 72(48%). The mean range of BMI was 26.81±2.92 kg/m (Table 1).

Table 1: Demographic Features of the Population

Variables	Mean ± SD	Range
Age (years)	47.21 ± 10.32	25–65
BMI (kg/m^2)	26.81 ± 2.92	21.33 – 29.92
Male (%)	78 (52)	–
Female (%)	72 (48)	–

The spinopelvic sagittal alignment parameters were evaluated using standing full-spine X-rays. The mean pelvic incidence (PI) was 50.31 ± 8.23°, pelvic tilt (PT) was 18.74 ± 5.13°, sacral slope (SS) was 31.62±7.41°, sagittal vertical axis (SVA) was 26.93± 8.64 mm, and lumbar lordosis (LL) was 42.41 ± 9.71° (Table 2).

Table 2: Spinopelvic Parameters of the Study Population

Parameters	Mean ± SD	Range
Pelvic Incidence (°)	50.31 ± 8.23	38–67
Pelvic Tilt (°)	18.74 ± 5.13	10–29
Sacral Slope (°)	31.62 ± 7.41	18–47
Sagittal Vertical Axis (mm)	26.93 ± 8.64	12–48
Lumbar Lordosis (°)	42.41 ± 9.71	25–60

Severity of the pain was evaluated by incorporating the visual analog scale (VAS), with a mean lumbar VAS score of 5.81±1.91 and a mean radicular VAS score of 4.31±2.11 (Table 3).

Table 3: Pain Severity Scores (VAS) Among Study Participants

Pain Type	Mean ± SD	Range
Lumbar VAS Score	5.81 ± 1.91	2–9
Radicular VAS Score	4.31 ± 2.11	1–8

Correlation analysis was performed between spinopelvic parameters and low back pain severity. A significant positive correlation was found among pelvic tilt and lumbar VAS scores ($r=0.52$, $p<0.001$), indicating that an increased PT was associated with greater pain severity. Similarly, sagittal vertical axis showed a weak positive correlation with lumbar VAS scores ($r=0.47$, $p<0.001$). Conversely, lumbar lordosis showed a significant negative correlation along with lumbar pain severity ($r=-0.49$, $p<0.001$), suggesting that reduced LL was linked to more severe pain. Pelvic incidence and sacral slope were not significantly correlated with pain scores ($p>0.05$) (Table 4).

Table 4: Correlation Between Spinopelvic Parameters and Pain Severity

Parameter	Lumbar VAS (r)	p-Value	Radicular VAS (r)	p-Value
Pelvic Incidence	0.12	0.14	0.09	0.21
Pelvic Tilt	0.52	<0.001	0.33	0.002*
Sacral Slope	0.08	0.26	0.10	0.18
Sagittal Vertical Axis	0.47	<0.001	0.38	0.001*
Lumbar Lordosis	-0.49	<0.001	-0.41	<0.001*

Values represent Pearson correlation coefficients (r) with corresponding p-values. A p-value <0.05 was considered

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statistically significant, shown with(*)
Representative imaging examples of MRI and standing full-spine X-rays showing lumbar disc degeneration and spinopelvic alignment parameters(Table 5).

Table 5: Representative Imaging Examples from Study Participants

Imaging Type	Description
MRI Lumbar Spine	L4-L5 disc bulge with nerve root compression and loss of disc height
MRI Lumbar Spine	L5-S1 disc desiccation with posterior protrusion
Standing Full-Spine changes X-ray	Increased pelvic tilt and reduced lumbar lordosis indicating sagittal imbalance
Standing Full-Spine X-ray	Normal spinopelvic alignment with balanced sagittal profile

DISCUSSIONS

When the body's center of gravity is maintained within a cone centered on the trunk, energy consumption is minimized, according to Muraoka's cone of economy concept [7]. Alterations in spinal alignment increase energy expenditure, pain, disability, and psychological distress. Lateral X-ray parameters such as pelvic tilt (PT), pelvic incidence–lumbar lordosis mismatch (PI-LL), and sagittal vertical axis (SVA) are closely linked with back pain and disability, and serve as sagittal modifiers in the SRS–Schwab classification for spinal deformity [2, 8]. Degenerative changes, including disc degeneration and facet joint arthritis, are also associated with sagittal misalignment [9]. In adults with spinal deformity, elevated SVA correlates with poor health-related quality of life and low back pain (LBP)[10]. Oakley *et al.* reported that kyphotic individuals experience greater back pain, impaired gait, reduced balance, and higher fall risk [11]. Consistent with previous findings, our results demonstrate that both mild degenerative changes and severe deformities are linked to higher SVA values, reflecting increased disability and pain. Although several studies have examined associations between spinopelvic parameters and LBP, results remain mixed. Moreno-Mateo *et al.* observed no significant sagittal parameter differences between asymptomatic individuals and LBP patients. Similarly, Sugavanam *et al.* found no sagittal alignment between patients with L5–S1 degeneration and those with normal radiographs [2, 12]. Conversely, Quintana *et al.* reported that patients with lumbar degenerative disease exhibited higher PT, lower sacral slope (SS), and reduced thoracic kyphosis compared with controls, while Cha and Park noted distinct lumbar lordosis differences between LBP patients and matched controls [13, 14]. Such discrepancies underscore the need for further research to clarify the precise role of spinopelvic parameters in LBP pathogenesis [15-17]. Current findings align with those studies reporting altered spinopelvic parameters among LBP patients, particularly increased SVA, decreased lumbar lordosis (LL), and elevated PT. According to Che *et al.*, reduced LL combined with higher PT and smaller SS produces greater compressive disc forces, promoting degeneration and discogenic back pain [18]. Sun *et al.* observed that individuals with type 2 LL had a higher incidence of LBP than controls (37.4% vs 23.3%, $p<0.05$), whereas Roussouly type 3 was more prevalent among controls (38.9% vs 47.7%, $p<0.05$) [19]. No significant differences were found for types 1 and 4 [20]. The authors concluded that LBP was more frequent in subjects with smaller SS and flatback morphology. Although PI did not differ between groups, their findings agree with ours, showing a correlation between PT and pain intensity (VAS), but not PI. We also noted a modest, though not statistically significant, association between disability and PI-LL ($p=0.08$), consistent with studies linking PI-LL mismatch to poor postoperative outcomes following spinal instrumentation [21]. Previous studies proposed that compensatory mechanisms driven by disc degeneration underlie type 2 LL in LBP patients [14]. Clinically, these results suggest that even in the absence of overt spinal deformity, altered sagittal balance, particularly increased SVA and PI-LL mismatch, may signal early spinal pathology. Thus, sagittal parameters should be incorporated into radiographic assessments of patients with non-specific LBP. For spine surgeons, the key message is that subtle imbalances in spinopelvic alignment should not be overlooked, as they may precede structural degeneration and chronic symptoms. The correlation between LBP and PI-LL supports previous studies that inherent spinopelvic configurations could predispose individuals to LBP [19]. Future longitudinal, multicenter studies are required to explore this hypothesis and relate spinopelvic parameters to long-term outcomes such as mobility, recurrence, and quality of life. The relatively low VAS scores in our cohort indicate mild symptoms and minimal functional impairment; yet, the observed associations between sagittal parameters and symptom severity highlight the importance of sagittal balance in the progression of spinal degeneration. This study's limitations include a small sample size, a single-center design, a lack of inter- or intra-observer reliability analysis, and the absence of a control group. Moreover, as a cross-sectional investigation, it cannot determine causality. Longitudinal research tracking patients over time could clarify whether specific sagittal morphologies predispose to chronic pain or degenerative progression, and whether early radiographic signs of imbalance predict future need for intervention or surgery. Such data would enhance early diagnostic and preventive strategies in degenerative lumbar disease. In

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summary, findings from this adult cohort without coronal deformity suggest that spinopelvic alignment has a significant influence on back pain and disability. While the relationship between sagittal parameters and health-related quality of life is not a novel concept, our results add to growing evidence supporting sagittal balance as a critical factor in the pathogenesis and clinical expression of LBP.

CONCLUSIONS

This study highlights a significant correlation between spinopelvic sagittal alignment parameters and low back pain severity. Increased pelvic tilt and sagittal vertical axis were related to higher pain scores, while reduced lumbar lordosis correlated with greater pain intensity. These findings underscore the position of sagittal balance in spinal biomechanics and pain perception. Early assessment and intervention may help prevent long-term complications. Future studies should explore these relationships in larger populations with longitudinal follow-up.

Authors Contribution

Conceptualization: AAJ
Methodology: MB, FAJ
Formal analysis: FAJ
Writing review and editing: MAQ, EA, AJ

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of Effectiveness of Intrathecal Tramadol versus Intravenous Tramadol in Prevention of Post-Anesthesia Shivering in Patients Undergoing Lower Limb Orthopedic Surgeries under Subarachnoid Block: A Comparative Study

Sameen Khalid[1], Humaira Ahmad[2], Muhammad Khalid[3] and Maliha Khalid[4*]

[1]District Headquarter Hospital, Faisalabad, Pakistan
[2]Department of Anesthesia, District Headquarter Hospital, Faisalabad, Pakistan
[3]Department of Anesthesia, Pakistan Air Force Teaching Hospital Mushaf, Sargodha, Pakistan
[4]Pakistan Air Force Teaching Hospital Mushaf, Sargodha, Pakistan

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***Corresponding Author:**
Maliha Khalid
Pakistan Air Force Teaching Hospital Mushaf, Sargodha, Pakistan
dowite18malyha@yahoo.com

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ABSTRACT

Shivering is a common spinal anesthetic side effect that occurs in 40-60% of people who have had subarachnoid block. Shivering is typified by spontaneous, involuntary, rhythmic fasciculation or skeletal muscular activation that resembles tremors. Hypothalamic thermoreceptors attempt to increase heat synthesis by shivering when they sense this drop in core body temperature due to peripheral heat redistribution. **Objectives:** To compare anti-shivering effects of intravenous versus intrathecal tramadol in patients receiving subarachnoid block for lower limb orthopedic operations. **Methods:** This Quasi-experimental study included 130 patients scheduled for elective orthopedic surgery under spinal anesthesia in the Operation Theater, Allied Hospital, Faisalabad. Patients were randomly divided into two groups: Group A (intrathecal tramadol with bupivacaine) and Group B (intravenous tramadol with intrathecal bupivacaine). The frequency of post-anesthesia shivering was recorded in both groups. **Results:** The mean ± SD of sensory and motor block duration in Group A was 331.72 ± 33.09 and 231.14 ± 11.22 minutes, respectively, while in Group B it was 228.12 ± 12.15 and 157.42 ± 10.02 minutes, respectively ($p<0.001$). Post-anesthesia shivering occurred in 9 (13.84%) patients in Group A and 23 (35.38%) patients in Group B ($p<0.05$). **Conclusions:** Post-anesthesia shivering was significantly higher in patients receiving intravenous tramadol (Group B) compared to those receiving intrathecal tramadol (Group A).

INTRODUCTION

Regional anesthesia is a conventional anesthesia technique which is comparatively easy with less complications [1]. Most of the orthopedic surgeries are done in spinal anesthesia because it provides excellent perioperative and postoperative analgesia with less blood loss [2]. However, one of the most common and challenging complication of this safer and preferred anesthesia technique is post spinal shivering (PSS) which occurs in 40-70% patients. Shivering is hypothesized to be a physiological response to perioperative hypothermia which occurs due to anesthesia induced inhibition of thermogenesis and peripheral vasodilatation causing heat loss. However, this thermoregulatory response has distressing effects on patients making vitals monitoring

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difficult [3]. Perioperative complications of shivering include increased oxygen consumption, hypercarbia, metabolic acidosis, tachycardia and hypertension which has deleterious effects especially on patients with reserved cardiac function [4]. Postoperative complications include delayed wound healing, increased wound pain and prolonged hospital stay. High incidence of PSS along with risk for several intra and post-operative complications makes its prophylaxis crucial. Several pharmacological and non-pharmacological interventions have been proposed for prevention of PSS. Non-pharmacological measures include use of blankets, surgical drapes, warm fluids, use of radiant heat and air warmers but are less effective and some are costly [5]. Pharmacological agents include pethidine, clonidine, low-dose ketamine, dexmedetomidine, dexamethasone, tramadol and magnesium sulfate [6-8]. There is no single globally agreed drug for prevention of PSS. However, tramadol is one of the most common agents used for shivering because of its low cost, easy availability and less side effects [9]. Tramadol is a weak synthetic opioid which acts as agonist of μ receptor and also inhibits reuptake of norepinephrine and 5-hydroxytryptamine which gives tramadol its thermoregulatory function [10]. There are many studies showing efficacy of intravenous tramadol in control of shivering. Previous studies compared intravenous nalbuphine 0.05 mg/kg to IV tramadol 1 mg/kg administered to treat post-spinal anesthesia shivering. He found that tramadol took less time to eliminate shivering than nalbuphine. Both medications had modest side effects and hemodynamic abnormalities. Recent researches have sparked interest in using tramadol as an adjuvant to bupivacaine given intrathecally, despite the fact that tramadol has been used intravenously for a long time to prevent and cure shivering. However, data in our local population is scarce. According to Abd El Azeem and his colleagues, they found that 8 patients (18.6%) in the intravenous group and 2 patients (4.6%) in the intrathecal group had post spinal shivering. (p=0.047).

This study aims to compare anti-shivering effects of intravenous versus intrathecal tramadol in patients receiving subarachnoid block for lower limb orthopedic operations.

METHODS

This Quasi-experimental study was conducted over six months from May 2024 to October 2024 at Allied Hospital, Faisalabad, after approval from the Institutional Ethical Committee (Ref. No. 48.ERC/FMU/2022-23/286), Faisalabad Medical University. A consecutive sampling technique was used to enroll 130 patients undergoing elective orthopedic surgery. Informed consent was obtained, and patients underwent pre-anesthesia evaluation a day before surgery and were instructed to fast for at least 8 hours. Randomization was done using random table number sequence using sealed envelopes, opened by the anesthesia team member to determine group allocation and prepare medications, ensuring blinding and minimizing bias. On the day of surgery, all patients received intravenous access, preloading with warmed Ringer's lactate (15 ml/kg) over 30 minutes, and standard monitoring was attached including heart rate, blood pressure, oxygen saturation, ECG, and temperature. Metoclopramide (10 mg) was given intravenously before surgery, and spinal anesthesia was given in sitting position with a 25-gauge Quincke needle. Patients were maintained on warmed intravenous fluids and closely monitored. Hypotension and bradycardia were defined as a 20% fall in systolic blood pressure and heart rate <50 beats/min, respectively, and treated accordingly. Post-spinal shivering was assessed using the Bedside Shivering Assessment Score (BSAS) within 24 hours, with grade 3 or 4 shivering treated using intravenous tramadol (0.5 mg/kg). The inclusion criteria were patients aged 21–60 years of either gender with ASA grades I and II, while exclusion criteria included uncontrolled comorbidities, major systemic disease, allergy to tramadol or bupivacaine, drug abuse, contraindications to spinal anesthesia, surgeries lasting >120 minutes, or failed spinal anesthesia requiring conversion to general anesthesia. Patients were divided into two groups: Group A (intravenous tramadol 25 mg) and Group B (intrathecal tramadol 10 mg with bupivacaine 15 mg). Sample size was calculated using the WHO calculator for two proportions with 95% confidence level, 80% power, P1=18.6% and P2=4.6% [11], yielding 130 patients. Data were analyzed using IBM-SPSS version 23.0, with quantitative variables (age, BMI, onset of block, duration of analgesia) expressed as Mean ± SD and qualitative variables (ASA grade, gender, shivering, complications) as frequencies and percentages. Chi-square test was applied with significance at $p < 0.05$.

RESULTS

The mean ± SD age of patients was 40.38 ± 10.56 years in Group A and 38.14 ± 7.53 years in Group B (p = 0.166). The gender distribution was comparable between the groups (31 males and 34 females in Group A; 27 males and 38 females in Group B, p = 0.597). ASA grade I and II were distributed as 30 and 35 in Group A, and 31 and 34 in Group B, respectively (p = 1.000). The mean ± SD BMI was 24.54 ± 2.13 kg/m^2 in Group A and 24.96 ± 2.06 kg/m^2 in Group B (p = 0.264)(Table 1).

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Table 1: Clinic-Demographics of Both Groups of Patients N=130

Variables	Group A (Intrathecal Tramadol, N=65)	Group B (Intravenous Tramadol, N=65)	p-Value
Age (years, Mean ± SD)	40.38 ± 10.56	38.14 ± 7.53	0.166
Gender (Male: Female)	31: 34	27: 38	0.597
ASA grade (I: II)	30: 35	31: 34	1.000
BMI (kg/m^2, Mean ± SD)	24.54 ± 2.13	24.96 ± 2.06	0.264

The mean ± SD of sensory and motor block duration in Group A was 331.723 ± 33.09 and 231.138 ± 11.22 minutes and in Group B was 228.123 ± 12.15 and 157.415 ± 10.02 minutes respectively (p-value <0.001) (Table 2).

Table 2: Comparison of Subarachnoid Block Characteristics Between the Two Groups (N=130)

Subarachnoid block characteristics	Group A (Intrathecal Tramadol, n=65) Mean ± SD	Group B (Intravenous Tramadol, n=65) Mean ± SD	p-Value
Duration of surgery (minutes)	91.15 ± 5.04	90.43 ± 5.05	0.416
Motor block duration (minutes)	231.14 ± 11.22	157.42 ± 10.02	<0.001*
Sensory block duration (minutes)	331.72 ± 33.09	228.12 ± 12.15	<0.001*
Frequency of analgesic demand (24h)	2.09 ± 0.42	3.80 ± 1.07	<0.001*

*p-value ≤ 0.05 considered significant

Post-anesthesia complications were mostly comparable between the two groups, except for shivering which was more frequent in Group B (Table 3).

Table 3: Complications after Subarachnoid Block (N=130)

Complications	Group A (n=65)	Group B (n=65)	p-Value
Post-anesthesia shivering	9	23	0.064
Bradycardia	1	1	
Hypotension	1	2	
Nausea and vomiting	9	6	

*p ≤ 0.05 considered statistically significant

Post-anesthesia shivering, assessed using the Bedside Shivering Assessment Score (BSAS), occurred in 13.84% of patients in Group A and 35.38% in Group B, showing a statistically significant difference (p=0.008) (Table 4).

Table 4: Post-Anesthesia Shivering Comparison Between Groups (N=130)

Shivering Status	Group A (n=65)	Group B (n=65)	p-Value
Present	9 (13.84%)	23 (35.38%)	0.008*
Absent	56 (86.15%)	42 (64.61%)	

*p-value ≤ 0.05 considered significant

DISCUSSIONS

Post-anesthesia shivering is a complex phenomenon influenced by various factors, including operating room temperature, patient heat distribution, pain, and sympathetic activity. Tramadol, a synthetic opioid, has been shown to effectively prevent shivering due to its unique mechanism of action. Oral tramadol has been reported to significantly reduce post-anesthetic shivering, with only 7.5% of patients experiencing shivering compared to 40% in the placebo group [12]. Multiple studies have examined different doses of intrathecal tramadol in patients undergoing urological procedures, cesarean sections, and for shivering prophylaxis in comparison to other adjuvants or placebo [13-15]. Additional evidence supports its role in cesarean section patients, and both tramadol and nalbuphine have been shown to be effective in controlling post-spinal shivering [16, 17]. The present study compared the analgesic effects of intrathecal tramadol (10 mg) versus intravenous tramadol (25 mg) in preventing post-anesthesia shivering in patients undergoing elective lower limb surgeries. Results showed that patients receiving intrathecal tramadol experienced significantly less shivering compared to those receiving intravenous tramadol, which is consistent with previously published findings [2, 18]. When compared with intrathecal dexmedetomidine added to bupivacaine, tramadol as an adjuvant with bupivacaine for the intrathecal route significantly extended the duration of the pain-free period after subarachnoid anesthesia [19]. Furthermore, this study found that the intrathecal group had longer sensory and motor block duration and postoperative analgesia, consistent with earlier reports [20]. Intrathecal tramadol has also been shown to be superior to intrathecal fentanyl in preventing shivering during cesarean section [21]. This study used a fixed dose of 25 mg intravenous tramadol and 10 mg intrathecal tramadol, consistent with the recommended dosage range for shivering prophylaxis. The results support the use of intrathecal tramadol as a safe and effective method for preventing post-anesthesia shivering and providing postoperative analgesia. A single dose of intrathecal tramadol may reduce the need for systemic intravenous supplementation, making it a convenient and efficient treatment option. The main limitation of this study was that it was conducted at a single center. Further multicenter studies with larger sample sizes are recommended to strengthen the clinical evidence.

CONCLUSIONS

Current study found that administering 10 mg of tramadol intrathecally as a prophylactic effectively prevents postoperative shivering in patients having lower limb procedures that need large amount of fluids for cleaning during debridement cases. Intrathecal tramadol increases motor block time and duration of analgesia, reducing the need for post-operative analgesics while minimizing adverse effects such nausea, vomiting, and hypotension. It is recommended to compare the antishivering effect of tramadol at different intrathecal dosages to find out the optimum dose for better results.

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Authors Contribution

Conceptualization: SK
Methodology: HA
Formal analysis: HA
Writing review and editing: MK[1], MK[2]

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Combination Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction in Infertile Women with Polycystic Ovarian Syndrome

Shagufta Tabassum[1*], Amna Aziz[1], Syeda Ali[1], Faiza Suman[1] and Ayesha Uzaima Tarin[1]

[1]Department of Obstetrics and Gynecology, Nishtar Hospital, Multan, Pakistan

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***Corresponding Author:**
Shagufta Tabassum
Department of Obstetrics and Gynecology, Nishtar Hospital, Multan, Pakistan
dr.shaguftatabassum@hotmail.com

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ABSTRACT

Infertility is a devastating health issue with widespread psychological effects. The most common reason for female infertility is polycystic ovary syndrome. The treatment revolves around Clomophene Citrate (CC) and Letrozole individually, but the combination has not been studied in our population. **Objectives:** To find if the combination of CC and Letrozole has better ovulation efficacy as compared to Letrozole alone. **Methods:** The foregoing quasi-experimental study was organized in the Department of Gynaecology at Nishtar Hospital of Pakistan. A total of 70 participants fulfilling the inclusion criteria were divided into two equal groups. Group A was prescribed 2.5 mg Letrozole daily, while Group B was given the composite 2.5 mg letrozole + 50 mg CC per day from the 3rd to the 7th cycle day for one treatment cycle. **Results:** The combination group yielded ovulation in 65.7% infertile women, while Letrozole alone in 37.1% of the cases, making a net difference of 28.6% which is quite significant. The conception was achieved in 17.1% of the combination group cases and 14.2% of the Letrozole alone group, making a net difference of 2.9%. The clinical pregnancy was diagnosed in 14.2% of the combination group cases and 11.1% of the Letrozole alone cases, with a net difference of 3.1%. **Conclusions:** Our findings endorsed the hypothesis that using combined CC + Letrozole leads to a better ovulation rate than Letrozole alone in women experiencing infertility due to polycystic ovary syndrome (PCOS).

INTRODUCTION

Infertility continues to be a devastating health issue. Infertility refers to the lack of ability to conceive after a couple has practiced regular, unprotected sexual intercourse for a period of 12 months [1]. Universally, it is estimated that every one in six couples of reproductive age group experience this issue at some stage of their life, making it as prevalent as approximately 13-15% [2]. Infertility is also a matter of concern in our country, Pakistan, where its prevalence is 18.67% [3]. The stress and emotional aspects associated with this issue have both hurtful and counter-productive effects on the mental and physical health of the experiencing couples. The main etiological factors for this distressing condition comprise a long list; male factor, polycystic ovarian syndrome, and tubal factor being the common ones [4]. PCOS is currently recognized as the most prevalent endocrine disorder affecting the fertility of women [5]. It is also a leading cause of infertility, contributing to nearly 70% of anovulation-related cases. The Rotterdam criteria define PCOS based on the presence of at least two of the following three features: (a) Infrequent/absent ovulation, typically indicated by menstrual cycles longer than 35 days or less than eight periods per year. (b) Signs of elevated androgen levels, which may be clinical (such as acne, excessive hair growth, or hair thinning) or biochemical (raised testosterone levels). (c) Polycystic ovarian morphology,

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identified as having 12 or more follicles, each 2–9 mm in diameter, and/or at least one ovary having a volume in excess of 10 mL [6]. The treatment of PCOS-related infertility aims to induce ovulation [7]. Various pharmacological agents have been employed to enhance not only ovulation, conception, and clinical pregnancy but also live birth rates, with differing levels of effectiveness. Among these, Clomiphene Citrate (CC) remains the most widely utilized. Its mode of action is as a selective estrogen receptor modulator [8], competing with estrogen for receptor sites both in the hypothalamus and pituitary gland. This disruption of the normal negative feedback from endogenous estrogen steers an increased release of two hormones, namely follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn promote the development of ovarian follicles and induce ovulation [9]. Despite its efficacy in triggering ovulation, CC can exert anti-estrogenic effects on the endometrium as well as cervical mucus, which may lower conception rates [10]. The other drug for ovulation induction is Letrozole, which is a highly selective aromatase inhibitor and has got dual effect [11]. Letrozole inhibits the enzymatic transformation of androstenedione to estrone and testosterone to estradiol, thereby reducing the endogenous estrogen formation. The resulting low estrogen levels create a positive feedback loop within the hypothalamic-pituitary-ovarian axis, promoting the release of GnRH and, consequently, increasing FSH secretion. One proposed additional mechanism for improved ovulation rates with Letrozole is the temporary rise in intraovarian androgens, which may enhance follicular responsiveness to FSH. Unlike clomiphene citrate (CC), Letrozole does not occlude estrogen receptors sited in central or peripheral tissues, allowing the body's natural feedback systems to remain functional [12]. In women with PCOS, the hormonal profile, particularly FSH, LH, estradiol, and testosterone levels, can influence the ovulatory response to both Letrozole alone and Letrozole combined with Clomiphene Citrate. Letrozole, by inhibiting aromatase and reducing estrogen levels, can lead to a rise in FSH and LH, potentially promoting follicle development and ovulation. However, the extent of this effect can vary based on the baseline FSH levels. The study postulates that the combined Letrozole + CC is superior to Letrozole alone while considering ovulation rates. The basis of our postulation is that both drugs have different mechanism of action and their combination can have a synergistic effect, resulting in better results. This hypothesis has been explored in only a small number of studies across the world. The use of Clomiphene Citrate versus Letrozole for infertility has been researched in many studies in Pakistan. After extensive online research, it was found that the combined use of Letrozole+CC for anovulatory infertility has not been studied in our local population of Pakistan. This finding provoked us to conduct a study to test the hypothesis that the combination of Clomiphene Citrate and Letrozole results in a higher ovulation rate in comparison to Letrozole alone. The results of this study generated a useful database of our local population and will prove to be beneficial for the infertile couples.

This study aimed to find if the combination of CC and Letrozole has better ovulation efficacy as compared to Letrozole alone.

METHODS

The quasi-experimental study was conducted in the Department of Gynecology at Nishtar Hospital, Multan, Pakistan. The Ethical Review Board of Nishtar Medical University acknowledged permission for this study (Reference letter number 18984/NMU). Eligible women presenting for ovulation induction between December 2024 and May 2025 were enrolled at the start of a treatment cycle and followed through outcome assessment. Treatment (combined Letrozole + CC vs Letrozole alone) was determined by treating clinicians as part of routine care; the study recorded exposures and outcomes without intervention by the investigators. Women aged 17–40 years with infertility (failure to conceive after ≥12 months of regular unprotected intercourse) and diagnosed with polycystic ovary syndrome (PCOS) according to the Rotterdam criteria were eligible if no other identifiable cause of infertility was present. Male partners required a sperm concentration >15 million/mL and progressive motility >40%. Exclusion criteria were pregnancy, recent hormonal contraceptive use, known adrenal or thyroid dysfunction or hyperprolactinemia, prior ovarian surgery, and known allergy or contraindication to letrozole or clomiphene citrate. The WHO calculator was used to gauge the sample size. The total number of samples was 70. The sample size of 35 participants in each group was needed to achieve a statistical power of 80% for detecting a clinically significant absolute difference of 35% in ovulation rates between the treatment arms. This calculation assumed ovulation rates of 38% with letrozole alone and 73% with the combined Letrozole+CC. The anticipated 35% difference was derived from prior research that evaluated ovulation induction using the combined regimen versus letrozole alone [13]. The candidates gave voluntary consent for their participation in the study. They were briefed about the study's objectives, with assurances of confidentiality and non-maleficence. Those meeting the inclusion criteria were enrolled, and all relevant information was recorded on a proforma. Demographic data, including age, address, BMI, and duration of subfertility, were collected. Group A "Letrozole alone"

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included women who received oral letrozole 2.5 mg daily; Group B "Combined" included women who received letrozole 2.5 mg daily + clomiphene citrate 50 mg daily from cycle day 3 to 7 in the same cycle. In the prospective scenario, treatment assignment was performed by the treating physician and documented in the clinic record; the research team did not allocate treatments. The primary outcome was ovulation during the index cycle, defined as mid-luteal serum progesterone >3.0 ng/mL. For regular cycles, 5 mL venous blood was obtained on cycle day 21 (day 1 = first day of menses). For irregular cycles, samples were taken weekly from day 21 until either the ovulatory progesterone value was detected or menstruation occurred. Serum was processed (clot 30 min; centrifuge 1,500 × g for 10 min); serum was analyzed immediately or stored at −20°C (≤2 weeks) or −70°C for longer storage. Serum progesterone was measured using chemiluminescent microparticle immunoassay (CMIA) on the Abbott Architect; internal quality controls (low and high) were run with each assay and accepted when within ±2 SD. Mid-cycle transvaginal ultrasound (day 12–14) was used to record dominant follicular size; follicle ≥18 mm was considered mature. Ultrasound scans were performed by the principal investigator utilizing a Mindray DP-50 to maintain consistency. A urinary pregnancy test was performed 7 days after ovulation, and clinical pregnancy was defined as an intrauterine fetal pole with cardiac activity on ultrasound. Continuous variables are presented as mean ± SD or median (IQR) as appropriate; categorical variables as n (%). Group comparisons used Student's t-test or Mann–Whitney U test for continuous variables and χ^2 or Fisher's exact test for categorical variables. To estimate the association between treatment (combined vs letrozole alone) and ovulation, we fitted multivariable logistic regression models adjusting a priori for age, BMI, and infertility duration; All tests were two-sided, and $p<0.05$ was considered statistically significant. Analyses were performed in IBM SPSS Statistics 26.0.

RESULTS

Out of the total 70 participants, most were of age around 30 years, with a mean age of 29.32 years in Group A and 30.01 years in Group B. BMI was also around 30 kg/m2, with a mean of 29.72 in Group A and 29.21 in Group B (Table 1).

Table 1: Demographics of Participants

Characteristics	Group A Letrozole (n= 35), Mean ± SD	Group B Letrozole + CC (n= 35), Mean ± SD
Age (Years)	29.32 ± 3.532	30.01 ± 4.23
BMI (kg/m^2)	29.72 ± 3.38	29.21 ± 3.46
Duration of Marriage (Years)	6.44 ± 3.21	5.92 ± 2.815

Ovulation was observed among 37.1% in Group A and 65.7% in Group B. The same data findings were observed for mid-cycle follicular size >18mm (Table 2).

Table 2: Reproductive Outcomes

Outcomes	Group A Letrozole, n= 35 (%)	Group B Letrozole + CC, n= 35 (%)	p-Value
Mid Cycle Follicle>18 mm	13 (37.1%)	23 (65.7%)	0.030*
Ovulation	13 (37.1%)	23 (65.7%)	0.030*
Conception	05 (14.2%)	06 (17.1%)	0.50
Clinical Pregnancy	04 (11.4%)	05 (14.2%)	0.50

*: statistically significant

DISCUSSIONS

Infertility is a crucial issue due to its considerable impact on couples as well as society. Many treatment modalities have been tried for this problem with variable success rates. However, the idea of combined Letrozole and Clomiphene Citrate may add up as a novel regime to the existing treatment therapies. Our findings confirmed that using a combination of Clomiphene Citrate+ Letrozole leads to a better ovulation rate than Letrozole alone in women experiencing infertility due to polycystic ovary syndrome. The combination group yielded ovulation in 65.7% infertile women, while Letrozole alone was successful in inducing ovulation in 37.1 % of the cases, making a net difference of 28.6% which is quite significant. The conception was achieved in 17.1% of the combination group cases and 14.2% of the Letrozole alone group, making a net difference of 2.9%. The clinical pregnancy was diagnosed in 14.2% of the combination group cases and 11.4% of the Letrozole alone cases, with a net difference of 2.8%. An analogous study was organized by Mejia et al. where ovulation was found to occur in 77% of the combined Letrozole and Clomiphene citrate group and 43% of the letrozole group, with a net difference of 34% [14]. The results of this study regarding ovulation are quite close to our study. However, Mejia found no difference between the groups as regards the conception and the clinical pregnancy rates. The difference in conception and clinical pregnancy rate between the two groups in our study is also not marked enough, thus almost matching the results of Mejia. Similarly, the side effect profile of the two groups was found to be the same in Mejia's study, thus supporting our findings regarding the side effect profile. The closely similar results between our study and that of Mejia might be due to the same sampling technique adoption based on age and BMI. Another study was organized by Panda et al. in India to evaluate the same as our study. They obtained ovulation in 72.5% of the combined group participants and 37.5% of the Letrozole group [13]. Their findings also lie alongside our results. Their study resulted in conception in 10% of the combined group and 7.5% of the Letrozole group. Clinical pregnancy was confirmed in 7.5% of the combined group and 5% of the Letrozole group. Both the conception and the clinical pregnancy rates revealed a net

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difference of 2.5% between the two groups. This result figure approximates our findings, thus endorsing our results. Also, though they found differences in side effects between the two groups but it was not statistically significant. Khodary *et al.* organized a similar research in Egypt [15]. They concluded that the Letrozole only group had ovulation in 79% cases and the combined Letrozole +CC had ovulation in 81% cases. Their resulting ovulation rate is quite high compared to our study. It might be because they used double the dose of lertozole (5 mg) and CC (100 mg) than that given in our study. Also, they included only those women who were up to 35 years of age and had a BMI less than 30 kg/m^2. These women have more chances of ovulation due to relatively younger age and appropriate BMI. A study was carried out by Ibrahem in Egypt using the same medication as our study [16]. However, they had a similar ovulation rate (63.3%) in both the Letrozole only and the Letrozole +CC group. So they concluded that the addition of CC to Letrozole poses no benefit. Their results were contrary to ours. However, it was quite expected as Ibrahem included those cases who were CC resistant. In his study, a combination of Letrozole + CC meant the same as Letrozole alone due to proven CC resistance of the participants. Ashkar *et al.* conducted a systematic review and meta-analysis by examining five different databases to validate the efficacy of combining Letrozole and Clomiphene Citrate (CC) compared to using either drug individually [17]. Their findings indicated that the combination therapy was more effective for inducing ovulation in sub-fertile women diagnosed with PCOS. Thus, their study supports our results regarding ovulation. However, they found no difference between the groups as regards conception and clinical pregnancy. Similarly, Sarkar *et al.* [18] and Eskandar *et al.* [19] also found the combination to be superior to Letrozole alone as regards ovulation. While the above studies concluded a better ovulation rate in the combination group, this does not always lead to higher conception and clinical pregnancy rates due to several reasons. The CC exerts anti-estrogenic effects on the endometrial lining, resulting in its thinning and reduced implantation. Also, the possibility of multiple pregnancies is increased with CC, with all the anticipated complications [20]. As far as the optimal dose of Letrozole+CC for maximizing ovulation without adverse effects is concerned, the various studies have suggested different dosage schedules. However, more large-scale studies are required to reach any evidence-based conclusion.

CONCLUSIONS

Our findings endorsed the hypothesis that using combined CC + Letrozole leads to a better ovulation rate than Letrozole alone in women experiencing infertility due to PCOS. The findings suggest that this low-cost treatment can be an effective option for the despair infertile couples, with promising results. Additional research studies are needed to observe the effects on conception and live pregnancy rate.

Authors Contribution

Conceptualization: ST
Methodology: FS, AUT
Formal analysis: AA
Writing review and editing: ST, SA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Hyperemesis Gravidarum in the Second Trimester as a Risk Indicator for Preterm Birth

Shumaila Asghar[1*], Mahpara Shaukat[2] and Qaiser Javed[3]

[1]Department of Gynaecology and Obstetrics, Tehsil Headquarter Hospital, Chichawatni, Pakistan
[2]Department of Gynaecology and Obstetrics, Sahiwal Medical College, Sahiwal, Pakistan
[3]Department of Gynaecology and Obstetrics, Services Institute of Medical Sciences, Lahore, Pakistan

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***Corresponding Author:**
Shumaila Asghar
Department of Gynaecology and Obstetrics, Tehsil Headquarter Hospital, Chichawatni, Pakistan
dr.shumailaasghar@yahoo.com

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ABSTRACT

A severe type of nausea and vomiting during the early stages of pregnancy is called hyperemesis gravidarum. Preterm delivery has been reported to be significantly associated with hyperemesis gravidarum. **Objectives:** To determine the association between preterm birth and hyperemesis gravidarum in female attending an antenatal care clinic in the second trimester. **Methods:** This Cohort1study was carried out at the Department of Obstetrics and Gynaecology, Sahiwal Teaching Hospital, Sahiwal. A total of 200 female were enrolled and divided into two groups with and without hyperemesis gravidarum. Then female were followed up in OPD until delivery. If female had a delivery before 37 weeks of gestation, then preterm birth was labelled. Data were analyzed in SPSS version 23.0. **Results:** The mean age of the female was 31.25 ± 5.98 years. In our study, 40 (40%) female were primigravida. The mean gestational age at presentation was 17.47 ± 3.51 weeks, while at delivery it was 37.27 ± 1.94 weeks. In the exposed group, preterm birth was noted in 45 (45%) cases, while in the unexposed group, preterm birth was noted in 15% cases. Thus, there was 1.909 times more risk of preterm birth in females with hyperemesis gravidarum as compared with female without hyperemesis gravidarum, i.e., RR=1.909 (95% CI; 1.483, 2.457, p<0.001). **Conclusions:** There is more than about two times greater risk of preterm birth in female with hyperemesis gravidarum during the second trimester of their pregnancy.

INTRODUCTION

During the first 20 weeks of pregnancy, morning sickness affects the majority of pregnant women [1, 2]. A severe type of nausea and vomiting that is common in the early stages of pregnancy is called hyperemesis gravidarum. It can cause dehydration, ketonuria, weight loss, and necessitate hospitalization [3, 4]. In the early stages of pregnancy, around half of women have both nausea and vomiting, while another quarter experience just nausea. Hyperemesis gravidarum has a reported incidence of 0.3% to 1.0%. Preterm delivery and low birth weight are adverse obstetric outcomes associated with hyperemesis gravidarum. The cause is not known. According to reports, more than 16% of babies could be delivered at a preterm stage [5, 6]. The risk of unfavorable perinatal outcomes might be increased by undernutrition and inadequate maternal weight gain throughout pregnancy, according to prior epidemiologic and animal research [7] involving preterm delivery and low birth weight [8]. The relationship between hyperemesis gravidarum and premature delivery might be explained by several processes. A well-known cause of malnourishment, dehydration, inadequate weight growth, and even weight loss is hyperemesis gravidarum. According to studies, women who suffer from hyperemesis gravidarum frequently consume inadequate amounts of calories and nutrients, sometimes falling short of 50% of the necessary diet [9, 10]. Due to a lack of evidence, often

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hyperemesis gravidarum remains neglected, which may lead to more severe outcomes, as preterm birth is associated with many other complications. So want to conduct this study to confirm the association of preterm birth with hyperemesis gravidarum. This study guides us to improve local guidelines and help to adopt a new strategy for management and prevention of hyperemesis gravidarum so that hazardous outcomes can be prevented. This study aims to find out the association of hyperemesis gravidarum in women who manifest in the second trimester of pregnancy is linked to an early birth.

METHODS

After taking approval from the hospital ethical review committee (158/IRB/SLMC/SWL), this cohort study was conducted at the Department of Obstetrics and Gynaecology, Sahiwal Teaching Hospital, Sahiwal, from November 2024 to April 2025. A sample size of 200 female; 100 female for both groups, was estimated by fixing the power of the study at 80%, significance level at 5% and percentage of preterm birth, i.e. 31.1% in exposed and 4.9% in unexposed cases in the second trimester of pregnancy [11]. The non-probability purposive sampling technique was used to include female, who fulfilled the following criteria. Female aged 20-40 years of parity <5 presenting during the second trimester of pregnancy (gestational age 12-24 weeks on USG) were included. Exposed Group: Female with Hyperemesis gravidarum, i.e. nausea and vomiting in the 2nd trimester. Female with a PUQE-24 (Pregnancy-Unique Quantification of Emesis) score of 13 or higher will be enrolled in the study. Unexposed Group: Female without Hyperemesis Gravidarum. At the same time, female with gestational or chronic Hypertension, diabetes, cardiac problems, asthma, multiple pregnancy or congenital abnormalities in the fetus after 23 weeks of gestation were not included. Informed written consent was taken to accomplish the research. A demographic profile with contact details was also obtained. Then female were separated into two groups with or without hyperemesis gravidarum. Then female were followed up in OPD every month until delivery of the fetus. At the time of delivery, an ultrasound was performed by the researcher to confirm the gestational age. If a female had a delivery before 37 weeks of gestation, then preterm birth was labelled. Female, who did not present for delivery and were lost to follow-up were replaced by new cases. All this procedure was recorded on a proforma and analyzed by SPSS version 23.0. Relative Risk was measured to assess the association between preterm birth and hyperemesis gravidarum. RR>1 was kept as significant (Figure 1).

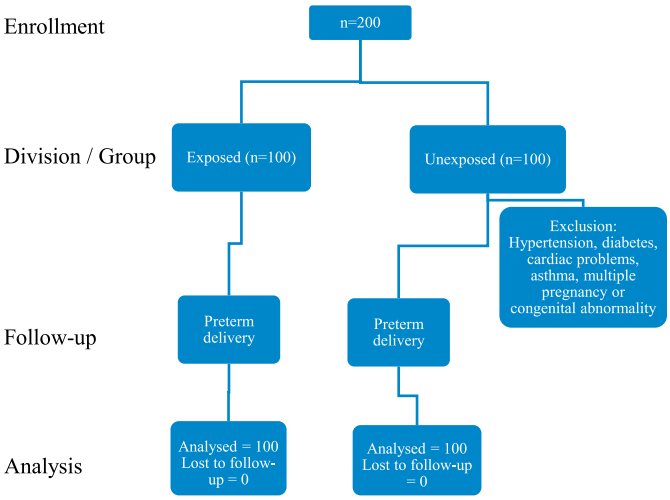

Figure 1: Patient Flow Diagram (n=200)

RESULTS

In the exposed group, the mean age of females was 26.25 ± 4.21 years, while in the unexposed group, the mean age was 36.25 ± 1.96 years. In the exposed group, the mean BMI of female was 26.88 ± 4.93 kg/m2, while in the unexposed group, the mean BMI was 26.59 ± 5.14 kg/m2. In the exposed group, 40 (40%) female were primigravida, 35 (35%) female were primiparous, and 25 (25%) were multiparous. In the unexposed group, 0 (%) female were primigravida, 15 (15%) female were primiparous, and 85 (85%) were multiparous. In the exposed group, 73 (73%) females were housewives, while 27 (27%) were working women. In the exposed group, 16 (16%) female had active lifestyle, 69 (69%) had a sedentary lifestyle, while 15 (15%) were doing gym/exercise. In the unexposed group, 17 (17%) female had an active lifestyle, 53 (53%) had a sedentary lifestyle, while 30 (30%) were doing gym/exercise. In the exposed group, 58 (58%) female were taking home-made food, 13 (13%) were taking fast food >3 times a week, 23 (23%) were taking street food >3 times a week, while 6 (6%) were following a diet plan. In the unexposed group, 58 (58%) female were taking home-made food, 19 (19%) were taking fast food >3 times a week, 18 (18%) were taking street food >3 times a week, while 5 (5%) were following a diet plan. In the exposed group, 30 (30%) were living in urban areas, 37 (37%) were coming from rural areas, while 33 (33%) were living in semi-urban areas. In the unexposed group, 31 (31%) were living in urban areas, 37 (37%) were coming from rural areas, while 32 (32%) were living in semi-urban areas. In the exposed group, 43 (43%) female had low socioeconomic class, 41 (41%) were from middle-class families, and 16 (16%) were from high socioeconomic class. In the unexposed group, 34 (34%) female had low socioeconomic class, 37 (37%) were from middle-class families, and 29 (29%) were from high socioeconomic class. The mean gestational age at enrolment was 17.85 ± 3.57 weeks in the exposed group,

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while 17.10 ± 3.42 weeks in the unexposed group. The mean gestational age at delivery was 36.60 ± 1.99 weeks in the exposed group, while 37.95 ± 1.64 weeks in the unexposed group (Table 1).

Table 1: Socio-demographic Characteristics of the Participants (n=200)

Characteristics	Groups	
	Exposed (n=100)	Unexposed (n=100)
Age		
Years	26.25 ± 4.21	36.25 ± 1.96
BMI		
Kg/m^2	26.88 ± 4.93	26.59 ± 5.14
Primigravida		
Parity=nil	40 (40%)	0 (%)
Primiparous		
Parity=1	35 (35%)	15 (15%)
Multiparous	-	-
Parity=2-4	25 (25%)	85 (85%)
Occupation		
Housewife	73 (73%)	68 (68%)
Working women	27 (27%)	32 (32%)
Life Style		
Active	16 (16%)	17 (17%)
Sedentary	69 (69%)	53 (53%)
Gym / Exercise	15 (15%)	30 (30%)
Dietary Habits		
Homemade Food	58 (58%)	58 (58%)
Fast Food	13 (13%)	19 (19%)
Street Food	23 (23%)	18 (18%)
Following A Diet Plan	6 (6%)	5 (5%)
Residence		
Urban	30 (30%)	31 (31%)
Rural	37 (37%)	37 (37%)
Semi-Urban	33 (33%)	32 (32%)
Socioeconomic Status		
Low	43 (43%)	34 (34%)
Middle	41 (41%)	37 (37%)
High	16 (16%)	29 (29%)
Gestational Age		
At Presentation	17.85 ± 3.57	17.10 ± 3.42
At Delivery	36.60 ± 1.99	37.95 ± 1.64*

*Significance (p-value)<0.0001 (Independent samples t-test)

In our study, preterm birth was noted in 60 (30%) cases, out of which 45 (45%) cases were exposed to hyperemesis gravidarum and 15 (15%) were unexposed. There was about two times more risk of preterm birth in exposed females compared to unexposed females, i.e. OR=1.909 (Table 2).

Table 2: Association of Preterm Birth with Hyperemesis Gravidarum (n=200)

Characteristics		Groups		Total
		Unexposed	Exposed	
Preterm Birth	Yes	45 (45%)	15 (15%)	60 (30%)
	No	55 (55%)	85 (85%)	140 (70%)
Total		100	100	200

RR = 1.909 (95% CI; 1.483, 2.457, p<0.001)

The data were stratified for the age of female, and it was observed that younger female, less than 30 years of age, all presented with hyperemesis gravidarum, and most of them had preterm births (56.3%). But in advanced age (above 30 years), there was no preterm birth in female exposed to hyperemesis gravidarum. While in the unexposed female, preterm birth occurred in 15% cases only. Among primigravida exposed to hyperemesis gravidarum, 40 (100%) female had preterm birth, while none in the unexposed primigravida female. In primiparous exposed female, preterm birth was noticed in 5 (14.3%) cases, while in 15 (100%) cases in unexposed primiparous female. Although the risk was insignificant (RR: 0.250 (95% CI: 0.117, 0.534)). Among multigravida, there was no preterm birth, whether the female had hyperemesis gravidarum or not. In female with an active lifestyle, preterm birth occurred in 5 (31.3%) exposed female, while in 2 (11.8%) unexposed female, depicting the relative risk of 1.688. In female with a sedentary lifestyle, preterm birth occurred in 35 (50.7%) exposed female, while in 9 (17.0%) unexposed female, depicting the relative risk of 1.825. This showed that if female had hyperemesis gravidarum and having a sedentary lifestyle, the risk is also doubled for preterm birth. While female doing exercise during pregnancy or going gym are also at doubled risk of preterm birth (RR: 2.00 (95% CI: 0.911, 4.392) (Table 3).

Table 3: Association of Preterm Birth with Hyperemesis Gravidarum When Controlled for Effect Modifiers (n=200)

Variables	Preterm Birth	Groups		RR (95% CI)
		Exposed	Unexposed	
Age 20-30 Years	Yes	45 (56.3%)	0 (0%)	NA
	No	35 (43.8%)	0 (0%)	
Age 31-40 Years	Yes	0 (0%)	15 (15%)	1.235 (1.126, 1.355)
	No	20 (100%)	85 (85%)	
Primigravida	Yes	40 (100%)	0 (0%)	NA
	No	0 (0%)	0 (0%)	
Primiparous	Yes	5 (14.3%)	15 (100%)	0.250 (0.117, 0.534)
	No	30 (85.7%)	0 (0%)	
Multigravida	Yes	0 (0%)	0 (0%)	NA
	No	25 (100%)	85 (100%)	
Active Lifestyle	Yes	5 (31.3%)	2 (11.8%)	1.688 (0.882, 3.230)
	No	11 (68.8%)	15 (86.2%)	
Sedentary Lifestyle	Yes	35 (50.7%)	9 (17.0%)	1.825 (1.361, 2.448)
	No	34 (49.3%)	44 (83.0%)	

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Gym / Exercise	Yes	5 (33.3%)	4 (13.3%)	2.00 (0.911, 4.392)
	No	10 (66.7%)	26 (86.7%)	

DISCUSSIONS

In our study, we observed preterm births in 60 (30%) female. The female in the exposed group had 1.909 times more risk of preterm births (45% cases) as compared to unexposed female (15% cases). Thus, this study observed RR=1.909 (95% confidence interval: 1.483, 2.457). In many studies, hyperemesis gravidarum has been linked to a higher risk of unfavorable obstetric outcomes, like preterm birth, low birthweight, and small-for-gestational-age babies [12, 13]. According to prospective cohort study by McCarthy and fellows, women with severe hyperemesis gravidarum were more likely than those without the condition to give birth spontaneously before their due date (adjusted OR, 2.6; 95% CI: 1.2–5.7) [14]. These findings are almost similar to our study, confirming that the risk of preterm birth doubled in the presence of hyperemesis gravidarum. Placental abruption and undersized for gestational age newborns are among the linked placental dysfunction diseases that are much more likely to occur in pregnancies complicated by hyperemesis gravidarum in the second trimester of pregnancy [15]. During the research period, the overall prevalence of hyperemesis gravidarum among primiparous women in Norway was 0.89% (95% CI: 0.88–0.92). Hyperemesis gravidarum was most common in women born in India and Sri Lanka (3.2%), whereas it was least common in women born in Western Europe (0.8%). The odds of developing hyperemesis gravidarum were 3.4 (95% CI: 2.7-3.5) and 3.3 (95% CI: 2.6-3.4) times higher for women born in Africa (excluding North Africa) and India or Sri Lanka, respectively [16, 17]. These studies also showed a significant association of hyperemesis gravidarum with preterm birth, as we observed in our study. One study reported that the frequency of preterm birth was 3.0% in females with hyperemesis gravidarum, while 2.8% in female without hyperemesis gravidarum [18]. Other studies supported this evidence and reported that preterm birth was found to be 7.4-7.6% among hyperemesis gravidarum female, while 5.7-5.8% among controls [19, 20]. Paauw *et al.* observed a very high risk of preterm birth in the presence of hyperemesis gravidarum. They observed that the frequency of preterm birth was very high among females with hyperemesis gravidarum (31.1%) as compared to controls (4.8%) [21]. In a study by Vandraas *et al.* reported that reduced risk of very preterm birth (OR=0.66; 95% CI: 0.5-0.9) and large-for-gestational-age (OR=0.9; 95% CI: 0.8-0.9) in female having hyperemesis gravidarum [22]. Other studies supported this evidence and reported that preterm birth was found to be 7.4-7.6% among hyperemesis gravidarum female, while 5.7-5.8% among controls [19, 21]."A study by Bolin et al. showed that the risk of preterm (<37 weeks) pre-eclampsia was more than doubled, the risk of placental abruption was three times higher, and the risk of a small for gestational age birth was 39% higher for women with hyperemesis gravidarum who were admitted for the first time in the second trimester (adjusted OR; (95% CI) were: 2.09 (1.38-3.16), 3.07 (1.88-5.00), and 1.39 (1.06-1.83), respectively) [18]. Reduced gestational age and longer hospital stays are more common among infants born to mothers who experienced hyperemesis gravidarum. The most frequent cause of hospitalization during the first trimester of pregnancy is hyperemesis gravidarum, which is surpassed only by premature labor for the whole pregnancy [11]."

CONCLUSIONS

It was concluded that there is about a two times greater risk of preterm birth in females having hyperemesis gravidarum in the second trimester. Consequently, hyperemesis gravidarum can lead to adverse pregnancy outcomes and can cause complications to the neonate in the neonatal period and beyond. So in future, keeping in mind the risk of preterm birth, we will plan and implement strategies to manage female with hyperemesis gravidarum to prevent preterm labor and delivery and reduce life-threatening risks to neonates.

Authors Contribution

Conceptualization: SA
Methodology: MS, QJ
Formal analysis: QJ
Writing review and editing: QJ

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Efficacy of Topical Testosterone in Hypospadias Patients Presenting with Microphallus

Shahid Khan[1*], Amber Azam[1], Umama Jelani[1], Zaibi Zara[2], Waleed Anjum Qureshi[1] and Muhammad Ahsan Khan[1]

[1]Department of Plastic Surgery, Northwest General Hospital and Research Centre, Peshawar, Pakistan
[2]Burns and Plastic Surgery Centre, Hayatabad Medical Complex, Peshawar, Pakistan

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***Corresponding Author:**
Shahid Khan
Department of Plastic Surgery, Northwest General Hospital and Research Centre, Peshawar, Pakistan
shaahidkhan105@gmail.com

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ABSTRACT

Hypospadias, a common congenital anomaly in males, is often linked with microphallus, complicating surgery. Preoperative androgen therapy may enhance penile size and outcomes, though most studies focus on intramuscular routes. Limited data exist on topical testosterone, especially locally. **Objectives:** To assess the effectiveness of topical testosterone in increasing penile length in children with hypospadias and microphallus. **Methods:** This quasi-experimental study was conducted at the Department of Plastic Surgery, Northwest General Hospital, spanned six months from November 2024 till May 2025. A total of 195 boys aged 1–10 years with hypospadias and microphallus received 5% topical testosterone cream, applied four times daily for 45 days. Stretched penile length was measured before and after treatment. A ≥50% increase defined treatment success. Data were analyzed using SPSS version 25.0; significance was set at p≤0.05. **Results:** Median penile length increased from 42 mm (IQR: 8 mm) to 60 mm (IQR: 21 mm). Mean length rose from 41.32 mm to 59.18 mm ($p < 0.001$). A ≥50% increase was seen in 52.3% of patients. No significant link was found between efficacy and age ($p = 0.316$) or hypospadias type ($p=0.118$). **Conclusions:** Topical testosterone effectively increases penile length in children with hypospadias and microphallus, regardless of age or subtype.

INTRODUCTION

Hypospadias is defined as an abnormal opening of the urethra along the ventral aspect of the penis, starting from the glans up to the perineum. Its incidence is 1 in every 250 newborn males. Usually, there are three anatomic abnormalities present, hooded skin with deficient ventral foreskin, abnormal curvature of the skin toward the ventral area called Chordee and ventrally opened urethral orifice below the normal position [1, 2]. Hypospadias one of the most common male congenital anomalies often coexists with a small penile size (microphallus or "hypospadias with small penis"), which can complicate tissue handling, glans approximation, and flap perfusion during repair. Pre-operative androgen stimulation (PAS), most commonly with topical or systemic testosterone or dihydrotestosterone (DHT), has been proposed to enlarge penile length and glans width, improve vascularity, and potentially reduce complications. Contemporary hypospadias reviews highlight a resurgence of interest in PAS as part of peri-operative optimization, particularly for distal repairs with small glans and for selected proximal cases [3, 4]. Quantitative syntheses now provide stronger estimates of PAS effects. A 2023 systematic review and meta-analysis reported that pre-operative testosterone increased stretched penile length by ~9.3 mm and glans

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width by ~3.3 mm, with a possible reduction in urethrocutaneous fistula risk and no signal for higher overall complications [5]. Prospective and dose-response work shows that testosterone-associated glans growth is measurable, dose dependent, and persists beyond the peri-operative window—supporting a biologically meaningful effect on surgical anatomy [6]. More recently, a multicenter study of pre-operative topical DHT for hypospadias reported favorable increases in penile dimensions without excess early complications, further expanding the topical options under evaluation [7]. The most appropriate time for hypospadias repair has been controversial; however, the majority of surgeons prefer to do hypospadias repair between 6 months and 5 years of age. It is because it is believed that in the future the boy will not remember the surgery and will not have any effect on his psychological health. Operating on a small hypospadias phallus can be technically challenging [7, 8]. Achieving normal function and a natural appearance are the main objectives of surgical correction. Although hypospadias repair is widely and frequently performed, there is no consensus on the best practice guidelines to improve the clinical outcomes. One of the controversial topics involving hypospadias surgery is the use of preoperative testosterone. Typically, testosterone is offered to patients who require a technically challenging repair, such as those with proximal hypospadias and/or with small phallus [9]. The young age of the patient combined with a very small area of surgery make the repair challenging as the complications are related to the size and length of the penis. As a result, many surgeons focus on the role of testosterone either intramuscular or topical on the circumference and length of the penis and its relation with the overall outcome [2]. Various researchers presented contradictory results regarding the use of testosterone to increase the length of microphallus preoperatively. Most of the researchers have used intramuscular testosterone for this purpose. Only in a few studies, we have found the use of topical testosterone for the enlargement of penile length. Chalapathi used topical testosterone cream in 13 patients with hypospadias and microphallus and found that 7 (53.84%) of them improved in length by 50% or more [10]. Beyond high-income settings, regional series echo these benefits while underscoring heterogeneity in protocols. In a 2024 African cohort of proximal hypospadias, intramuscular testosterone given pre-operatively was associated with improved penile dimensions and acceptable complication rates [11]. Egyptian single-center experience in 2024 also found that pre-operative topical testosterone enlarged penile/glans size and aided technical ease, though the authors emphasized the need for standardized dosing and timing [12]. From South Asia, an Indian prospective study (2019–2021) using parenteral testosterone documented significant pre-operative gains in penile length and glans diameter that translated into technically easier repairs [13].

Collectively, these regional data support feasibility of PAS across resource settings while highlighting protocol variability (drug, route, dose, and treatment interval). For this study, microphallus was defined as hypospadias associated with a stretched penile length below the normal mean for age, as per standard reference values. Hypospadias itself refers to a congenital anomaly in boys in which the urethral opening is ectopically located anywhere from just below the glans to the scrotum. The efficacy of topical testosterone was operationalized as a ≥50% increase in penile length following therapy, measured in the stretched condition using a standard measuring tape. The working hypothesis was that topical testosterone would be effective in increasing penile length in this group of patients. This study was aimed to determine the efficacy of topical testosterone in hypospadias patients presenting with microphallus.

METHODS

This quasi-experimental study was conducted in the Department of Plastic Surgery at Northwest General Hospital and Research Center. The study duration was a minimum of six months, starting from November 2024 to May 2025. Ethical Approval was obtained from the hospital's ethical review committee (Ref. No. IRB & EC/2024-GH/0137). A total of 195 patients were enrolled, calculated using the Raosoft online sample size calculator by taking the expected efficacy of topical testosterone in penile length enlargement as 53.84%, at 95% confidence interval, and a margin of error of 7% [10]. Consecutive non-probability sampling was employed for patient recruitment. Male children aged 1–10 years with hypospadias associated with microphallus (penile length less than normal for age, measured in stretched condition as per standard reference values). Patients with severe proximal or penoscrotal hypospadias, previously circumcised patients, those with chordee requiring interruption of the urethral plate, and those undergoing redo hypospadias repair were excluded. After obtaining written informed consent from parents or guardians, all eligible patients underwent detailed history such as age, residence, socioeconomic status, family history, clinical examination e.g. (stretched penile length) and type of hypospadias were recorded (based on the anatomical location of the external urethral meatus observed during examination). Penile length was measured in stretched condition from the base to the tip of the glans using a measuring tape. Glans width was not included in the present study, as the primary objective was to evaluate the

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efficacy of topical testosterone in increasing penile length. Accurate and reproducible measurement of glans width requires specialized calipers and observer calibration, which were not feasible within the scope of this project. Moreover, stretched penile length is a validated and widely used parameter for assessing androgen response, and limiting the outcome assessment to penile length reduced variability and improved methodological consistency. All patients received 5% topical testosterone cream, initially applied under supervision during the first visit. Parents were instructed to continue applying the cream four times daily for 45 consecutive days. On the 46th day, penile length was measured again in the same standardized manner. Efficacy was defined as a ≥50% increase in penile length compared to baseline. Data were analyzed using SPSS version 25.0. Continuous variables such as age and penile length were expressed as median with Interquartile Range (IQR), after checking for normality of distribution assessed by the Shapiro-Wilk test. Categorical variables such as hypospadias type and treatment efficacy were summarized as frequencies and percentages. Efficacy was stratified by age and hypospadias type. Post-stratification comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. A p-value ≤0.05 was considered statistically significant. Results were presented in tables and figures.

RESULTS

A total of 195 patients with hypospadias and microphallus were included in the study. The median age of participants was 6 years (interquartile range (IQR)=5 years). At baseline, the median penile length was 42 mm (IQR = 8 mm), which increased to 60 mm (IQR=21 mm) following topical testosterone therapy. A median Increase in penile length by 20mm (IQR=20) was observed in the participants. Furthermore, the median percent increase as compared to penile length before Testosterone intervention was recorded as 51.08(IQR=48.23). The Shapiro-Wilk test indicated that the data were not normally distributed ($p < 0.05$)(Table 1).

Table 1: Age, Penile Length of the Participants

Characteristics	Median (IQR)	p-Value (Shapiro wilk)
Age of the participant (in years)	6 (5.00)	<0.001
Penile length before Testosterone (mm)	42 (8.00)	0.003
Penile length After Testosterone (mm)	60 (21.00)	0.033
Increase in Penile Length after Testosterone (mm)	20 (22)	<0.001
Percent Increase in Penile Length	51.08 (48.23)	<0.001

Regarding demographic distribution, more than half of the children (54.4%) resided in rural areas, while 45.6% were from urban areas. The majority (75.4%) had a monthly household income ≤100,000 PKR, and most belonged to the middle socioeconomic class (57.9%), followed by the lower class (36.9%) and the upper class (5.1%). A family history of hypospadias was reported in 17.4% of cases. In terms of hypospadias subtypes, glandular hypospadias was the most common (28.7%), followed by coronal (25.6%), distal penile (21.5%), mid penile (13.8%), and proximal penile (10.3%). Over 52.3% (102) patients reported an increase in penile length by more than 50% while 47.7% (93) were recorded as increase in penile length less than 50% of the baseline. Overall, the efficacy of topical testosterone, (defined as a ≥50% increase in penile length as compared to Baseline) was achieved in 52.3% (102 out of 195) patients, whereas in 47.7% (93 out of 195) of the participants, the increase in penile length was less than 50% of the baseline. The age distribution was nearly balanced, with 48.2% of children aged ≤5 years and 51.8% aged >5 years (Table 2).

Table 2: Demographics, Hypospadias Types and Efficacy

Demographics, Hypospadias types and efficacy (N=195)		Frequency N (%)
Residence	Rural	106 (54.4%)
	Urban	89 (45.6%)
Monthly income	≤ 100000	147 (75.4%)
	> 100000	48 (24.6%)
Socioeconomic status	Lower class	72 (36.9%)
	Middle class	113 (57.9%)
	Upper class	10 (5.1%)
Family history	Yes	34 (17.4%)
	No	161 (82.6%)
Type of Hypospadias	Coronal	50 (25.6%)
	Distal penile	42 (21.5%)
	Glandular	56 (28.7%)
	Mid penile	27 (13.8%)
	Proximal penile	20 (10.3%)
Percent Increase in Penile Length after Testosterone Therapy as compared to baseline	< 50% increase	93 (47.7%)
	>50% Increase	102 (52.3%)
Efficacy of topical testosterone (≥50% increase in penile length)	Yes	102 (52.3%)
	No	93 (47.7%)
Age Categories	≤ 5 years	94 (48.2%)
	> 5 years	101 (51.8%)

Analysis of efficacy in relation to hypospadias type revealed no statistically significant association (p=0.118). Although children with glandular and distal penile hypospadias showed relatively higher response rates, the difference did not reach statistical significance. Similarly, the efficacy of testosterone therapy did not differ significantly between age groups (≤5 years vs. >5 years; p=0.316), indicating that response to treatment was independent of both hypospadias type and age (Table 3).

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Table 3: Association Between Hypospadias Types, Age and Efficacy

Variables	Category	Efficacy of topical testosterone (≥50% increase)		Total	Chi-Square/ p-Value (<0.05)
		Yes	No		
Type of Hypospadias	Coronal	22	28	50	0.118
	Distal penile	27	15	42	
	Glandular	33	23	56	
	Mid penile	13	14	27	
	Proximal penile	07	13	20	
	Total	102	93	195	
Age	≤ 5 years	53	41	94	0.316
	> 5 years	49	52	101	
	Total	102	93	195	

When comparing penile length before and after treatment, the mean increased from 41.32 mm to 59.18 mm. A paired t-test demonstrated that this difference was highly significant ($p < 0.001$). This finding confirms that topical testosterone significantly enhances penile growth in children with hypospadias and microphallus, supporting its use as an effective preoperative intervention (Table 4).

Table 4: Mean Comparison Before and After Testosterone

Parameter	Mean Before Topical Testosterone	Mean After Topical Testosterone	Paired t-Test / p-Value
Penile Length (in mm)	41.32	59.18	<0.001

DISCUSSIONS

In the present study, topical testosterone therapy produced a significant increase in penile length among children with hypospadias and microphallus. The mean penile length improved from 41.32 mm before treatment to 59.18 mm after treatment, with the difference being highly significant ($p<0.001$). More than half of the participants (52.3%) demonstrated an effective response, defined as a ≥50% increase in penile size. Importantly, no statistically significant association was observed between treatment efficacy and either the type of hypospadias ($p=0.118$) or the age category of patients ($p=0.316$), suggesting that the benefits of testosterone were consistent across different subgroups no adverse effects were reported. In comparison to our study, Preoperative androgen stimulation (PAS) has emerged as a valuable adjunct in the management of hypospadias, particularly in children with microphallus. Evidence from systematic reviews suggests that both topical and intramuscular testosterone reliably increase stretched penile length and glans width, providing a more favorable surgical field. A 2023 meta-analysis demonstrated significant penile growth with PAS and suggested a potential reduction in urethrocutaneous fistula formation, though long-term outcomes remain under study [5]. Lucaccioni *et al.* reported one of the more recent experiences with transdermal testosterone gel as a preoperative intervention in boys with severe hypospadias. Their small series of 10 patients showed an average increase of 0.76 cm in penile length and 0.42 cm in glans width following about six weeks of daily application. This represented nearly a 40% increase from baseline. Although no adverse effects were observed, surgical complications still occurred in 30% of cases, indicating that the effect in preventing surgical complications is still not clear [14]. Jackson *et al.* investigated the long-term effects of topical testosterone versus topical dihydrotestosterone (DHT) in boys with proximal hypospadias. They found that DHT was particularly effective, with glans width nearly doubling from 6.1 mm to 14.9 mm, while testosterone also produced significant increases from 10.5 mm to 14.6 mm [15]. Prospective clinical data further support these findings. Mittal *et al.* quantified a dose-dependent rise in glans width following testosterone therapy, highlighting its biological efficacy and potential to reduce technical challenges during repair [4]. Regional experience from Egypt also confirmed that topical testosterone enhanced penile and glans size, which surgeons perceived as beneficial for operative handling, though the authors emphasized the need for standardized dosing protocols [12]. Another meta-analysis by Do *et al.* found that testosterone therapy demonstrated a mean increase in stretched penile length of 9.3 mm (95% CI: 6.7–12.0 mm) and a glans width gain of 3.3 mm (95% CI: 2.5–4.0 mm) [5]. In a cohort of 368 patients undergoing distal hypospadias repair where two groups (testorserone vs controls) were compared, results showed that testosterone patients demonstrated significantly larger glans width (17.1 mm vs 14.6 mm, p=0.001). After adjusting for age, baseline glans width, testosterone exposure, and urethroplasty length, testosterone therapy was shown to be significantly associated with a reduced risk of postoperative complications (OR 0.4, p=0.039) [16]. Sembiring *et al.* compared post hypospadias repair complication rates between children who received testosterone therapy and controls. The study found that the testosterone group had a significantly lower rate of glans dehiscence (OR 0.40, 95% CI 0.17–0.97) compared to controls [17]. Another meta-analysis by Munawwir *et al.* found that PAS not only has an effect on the penile length but also as significant effect on the overall complication rate (OR=0.68, 95% CI: 0.48-0.96; p=0.03) compared to controls. Analysis showed protective effects against several specific complications e.g. meatal stenosis (OR=0.66, 95% CI: 0.44–0.98), glans dehiscence (OR=0.46, 95% CI: 0.30–0.71; p<0.001), and urethrocutaneous fistula (OR=0.58, 95% CI: 0.36–0.94; p=0.03) [18]. Despite the growing international evidence base, national studies from Pakistan continue to focus predominantly on surgical

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outcomes of urethroplasty, with limited evaluation of preoperative hormonal strategies [19, 20]. This evidentiary gap underscores the importance of local data to assess efficacy, safety, and applicability of topical testosterone in Pakistani children presenting with hypospadias and microphallus.

CONCLUSIONS

In conclusion, topical testosterone had a significant effect in increasing penile length in children with hypospadias and microphallus. Around half of the children achieved a ≥50% gain in penile length as compared to base line.

Authors Contribution

Conceptualization: SK, UJ
Methodology: SK, AA, MAK
Formal analysis: UJ
Writing review and editing: SK, AA, ZZ, WA, MAK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Risk Factors and Survival Outcomes Associated with Breast Cancer Recurrence

Syed Saad Gardezi[1*], Muhammad Sami Ullah[2], Mehroosh Shakeel[3], Sadaf Shafique[4], Badar Masood[5] and Bushra Nisar[6]

[1]Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur, Pakistan
[2]Department of Pathology, Nishtar Medical University, Multan, Pakistan
[3]Department of Histopathology, Shalamar Medical and Dental College, Lahore, Pakistan
[4]Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur, Pakistan
[5]Department of Clinical Oncology, Bahawalpur Institute of Nuclear Medicine and Oncology Cancer Hospital, Bahawalpur, Pakistan
[6]Department of Pathology, Ameer ud Din Medical College, Postgraduate Medical Institute, Lahore General Hospital, Lahore, Pakistan

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Corresponding Author:
Syed Saad Gardezi
Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur, Pakistan
saadgardezi@gmail.com

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ABSTRACT

Breast cancer recurrence remains a major clinical challenge, despite advancements in diagnosis and treatment. Identifying reliable clinicopathological predictors is essential for improving long-term outcomes and guiding individualized treatment. **Objective:** To assess the clinicopathological characteristics and risk factors associated with breast cancer recurrence and evaluate survival outcomes in patients with operable breast cancer. **Methods:** This retrospective study included 281 patients diagnosed with operable primary breast cancer at a tertiary care center. Data were collected on demographic, histopathological, and treatment-related variables. Recurrence was defined as any documented local, regional, or distant relapse after initial treatment. Statistical analyses included chi-square tests for categorical variables and independent-samples t-tests for continuous variables to assess associations with recurrence. A p-value<0.05 was considered statistically significant. **Results:** The overall recurrence rate was 31.7 %, with distant metastasis being the most common type. Odds ratios with 95 % confidence intervals for categorical variables (molecular subtype, hormone receptor status, tumor size category, histological grade, Ki-67 index, and lymphovascular invasion) showed no statistically significant associations with recurrence. Likewise, mean differences with 95 % confidence intervals for continuous variables (age, tumor size, Ki-67 index, and disease-free survival) revealed no significant differences between recurrence and non-recurrence groups. **Conclusions:** No clinicopathological factor was found to be a statistically significant predictor of breast cancer recurrence in this cohort. These findings highlight the limitations of traditional pathological markers and underscore the need to integrate molecular and genomic profiling for more accurate recurrence risk assessment and personalized treatment planning.

INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer and the leading cause of cancer-related death among women worldwide. Despite advances in early detection and therapy, recurrence continues to be a major clinical concern, significantly affecting survival outcomes and quality of life [1-3]. Recurrence may occur locally, regionally, or as distant metastases, and is often influenced by a complex interplay of demographic, pathological, and molecular factors. Understanding the risk factors associated with breast cancer recurrence is critical for tailoring treatment strategies and improving long-term outcomes. Age has been shown to significantly impact recurrence and survival. Younger women, particularly those under 40, often present with more aggressive tumor subtypes and higher proliferation indices such as Ki-67, resulting in higher recurrence rates and

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worse disease-free survival (DFS) [4, 5]. Conversely, older age (>65) is associated with distinct recurrence patterns and often comorbidities that complicate prognosis and treatment [6]. Molecular subtype plays a pivotal role in recurrence patterns. Triple-negative breast cancer (TNBC) and HER2-positive subtypes are linked with higher recurrence risks and poorer prognosis compared to luminal A and B subtypes, which tend to recur later and are generally associated with better survival outcomes [4, 7]. A recent study found the time to recurrence was shortest in TNBC and HER2-positive patients, with longer recurrence-free intervals seen in hormone receptor-positive subtypes [6]. Pathological features such as tumor size, lymph node involvement, histologic and nuclear grade, and lymphovascular invasion (LVI) are also strong predictors of recurrence [1, 8]. A large meta-analysis of hormone receptor-positive, HER2-negative breast cancer patients in Japan revealed that lymph node metastasis and high tumor grade significantly reduced relapse-free survival [1]. Similarly, high Ki-67 expression has been shown to increase the likelihood of local or regional recurrence [9]. Treatment-related factors further influence survival and recurrence. Adjuvant chemotherapy, hormone therapy, and radiotherapy significantly reduce recurrence risk and improve survival when administered appropriately based on tumor characteristics [7, 10]. A study from Saudi Arabia reported that patients who did not receive adjuvant chemotherapy had significantly worse DFS and higher recurrence rates [3]. In addition, limited post-operative follow-up was also associated with a greater risk of recurrence, underlining the importance of long-term monitoring [3]. Recent advancements in predictive modeling have further enhanced recurrence risk stratification. Clinical risk scoring systems and machine learning models incorporating both molecular and clinical data have demonstrated promising accuracy in predicting recurrence and survival outcomes [9, 11]. Breast cancer recurrence remains a critical challenge despite advances in treatment, significantly impacting patient survival. While various risk factors like age, tumor subtype, and pathological features have been linked to recurrence, evolving therapies and population differences highlight the need for updated analysis.

This study aims to identify key predictors of recurrence and their effect on survival to help improve patient monitoring and treatment planning.

METHODS

This retrospective cohort study was conducted at the Department of Histopathology, Quaid-e-Azam Medical College, Bahawalpur, after obtaining approval from the Institutional Review Board (2507/DME/QAMC Bahawalpur). The study included breast cancer cases diagnosed and treated between January 2020 and June 2024. Data abstraction from hospital records, pathology reports, and follow-up registries was carried out for 3 months (August 2024 to October 2024) following IRB approval. The objective was to evaluate the risk factors associated with breast cancer recurrence and their impact on survival outcomes. The sample size was calculated using the formula: $n = (Z^2 \times p \times (1 - p)) / d^2$, where $Z = 1.96$ for a 95% confidence level, $p=0.76$ (the 5-year disease-free survival rate reported by Chen et al.), and $d = 0.05$ (5% margin of error). This yielded a required sample size of approximately 281 patients [4]. Eligible participants were female patients aged 18 years and above, with histologically confirmed primary breast carcinoma who had undergone definitive surgery, including either breast-conserving surgery or mastectomy. Patients with complete clinicopathological and follow-up records and a minimum follow-up period of six months were included. Written informed consent was taken. Exclusion criteria comprised those with metastatic disease at the time of diagnosis, recurrent breast cancer or second primary tumors, incomplete records, or patients lost to follow-up within six months after treatment. Data were collected retrospectively using a structured data abstraction form from hospital records, pathology reports, and follow-up registries. The predictor variables recorded included age at diagnosis, tumor size, lymph node involvement, histological grade, and molecular subtype (Luminal A/B, HER2-enriched, Triple-negative), which was assigned strictly using immunohistochemical (IHC) surrogates based on ER, PR, HER2, and Ki-67 status according to established criteria; no additional genomic profiling was performed. Hormone receptor status (estrogen and progesterone receptors), HER2 status, and Ki-67 proliferation index, which was recorded as a continuous percentage and, for subgroup analyses, categorized as low (≤20%) versus high (>20%) expression based on established guidelines, were also included. Additional variables included type of surgery, type of adjuvant therapies (chemotherapy, radiotherapy, hormone therapy), which were recorded to account for potential confounding effects of standardized multimodal treatment on recurrence risk, presence of lymphovascular invasion, and menopausal status. Outcome variables included recurrence status (yes/no), type of recurrence (local vs distant), time to recurrence, disease-free survival (DFS), and overall survival (OS). All data were entered and analyzed using IBM SPSS version 25.0. Descriptive statistics summarized patient demographics and clinical variables. Continuous variables were reported as mean ± standard deviation, and categorical variables as frequencies and percentages. For subgroup analysis, the Ki-67 proliferation index was dichotomized into low (≤20%) and high (>20%)

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expression. Associations between categorical variables (including Ki-67 category and adjuvant therapy type) and recurrence were analyzed using the Chi-square test or Fisher's exact test where appropriate. Differences in means of continuous variables between recurrence and non-recurrence groups were assessed using the independent samples t-test. Recurrence-free survival (RFS) was defined as the time from definitive surgery to the first documented local, regional, or distant recurrence or last follow-up. RFS was estimated using the Kaplan–Meier method, and survival distributions between groups were compared using the log-rank (Mantel–Cox) test. A p-value<0.05 was considered statistically significant.

RESULTS

A total of 281 patients were included in the analysis. The mean age at diagnosis was 51.74 ± 13.52 years, and the average tumor size was 5.47 ± 1.48 cm. The mean Ki-67 proliferation index was 33.37 ± 16.11%, indicating a moderate level of tumor cell proliferation across the cohort. The mean disease-free survival (DFS) duration was 41.72 ± 17.19 months. The study summarizes the frequency distribution of key clinicopathological variables among 281 breast cancer patients. A majority of tumors were histologically high grade, with Grade III reported in 172 (61.2%) patients, followed by Grade II in 93 (33.1%) and Grade I in only 16 (5.7%), indicating a predominance of aggressive histological profiles within the study cohort. In terms of molecular subtype, Luminal A was the most common, observed in 104 (37.0%) cases, followed by Luminal B in 72 (25.6%), and Triple-negative in 67 (23.8%). The HER2-enriched subtype was the least frequent, comprising 38 (13.5%) of the cases. This distribution suggests a notable proportion of hormone receptor-positive tumors, although a substantial number of patients also had more aggressive phenotypes such as triple-negative and HER2-enriched subtypes. Regarding hormone receptor status, estrogen receptor (ER) positivity was seen in 176 (62.6%) patients, while ER-negative tumors were identified in 105 (37.4%). Similarly, progesterone receptor (PR) positivity was found in 158 (56.2%) patients, compared to 123 (43.8%) who were PR-negative. HER2 overexpression was present in 86 (30.6%), while the remaining 195 (69.4%) were HER2-negative. These figures reflect a typical distribution pattern seen in operable breast cancer cases and support the clinical utility of targeted hormonal and HER2-based therapies. When evaluating adjuvant treatment modalities, 183 (65.1%) patients received a combination of chemotherapy, radiotherapy, and hormone therapy, representing a multimodal approach tailored to tumor biology. Chemo-radiotherapy without hormone therapy was administered in 61 (21.7%) cases, while chemotherapy alone was given to 34 (12.1%) patients. Only 3 (1.1%) patients did not receive any form of adjuvant therapy. This reflects a strong inclination toward comprehensive treatment regimens among the study population. Lymphovascular invasion (LVI), a known marker of poor prognosis, was present in 127 (45.2%) patients and absent in 154 (54.8%). This near-equal distribution suggests heterogeneity in tumor aggressiveness. In terms of disease outcomes, recurrence occurred in 89 (31.7%) patients, while 192 (68.3%) remained recurrence-free during the follow-up period. Among those who experienced recurrence, distant metastasis was more common, affecting 62 (22.1%), followed by local recurrence in 27 (9.6%) patients. These figures highlight that distant recurrence is the predominant mode of relapse in operable breast cancer and remains a major clinical challenge despite standard treatment. Using the predefined cut-off (≤20% for low expression and >20% for high expression), 72 patients (25.6%) were classified as having low Ki-67 expression and 209 patients (74.4%) as having high Ki-67 expression. This distribution indicates that the majority of tumors in this cohort exhibited a high proliferative index (Table 1).

Table 1: Frequency Distribution of Categorical Variables (n=281)

Variables	Category	n (%)
Histological Grade	Grade I	16 (5.7%)
	Grade II	93 (33.1%)
	Grade III	172 (61.2%)
Molecular Subtype	Luminal A	104 (37.0%)
	Luminal B	72 (25.6%)
	HER2-Enriched	38 (13.5%)
	Triple-Negative	67 (23.8%)
ER Status	Positive	176 (62.6%)
	Negative	105 (37.4%)
PR Status	Positive	158 (56.2%)
	Negative	123 (43.8%)
HER2 Status	Positive	86 (30.6%)
	Negative	195 (69.4%)
Adjuvant Therapy	Chemo + Radio + Hormone	183 (65.1%)
	Chemo + Radio	61 (21.7%)
	Chemo only	34 (12.1%)
	None	3 (1.1%)
Lymphovascular Invasion	Present	127 (45.2%)
	Absent	154 (54.8%)
Recurrence Status	Yes	89 (31.7%)
	No	192 (68.3%)
Type of Recurrence	Local	27 (9.6%)
	Distant	62 (22.1%)
	None	192 (68.3%)
Ki67 Category	Low (≤20%)	72 (25.6%)
	High (>20%)	209 (74.4%)

Findings summarize the association between clinicopathological variables and breast cancer recurrence, now including odds ratios (ORs) with 95 %

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confidence intervals to reflect effect size and precision. Across all evaluated categories, none of the associations reached statistical significance. For histological grade, recurrence occurred in 5 (31.3 %) patients with Grade I, 28 (30.1 %) with Grade II, and 56 (32.6 %) with Grade III tumors. Compared with Grade I, the odds of recurrence were similar for Grade II (OR 0.95, 95 % CI 0.30–2.98) and Grade III (OR 1.06, 95 % CI 0.35–3.20; p=0.919). Among molecular subtypes, recurrence was most frequent in Luminal A cases (38 (36.5 %)), followed by HER2-enriched (12 (31.6 %)), triple-negative (21 (31.3 %)), and Luminal B (18 (25.0 %)). Compared with Luminal A, the odds of recurrence were lower for Luminal B (OR 0.58, 95 % CI 0.30–1.13), HER2-enriched (OR 0.80, 95 % CI 0.36–1.77), and triple-negative (OR 0.79, 95 % CI 0.41–1.52; overall p=0.454). Regarding hormone receptor status, recurrence occurred in 55 (31.3 %) of ER-positive and 34 (32.4 %) of ER-negative patients (OR 1.05, 95 % CI 0.63–1.77; p=0.844), and in 51 (32.3 %) of PR-positive versus 38 (30.9 %) of PR-negative patients (OR 0.94, 95 % CI 0.56–1.56; p=0.805). Similarly, HER2-positive tumors showed 31 recurrences (36.0 %) compared with 58 (29.7 %) in HER2-negative tumors (OR 1.33, 95 % CI 0.78–2.28; p=0.295), indicating no significant difference. When examining adjuvant therapy, recurrence rates were 55 (30.1 %) among those receiving chemo + radio + hormone therapy, 20 (32.8 %) for chemo + radio, 13 (38.2 %) for chemo only, and 1 (33.3 %) for no adjuvant treatment. Compared with the multimodal group, the odds of recurrence were 1.14 (95 % CI 0.61–2.11) for chemo + radio and 1.44 (95 % CI 0.67–3.08) for chemo only (p=0.817). Interestingly, lymphovascular invasion showed recurrence in 35 (27.6 %) patients with LVI present versus 54 (35.1%) without LVI, corresponding to an OR of 1.42 (95 % CI 0.85–2.37; p=0.178). Although counterintuitive, this trend remained statistically non-significant and may reflect treatment confounding or variable follow-up durations. Finally, using the ≤20 % cut-off for Ki-67 expression, 20 of 72 patients (27.8 %) with low Ki-67 experienced recurrence compared to 69 of 209 (33.0 %) with high Ki-67 expression (OR 1.28, 95 % CI 0.71–2.31; p=0.410). This indicates no measurable association between Ki-67 category and recurrence status in this cohort. Overall, the inclusion of odds ratios with confidence intervals confirms that none of the clinicopathological factors evaluated showed a statistically significant association with recurrence (Table 2).

Table 2: Association of Clinicopathological Variables with Recurrence Status (n=281)

Variable (Reference Category)	Recurrence: Yes n (%)	Recurrence: No n (%)	OR (95 % CI)	p-Value
Histological Grade				
Grade II vs Grade I	28 (30.1) vs 5 (31.3)	65 (69.9) vs 11 (68.7)	0.95 (0.30–2.98)	0.919
Grade III vs Grade I	56 (32.6) vs 5 (31.3)	116 (67.4) vs 11 (68.7)	1.06 (0.35–3.20)	0.919
Molecular Subtype (vs Luminal A)				
Luminal B	18 (25.0) vs 38 (36.5)	54 (75.0) vs 66 (63.5)	0.58 (0.30–1.13)	0.454
HER2-Enriched	12 (31.6) vs 38 (36.5)	26 (68.4) vs 66 (63.5)	0.80 (0.36–1.77)	0.454
Triple-Negative	21 (31.3) vs 38 (36.5)	46 (68.7) vs 66 (63.5)	0.79 (0.41–1.52)	0.454
ER Status (Negative vs Positive)	34 (32.4) vs 55 (31.3)	71 (67.6) vs 121 (68.8)	1.05 (0.63–1.77)	0.844
PR Status (Negative vs Positive)	38 (30.9) vs 51 (32.3)	85 (69.1) vs 107 (67.7)	0.94 (0.56–1.56)	0.805
HER2 Status (Positive vs Negative)	31 (36.0) vs 58 (29.7)	55 (64.0) vs 137 (70.3)	1.33 (0.78–2.28)	0.295
Adjuvant Therapy (vs Chemo + Radio + Hormone)				
Chemo + Radio	20 (32.8) vs 55 (30.1)	41 (67.2) vs 128 (69.9)	1.14 (0.61–2.11)	0.817
Chemo Only	13 (38.2) vs 55 (30.1)	21 (61.8) vs 128 (69.9)	1.44 (0.67–3.08)	0.817
Lymphovascular Invasion (Absent vs Present)	54 (35.1) vs 35 (27.6)	100 (64.9) vs 92 (72.4)	1.42 (0.85–2.37)	0.178
Ki-67 Category (High >20 % vs Low ≤20 %)	69 (33.0) vs 20 (27.8)	140 (67.0) vs 52 (72.2)	1.28 (0.71–2.31)	0.410

OR = Odds Ratio for recurrence in the category shown compared with the reference category.

The study compares continuous clinicopathological variables between patients who experienced recurrence and those who did not, now including mean differences with 95 % confidence intervals. None of the variables demonstrated a statistically significant difference between the two groups. The mean age at diagnosis was slightly higher in the recurrence group (53.11 ± 13.69 years) than in the non-recurrence group (51.11 ± 13.43 years), but the mean difference of +2.00 years (95 % CI –1.44 to +5.44) was not statistically significant (p=0.249). Tumor size was marginally smaller in the recurrence group (5.23 ± 1.50 cm) compared to the non-recurrence group (5.59 ± 1.46 cm), with a mean difference of –0.36 cm (95 % CI –0.74 to +0.02; p=0.059), approaching but not reaching statistical significance. The Ki-67 proliferation index was comparable between groups (33.92 ± 15.79 % vs 33.11 ± 16.28 %), with a mean difference of +0.81 % (95 % CI –3.22 to +4.84; p=0.698). Disease-free survival (DFS) duration was virtually identical (41.67 ± 16.72 vs 41.73 ± 17.45 months), with a mean difference of –0.06 months (95 % CI –4.34 to +4.22; p=0.978).

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Overall, these findings show that none of the continuous baseline variables examined were significantly associated with recurrence, and the inclusion of mean differences with confidence intervals confirms the absence of clinically meaningful differences between groups (Table 3).

Table 3: Comparison of Continuous Variables Between Recurrence Groups (n=281)

Variables	Recurrence, Yes (n=89), Mean ± SD	Recurrence, No (n=192), Mean ± SD	Mean Difference (95 % CI)*	p-Value
Age at Diagnosis (Years)	53.11 ± 13.69	51.11 ± 13.43	+2.00 (-1.44 to +5.44)	0.249
Tumor Size (cm)	5.23 ± 1.50	5.59 ± 1.46	-0.36 (-0.74 to +0.02)	0.059
Ki-67 Index (%)	33.92 ± 15.79	33.11 ± 16.28	+0.81 (-3.22 to +4.84)	0.698
DFS (Months)	41.67 ± 16.72	41.73 ± 17.45	-0.06 (-4.34 to +4.22)	0.978

*Mean difference

Recurrence-free survival (RFS) was further evaluated using Kaplan–Meier analysis, which demonstrated a steady decline in RFS over time with a median RFS of approximately 41 months. No statistically significant differences in RFS were observed across molecular subtypes, histological grades, or lymphovascular invasion groups (log-rank p>0.05 for all comparisons), calculated as Recurrence Yes Minus Recurrence No. Tick marks indicate censored observations (Figure 1).

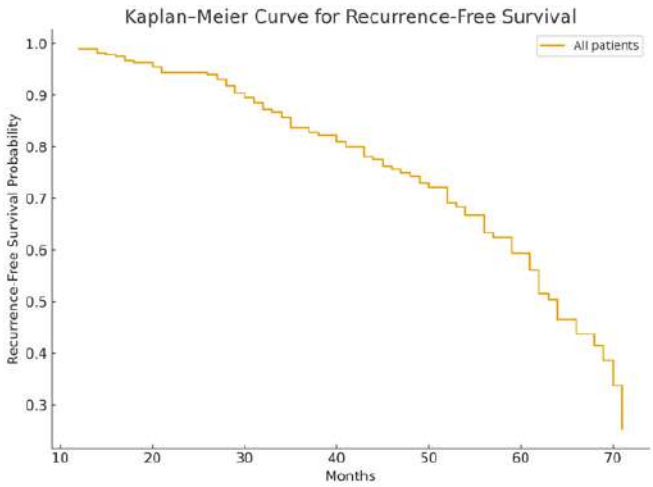

Figure 1: Kaplan–Meier Curve Showing RFS among 281 Patients with Operable Breast Cancer

DISCUSSIONS

This study analyzed recurrence patterns in a cohort of 281 breast cancer patients by evaluating a wide range of clinicopathological variables. The observed recurrence rate of 31.7% aligns with previous findings in similar cohorts, particularly among patients with aggressive molecular subtypes such as HER2-enriched and triple-negative breast cancer [12]. However, in our study, molecular subtype was not statistically associated with recurrence. Although recurrence was numerically more frequent in Luminal A and HER2-enriched tumors, these differences were not significant. This lack of association may be due to uniform application of treatment modalities across subtypes or unmeasured biological heterogeneity. The Ki-67 proliferation index showed a mean of 33.37%, reflecting moderate tumor proliferation overall. Yet, there was no significant difference in Ki-67 levels between recurrence and non-recurrence groups, consistent with studies reporting its limited predictive value when used independently [13]. While Ki-67 has been recognized as a marker of biological aggressiveness, its prognostic utility improves when integrated into multigene assays such as Oncotype DX, which better stratify recurrence risk in hormone receptor-positive breast cancer [14]. None of the traditional clinicopathological variables, including histological grade, hormone receptor status, HER2 expression, lymphovascular invasion, or type of adjuvant therapy, showed a statistically significant association with recurrence. These findings support previous research suggesting that individual pathological markers may have limited prognostic value in isolation, especially in the era of comprehensive multimodal treatment [15, 16]. An unexpected observation was the higher recurrence rate in patients without lymphovascular invasion (35.1%) compared to those with LVI (27.6%), though this trend was not statistically significant (p=0.178). This finding contradicts established literature that classifies LVI as an adverse prognostic factor [15, 16] and may be influenced by confounding factors such as tumor biology, differential follow-up, or treatment intensity. Further large-scale studies are needed to explore this paradox. Continuous variables, including age, tumor size, Ki-67 index, and DFS, also showed no significant differences between recurrence and non-recurrence groups. Interestingly, tumor size was marginally smaller in the recurrence group, though the difference approached but did not reach significance (p=0.059). This may suggest the influence of molecular or genetic factors not captured by baseline pathology alone. The nearly identical DFS duration between groups reinforces the concept that standard clinicopathological features may not sufficiently explain individual recurrence risk [17]. Furthermore, the lack of significant difference in recurrence across adjuvant therapy groups may reflect the equalizing effect of standardized, multimodal treatment regimens. This is consistent with previous studies indicating that, when systemic therapy is appropriately administered, recurrence rates can be similar across surgical modalities and molecular subtypes [18]. Overall, while recurrence rates varied across clinical subgroups, no statistically significant predictors emerged in our analysis. These findings underscore the limitations of relying solely on conventional clinicopathological markers and support the

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integration of molecular profiling, tumor microenvironment characteristics, and emerging biomarkers to improve recurrence risk prediction in breast cancer management [19–22].

CONCLUSIONS

In this study involving 281 patients with operable breast cancer, no clinicopathological variable, including tumor grade, molecular subtype, hormone receptor status, HER2 expression, tumor size, Ki-67 index, or lymphovascular invasion, demonstrated a statistically significant association with recurrence. Additionally, none of the continuous parameters, such as age, tumor size, Ki-67 index, or disease-free survival, differed significantly between recurrence groups. These findings highlight the limitations of relying solely on traditional pathological markers for recurrence prediction and underscore the need for incorporating molecular profiling and personalized risk assessment tools into clinical practice to enhance prognostication and guide individualized treatment strategies.

Authors Contribution

Conceptualization: SSG
Methodology: SSG, SS
Formal analysis: SSG
Writing review and editing: MSU, MS, SS, BM, BN

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Impact of Maternal Obesity on Pregnancy Outcomes: A Hospital-Based Study

Talat Parveen[1*], Quratulain[1], Saba Yasmin Usmani[2], Samina[1], Sadaf Un Nisa[1] and Nergis Taj[2]

[1]Department of Obstetrics and Gynaecology, Bahawal Victoria Hospital, Bahawalpur, Pakistan
[2]Department of Obstetrics and Gynaecology, Sadiq Abbasi Hospital, Quaid e Azam Medical College, Bahawalpur, Pakistan

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***Corresponding Author:**
Talat Parveen
Department of Obstetrics and Gynaecology, Bahawal Victoria Hospital, Bahawalpur, Pakistan
talatjalal1964@gmail.com

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ABSTRACT

Obesity among pregnant women has emerged as a major global health issue and is closely associated with unfavorable outcomes for both the mother and the newborn. **Objectives:** To assess how maternal obesity influences pregnancy-related outcomes in both mothers and their newborns at a tertiary care facility. **Methods:** This hospital-based descriptive cross-sectional research was carried out in the Obstetrics and Gynaecology Department of Bahawal Victoria Hospital, Bahawalpur, during the period from 23-04-2024 to 22-10-2024. A total of 153 pregnant women with obesity (BMI ≥30 kg/m^2) and singleton pregnancies beyond 28 weeks of gestation were selected through non-probability consecutive sampling. Women with multiple gestations, fetal anomalies, or chronic illnesses unrelated to obesity were excluded. Data on maternal demographics, obstetric history, and outcomes were collected using a structured proforma. The evaluated outcomes comprised gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), type of delivery, preterm labor, postpartum hemorrhage (PPH), stillbirth, macrosomia, Apgar scores, neonatal intensive care unit (NICU) admissions, and congenital abnormalities. Data analysis was performed using SPSS-26, with a p-value less than 0.05 considered statistically significant. **Results:** The mean maternal age was 29.99 ± 6.26 years. GDM occurred in 26.8% and PIH in 15.0% of participants. Cesarean delivery was performed in 44.4%, and macrosomia was observed in 23.5% of neonates. Significant associations were noted between parity and PIH (p=0.024), ANC visits and NICU admission (p=0.005), and chronic illness with congenital anomalies (p=0.041). **Conclusions:** Maternal obesity is associated with increased risks of metabolic, obstetric, and neonatal complications.

INTRODUCTION

Rising rates of obesity among women of childbearing age have made maternal obesity a growing global health concern, with considerable implications for both maternal and neonatal well-being. As more pregnancies occur in the context of elevated maternal weight, complications linked to obesity have become increasingly common. A pre-pregnancy body mass index (BMI) of 30 kg/m^2 or higher is used to define maternal obesity, which has been correlated with numerous unfavorable health outcomes for both the mother and the developing fetus [1]. Pregnant women with obesity are more prone to developing complications such as gestational diabetes mellitus (GDM), hypertensive disorders, and preeclampsia [2, 3]. These maternal conditions contribute to an increased likelihood of cesarean section, early delivery, and greater maternal health risks [4]. One hospital-based cohort study documented notably higher incidences of GDM (23.7%) and hypertensive disorders (18.3%) among obese patients when compared with women of normal weight [5]. Such evidence supports the broader consensus that excess maternal weight amplifies metabolic disturbances during pregnancy [6]. In addition to maternal complications, obesity also imposes substantial risks on fetal health. Adverse neonatal outcomes such as macrosomia, low Apgar scores, stillbirth, and NICU admissions are frequently observed in pregnancies complicated by

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obesity [7, 8]. For instance, infants born to obese mothers are more likely to require neonatal resuscitation and intensive care, and they face a higher risk of metabolic disorders later in life [9]. Placental pathology studies also confirm abnormal changes such as increased chorangiosis and infarction in obese pregnancies, further linking maternal adiposity to poor fetal outcomes [10]. At the immunological level, maternal obesity fosters a pro-inflammatory state that disrupts the normal immunometabolic adaptations required for a successful pregnancy [11]. Obese women tend to exhibit elevated levels of IL-6, leptin, and MCP-1, contributing to chronic low-grade inflammation. This environment may impair placental function and fetal development by shifting immune responses from Th2-dominant to Th17-biased profiles, thereby increasing the risk of miscarriage and preeclampsia [11]. Moreover, the consequences of maternal obesity are not limited to the perinatal period. Longitudinal studies suggest that children born to obese mothers are more susceptible to obesity, insulin resistance, and neurodevelopmental disorders later in life, perpetuating a cycle of poor health across generations [12]. Given these extensive and multifactorial impacts, early identification and intervention are critical. Clinical management strategies should include preconception counseling, weight optimization, and tailored antenatal care to mitigate obesity-related risks.

This study aimed to explore the specific impact of maternal obesity on pregnancy outcomes, thereby contributing to evidence-based practices and policy formulation in maternal health care.

METHODS

A descriptive cross-sectional study was carried out in the Obstetrics and Gynaecology Department of Bahawal Victoria Hospital, Bahawalpur, spanning a duration of six months from 23-04-2024 to 22-10-2024. Ethical approval for the study was obtained from the Institutional Ethical Review Committee (Approval No.2386/DME/QAMC Bahawalpur), and written informed consent was secured from all participants. Patient confidentiality was maintained throughout the study. The primary aim was to assess both maternal and neonatal outcomes in women with obesity during pregnancy. The sample size was calculated using Open Epi version 3.01, referring to the findings of Neal et al. who reported a pregnancy-induced hypertension (PIH) rate of 11.2% among obese expectant mothers. With a 95% confidence level, a 5% margin of error, and a power of 80%, the required sample size was estimated to be 153. This ensured adequate power to detect significant associations between maternal obesity and adverse pregnancy outcomes [13]. A non-probability consecutive sampling technique was used. All pregnant women presenting during the study period who fulfilled the inclusion criteria were enrolled until the desired sample size was reached. Inclusion criteria were pregnant women with a BMI of 30 kg/m^2 or more, singleton pregnancy, gestational age of 28 weeks or more, and willingness to provide informed consent. Women with multiple gestations, known fetal anomalies diagnosed on ultrasound, or pre-existing chronic illnesses unrelated to obesity, such as type 1 diabetes, chronic hypertension, thyroid disorders, or renal disease, and those with incomplete records were excluded. Data were collected using a structured proforma that was developed after reviewing relevant literature and in consultation with subject experts. The proforma was pretested on 10 cases (not included in the final analysis) to ensure clarity and comprehensiveness. Gestational diabetes mellitus (GDM) was diagnosed according to WHO/ADA criteria based on oral glucose tolerance testing, while pregnancy-induced hypertension (PIH) was defined as new-onset hypertension (≥140/90 mmHg) after 20 weeks of gestation, in line with ACOG guidelines. Other maternal and neonatal outcomes were recorded from hospital records and cross-verified by the attending obstetrician to enhance reliability. Maternal characteristics recorded included age, parity, gestational age at delivery, number of antenatal visits, history of chronic illness, and socioeconomic status. Maternal outcomes studied were gestational diabetes mellitus, pregnancy-induced hypertension or preeclampsia, mode of delivery, preterm delivery, postpartum hemorrhage, and stillbirth. Fetal and neonatal outcomes included macrosomia, Apgar score at 5 minutes, NICU admission, and presence of congenital anomalies. Families with an income of ≤30,000 PKR/month were categorized as low, those with 30,001–70,000 PKR/month as middle, and those earning >70,000 PKR/month as high socioeconomic status. Data were compiled and analyzed using SPSS version 26.0. For continuous variables such as maternal age, gestational age, and neonatal birth weight, results were presented as mean ± standard deviation. Categorical variables, including parity, mode of delivery, and various outcomes, were described using frequencies and percentages. To identify possible effect modifiers, stratification was applied across variables such as maternal age, parity, number of antenatal visits, existing chronic illnesses, and socioeconomic status. Associations between maternal factors and pregnancy outcomes were examined using the chi-square test or Fisher's exact test for categorical data, and the independent t-test or Mann–Whitney U test for continuous data, depending on normality. A p-value below 0.05 was regarded as statistically significant.

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RESULTS

The study comprised 153 obese pregnant women. The mean maternal age was 29.99 ± 6.26 years. The average gestational age at delivery was 38.04 ± 1.51 weeks, and the mean number of antenatal care (ANC) visits was 4.14 ± 1.48. Among the participants, 74 (48.4%) were primigravida and 79 (51.6%) were multigravida. Chronic medical illness was reported in 33 (21.6%) women, while the remaining 120 (78.4%) had no comorbidities. Regarding socioeconomic status, 52 (34.0%) belonged to the low-income group, 72 (47.1%) to the middle-income group, and 29 (19.0%) to the high-income group. In terms of maternal outcomes, gestational diabetes mellitus (GDM) was observed in 41 (26.8%) participants, and pregnancy-induced hypertension (PIH) occurred in 23 (15.0%). Cesarean section was performed in 68 (44.4%) cases, while 85 (55.6%) underwent vaginal delivery. Preterm birth was documented in 17 (11.1%) women, postpartum hemorrhage in 16 (10.5%), and stillbirth in 6 (3.9%) cases. Regarding fetal and neonatal outcomes, macrosomia was identified in 36 (23.5%) newborns. NICU admission was required for 19 (12.4%) neonates, Low Apgar scores (<7 at 5 minutes) were recorded in 138 (90.2%) of neonates, which is substantially higher than rates reported in the general obstetric population (typically 1–10% at 5 minutes in large-scale studies). This finding underscores the markedly increased risk of neonatal compromise associated with maternal obesity and congenital anomalies were present in 10 (6.5%) neonates (Table 1).

Table 1: Frequency Distribution of Maternal and Fetal Variables (n=153)

Variables	Category	n (%)
Parity	Primigravida	74 (48.4%)
	Multigravida	79 (51.6%)
Chronic Illness	No	120 (78.4%)
	Yes	33 (21.6%)
Socioeconomic Status*	Low	52 (34.0%)
	Middle	72 (47.1%)
	High	29 (19.0%)
Maternal Outcomes		
GDM	No	112 (73.2%)
	Yes	41 (26.8%)
PIH	No	130 (85.0%)
	Yes	23 (15.0%)
Mode of Delivery	Vaginal	85 (55.6%)
	Cesarean	68 (44.4%)
Preterm Delivery	No	136 (88.9%)
	Yes	17 (11.1%)
Postpartum Hemorrhage	No	137 (89.5%)
	Yes	16 (10.5%)
Fetal/Neonatal Outcomes		
Stillbirth	No	147 (96.1%)
	Yes	6 (3.9%)
Macrosomia	No	117 (76.5%)
	Yes	36 (23.5%)
NICU Admission	No	134 (87.6%)
	Yes	19 (12.4%)
Apgar Score (5 min)	Low (<7)	138 (90.2%)
	Normal (≥7)	15 (9.8%)
Congenital Anomalies	No	143 (93.5%)
	Yes	10 (6.5%)

*Socioeconomic status was classified based on monthly household income: Low (≤30,000 PKR), Middle (30,001–70,000 PKR), High (>70,000 PKR).

Subgroup analysis revealed a statistically significant association between parity and PIH, with 9 (12.2%) cases among primigravidas and 14 (17.7%) among multigravidas (p=0.024). GDM was more prevalent in women with chronic illness (25; 75.8%) compared to those without (16; 13.3%) (p = 0.063). Cesarean deliveries were more frequent in women aged ≥30 years (40; 63.5%) versus those aged <30 years (28; 31.1%) (p=0.072). No significant association was noted between parity and macrosomia (p=0.119) (Table 2).

Table 2: Association of Independent Variables with Maternal Outcomes among Obese Mothers (n=153)

Outcomes	Independent Variable	Category	Yes, n (%)	No, n (%)	p-Value
PIH	Parity	Primigravida (n=74)	9 (12.2%)	65 (87.8%)	0.024
		Multigravida (n=79)	14 (17.7%)	65 (82.3%)	
GDM	Chronic Illness	No (n=120)	16 (13.3%)	104 (86.7%)	0.063
		Yes (n=33)	25 (75.8%)	8 (24.2%)	
Cesarean Delivery	Age Group	<30 years (n=90)	28 (31.1%)	62 (68.9%)	0.072
		≥30 years (n=63)	40 (63.5%)	23 (36.5%)	
Macrosomia	Parity	Primigravida (n=74)	18 (24.3%)	56 (75.7%)	0.119
		Multigravida (n=79)	18 (22.8%)	61 (77.2%)	

Preterm birth showed no significant difference by socioeconomic status, occurring in 5 (9.6%) women from the low-income group and 12 (11.9%) from the middle/high-income group (p=0.385). NICU admission was significantly more common in neonates of mothers who had ≥4 ANC visits (15; 16.1%) compared to those with <4 visits (4; 6.7%) (p=0.005). A statistically significant association was also observed between maternal chronic illness and congenital anomalies, which were present in 7 (21.2%) neonates of affected mothers versus 3 (2.5%) of those without comorbidities (p=0.041) (Table 3).

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Table 3: Association of Independent Variables with Fetal Outcomes among Obese Mothers (n=153)

Outcomes	Independent Variable	Category	Yes, n (%)	No, n (%)	p-Value
Preterm Delivery	Socioeconomic Status	Low (n=52)	5 (9.6%)	47 (90.4%)	0.385
		Middle/High (n=101)	12 (11.9%)	89 (88.1%)	
NICU Admission	ANC Visits	<4 visits (n=60)	4 (6.7%)	56 (93.3%)	0.005
		≥4 visits (n=93)	15 (16.1%)	78 (83.9%)	
Congenital Anomalies	ChronicIllness	No (n=120)	3 (2.5%)	117 (97.5%)	0.041
		Yes (n=33)	7 (21.2%)	26 (78.8%)	

DISCUSSIONS

The findings of our study affirm the well-documented association between maternal obesity and adverse pregnancy outcomes. In our cohort of obese pregnant women, the prevalence of gestational diabetes mellitus (26.8%) and pregnancy-induced hypertension (15.0%) was comparable to global data, underscoring obesity as an independent risk factor for metabolic complications [13]. Cesarean section was required in 44.4% of cases, consistent with prior reports linking obesity with increased surgical deliveries [14, 15]. Macrosomia was observed in 23.5% of neonates, in line with previous evidence showing maternal obesity as a major driver of excessive birth weight, even in the absence of gestational diabetes [16, 17]. NICU admissions were reported in 12.4% of neonates, comparable with literature describing higher morbidity in infants of obese mothers [18, 19]. A particularly striking finding of our study was the disproportionately high rate of low Apgar scores at 5 minutes (90.2%), far exceeding the 1–10% generally reported in population-based cohorts. This highlights the significant compromise in neonatal adaptation associated with maternal obesity. Congenital anomalies were identified in 6.5% of neonates, with a significant association in mothers with chronic illnesses. This finding aligns with previous reports that maternal obesity increases the risk of structural malformations, particularly neural tube defects, congenital heart disease, and orofacial clefts. Several mechanisms may contribute, including maternal hyperglycemia, altered folate metabolism, oxidative stress, and chronic low-grade inflammation that disrupts normal embryogenesis. Placental dysfunction in obese pregnancies, characterized by abnormal angiogenesis and increased inflammatory cytokines, may further impair fetal development. Neal et al. similarly reported higher rates of congenital malformations in class III obesity, independent of maternal diabetes [13]. Other studies have confirmed that obesity compounds risks in women with coexisting chronic conditions such as diabetes and hypertension, which may explain the stronger association in our cohort [20-22]. Other maternal complications included postpartum hemorrhage (10.5%); although consistent with international evidence that obesity predisposes to uterine atony, operative delivery, and prolonged labor, the limited number of cases in our study did not allow detailed subgroup analysis. This limitation has been acknowledged, and larger studies are needed to further explore the association between obesity and PPH. Preterm birth (11.1%) was also observed, aligning with prior data linking maternal obesity to increased risk of adverse obstetric outcomes [21]. Our study also provides insight into modifying factors. Parity was significantly associated with PIH, echoing systematic reviews that identify maternal age and parity as important risk modifiers in obese women [18]. Furthermore, socioeconomic disparities emerged, with low- to middle-income women disproportionately affected, consistent with global data that link obesity and adverse perinatal outcomes to lower socioeconomic strata [23]. Lastly, our results are aligned with longitudinal studies showing that both prepregnancy obesity and excessive gestational weight gain increase risks across successive pregnancies, reinforcing the need for early counseling and weight optimization before conception [24]. Collectively, these findings confirm obesity as a major, yet modifiable, public health risk factor while also highlighting unique aspects of our population, such as markedly elevated rates of low Apgar scores and SES-related differences in outcome

CONCLUSIONS

In conclusion, our study reinforces that maternal obesity significantly increases the risk of adverse pregnancy and neonatal outcomes, including gestational diabetes, pregnancy-induced hypertension, cesarean delivery, macrosomia, and NICU admissions. These findings are consistent with published literature highlighting the independent impact of obesity on both maternal and fetal health, even in the absence of other comorbidities. The significant associations observed in our cohort, particularly the influence of parity, chronic illness, and antenatal care on outcomes, underscore the multifactorial nature of obesity-related risks. These results emphasize the need for early identification, preconception counseling, and targeted interventions to optimize weight before and during pregnancy, thereby reducing the burden of obesity-associated complications and improving maternal and neonatal health outcomes.

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Authors Contribution

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Methodology: TP, Q
Formal analysis: TP
Writing review and editing: SYU, S, SUN, NJ

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of Thyroid Dysfunction in Patients with Controlled Versus Uncontrolled Diabetes Mellitus: A Comparative Cross-Sectional Study

Khansa Qamar[1*], Masud Ali Ansari[1], Mahneem Tofique[1], Jannat Naeem[1], Sara Shams[1] and Fizza Fatima[2]

[1]Department of Chemical Pathology, Nishtar Hospital, Multan, Pakistan
[2]Department of Chemical Pathology, Bakhtawar Amin Medical and Dental College, Multan, Pakistan

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***Corresponding Author:**
Khansa Qamar
Department of Chemical Pathology, Nishtar Hospital, Multan, Pakistan
khanxa.taurus@gmail.com

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ABSTRACT

Thyroid dysfunction (TD) and type 2 diabetes mellitus (DM) are the two endocrine conditions most frequently encountered in clinical settings. **Objectives:** To compare the frequency of thyroid dysfunction in patients with controlled versus uncontrolled DM. **Methods:** This comparative cross-sectional study was conducted at the Pathology Department of Nishtar Hospital, Multan, from February to July 2025. Diabetic patients aged 30–70 years of both genders were enrolled in the study as uncontrolled diabetes (n=124) and controlled diabetes (n=124). Patients with pre-existing TD, on its treatment, or using medications known to alter thyroid function were excluded. Demographic details, including age, gender, duration of diabetes, and hypertension status, were recorded. TD was categorized into subclinical hypothyroidism, clinical hypothyroidism, subclinical hyperthyroidism, and hyperthyroidism. Descriptive statistics were run through SPSS version 23.0, and the Shapiro-Wilk test for normality. Chi-square test at 5% significance level was used for comparisons, with stratification done to control confounding. **Results:** Among 248 participants, the mean age was 49.2 ± 10.3 years. Males constituted 48% and 73.4% had hypertension. TD was found in 14.5% of diabetics, more common in uncontrolled (69.4%) than controlled diabetes (30.6%) (p=0.012). Most frequent type was subclinical hypothyroidism (6%), followed by hypo- and hyperthyroidism (3.2% each), and subclinical hyperthyroidism (2%). TD was high in uncontrolled diabetics ≥50 years, females, and hypertensive patients. **Conclusions:** Thyroid dysfunction was remarkably more common in persons with uncontrolled diabetes, particularly in older age, females, and hypertensives.

INTRODUCTION

Thyroid dysfunction (TD) and type 2 diabetes mellitus (DM) are the two most common endocrine conditions that endocrinologists encounter in their clinical work [1]. Because thyroxin and insulin both are important in controlling cellular metabolism, and one of them acts in a counter-regulatory way against the other, the link between thyroid impairment and DM is well established [2]. Along with the detrimental impact thyroid dysfunction has on glucose balance, numerous investigations have shown that TD is more prevalent in diabetic patients than in normal healthy individuals [3]. A study carried out in Karachi, Pakistan, revealed that 36.9% of persons with type 2 DM had thyroid abnormalities [4]. Thyroid hormones influence glucose metabolism in a variety of ways. It has long been known that hyperthyroidism contributes to poor glycemic control; in this condition, the half-life of insulin is shortened. This shorter half-life is most likely caused by a greater breakdown and increased production of insulin precursors that are physiologically inactive [5]. It has been demonstrated that both subclinical and clinical hypothyroid conditions are linked to elevated insulin resistance, even though hypothyroidism can result in a

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decreased rate of hepatic glucose synthesis [6]. Al-Rubaye et al. conducted a study on 500 cases with type 2 DM. Out of those, 364 patients (72.8%) had poor glycemic control. Thyroid dysfunction was diagnosed in 67/364 patients (18.4%) with uncontrolled DM and 9/136 (6.6%) patients with controlled DM. The frequency of subclinical hypothyroidism, primary hypothyroidism, subclinical hyperthyroidism, and clinical hyperthyroidism was 38.8%, 19.4%, 23.8% and 17.9% in uncontrolled DM cases versus 33.3%, 22.2%, 11.1%, and 33.3% in controlled DM cases, respectively [7]. Alo et al. included a total of sixty subjects in their study. Out of all, 30 patients were diabetic, both controlled and uncontrolled, and 30 were healthy individuals. Mean levels of serum TSH were markedly high (4.77 ± 3.12 vs. 2.52 ± 1.46), and mean serum FT4 level (10.64 ± 1.29 vs. 12.21 ± 2.21) was substantially lower in uncontrolled diabetic persons as compared to those who had controlled diabetes [8]. By knowing the relationship between the status of thyroid function and glycemic control, physicians would be more careful in the future to prevent thyroid dysfunction by maintaining good control of diabetes in their patients. Moreover, early screening will be helpful in timely diagnosis and appropriate treatment, thus positively affecting the health of diabetic patients.

This study aims to determine the magnitude of TD and its types in patients presenting with controlled versus uncontrolled T2DM in our local setting.

METHODS

This comparative cross-sectional study was performed at the Department of Chemical Pathology, Nishtar Hospital, Multan, from 1st February 2025 to 31st July 2025 after approval from the institutional ethics review committee (ERC no: 1553/NMU). Patients 30 - 70 years of age, either male or female gender and diabetic for ≥5 years were approached. All patients underwent HbA1c% measurement from a single laboratory. Diabetic patients with HbA1c ≥ 7% were taken as uncontrolled diabetes, and <7% as controlled diabetes. A total of 124 controlled and 124 uncontrolled diabetes patients were enrolled through non-probability consecutive sampling in the study after informed consent. Based on history and medical record reviews, patients with thyroid dysfunction before the onset of diabetes mellitus, already on treatment for thyroid dysfunction and using medications like amiodarone, nitroprusside, sulfonylurea, thalidomide, interleukin, lithium, perchlorate, and interferon-alpha treatment were excluded. Patient characteristics like age, gender, duration of diabetes, and hypertension were recorded. All the patients underwent venous blood sampling aseptically for the assessment of thyroid functions (TSH, T3, and T4) measured by chemiluminescence immunoassay (CLIA). Thyroid dysfunction was labelled if any of the following abnormality was identified on thyroid profile; subclinical hypothyroidism: serum TSH values >4.2 mU/L and normal free T3 (210-440pg/dl) and free T4 levels (0.8-2.7ng/dl), hypothyroidism: if free T4 is low (ng/dl)<0.8 and serum TSH level is high (21 - 54yrs - >4.2 mU/L, 55 - 87 yrs - >8.9mU/L), subclinical hyperthyroid: serum TSH values <0.4 mU/l in 21-54 years and <0.5 mU/l in 55-87 years, normal free T3 and free T4 levels and hyperthyroidism as high free T3 (>440pg/dl), free T4 (>2.7 ng/dl) and low TSH (<0.4 mU/l in 21-54 years and <0.5 mU/l in 55-87 years). A minimum sample size of 248 (124 uncontrolled and 124 controlled diabetes) was calculated through Open Epi online software using formula for comparative cross-sectional study [9]: n = (Zα/2 + Z1-β)2 p̄q̄(r+1) / r (p1 – p2)2, assuming thyroid dysfunction of 6.6% in uncontrolled diabetics, 18.4% in controlled diabetics at 80% power and 95% confidence interval [7]. SPSS version 25.0 was used for data analysis. The Shapiro-Wilk test was used for normality assessment. Mean and standard deviation are presented for quantitative data like age and duration of diabetes. Numerical data between the groups was compared through an independent sample t-test. Frequency and percentages for categorical data like gender, hypertension, thyroid dysfunction, and type of thyroid dysfunction. Thyroid dysfunction between the uncontrolled and controlled diabetics was compared through a chi-square test at 5% significance level and 95% confidence level. Confounding was controlled through stratification on demographic factors. The p-value<0.05 was considered significant for all comparisons. The study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for a cross-sectional study [10].

RESULTS

The mean age of the participants was 49.2 ± 10.3 years, and 133 (53.6%) were <50 years old. There were 129 (48%) male and 129 (52%) female participants. Hypertension was identified in 182 (73.4%) of the participants. The mean duration of diabetes mellitus was 9.0 ± 3.1 years, and in 158 (63.7%) of participant's duration of diabetes was <10 years. The demographic characteristics were comparable between uncontrolled and controlled diabetics (Table 1).

Table 1: Characteristics of Patients with Diabetes Mellitus (n=248)

Characteristics	All (n=248)	Uncontrolled Diabetes (n= 124)	Controlled Diabetes (n= 124)	p-Value*
Age				
Year	49.2 ± 10.3	48.3 ± 10.9	50.2 ± 9.5	0.152
<50-Years	133 (53.6%)	73 (54.9%)	60 (45.1%)	0.098
≥50-Years	115 (46.4%)	51 (44.3%)	64 (55.7%)	
Gender				
Male	119 (48%)	61 (51.3%)	58 (48.7%)	0.703
Female	129 (52%)	63 (48.8%)	66 (51.2%)	

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Hypertension				
Yes	182 (73.4%)	91 (50%)	91 (50%)	1.00
Diabetes				
Duration	9.0 ± 3.1	9.4 ± 3.6	8.7 ± 2.6	0.083
<10-Years	158 (63.7%)	75 (47.5%)	83 (52.5%)	0.291
≥10-Years	90 (26.6%)	49 (54.4%)	41 (45.6%)	

*t-test for numerical and chi-square test for categorical comparison

Thyroid dysfunction was diagnosed in 36 (14.5%) diabetic patients. Prevalence of TD was significantly more frequent in uncontrolled diabetics compared to controlled diabetics (69.4% vs. 30.6%). Subclinical hypothyroid was diagnosed in 15 (6%), hypo- and hyperthyroid in 5 each (3.2%), and subclinical hyperthyroid in 5 (2%) of diabetic patients. Types of thyroid dysfunction were comparable in uncontrolled and controlled diabetics (p-value >0.05) (Table 2).

Table 2: Thyroid dysfunction in Patients with Diabetes Mellitus (n=248)

Characteristics	All (n=248)	Uncontrolled Diabetes (n=124)	Controlled Diabetes (n=124)	p-Value*
Thyroid Dysfunction				
Yes	36 (14.5%)	25 (69.4%)	11 (30.6%)	0.012¥
No	212 (85.5%)	99 (46.7%)	113 (53.3%)	
Type of Thyroid Dysfunction				
Hypothyroid	08 (3.2%)	5 (62.5%)	3 (37.5%)	0.882
Subclinical Hypothyroid	15 (6.0%)	11 (73.3%)	4 (26.7%)	
Hyperthyroid	08 (3.2%)	5 (62.5%)	3 (37.5%)	
Subclinical Hyperthyroid	05 (2.0%)	4 (80%)	1 (20%)	

* chi-square test (Fisher's exact test where cell count <5), ¥ statistically significant

Thyroid dysfunction was significantly higher in uncontrolled diabetics ≥50 years in contrast to controlled diabetics (65.6% vs. 34.4%, p-value<0.004). Similarly, in uncontrolled diabetics, TD was significantly high in females (70% vs. 30%, p-value <0.039) and in hypertensive patients (69.4% vs. 30.6%, p-value<0.009) compared to controlled diabetics (Table 3).

Table 3: Factors Associated with Thyroid Dysfunction in Diabetic Patients (n=248)

Associated Factors		Thyroid Dysfunction	Uncontrolled Diabetes (n=124)	Controlled Diabetes (n=124)	p-Value*
Age	<50-Years	Yes	4 (100%)	0 (0.0%)	0.127
		No	69 (53.5%)	60 (46.5%)	
	≥50-Years	Yes	21 (65.6%)	11 (34.4%)	0.004¥
		No	30 (36.1%)	53 (63.9%)	
Gender	Male	Yes	11 (68.8%)	5 (31.3%)	0.132
		No	50 (48.5%)	53 (51.5%)	
	Female	Yes	14 (70%)	6 (30%)	0.039¥
		No	49 (45%)	60 (55%)	
Diabetes Duration	<10-Year	Yes	3 (100%)	0 (0.0%)	0.105
		No	72 (46.5%)	83 (53.5%)	
	≥10-Year	Yes	22 (66.7%)	11 (33.3%)	0.076
		No	27 (47.4%)	30 (52.6%)	
Hypertension	Yes	Yes	25 (69.4%)	11 (30.6%)	0.009¥
		No	66 (45.2%)	80 (54.8%)	
	No	Yes	–	–	–
		No	33 (50%)	33 (50%)	

* chi-square test (Fisher's exact test where cell count < 5), ¥ statistically significant

DISCUSSIONS

In this study, we observed that TD was frequently common in diabetic patients. Frequency of TD was more commonly seen in patients with uncontrolled diabetes, in contrast to controlled diabetes. The most common dysfunction was subclinical hypothyroidism, followed by hypo- and hyperthyroidism and subclinical hyperthyroidism. Al-Rubaye *et al.* reported in their study that the frequency of thyroid impairment was 18.4% in patients with uncontrolled diabetes and 7.6% of all type 2 diabetics [7]. Díez *et al.* documented that the overall magnitude of TD was 13.4% in diabetic cases. It was low in Type 2 diabetes men (7%) and greatest in Type 1 diabetic women (31.4%). Subclinical hypothyroidism (4.8%), hypothyroidism (0.9%), hyperthyroidism (0.5%), and subclinical hyperthyroidism (0.5%) were the most frequently diagnosed conditions [11]. Our findings are very close to these observations. Ghimire *et al.* observed that thyroid problems were seen in 27.9% of patients with type-2 DM. Subclinical hypothyroidism was the most prevalent thyroid condition, affecting 14.71% of persons [12]. In a meta-analysis, Hadgu *et al.* included 38 studies. Thyroid dysfunction was present in 20.24% of cases. Subclinical hyperthyroidism, hypothyroidism, hypothyroidism, and subclinical hypothyroidism were shown to have respective pooled prevalences of 11.87%, 7.75%, 2.49%, and 2.51% [13]. Since most of the individuals were previously diagnosed with thyroid dysfunction before their inclusion in the study, the discrepancy can be explained by the disparities in health systems and the referral of complex cases to diabetes clinics in tertiary care facilities. Similar to our results, according to Al-Rubaye *et al.* hypothyroidism was present in 58.2% of uncontrolled individuals, and subclinical hypothyroidism was seen in around two-thirds of these patients (26 patients, 38.81% of patients with thyroid dysfunction and poor glycaemic control) [7]. Similar results were also shown by Akbar *et al.* and Palma *et al.* [14, 15]. In a meta-analysis published by Han *et al.* showed that the frequency of subclinical hypothyroidism ranged between 4.69% and 18.86% regardless of whether the patients had poor or good glycemic control. In this study, the frequency of subclinical hypothyroidism was 7.14% of those with uncontrolled

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diabetes mellitus [16]. A case-control study, which found that HbA1c levels above 7% are a significant risk factor for thyroid dysfunction, with adjusted odds ratio (OR) of 2.553 (95% CI: 1.472–4.429; p=0.001), further supports the link between thyroid dysfunction and poor glycaemic management [17]. It has been demonstrated by researchers that the thyroid hormone controls the pancreas and glucose metabolism, and DM may alter thyroid function. For instance, it has been discovered that diabetes lowers the "TSH to thyrotropin-releasing hormone response," which results in hypothyroidism and lower T3 levels [18]. Numerous studies have also demonstrated that this pathophysiological association is mimicked by a variety of intricately linked hormonal, genetic, and biochemical problems. For instance, the primary target for modifying insulin sensitivity control and thyroid hormone feedback associated with hunger and energy utilization is the "5′ adenosine monophosphate-activated protein kinase" (AMPK) [19, 20]. Furthermore, the main cause of diabetes mellitus associated with thyroid problems is autoimmune. Additionally, some genetic changes, such as a mutation in GLUT4 [21], have also been related to thyroid issues and type 2 DM. Concordant with our study, age above 50 years was a significant predictor of thyroid dysfunction, with adjusted odds ratio (OR) of 3.89 (95% CI: 2.15–7.05; p<0.001), in a case-control study that enrolled 998 persons with type 2 DM [15]. This implies that the interaction between thyroid function and glycaemic management may worsen with age. According to the same study, thyroid dysfunction was more likely to be seen in women (OR 1.75; 95% CI: 1.12–2.74; p=0.013) [17]. Furthermore, a Saudi Arabian study reported that female type 2 DM patients, especially those with hypertension, had a higher prevalence of thyroid dysfunction [22]. These results highlight how crucial it is to evaluate TD in diabetic persons while taking gender and concomitant diseases like hypertension into account. The strengths of our study were that it was a case-control design, which effectively allowed comparison between controlled and uncontrolled diabetics, highlighting the association of TD with glycemic control. The study differentiated between subclinical and clinical forms of both hypo- and hyperthyroidism, adding granularity and clinical relevance to the findings.

CONCLUSIONS

Thyroid dysfunction is more prevalent in individuals with uncontrolled diabetes, especially in patients who are over 50, female, or have high blood pressure. The significance of routine thyroid function monitoring in high-risk diabetes groups is highlighted by these findings. The findings highlight the importance of considering routine thyroid screening in patients with poorly controlled diabetes, especially women and those over 50 years of age, to enable earlier detection and timely management. The necessity for integrated care approaches in diabetes management is further supported by the possibility that early detection and treatment of thyroid abnormalities may improve glycaemic control and lower the risk of complications.

Authors Contribution

Conceptualization: KQ
Methodology: KQ, MAA, MT, JN, SS, FF
Formal analysis: MT, JN
Writing review and editing: KQ, MAA, FF

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

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All the authors declare no conflict of interest.

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Assessment of the Relationship Between Student-Teacher Interactions and Professional Development among Nursing Students in Karachi, Pakistan

Muhmooda Abdul Razzaque[1*], Rukhsana Muhammad Haroon[1], Rubina Hafeez[2] and Tanseer Ahmed[1]

[1]Dow Institute of Nursing and Midwifery, Dow University of Health Sciences, Karachi, Pakistan
[2]Institute of Nursing and Midwifery, Jinnah Sindh Medical University, Karachi, Pakistan

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Corresponding Author:
Muhmooda Abdul Razzaque
Dow Institute of Nursing and Midwifery, Dow University of Health Sciences, Karachi, Pakistan
muhmooda.abdulhaleem@duhs.edu.pk

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ABSTRACT

Student-teacher interactions (STIs) and professional development (PD) are a crucial part of nursing education. Both contribute to enhancing self-efficacy among nursing students by fostering knowledge, skills, and professional identity. Objectives: To assess the relationship between student-teacher interactions and professional development among nursing students in Karachi, Pakistan. **Methods:** A cross-sectional analytical study was conducted between November 2024 and January 2025 at two nursing institutions: Dow Institute of Nursing and Midwifery and the College of Nursing, Dr Ruth Pfau Civil Hospital, Karachi. A purposive sample of 235 Bachelor of Science in Nursing (BSN) students was included from the 2nd to 4th years of nursing students. After getting ethical approval and consent from the participants. Data were gathered using a structured, self-developed questionnaire. Data were analyzed using SPSS version 26.0. **Results:** Out of 235, the mean age (25.9 ± 0.891) of the participants, and a majority were female (n=157, 66.8%), and were studying in their 4th year (n=122, 51.9%). A bulk of participants were not aware of the hidden curriculum. They found a significant positive correlation between STIs and PD (Spearman's ρ = 0.789, $p<0.01$) among respondents. **Conclusions:** This study found a strong relationship between student-teacher interactions and professional development among nursing students in Karachi, Pakistan. It is recommended to conduct longitudinal and qualitative studies to gain deeper insights into student-teacher interactions and their relationship with professional development among nursing students.

INTRODUCTION

Nursing education mainly encompasses formal and informal training; both play an important role in guiding nursing students throughout their nursing journey [1]. A formal curriculum includes a written syllabus for nursing students to qualify to become professional nurses. Informal curriculum helps students to understand the complexities of patient care and professional conduct that are not always covered in textbooks or lectures. Student-teacher interaction (STI) is a crucial part of the hidden curriculum that enhances the engagement and self-efficacy of nursing students [3]. Usually, students interact with teachers in the classroom and during their clinical duties [2]. Previous research has shown that STIs engage students in learning constantly [1]. It also motivates students to discuss assignments and queries openly. Constructive feedback from teachers has a significant place in improving the academic performance of students [1, 2]. Moreover, nursing students who are well-guided by their educators become competent in decision-making and problem-solving. A study has shown that 93.2% of nursing students perceived their academic success as linked with positive interactions with faculty [3]. Professional development (PD) refers to acquiring knowledge, skills, and a professional identity that

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comprises formal and informal education [4]. It provides platforms for nursing students to understand values and ethics and develop self-efficacy. PD aims to equip student nurses with the prerequisite professional standards. Major elements of PD include the development of clinical reasoning and reflection, and it enhances professional integrity through observation and the preceptorship model. PD is a multifaceted process that is strongly related to student-teacher interactions [3, 4]. These relationships have several attributes, such as caring, reciprocal respect, and open communication, that promote individual and professional growth. The most important part of the learning environment is the teacher, rather than the student. Competent teachers always exhibit high confidence in their students. They understand the significance of student involvement in the learning process [5]. A teacher's first responsibility is to motivate students to be major participants in their learning by providing a conducive learning environment. Finally, when students achieve success in academic learning, it builds a positive relationship between the student and teacher [6]. STI is an ideal situation that allows both teachers and students to work efficiently. Also, the student and teacher can enjoy the learning process and resolve conflicts easily [4]. Previous studies have endorsed that often, teachers impart their students' unforgettable lessons through actions rather than words. When teachers address multiple challenging situations, students find inspiration [7].

Moreover, there are limited studies related to student-teacher interactions and their association with professional development in nursing education, specifically in Karachi, Pakistan. This study aimed to assess the relationship between student-teacher interactions and professional acquisition among nursing students in Karachi, Pakistan.

METHODS

A cross-sectional analytical study was conducted among nursing students studying at the Dow Institute of Nursing and Midwifery and the College of Nursing at Dr Ruth Pfau Civil Hospital, Karachi, by using a purposive sampling technique. The duration of the study was three months from November 2024 to January 2025. The study population comprised 450 BS Nursing students, with 300 from Dow Institute of Nursing and Midwifery and 150 from the College of Nursing at Dr. Ruth Pfau Civil Hospital, Karachi. This study included nursing students who were currently enrolled in the 2nd to 4th year at the time of data collection. However, students enrolled in their first year of studies, absent during data collection, and who did not provide consent were excluded. An ethical approval was obtained from the Institutional Review Board of Dow University of Health Sciences (IRB-2434/DUHS/Approval/2022/776). Written informed consent was obtained from all participants. A sample size was calculated using Open-Epi software by estimating a population proportion with a finite population: Using the formula n = (DEFFN p (1-p)])/ $((d^2/Z^2_{1-}\alpha/_2)(N-1)+p(1-p))$. Where: n = required sample size, N = population size, p = estimated proportion of nursing students demonstrating professional development (main outcome), d = margin of error, Z = Z-score at 95% confidence (1.96), DEFF = design effect (set to 1) [8]. Since no previous data were available, a conservative value of p = 0.5 was chosen to maximize the sample size. The parameters were set at d = 0.05, Z = 1.96, and DEFF = 1. With a population of 450 students, the required sample size was 208. To account for a possible 20% dropout, the sample was increased to 248. Out of this, 13 participants were excluded due to missing data, leaving 235 participants for the final analysis. Data were collected through a structured, self-administered questionnaire developed through an extensive literature review [1-16]. The questionnaire consisted of three sections: The first section included demographic information such as age, gender, year of study, and knowledge about the hidden curriculum. The second section has two domains. 1) Student-teacher interactions have 06 items, and 2) professional development of the nursing students has 6 items. Responses of the participants were recorded on a five-point Likert scale. It ranges from 1 = Strongly Disagree to 5 = Strongly Agree. A pilot test involving 10% (n=24) of the sample size of the present study was conducted to assess the instrument's reliability. A Cronbach's alpha of 0.78 confirmed the acceptable internal consistency of the study tool. Data were analyzed using IBM SPSS version 26.0. Descriptive statistics were applied for age, gender, study year, and knowledge about the hidden curriculum. The relationship between Student-Teacher Interactions and Professional Development was checked by using Spearman's correlation test. Total scores for each variable were obtained by summing the responses to their respective items, resulting in overall scores for STIs and PD for each participant. Spearman's rho (ρ) was then computed to determine the strength and direction of the relationship between student-teacher interactions and the professional development of nursing students. A p-value of less than 0.05 was considered statistically significant. The correlation strength was interpreted using the following guidelines: if the value is 0.00–0.19 = very weak, 0.20–0.39 = weak. 0.40–0.59 = moderate,0.60–0.79 = strong and 0.80–1.00 = very strong.

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RESULTS

A total of 235 participants, mean age of participants was 25.9 ± 0.891, and a majority of participants were female (n=157, 66.8%), and most were studying in their 4th year (n=122, 51.9%). A bulk of students don't know about the hidden curriculum (n=140, 59.5%) (Table 1).

Table 1: Demographic Characteristics of the Nursing Students

Variables	Frequency (%)
Age	25.9 ± 0.891
Gender	
Male	78 (33.1%)
Female	157 (66.8%)
Year of Study	
2nd Year	53 (22.5%)
3rd Year	60 (25.5%)
4th Year	122 (51.9%)
Do You Know About the Hidden Curriculum?	
Yes	95 (40.42%)
No	140 (59.5%)

The highest-rated items on the student-to-teacher interactions were found: the clinical instructors were approachable and available during clinical practice (Mean ± SD = 4.41 ± 1.108), and teachers encourage students to discuss their learning issues openly (Mean± SD=4.02±1.156). The lowest-rated items, teachers recognized the learning capacity of students (Mean ± SD = 2.14 ± 1.437) (Table 2).

Table 2: Student–Teacher Interactions (STIs) among Nursing Students

Items	Mean ± SD
My clinical instructor is approachable and available during clinical practice	4.41 ± 1.108
Teachers acknowledge students' valid opinions in their learning	3.19 ± 1.501
Teachers' feedback is constructive and timely	3.27 ± 1.299
Teachers encourage students to openly discuss their learning issues	4.02 ± 1.156
Teachers provide students with ongoing support during difficult tasks	3.22 ± 1.351
Teachers can recognize the learning capacity of students	2.14 ± 1.437

The highest-rated aspects on professional development (PD) were students' know-how to communicate with patients and families in various situations during their clinical rotations (Mean ± SD = 4.09 ± 0.969), and students have learned to respect patients' cultural competence (Mean ± SD = 4.04 ± 1.014). The lowest-rated responses were simulation-based learning strengthened my clinical skills (Mean ± SD = 2.99 ± 1.267) (Table 3).

Table 3: Professional Development (PD) of the Nursing Students

Items	Mean ± SD
I can perform nursing procedures independently, and I have Learnt	3.67 ± 1.03
I am confident in interpreting clinical data for patient care	3.02 ± 0.27
Simulation-based learning has strengthened my clinical skills	2.99 ±1.32
I am aware of the ethical principles that guide nursing practice	3.65 ± 1.07
I know how to communicate with patients and families in various situations during their clinical rotations	4.09 ± 0.97
I have learned to respect patients' cultural competence	4.04 ± 1.01

A Correlation Coefficient (Spearman's rho) test showed a strong, statistically significant positive correlation (r=0.789, p<0.01) observed between student-teacher interaction and professional development of the nursing students (Table 4).

Table 4: Relationship Between Student—Teacher Interactions and Professional Development among Nursing Students

Domains	Student–Teacher Interaction	Professional Development
Student–Teacher Interaction	1.000	0.789
Professional Development	0.789	1.000

p<0.01 (2-tailed)

DISCUSSIONS

The present study aimed to assess the relationship between student-teacher interactions and professional development among nursing students in Karachi, Pakistan. The study found a positive correlation between student-teacher interaction and professional development among nursing students. These findings were congruent with previous literature that indicated a significant role of teacher-student interactions in professional development [1-4]. A similar finding was supported that students and teachers' positive relationship profound influence on the academic and professional growth of the students [5]. Moreover, a few studies have highlighted that students' positive behavior modifications were influenced by mentorship and students' engagement in the learning process [5, 6]. In the same way, a study found a positive correlation between teacher and student interaction during academic engagement in administration courses among nursing students [3]. Another study also concluded that a positive relationship between student-to-teacher interaction can enhance the professional and personal skills of students long long-lasting [7]. A positive association between student–teacher interactions and professional development highlights the need to strengthen interpersonal engagement within academic and clinical environments. Moreover, these findings emphasize that a conducive learning environment is a major attribute to support nursing students in learning both theory and clinical practice. About student–teacher interactions, the majority of participants reported in this study was the availability and approachability of clinical faculty during their clinical duties. It encouraged nursing students to discuss their clinical issues openly. These

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findings were in line with many studies, that clinical instructor availability can influence students' learning and acquisition of skills. It also fosters support and provides a conducive learning environment [9-11]. A previous study found that clinical practice under the supervision of a clinical teacher showed significant relationships between competence and skills development. Nursing students perceived positive interactions with their teachers by following their guidelines in solving their queries [9]. One of the studies has found that clinical instructors' approachability enhances nursing students' confidence level to perform clinical practice [10]. Teachers' availability during the clinical settings influences on satisfaction of nursing students' learning [11]. In contrast, a study had found that teachers were limited in their progress in professional development, and their students' approach was subjected to specific [12]. Another study focused on teachers' motivations to encourage students to openly discuss their learning issues and the usage of different strategies to solve students' queries on time. Hence, it concluded that teachers' encouragement plays a significant role in shaping student and teacher interactions during class [13]. Another study also explored that teachers' supportive attitude enhances students' confidence to share their thoughts in class during discussions. And students take an interest in justifying their answers by referring to their ideas and opinions. It was concluded that students' engagement in discussion increases when their participation in the class is valued by the teachers [14]. In contrast, many studies have found that most teachers do not hold sessions for discussion during class due to maintaining discipline in the class, time management, and completion of curriculum content within a timeframe. Therefore, teachers have struggled to follow academic calendars and are least interested in spending time on the discussions [6, 13]. Educators should prioritize availability, approachability, and meaningful feedback, as these factors contribute to students' confidence, motivation, and competence. Our study has found highest response was rated by participants in professional development. Such as how to communicate with patients and families, and students learnt to respect patients' cultural competence. Few congruent studies have found that the communication patterns of nursing students were highest who were competent in clinical practice [11, 15]. When a nursing student can do an assigned task clinically, they gradually become confident in their communication. Therefore, a significant relationship between the readiness of clinical practice and communication skills is an important factor [11]. Incongruent finding from previous study that those nursing students who are not competent in clinical skills face challenges while they are communicating with patients and their relatives [16, 17]. According to one of the studies that nursing students were in trouble as they step forward to professional life. This is due to a huge difference between what they had learned during the nursing degree and the clinical skills that are required in real patient care. At the end, nursing students perceived themselves as unprepared to handle complexities in real scenario of patients. These findings conveyed the importance of pedagogical approaches that are aligned with both theory and practice in nursing education [17]. Furthermore, studies have shown that nursing students' knowledge of cultural competence is essential to dealing with the diverse needs of patients. Few demographic factors significantly influence students' nurse awareness like "age, studying year, and cultural content "[18]. Studies have emphasized that nursing students should know the emotional needs of patients according their cultural differences. So, they become competent to give culturally sensitive care to the patients. The concept of cultural competency as necessary to facilitate patients' culturally sensitive needs in today's era it includes “empathy, cultural sensitivity, and compassionate care” [18, 19] Another study explored that student nurses were not confident for culturally sensitive care even though they had adequate knowledge about domains of cultural diversity. Therefore, educational interventions are needed to develop the concept of transcultural care and its implications among student nurses [20]. This study underscores the necessity of integrating cultural competence into the nursing curriculum. Also, provide structured learning experiences through real-world clinical exposure and reflective practice that can bridge the gap between theoretical knowledge and practical application, particularly in diverse healthcare settings.

CONCLUSIONS

This study found a strong relationship between student-teacher interactions and professional development among nursing students in Karachi, Pakistan. It is recommended to conduct longitudinal and qualitative studies to gain deeper insights into student-teacher interactions and their relationship with professional development among nursing students.

Authors Contribution

Conceptualization: MAR
Methodology: MAR, RMH
Formal analysis: TA
Writing review and editing: RMH, RH, TA

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

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Original Article

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Outcome of Topical Dapsone 5% Versus Topical Clindamycin 1% in Treatment of Mild to Moderate Acne Vulgaris

Muhammad Bilal Iftikhar[1*], Zareen Saqib[1] and Bushra Bashir[1]

[1]Department of Dermatology, Khawaja Muhammad Safdar Medical College, Sialkot, Pakistan

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***Corresponding Author:**
Muhammad Bilal Iftikhar
Department of Dermatology, Khawaja Muhammad Safdar Medical College, Sialkot, Pakistan
bilaliftikhar28@gmail.com

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ABSTRACT

Acne vulgaris is a common inflammatory skin disorder, and increasing resistance to conventional topical antibiotics has highlighted the need for alternative therapies such as dispone. **Objective:** To compare the outcome of topical dapsone 5% gel versus topical clindamycin 1% gel in the treatment of mild to moderate acne vulgaris. **Methods:** A Randomized Controlled trial was conducted in the Dermatology Department of Allama Iqbal Memorial Teaching Hospital, Sialkot, from February 2025 to July 2025. A total of 131 patients aged between 18 and 60 years, diagnosed with mild to moderate acne vulgaris based on the Global Acne Grading System (GAGS), were consecutively enrolled. Participants were randomly allocated into two groups (Group A: clindamycin 1% gel twice daily, Group B: dapsone 5% gel once daily). Both regimens were continued for 12 weeks. Mean difference and percentage reduction in GAGS scores, along with adverse events, were noted as outcomes. **Results:** Both groups had similar baseline characteristics without significant differences ($p>0.05$). At 12 weeks, mean GAGS scores were significantly lower in the clindamycin group (9.27 ± 2.95) than in the dapsone group (10.57 ± 4.33; $p=0.047$). Percent reduction in GAGS score was also significantly greater with clindamycin (44.97 ± 14.37) compared to dapsone (38.72 ± 18.52; $p=0.033$). No adverse events occurred in the Clindamycin 1% gel group, while 5 (7.6%) in the Dapsone 5% gel group reported oily skin, pruritus, or irritation. **Conclusions:** Clindamycin 1% gel demonstrated superior efficacy and tolerability compared to Dapsone 5% gel in reducing acne severity over 12 weeks.

INTRODUCTION

Acne vulgaris is a common chronic inflammatory disorder affecting the pilosebaceous unit, arising from a combination of mechanisms such as excessive sebum secretion, obstruction of the follicular canal due to hyperkeratinization, proliferation of Cutibacterium acnes, and the resulting inflammatory cascade [1]. Clinically, it is characterized by recurrent comedones along with inflammatory papules and pustules. These lesions are commonly found on the face, but they can also develop on areas such as the trunk, neck, and Proximal arms [2]. While often considered a self-limiting ailment during adolescence and early adulthood, acne can cause lasting disfigurement in the form of scars and may contribute to considerable psychological morbidity, underscoring the importance of effective treatment strategies [3]. There are various treatment options available for acne, ranging from topical medications to systemic treatments. Topical therapies, typically preferred for managing mild to moderate cases, include combinations of antibiotics and anti-inflammatory agents that offer ease of application and lower risk of systemic side effects [4]. Clindamycin 1% gel is a commonly used topical antibiotic [5]. It has demonstrated efficacy in managing mild to moderate acne [6]. However, the increasing resistance to Clindamycin is now a concern [7], even as a standalone therapy or in combination with systemic treatments [8]. The rise of

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bacterial resistance linked to topical antibiotic use and side effects in a few cases emphasizes the need for alternative therapies [9]. Dapsone, classified as a sulfone, provides both anti-inflammatory and antimicrobial effects [10]. Although historically used as an oral treatment for acne, the risk of systemic toxicity limited its use [11]. Although various treatment modalities exist, there is limited regional evidence comparing topical clindamycin and dapsone, with few studies conducted in South Asia, including Pakistan [12] and neighboring countries [13]. Genetic predisposition, environmental exposures, and lifestyle habits unique to Pakistani patients are likely to influence acne severity and therapeutic response. Locally conducted studies are therefore essential to validate international findings and guide context-specific treatment strategies. Comparing topical dapsone and clindamycin is clinically significant, as increasing antibiotic resistance has reduced the long-term effectiveness of clindamycin, while dapsone offers an alternative with both antimicrobial and anti-inflammatory properties. Furthermore, adherence and cost considerations are critical in resource-constrained settings, underscoring the need for evidence to identify effective, practical, and sustainable treatment options.

This study aimed to evaluate the efficacy and safety of 5% topical dapsone versus 1% topical clindamycin in mild to moderate acne vulgaris, thereby generating locally relevant data to inform dermatologic practice.

METHODS

This randomized controlled trial was conducted in the Dermatology Unit of Allama Iqbal Memorial Teaching Hospital, Sialkot, from February 2025 to July 2025. Before initiation, the study received ethical approval from the Institutional Review Board of Government Khawaja Muhammad Safdar Medical College, Sialkot (IRB No: 47/REC/KMSMC) and was registered in the Iranian Registry of Clinical Trials (IRCT No: IRCT20250124064503N1). No modification to the study was made after commencement. Patients aged 18 to 60 years of both genders, clinically confirmed as mild to moderate acne vulgaris, were screened for inclusion. Acne was classified into mild to moderate severity using the Global Acne Grading System (GAGS), and patients with scores between 0 and 30 were enrolled. Individuals with severe acne (GAGS ≥ 31), other facial dermatoses such as rosacea, pregnancy, lactation, known hypersensitivity to the study medications, recent systemic antibiotics (within four weeks) or topical antibiotics (within two weeks), and current use of medications that could exacerbate acne (e.g., glucocorticoids, phenytoin, isoniazid, lithium) were excluded. Sample size calculation was performed using Open Epi software, aiming to detect a difference in mean GAGS scores between both groups at the 12th week follow-up. Based on prior data, the anticipated mean GAGS scores were 5.0 ± 2.5 for the clindamycin group and 2.5 ± 4.1 for the dapsone group [14]. With a two-sided alpha of 0.05 and 80% power, 66 participants per group were required, totaling 132. One participant in the dapsone group withdrew, leaving 131 patients for analysis. After obtaining written informed consent, baseline demographic and clinical data were recorded. All eligible patients presenting during the study period were enrolled consecutively and then randomized into the two treatment groups, ensuring equal allocation and minimizing selection bias. Randomization was achieved via a computer-generated sequence, and assignment was performed by a separate staff member not involved in outcome assessment. Participants were allocated to one of two intervention arms using sealed opaque envelopes: Clindamycin 1% gel was prescribed for Group A to be applied twice per day, and dapsone 5% gel was given to Group B for once nightly application over 12 weeks. A CONSORT flow diagram has been provided to depict the screening, randomization, and allocation of participants (Figure 1).

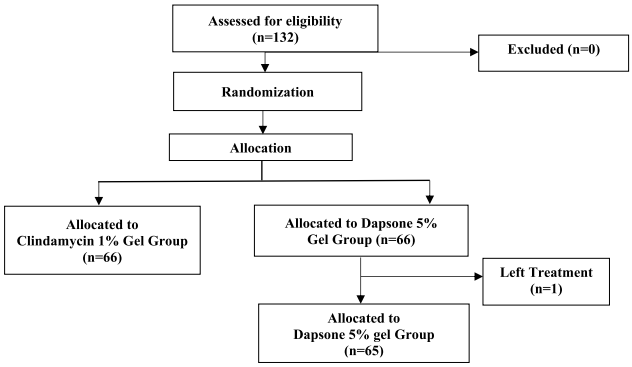

Figure 1: Consort Flow Showing Recruitment of Patients

Although differences in dosage frequency and formulation precluded double blinding, both the outcome assessor and the statistician remained blinded to group allocation. Patients were instructed on proper application techniques and dosing schedules. Follow-up assessments were conducted at the baseline and at weeks 4, 8, and 12. Adherence was monitored by checking returned medication tubes and residual content, supplemented by a treatment diary maintained by each participant, recording the date and time of applications. Clinical assessments were performed at baseline and at 12 weeks. The primary outcome was the mean difference in GAGS scores between groups, with greater reductions indicating higher efficacy. Secondary outcomes included the incidence of adverse events, documented through patient self-reports and clinical evaluation. Adverse events, defined in advance to ensure consistency, included skin irritation (stinging,

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tingling, itching), burning sensation, pruritus, erythema, and increased oiliness. No changes were made to pre-specified outcomes after trial initiation. Data were analyzed using IBM SPSS Statistics version 26.0 on a per-protocol basis, including only participants who completed the study as per the assigned treatment. No imputation methods (e.g., last observation carried forward) were applied for missing data. As attrition was minimal, the risk of attrition bias was considered low. Continuous variables, like age and how long participants had acne, were expressed as mean ± standard deviation (SD) and compared between the two groups using the independent samples t-test. Categorical data, including variables like gender, residential status, and acne severity, were expressed as frequencies and percentages, and analyzed using either the Chi-square test or Fisher's exact test, based on suitability. The Primary outcome, defined as the mean difference in GAGS score from the start of the study to week 12, was analyzed using the independent sample t-test to compare results between the two groups. Changes within each group over time were assessed using the paired samples t-test. The percentage reduction in GAGS scores was also calculated and analyzed between the groups using the independent t-test. All statistical analyses were two-sided, with a p-value<0.05 considered statistically significant. Additionally, 95% confidence intervals (CIs) were calculated for all mean differences.

RESULTS

The study was completed by 131 participants, with 66 receiving clindamycin 1% (Group A) and 65 assigned to the dapsone 5% treatment group (Group B). Study provides a summary of the Pre-treatment demographic and clinical characteristics. There were no significant differences between the two groups in terms of age, gender distribution, acne duration, place of residence, or baseline acne severity (p>0.05 for all), indicating that the two groups were statistically similar at baseline (Table 1).

Table 1: Initial Demographic and Clinical Profiles of Participants in the Clindamycin 1% and Dapsone 5% Treatment Groups

Variables	Total (n=131)	Clindamycin 1% (n=66)	Dapsone 5% (n=65)	p-Value
Age				
Years	21.57 ± 3.87	22.20 ± 4.30	20.94 ± 3.28	0.062α
≤22	88 (67.2%)	41 (46.6%)	47 (53.4%)	0.214β
>22	43 (32.8%)	25 (58.1%)	18 (41.9%)	
Gender				
Male	27 (20.6%)	11 (40.7%)	16 (59.3%)	0.261β
Female	104 (79.4%)	55 (52.9%)	49 (47.1%)	
Duration of Acne				
Years	2.12 ± 1.99	2.11 ± 1.96	2.12 ± 2.04	0.981α
≤2	90 (68.7%)	45 (50.0%)	45 (50.0%)	0.897β
>2	41 (31.3%)	21 (51.2%)	20 (48.8%)	
Residence				
Urban	105 (80.2%)	51 (48.6%)	54 (51.4%)	0.405β
Rural	26 (19.8%)	15 (57.7%)	11 (42.3%)	
Severity of Acne				
Mild	70 (53.4%)	36 (51.4%)	34 (48.6%)	0.797β
Moderate	61 (46.6%)	30 (49.2%)	31 (50.8%)	

Values are displayed as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. The p-values are calculated to assess baseline comparability between groups. αIndependent t-test applied. βChi-square/Fisher-Exact test applied. At study initiation, the mean GAGS scores were 17.67 ± 5.80 for the Clindamycin group and 18.18 ± 6.57 for the Dapsone group, with no statistically significant difference (p=0.633). At the end of the 12-week treatment period, both groups demonstrated a noticeable improvement in their GAGS scores. However, the clindamycin group exhibited a significant reduction, with a mean score of 9.27 ± 2.95, compared to 10.57 ± 4.33 in the dapsone group (p=0.047). A greater mean percentage decrease in GAGS scores was also observed in the Clindamycin group (44.97 ± 14.37) compared to the Dapsone group (38.72 ± 18.52), with a difference in means of 6.25 (95% CI: 0.52–11.97, p=0.033) (Table 2).

Table 2: Comparison of Mean GAGS Scores Between Clindamycin 1% and Dapsone 5% Groups at Baseline and After 12 Weeks

Time Point	Group	N	Mean ± SD	Mean Difference	95% CI of Difference	t (df)	p-Value
Baseline	Clindamycin 1%	66	17.67 ± 5.80	-0.52	-2.66 to 1.62	-0.478 (129)	0.633
	Dapsone 5%	65	18.18 ± 6.57				
12 Weeks	Clindamycin 1%	66	9.27 ± 2.95	-1.30	-2.58 to -0.02	-2.007 (129)	0.047*
	Dapsone 5%	65	10.57 ± 4.33				
Percent Reduction	Clindamycin 1%	65	44.97 ± 14.37	6.25	0.52 to 11.97	2.159 (129)	0.033*
	Dapsone 5%	66	38.72 ± 18.52				

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SD = Standard deviation; CI = Confidence interval; df = Degrees of freedom; $p < 0.05$ considered statistically significant. *Statistically significant difference.

No adverse events were reported in the Clindamycin group. In contrast, 5 participants (7.6%) in the Dapsone group reported adverse events. Among these, oily skin and pruritus were the most commonly observed, each occurring in 2 participants (40%), while one participant (20%) experienced skin irritation (Table 3).

Table 3: Frequency and Percentage Distribution of Adverse Effects and Specific Adverse Events among Study Participants

Adverse Effects	Specific Event	Frequency (%)
Any Adverse Effect	Clindamycin 1% gel (n=66)	0 (0%)
	Dapsone 5% gel (n=65)	5 (7.6%)
Type of Adverse Effect in Dapsone 5% Gel (n=5)	Irritation	1 (20.0%)
	Oily skin	2 (40.0%)
	Pruritus	2 (40.0%)

DISCUSSION

This randomized controlled trial demonstrated that topical 1% clindamycin gel led to significantly greater improvement in acne severity compared to topical 5% dapsone gel, as measured by mean GAGS score reduction and percent reduction after 12 weeks, with both agents showing a favorable safety profile. Our findings differ from those of a clinical trial conducted in Bangladesh, which compared topical dapsone gel with clindamycin cream applied over a 4-week period in patients with mild to moderate acne vulgaris [15]. That study found no statistically significant variation between both groups in terms of comedone, papule, pustule counts, or total acne score at final follow-up. Though similar to the current study finding, percent reduction in acne severity was numerically higher for clindamycin (74.77%) than dapsone (69.20%), but this difference was not statistically significant [15]. Notably, the treatment period in that trial was shorter (4 weeks) compared to our 12-week intervention, which may partly explain why our study detected statistically significant differences favoring clindamycin. Additionally, the Bangladesh study used clindamycin cream rather than gel, which can have different skin penetration characteristics. Similarly, Iftikhar et al. (2025), in a Lahore-based study reported that dapsone 5% gel monotherapy significantly reduced total lesion counts after 12 weeks [16]. Another important point of notice is that in the current study Clindamycin 1% gel was given twice a day whereas Dapsone 5% gel once daily. This deviates from most studies which use once daily dose for both. The reason behind using Clindamycin 1% gel twice a day in the current study is because of its short half-life while Dapsone 1% gel longer half-life allows once daily dosing. Our results are partially aligned with those of Iqra et al. in Pakistan, who compared topical dapsone 5% gel and clindamycin 1% gel in mild to moderate acne vulgaris and reported clindamycin 1% gel as effective [17]. In contrast, earlier Indian studies, such as those reported by Verma et al. have found no significant difference between the two agents when used as monotherapy [18]. This variation may be explained by differences in treatment protocols, particularly our twice-daily clindamycin application versus once-daily dapsone and regional differences in Cutibacterium acnes resistance profiles. Several South Asian studies have evaluated only dapsone 5% gel or with other regimens, such as Fatima et al. who compared it to adapalene 0.1% gel [19]. Similar findings were reported by Darjani et al. from Iran who reported dapsone 5% gel as effective compared to benzoyl peroxide 5% in combination with doxycycline [20]. These trials demonstrated significant reductions in inflammatory and non-inflammatory lesions with dapsone, highlighting its safety and tolerability. With respect to safety, the low incidence of mild adverse effects in our trial (3.8%) is in line with prior reports, including the Bangladesh study [15] and trials by Iqra et al. [17]. Lastly, a previous study from Pakistan reported significant associations between acne occurrence and factors such as skin type, physical activity, menstrual cycle, and use of skincare products like toners. These population-specific and potentially modifiable factors warrant further exploration in relation to treatment response [21]. Most adverse events were mild and self-limiting, and no participant discontinued treatment due to side effects, reinforcing the tolerability of both agents. The study had several strengths, including an adequately calculated sample size, use of standardized and validated outcome measures (GAGS), and active compliance monitoring. The results of this study have important clinical and public health implications. Clinically, the superior efficacy of clindamycin 1% gel in reducing acne severity, combined with its favorable safety profile, supports its use as a first-line topical therapy for mild to moderate acne vulgaris. These findings provide evidence to guide dermatologists in selecting treatments that optimize patient outcomes, enhance adherence, and minimize adverse effects. From a public health perspective, acne represents a common chronic condition that can substantially affect psychosocial well-being and quality of life. Demonstrating effective and well-tolerated topical interventions, such as clindamycin, can contribute to reducing the overall burden of disease, improving patient satisfaction, and informing treatment guidelines in local clinical settings. Collectively, these results underscore the importance of evidence-based, context-specific approaches to acne management that address both individual patient care and broader public health priorities. Future research should focus on multi-center trials across Pakistan and neighboring countries to address regional variability in treatment

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response and resistance patterns. Studies comparing combination regimens such as clindamycin with benzoyl peroxide versus dapsone monotherapy could provide more practical clinical guidance. Extended follow-up studies are necessary to evaluate relapse rates and the long-term effectiveness beyond the 12 weeks.

CONCLUSIONS

This randomized controlled trial compared the efficacy and safety of topical clindamycin 1% gel and topical dapsone 5% gel in patients with mild to moderate acne vulgaris. Clindamycin demonstrated superior reduction in GAGS scores over 12 weeks, while both treatments were well tolerated with minimal adverse events.

Authors Contribution

Conceptualization: MBI
Methodology: MBL, ZS
Formal analysis: MBI
Writing review and editing: BB

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Impact of Acne Vulgaris on the Quality of Life of Patients Presented to Nishtar Hospital Multan Outpatient Department

Sidra Tahir[1*], Raheel Tahir[1], Noreen[1], Hurraira Bin Afzal[1], Muhammad Irfan Jamil[2] and Muhammad Shoaib[3]

[1]Department of Dermatology, Nishtar Hospital, Multan, Pakistan
[2]Department of Medicine, Lahore General Hospital, Lahore, Pakistan
[3]Department of Dermatology, Yeovil District Hospital, Somerset National Health Service Foundation Trust, Yeovil, United Kingdom

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Corresponding Author:
Sidra Tahir
Department of Dermatology, Nishtar Hospital, Multan, Pakistan
sidra.tahir77@yahoo.com

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ABSTRACT

Acne vulgaris is one of the most prevalent dermatological conditions globally, yet its psychosocial burden is often underestimated in clinical settings. **Objectives:** To assess the impact of acne vulgaris on quality of life of patients. **Methods:** This cross-sectional study enrolled 145 patients (aged 14–50 years) with acne vulgaris at the Dermatology OPD, Nishtar Hospital, Multan. Acne severity and quality of life were assessed using GAGS and DLQI, respectively. Statistical tests included chi-square, ANOVA, and logistic regression, with significance set at $p < 0.05$. **Results:** Of 145 patients, 81 (55.9%) were female and 64 (44.1%) male. Based on GAGS, 45 (31.0%) had mild, 63 (43.4%) moderate, and 37 (25.5%) severe acne; mean GAGS score was 23.12 ± 9.89. DLQI assessment revealed no impact in 13 (9.0%), mild in 33 (22.8%), moderate in 26 (17.9%), very large in 48 (33.1%), and huge in 25 (17.2%); mean DLQI was 11.79 ± 8.43. DLQI scores increased with acne severity: mild 8.40 ± 9.34, moderate 11.44 ± 7.53, severe 16.49 ± 6.54 ($F=10.71$, $p<0.001$). Very large DLQI impact was seen in 11.1%, 33.3%, and 59.5% of mild, moderate, and severe cases, respectively. Independent predictors of high DLQI impact included age 31–50 years, unemployment, and low socioeconomic status ($\chi^2=38.70$, $df=8$, $p<0.001$). **Conclusions:** This study demonstrates that the severity of acne vulgaris is significantly associated with greater impairment in dermatology-specific quality of life. Independent predictors of poor quality of life include age, gender, occupation, and socioeconomic status.

INTRODUCTION

Acne vulgaris is one of the most widespread dermatological conditions and has been ranked as the eighth most common disease globally. Its burden is particularly high among adolescents and young adults, with global age-standardized prevalence increasing from 8,563.4 per 100,000 in 1990 to 9,790.5 per 100,000 in 2021 [1]. Peak prevalence occurs during adolescence, especially in those aged 15–19 years, affecting up to 85% of late pubertal boys and a slightly lower proportion of girls [2, 3]. Among young adults aged 16–24, nearly 28% are affected, while in adults aged 25–39, the prevalence remains substantial at approximately 19% [2, 4]. In Pakistan, the estimated prevalence stands at 5%, making it a common reason for dermatological consultations [5]. Beyond its physical presentation, acne is strongly associated with psychological and social consequences that often exceed its clinical severity [6]. The quality-of-life impact of acne vulgaris is shaped by clinical severity, emotional health, self-perception, and demographic factors. Even mild acne can lead to significant distress due to perceived disfigurement. Anxiety, depression, and sleep disturbances are common and often influence life quality more than lesion count [7, 8]. Social withdrawal, impaired relationships, and reduced academic or professional performance are frequently reported. Females tend to be more affected by appearance concerns, while males report

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physical discomfort. Older adults often experience greater emotional burden than younger individuals [9]. The Dermatology Life Quality Index (DLQI) is a validated tool used to assess the impact of skin conditions like acne vulgaris on daily life. It covers symptoms, emotions, social and work activities, and treatment-related concerns. Widely used in both clinical and research settings, it offers a comprehensive measure of well-being [10]. Compared to other scales, the DLQI is more broadly validated. Higher scores reflect greater burden, especially with severe, long-standing acne, scarring, and pigmentation [11]. Given the high prevalence of acne vulgaris and its documented psychological and social burden, especially among adolescents and young adults in South Asia, there is a pressing need for local data to understand its broader impact. Despite being a common condition, limited research from Pakistan has explored how acne affects patients' quality of life using validated tools.

This study aims to assess the quality-of-life impact of acne vulgaris using the Dermatology Life Quality Index (DLQI) and to identify demographic and clinical factors that influence this burden, providing evidence to support more comprehensive, patient-centered acne care.

METHODS

This analytical cross-sectional study was carried out in the Dermatology Unit of Nishtar Hospital, Multan, a tertiary-level referral center serving a large population in southern Punjab. Data collection took place over six months from June to November 2024. Ethical approval was obtained from the Institutional Review Board (Ref. No. 7064). A total of 145 patients were enrolled through non-probability consecutive sampling. All dermatology outpatient attendees during the study period were evaluated, and those meeting the eligibility criteria were enrolled until the required number was reached. Informed consent was taken from all the participants. Sample size was calculated with a 95% confidence level, 9.7% prevalence, and 4.5% precision [12]. The sample size for this study was calculated using the standard formula for prevalence-based studies, expressed as $n = Z^2 \times P \times (1 - P) / d^2$ [13]. GAGS has demonstrated excellent psychometric properties with high internal consistency (Cronbach's α = 0.947) and excellent intra-rater reliability (ICC = 0.946, 95% CI: 0.918–0.966 [14]. The Dermatology Life Quality Index (DLQI) is a standardized and validated instrument consisting of 10 items designed to evaluate the quality-of-life impact of dermatological conditions such as acne. It assesses various domains, including emotional well-being, interpersonal interactions, daily routines, academic or occupational functioning, and treatment-related burden. Each item is rated on a 4-point Likert scale (0 to 3), producing a cumulative score between 0 and 30. Scores are interpreted as follows: 0–1 reflects no impact, 2–5 mild impact, 6–10 moderate impact, 11–20 substantial impact, and 21–30 denotes a very severe impact on the individual's quality of life [10]. Multiple validation studies have confirmed excellent psychometric properties, with internal consistency ranging from Cronbach's α=0.673 to 0.997 (mean = 0.834), with 95.3% of studies reporting values above the acceptable threshold of ≥0.70. Test-retest reliability shows strong correlations (ICC between 0.77-0.98) [11]. A face-to-face structured interview was conducted by the principal investigator in a dedicated consultation room to ensure privacy. Patients were asked a questionnaire in their preferred language. The answers were recorded directly into a predesigned data collection proforma. Data were analyzed using SPSS version 26.0. Continuous variables (e.g., age, GAGS, DLQI scores) were expressed as mean ± standard deviation, while categorical variables (e.g., gender, acne severity, DLQI categories) were presented as frequencies and percentages. Associations between acne severity and DLQI categories were assessed using Chi-square and one-way ANOVA. Before conducting ANOVA, normality of continuous variables was assessed using the Shapiro-Wilk test. Multivariable logistic regression to identify independent predictors of high QoL impairment. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Among the 145 patients enrolled, 80 (55.2%) were aged 14–30 years, and 81 (55.9%) were female. The most frequently involved site was the face and neck (76; 52.4%). Most had acne for 1–3 years (99; 68.3%). The mean Global Acne Grading System (GAGS) score was 23.12 ± 9.89. Moderate acne was most common (63; 43.4%). The Dermatology Life Quality Index (DLQI) revealed a mean score of 11.79 ± 8.43, with 48 (33.1%) reporting a very large impact and 25 (17.2%) reporting an extremely large impact on quality of life (Table 1).

Table 1: Baseline Characteristics of the Study Population (N = 145)

Variables	Frequency (%)
Age Group	
14–30 years	80 (55.2%)
31–50 years	65 (44.8%)
Gender	
Male	64 (44.1%)
Female	81 (55.9%)
Duration of Disease	
1–3 years	99 (68.3%)
More than 3 years	46 (31.7%)
Site of Acne Lesions	
Face and Neck	76 (52.4%)
Chest	43 (29.7%)

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Back	26 (17.9%)
Marital Status	
Married	63 (43.4%)
Unmarried	63 (43.4%)
Divorced/Widowed	19 (13.1%)
Educational Level	
Primary	33 (22.8%)
Matriculation	46 (31.7%)
Intermediate	41 (28.3%)
Graduation or Higher Education	25 (17.2%)
Occupation	
Student	40 (27.6%)
Employed	59 (40.7%)
Unemployed	23 (15.9%)
Homemakers / Non-Working Adults	23 (15.9%)
Socioeconomic Status	
Low (≤ PKR 50,000)	23 (15.9%)
Middle (50,001–120,000 PKR)	60 (41.4%)
High (> PKR 150,000)	62 (42.8%)
Acne Severity (GAGS Classification)	
Mild	45 (31.0%)
Moderate	63 (43.4%)
Severe	37 (25.5%)
DLQI-Based QoL Impact	
No Effect (0–1 score)	13 (9.0%)
Mild Effect (2–5 score)	33 (22.8%)
Moderate Effect (6–10 score)	26 (17.9%)
Very Large Effect (11–20 score)	48 (33.1%)
Extremely Large Effect (21–30 score)	25 (17.2%)

A significant association was observed between acne severity and quality-of-life impairment (χ^2=38.70, df=8, p<0.001). No DLQI impact was reported by 10 (22.2%) with mild acne, 3 (4.8%) with moderate, and none with severe acne. Very large DLQI impact was most frequent in severe acne (22; 59.5%) (Table 2).

Table 2: Association Between Acne Severity and Quality of Life Impact (DLQI Categories)

DLQI Impact on Life	Mild Acne (N=45)	Moderate Acne (N=63)	Severe Acne (N=37)	p-Value
No Effect (0–1)	10 (22.2%)	3 (4.8%)	0 (0.0%)	<0.001*
Mild Effect (2–5)	16 (35.6%)	16 (25.4%)	1 (2.7%)	
Moderate Effect (6–10)	7 (15.6%)	13 (20.6%)	6 (16.2%)	
Very Large Effect (11–20)	5 (11.1%)	21 (33.3%)	22 (59.5%)	
Extremely Large Effect (21–30)	7 (15.6%)	10 (15.9%)	8 (21.6%)	

p≤0.05 indicates statistical significance

A one-way ANOVA demonstrated a significant increase in DLQI scores with acne severity: 8.40 ± 9.34 (mild), 11.44 ± 7.53 (moderate), and 16.49 ± 6.54 (severe) ($F(2,142) = 10.71$, $p<0.001$), with acne severity explaining 13.1% of score variance ($\eta^2 = 0.131$). Another ANOVA across DLQI impact categories was also significant ($F(4,140) = 498.32$, $p<0.001$), with all pairwise comparisons showing statistically significant score differences. In the adjusted regression model, patients aged 31–50 years exhibited significantly higher odds of experiencing dermatology-specific quality-of-life (QoL) impairment compared to those aged 14–30 years (OR = 4.72, 95% CI: 1.35–16.51, p = 0.015). Male gender was also associated with increased DLQI burden (OR = 2.63, 95% CI: 1.06–6.54, p = 0.037). Occupational status revealed strong associations: unemployed individuals had 31.31 times higher odds (95% CI: 2.82–348.13, p = 0.005), and homemakers had 24.17 times higher odds (95% CI: 1.86–313.38, p = 0.015) of high QoL impact compared to students. High socioeconomic status was protective (OR = 0.16, 95% CI: 0.03–0.75, p = 0.020). Moderate acne showed lower odds of high DLQI scores versus mild acne (OR = 0.14, 95% CI: 0.04–0.53, p = 0.004). Other variables were not statistically significant (Table 3).

Table 3: Multivariable Binary Logistic Regression Predicting High DLQI Impact (DLQI >10) Among Acne Vulgaris Patients (N = 145)

Predictor Variable	B	S.E.	Wald	df	p-Value	Adjusted OR (Exp (B))	95% CI for OR
Age group (31–50 vs 14–30 years)	1.552	0.639	5.902	1	0.015*	4.721	1.350 – 16.514
Gender (Female vs Male)	-0.967	0.464	4.344	1	0.037*	0.380	0.153 – 0.943
Marital Status (reference: Married)	–	–	1.205	2	0.548	–	–
Unmarried vs Married	0.875	0.824	1.127	1	0.288	2.398	0.477 – 12.057
Divorced/Widowed vs Married	0.530	0.795	0.445	1	0.505	1.698	0.358 – 8.060
Site of Acne (reference: Face and Neck)	–	–	3.427	2	0.180	–	–
Chest vs Face and Neck	1.171	0.674	3.016	1	0.082	3.224	0.860 – 12.083
Back vs Face and Neck	0.529	0.738	0.514	1	0.473	1.698	0.399 – 7.215
Education (reference: Primary)	–	–	1.180	3	0.758	–	–
Matric vs Primary	0.741	0.772	0.920	1	0.338	2.098	0.462 – 9.534
Intermediate vs Primary	0.732	0.749	0.956	1	0.328	2.079	0.479 – 9.020
Graduation or Higher vs Primary	0.482	0.756	0.407	1	0.524	1.620	0.368 – 7.134
Occupation (reference: Student)	–	–	9.653	3	0.023*	–	–
Employed vs Student	2.508	1.386	3.276	1	0.070	12.282	0.812 – 185.661
Unemployed vs Student	3.444	1.204	8.205	1	0.005*	31.314	2.817 – 348.125

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Homemaker vs Student	3.185	1.307	5.934	1	0.015*	24.166	1.864 – 313.384
Socioeconomic Status (reference: Low)	—	—	7.120	2	0.028*	—	—
Middle vs Low	-0.976	0.517	3.559	1	0.059	0.377	0.137 – 1.039
High vs Low	-1.832	0.787	5.421	1	0.020*	0.160	0.034 – 0.748
Duration of Disease (≥3 vs <3 years)	-0.775	0.523	2.197	1	0.138	0.461	0.165 – 1.284
Severity of Acne (reference: Mild)	—	—	8.833	2	0.014*	—	—
Moderate vs Mild	-1.957	0.672	8.478	1	0.004*	0.141	0.038 – 0.528
Severe vs Mild	-1.032	0.611	2.853	1	0.091	0.356	0.108 – 1.180
Constant	-2.936	1.789	2.692	1	0.101	0.053	—

*Reference categories: Male (Gender), Married (Marital Status), Face & Neck (Site), Primary (Education), Student (Occupation), Low SES (Socioeconomic Status), Mild acne (Severity), <3 years (Duration). *p ≤ 0.05 indicates statistical significance

DISCUSSIONS

In the present study, a statistically significant association was observed between acne severity and impairment in quality of life, with the mean DLQI score rising from 8.40 ± 9.34 in mild cases to 16.49 ± 6.54 in severe cases (χ^2=38.70, df = 8, p<0.001). A greater proportion of patients with severe acne reported a very large (59.5%) or extremely large (21.6%) impact on daily functioning, compared to 11.1% and 15.6%, respectively, among those with mild acne. These findings align with previous studies, which reported a very large impact in 75.8% of patients with severe acne (mean DLQI: 13.29) and others who observed progressively worsening DLQI scores with increasing severity [15, 16]. Conversely, some studies reported a lower mean DLQI (3.05), likely due to a sample dominated by mild cases [17]. Other literature further supports this relationship; as acne severity increases, emotional distress, embarrassment, and social withdrawal become more common [18, 19]. In this study, patients aged 31–50 years exhibited significantly higher odds of quality-of-life (QoL) impairment than those aged 14–30 years, which contrasts with prevailing literature where adolescents and young adults typically report greater psychosocial burden due to heightened self-image concerns and social sensitivity [20, 21]. Several factors specific to our Pakistani context may explain this unexpected pattern. Older patients likely had prolonged acne with accumulated scarring and treatment failures, leading to psychological hopelessness. Working adults face greater occupational appearance pressures compared to students, while Pakistani culture views persistent adult acne as more socially stigmatizing than teenage acne. Many older patients also delayed treatment due to financial constraints or misconceptions that acne is only a teenage condition, resulting in more severe disease and cumulative psychological burden. This contrasts with previous findings highlighting higher DLQI scores in younger age groups, emphasizing the importance of considering cultural and socioeconomic contexts in QoL research. In terms of gender, the present findings revealed greater QoL disruption among male patients, diverging from studies that consistently show females experiencing higher psychological distress despite often having milder acne [22-24]. These inconsistencies may reflect context-specific factors such as healthcare-seeking behaviors, sociocultural expectations, or differential coping strategies. In the present study, neither duration of acne nor site of involvement showed a statistically significant association with DLQI scores in the adjusted model. This contrasts with findings from other studies that reported significantly higher QoL impairment in patients with longer disease duration [25] and those noting that facial or multisite acne was strongly associated with elevated DLQI scores due to the visibility of lesions [26]. In the current sample, this lack of association may be explained by the pattern of severe acne reported predominantly on the chest rather than the face, where its impact on appearance and social perception may be relatively less. Additionally, overlapping psychosocial burden in patients across different lesion sites might have diluted the independent effect of anatomical location on QoL. In the current study, marital status did not show a statistically significant association with quality-of-life impairment, which contrasts with findings where unmarried participants had higher DLQI scores [6, 23]. These differences may be attributed to variation in age distribution and cultural expectations regarding appearance. Regarding occupation, both unemployed individuals and homemakers were significantly more likely to report high DLQI scores compared to students. Socioeconomic status was found to be a strong predictor, with lower SES associated with increased QoL impairment, consistent with previous studies that highlighted financial constraints as a barrier to effective acne management [24]. This study offers valuable insights into the psychosocial burden of acne vulgaris in a local clinical context. The use of validated tools such as GAGS and DLQI strengthens the reliability of the findings. A major strength lies in the analysis of multiple demographic and socioeconomic factors as potential predictors. However, certain limitations must be

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acknowledged, including the single-center design, relatively modest sample size, the cross-sectional nature limiting causal interpretation, and the use of consecutive non-probability sampling, which may restrict generalizability. Despite these, the study emphasizes the need for dermatologists to routinely assess quality of life and address psychosocial concerns as part of comprehensive acne management, especially in vulnerable groups.

CONCLUSIONS

In conclusion, significant association between acne severity and quality-of-life impairment. Individuals aged 31–50 years, males, unemployed or homemaker groups, and those from lower socioeconomic backgrounds were more likely to experience greater psychosocial burden. These findings highlight the importance of considering both acne severity and sociodemographic factors in assessing quality-of-life impact. Future longitudinal studies are needed to establish causal relationships and track quality of life changes over time with treatment interventions. Clinical practice should incorporate routine DLQI screening in dermatology consultations to identify high-risk patients and implement comprehensive, patient-centered care that addresses both physical and psychosocial aspects of acne management.

Authors Contribution

Conceptualization: ST
Methodology: ST, N
Formal analysis: ST, MIJ
Writing review and editing: ST, RT, N, HBA, MS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Maternal Dietary Diversity in Pakistan: Influences of Education, Poverty, and Food Insecurity from a Cross-Sectional Survey

Ijaz Habib[1], Zia Ul Haq[1*], Ayesha Imtiaz[1], Muhammad Naseem Khan[2], Saima Afaq[3,1], Sheraz Fazid[4], Cecilia Garzon[5], Mahamadou Tanimoune[5] and Yasir Ihtesham[5]

[1]Institute of Public Health and Social Sciences, Khyber Medical University, Peshawar, Pakistan
[2]Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar
[3]Department of Health Sciences, University of York, United Kingdom
[4]Department of Epidemiology and Biostatistics, Institute of Public Health and Social Sciences, Khyber Medical University, Peshawar, Pakistan
[5]World Food Program, United Nations, Islamabad, Pakistan

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***Corresponding Author:**
Zia Ul Haq
Institute of Public Health and Social Sciences, Khyber Medical University, Peshawar, Pakistan
drzia@kmu.edu.pk

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ABSTRACT

Maternal nutrition strongly influences pregnancy outcomes. In Pakistan, poor dietary diversity and food insecurity remain key drivers of malnutrition, particularly in disadvantaged areas. **Objectives:** To assess dietary diversity, household food insecurity, and nutritional status among pregnant women in Kurram District, Pakistan, and examine their associations with maternal education and poverty. **Methods:** A community-based cross-sectional baseline survey, nested within a non-randomized, cluster-controlled trial (ISRCTN94319790), was conducted in Upper Kurram from January to April 2018, using multi-stage cluster sampling (80 clusters from 12 health facilities) and consecutive home-based enrolment of 1,209 pregnant women (15–49 years). Data were collected via structured questionnaires (HFIAS, MDD-W), standardized anthropometry, and analyzed in Stata 14. **Results:** Mean age was 27.9 ± 5.8 years; 68.9% of women and 24% of husbands were uneducated. Most households were non-poor (87.6%), and 77.4% were food secure (mean HFIAS 4.2 ± 5.2). Dietary diversity was low, with only 13.2% achieving MDD-W ≥5; diets were dominated by cereals (98.4%), low in fruits, vegetables, and animal-source foods. Mean BMI was 24.9 ± 4.5; 4.5% were underweight, 29.8% overweight, and 11.0% obese. In bivariate analyses, food insecurity was more common among women with no formal education, the poorest households, and those consuming <5 food groups (all $p<0.001$). **Conclusions:** Findings reveal a double burden of malnutrition, with overweight and obesity coexisting with poor dietary diversity. Food insecurity was strongly linked to poverty, low education, and limited dietary diversity. Interventions addressing education, poverty, and dietary diversity are critical to improve maternal nutrition in similar low-resource settings.

INTRODUCTION

Malnutrition remains a major threat to population health, and women of reproductive age are especially vulnerable during pregnancy because of higher nutrient requirements [1, 2]. Improving nutrition in the first 1,000 days, from conception to a child's second birthday, lays the foundation for lifelong health [3]. Yet across many settings, women's diets still fall short: meals are often dominated by staples with limited micronutrient density, and access is shaped by affordability, gender norms, and local food environments [2, 4]. In this context, assessing what women actually eat and how diet quality varies by social conditions is essential for guiding maternal nutrition policy and practice. Dietary diversity, a 24-hour count of distinct food groups, is a practical way to gauge whether pregnant women likely

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meet nutrient needs [5]. The FAO MDD-W uses 10 groups; intake of ≥5 denotes minimum diversity and proxy's micronutrient adequacy [2]. Maternal undernutrition remains prevalent in low- and middle-income countries (LMICs), with approximately 20% of women in Asia and 10% in Africa having a low body mass index; deficiencies of key micronutrients (iron, folate, calcium, vitamins A and D) are also widespread [6]. Conversely, overweight and obesity are rising, and women of reproductive age in Pakistan face a double burden of malnutrition [7]. Maternal malnutrition affects the health and well-being of both mothers and offspring [8]. Addressing it is essential for human capital, socioeconomic development, and long-term economic growth [9]. Regionally, Pakistan shows the coexistence of undernutrition with rising overweight and obesity in women of reproductive age, with Khyber Pakhtunkhwa (KP) and the newly merged districts exhibiting persistent structural disadvantages (low female literacy, limited services) [1]. Provincial data indicate substantial household food security alongside micronutrient gaps (NNS 2018) [7], while analyses from Peshawar link poverty and food insecurity across urban and rural households [10]. Urban studies (e.g., Islamabad/Rawalpindi) report comparatively higher dietary diversity during pregnancy, underscoring socioeconomic and educational gradients within Pakistan [5]. Most recent evidence from Karachi shows that dietary diversity was alarmingly low in pregnant women [11]. Comparable findings from neighboring LMIC contexts show low women's dietary diversity and strong associations with household food insecurity and maternal education [12, 13], alongside programmatic evidence on nutrition and food access during the first 1,000 days [14]. Together, these patterns highlight the need for district-level data from tribal settings such as Kurram to inform locally appropriate maternal nutrition strategies. Despite national and provincial reports, district-level evidence from KP's newly merged tribal districts is scarce, and large surveys (PDHS 2017–18; NNS 2018) may mask local heterogeneity in women's diet quality and food access [15]. Upper Kurram was purposively selected due to a culturally feasible setting for women-focused fieldwork, with community receptivity and established female health-worker networks enabling reliable household access and data collection [16]. In addition, undernutrition among pregnant and lactating women (PLWs) in Kurram exceeds the national average (NNS 2018) [7], highlighting an at-risk district within KP's newly merged areas. Coupled with very low female literacy and constrained services [16], these conditions plausibly shape dietary intake and food security differently than urban centers [5]. Generating baseline, community-based estimates of dietary diversity trends, food insecurity situation, and nutritional status in this tribal setting addresses a critical evidence gap and provides operational inputs for provincial strategies and social protection programming [17, 18]. Improving the diversity of diets is one approach to enhance micronutrient nutrition for women of reproductive age and promote sustainable, healthy diets; this can contribute to the Sustainable Development Goals and the World Health Assembly's 2030 nutrition-specific targets [2].

This study aims to assess dietary diversity, food insecurity, and nutritional status of pregnant participants in Kurram District. To fill a district-level evidence gap for KP's tribal districts and to inform targeting and counselling priorities under ongoing provincial nutrition and social protection initiatives.

METHODS

This study conducted a community-based cross-sectional baseline survey in Upper Kurram from January to April 2018, nested within a non-randomized, cluster-controlled trial (ISRCTN94319790). Using multistage cluster sampling, 80 clusters were drawn from 12 health-facility catchments, and 1,209 pregnant women (15–49 years) were enrolled consecutively during home visits. Trained staff administered the Household Food Insecurity Access Scale (HFIAS) and the Minimum Dietary Diversity for Women (MDD-W) and obtained standardized anthropometry. Analyses were performed in Stata 14 with descriptive and bivariate tests (chi-square; α=0.05); proportions are reported with one decimal, and BMI category estimates include 95% confidence intervals (Wilson method). The study complied with the Declaration of Helsinki and local regulations, with approval from the KMU Ethics Review Board (Ref DIR/KMU-EB/SP/000427-28-08-2017). Trained female staff provided information in Pashto/Urdu (objectives, procedures, risks/benefits, privacy, voluntariness). Participation was voluntary, with the right to decline/withdraw anytime. Written consent was obtained; for non-literate participants, forms were read with an impartial witness, and consent was recorded by thumbprint plus witness signature. For participants <18 years, parent/guardian consent and assent were obtained. Interviews were private; data were de-identified (unique IDs) and securely stored. No clinical interventions or specimens were collected; only aggregate, de-identified results are reported. Eligible participants were resident pregnant women, aged 15-49 years, in their first trimester. The required sample was estimated using the single-proportion formula: $n_o = Z^2p(1-p)/d^2$ assuming a 95% confidence level (Z = 1.96), expected prevalence $p=.40$, and precision d=0.04, yielding no ≈ 576 [19]. To adjust for multi-stage cluster sampling, a conservative design effect (DEFF = 2.0) was applied, giving n ≈ 1,152. Allowing for an estimated 5% non-response, the final target was 1,210, closely

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matching the achieved sample of 1,209 (30). Post-hoc Open Epi analysis indicated >90% power (α = 0.05, two-sided) to detect an approximate 19% prevalence difference between women consuming milk/milk products (n=488; 40.4%) and non-consumers (n = 721; 59.6%) [21]. A multi-stage cluster approach was applied to screen and register the study participants. A total of 122 clusters were formed in the catchment areas of selected health facilities (n=12) in Upper Kurram. Each cluster comprised, on average, 100-150 households based on the Lady Health Workers (LHWs) catchment area. Households were identified and selected based on the polio micro planning data of the Expanded Program on Immunization (EPI). Clusters (n=80) were randomly selected from the total clusters. A consecutive sampling technique was used to select the participants from selected clusters. Pregnant women aged 15–49 years registered with LHWs in the selected clusters were identified. The data collection teams visited the households in selected clusters and met the household members to enroll the eligible participants, using a social mapping approach. All the eligible participants (pregnant women) in the selected household were approached and enrolled in the study with appropriate written informed consent. Fewer than 3% of the Pregnant women refused participation, and reasons for non-participation were documented. This cross-sectional survey was conducted from January to April 2018 to assess the baseline characteristics of the pregnant women. Before inclusion, informed consent in written form was obtained from study participants after the provision of the information sheet and verbal explanation of the study objectives. Participants were apprised regarding their free will and withdrawal from the study without any reason. They were assured of the confidentiality of the data. The data collected on validated structured questionnaires on dietary diversity and food insecurity, along the basic demographic data. Anthropometric measurements were done following standard procedures as explained below. The questionnaires on the Household Food Insecurity Access Scale instrument (HFIAS-instrument) and Minimum Dietary Diversity for Women (MDD-W) were translated into Pashto and Urdu, translated back into English for accuracy, and pre-tested in a pilot survey. This ensured cultural relevance and validity. Information on participants' demographics was recorded, covering age, marital status, household composition, years, and occupation of both women and their spouses. Socioeconomic position was assessed using the Benazir Income Support Program poverty scale. Based on the poverty score, households were categorized into four groups: "Ultra poor (0-11)", "Vulnerable poor (12-18)", "Transitory poor (19-23)", and "non-poor (24-100)" [21]. Data on household food insecurity were collected using the "Household Food Insecurity Access Scale (HFIAS)". Based on the HFIAS score, households were categorized into four levels: "food secure", "mildly food insecure", "moderately food insecure", or "severely food insecure" [22]. "Minimum Dietary Diversity for Women (MDD-W)" was used for collecting data on dietary diversity. Dietary intake was assessed using a 24-hour interviewer-administered recall, minimizing misreporting. Recall bias was further reduced by prompting participants about specific meals, snacks, and seasonal food items. Based on Food and Agriculture Organization (FAO) cut-off points, dietary diversity was poor if less than five food groups were consumed and good if a woman ate at least five food groups in the last 24 hours [2]. Anthropometric measures of the pregnant women included height (cm), weight (kg). Measurements of BMI and MUAC were taken as indicators of maternal nutritional status. Weight was measured using the SECA 2 weighing scale. Height in centimeters was assessed using the standardized UNICEF SECA height boards. SECA weighing scales were calibrated daily. Height boards were standardized. Inter-observer reliability checks were performed weekly for MUAC and height to ensure consistency across data collectors. Maternal nutritional status was assessed using the BMI, calculated as weight in kilograms divided by height in meters squared (kg/m2), and classified under WHO reference values. Women were grouped as underweight if BMI was below 18.5, normal when between 18.5–24.9, overweight for values of 25–29.9, and obese when 30 or above [23]. MUAC was measured with non-stretchable plastic tapes for adults, developed by UNICEF. Pregnant women having MUAC <23 cm were classified as undernourished, and those with MUAC ≥23 cm were considered normal [12]. Data were collected by twenty data collectors. Each data collector was assigned four clusters. They were trained on questionnaires used for data collection and were also briefed on the study background, objectives, and methodology. The data collection process was supervised, and the data were double-checked to ensure the quality data. All the recruited participants in the baseline study were assigned unique IDs to ensure the privacy of the study participants. Data were analyzed and descriptive statistics were generated, with continuous measures expressed as mean ± SD, and categorical measures presented as frequencies and percent distributions. All statistical analysis was performed using STATA software (version 14.0).

RESULTS

Mean BMI was 24.9 ± 4.5; 4.5% were underweight, 29.8% overweight, and 11.0% obese. The mean height was 157.6 ± 5.7 cm, and the mean weight was 61.3 ± 11.2 kg. Figure 1 shows the BMI distribution: 4.5% underweight, 54.7% normal, 29.8% overweight (95% CI 27.3–32.4), and 11.0%

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obese (95% CI 9.4–12.9), indicating a double burden of malnutrition. The mean MUAC was 26.2 ± 3.3 cm, with 85.0% ≥ 23 cm, figure 1.

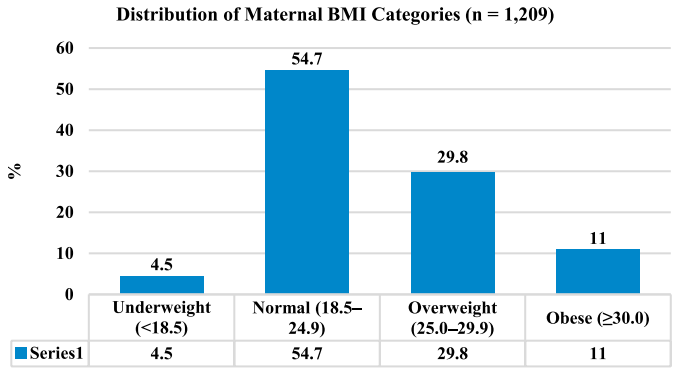

Figure 1: Distribution of Maternal BMI Categories among Pregnant Women in Kurram (n=1,209)

The 1,209 pregnant participants were predominantly 20–30 years (66.4% mean age 27.9 ± 5.8 years), with 68.9% of women having no formal schooling and 24.2% of husbands uneducated. Most households were non-poor (87.6%) and food secure (77.4%, 95% CI 75.0–79.8). Mean HFIAS was 4.2 ± 5.2. Four in five women lived in joint/extended families (83.5%), and nearly one-third of husbands were unemployed (29.3%), table 1.

Table 1: Socio-Demographic, Education, Occupation, Household Composition, Poverty, and Food Security of Pregnant Women (n=1,209)

Variables	n (%) / Mean ± SD
Age Groups	
Mean age	27.9 ± 5.8
<20 Years	75 (6.2%)
20–30 Years	803 (66.4%)
>30 Years	331 (27.4%)
Education (Women)	
No Schooling	833 (68.9%)
1–8 Years	202 (16.7%)
9–12 Years	129 (10.7%)
13–16 Years	45 (3.7%)
Years of Education	2.6 ± 4.3
Husband's Education	
No Schooling	293 (24.2%)
1–8 Years	338 (28.0%)
9–12 Years	467 (38.6%)
13–16 Years	111 (9.2%)
Years of Education	7.2 ± 4.9
Husband's Occupation	
Paid Work	209 (17.3%)
Self-Employed	259 (21.4%)
Non-Paid Work	57 (4.7%)
Unemployed	354 (29.3%)
Abroad	281 (23.2%)
Other	49 (4.1%)
Living Structure	
Nuclear/Single	200 (16.5%)
Joint/Extended	1,009 (83.5%)
Poverty (BISP Scorecard)	
Score	41.5 ± 14.8
Ultra-Poor	6 (0.5%)
Vulnerable Poor	49 (4.1%)
Transitory Poor	95 (7.9%)
Non-Poor	1,059 (87.6%)
Household Food Security (HFIAS)	
HFIAS Score	4.2 ± 5.2
Food Secure	936 (77.4%)
Mild Food Insecurity	145 (12.0%)
Moderate Food Insecurity	51 (4.2%)
Severe Food Insecurity	77 (6.4%)

PW = Pregnant Women, HFIAS = Household Food Insecurity Access Scale, BISP = Benazir Income Support Program, SD = Standard Deviation, CI = Confidence Interval. Note: Percentages are to one decimal place. Means are mean ± SD. Food security classification per HFIAS categories. Values are n (%) unless stated, continuous variables are mean ± SD.

Only 13% achieved MDD-W ≥5; cereals were near-universal (98%), while animal-source foods and fruit/vegetable groups were infrequent. Over half of the participants (54%) reported consuming oils and fats, followed by 40% who consumed milk and dairy products, and 35% who ate legumes, nuts, or seeds. Consumption of fish, eggs, flesh meat, and both vitamin-rich and other fruits was very low. The study enrolled 1,209 pregnant women (mean age 27.9 ± 5.8 years). Most had limited schooling: 68.9% of women and 24.0% of husbands had no formal education. Although 87.6% of households were categorized as non-poor and 77.4% were food secure (mean HFIAS 4.2 ± 5.2), diet quality was low. Only 13.2% met MDD-W ≥5, and diets were dominated by cereals (98.4%) with low intake of fruits, vegetables, and animal-source foods (Table 2).

Table 2: Dietary Diversity and 24-Hour Food Group Consumption among Pregnant Women (n=1,209)

Variables	Yes, n (%)	No, n (%)
Indicator (Minimum Dietary Diversity for Women)		
Adequate Dietary Diversity (≥5 Food Groups)	159 (13.2%)	1050 (86.8)
Food Groups Consumed in the Previous 24 Hours		
Cereals	1190 (98.4%)	19 (1.6%)
Roots and Tubers	353 (29.2%)	856 (70.80%)
Legumes, Nuts and Seeds	428 (35.4%)	781 (64.6%)
Milk and Dairy Products	488 (40.4%)	721 (59.6%)
Flesh Meat	205 (17.0%)	1004 (83.0%)
Fish	14 (1.2%)	1195 (98.8%)
Eggs	117 (9.7%)	1092 (90.3%)
Dark Green Leafy Vegetables	177 (14.6%)	1032 (85.4%)
Vitamin A Rich Vegetables	294 (24.3%)	915 (75.7%)
Other Vegetables Sources	468 (38.7%)	741 (61.3%)

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Vitamin A Rich Fruits	87 (7.2%)	1122 (92.8%)
Other Fruits Sources	220 (18.2%)	989 (81.8%)
Organ Meat	26 (2.2%)	1183 (97.9%)
Oils and Fats	658 (54.4%)	551 (45.6%)

MDD-W = Minimum Dietary Diversity for Women. (Percentages shown are one decimal. Categories reflect reported questionnaire groupings. Values are n (%) unless stated; dietary diversity based on MDD-W (10 food groups; ≥5 indicates minimum diversity).

The MDD-W <5 and household food insecurity were each strongly associated with lower maternal education and poverty (χ^2, p<0.001). Women with no formal schooling were far less likely to achieve adequate dietary diversity (11%) compared with those with ≥9 years of education (24%) (χ^2 = 28.0, p<0.001). Households in the poorest quartile were disproportionately food insecure (42%) compared to non-poor households (19%) (χ^2 = 39.5, p<0.001). Dietary diversity was also strongly linked to food security: women consuming <5 food groups were more often food insecure (60%), whereas those consuming ≥5 food groups reported substantially lower food insecurity (20%) (χ^2 = 87.0, p<0.001), Table 3.

Table 3: Minimum Dietary Diversity (≥5) By Maternal/Household Characteristics (n=1,209)

Variables	Category	Food Insecure, n (%)	Food Secure, n (%)	χ^2	p-Value
Minimum Dietary Diversity (≥5)					
Maternal Education	No Formal Schooling	741 (89.0%)	92 (11.0%)	28.0	<0.001
	≥9 Years of Schooling	223 (76.0%)	70 (24.0%)		
Household food insecurity (HFIAS)					
Poverty Status	Poorest Quartile	63 (42.0%)	87 (58.0%)	39.5	<0.001
	Non-Poor	201 (19.0%)	858 (81.0%)		
Dietary Diversity (MDD-W)	<5 Food Groups	630 (60.0%)	420 (40.0%)	87.0	<0.001
	≥5 Food Groups	32 (20.0%)	127 (80.0%)		

Abbreviations: MDD-W = Minimum Dietary Diversity for Women; HFIAS = Household Food Insecurity Access Scale. Values are n (%). Test: χ^2; p-values two-sided; α = 0.05.

Bars show % by WHO BMI category: BMI from standardized weight/height taken at home visits. 95% CIs: Underweight 54/1209, 3.4–5.8%; Normal 661/1209, 51.9–57.5%; Overweight 360/1209, 27.3–32.4%; Obese 133/1209, 9.4–12.9%. Food insecurity clustered among women with no schooling, households in the poorest category, and those consuming <5 food groups (all p<0.001). Food insecurity was more common among women with no schooling, households in the poorest quartile, and those consuming fewer than five food groups (Figure 2).

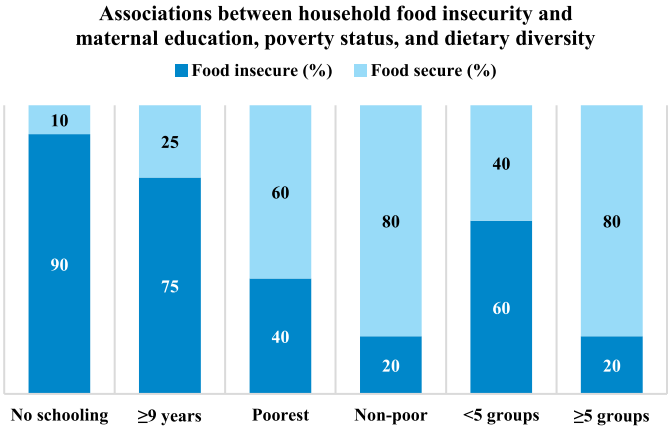

Figure 2: Associations Between Household Food Insecurity and Maternal Education, Poverty Status, and Dietary Diversity

DISCUSSIONS

This study shows a clear double burden among pregnant women in Upper Kurram: diet quality is poor while excess weight is common, and both patterns align with social disadvantage [17, 24]. Only a small share achieved MDD-W ≥5, indicating limited access to, or low prioritization of, micronutrient-dense foods [2]. At the same time, overweight and obesity suggest greater exposure to energy-dense, nutrient-poor diets that accompany the nutrition transition [7, 24]. Taken together, these findings point beyond food availability to the social and economic conditions that shape what women can purchase, prepare, and consume, underscoring the need for district-level strategies that strengthen diet diversity alongside poverty-sensitive support [16, 10]. Similar trends have been observed in other South-Asian contexts, where maternal dietary diversity significantly reduces with increasing household-level food insecurity during pregnancy and postpartum [14]. Two-thirds of women and one-fourth of husbands had no formal education. These gradients mirror PDHS patterns and underscore education-linked vulnerability in Kurram [14]. The mean poverty score (41.5 ± 14.8) and a high share of non-poor households resemble provincial heterogeneity reported in Peshawar [1], indicating that income alone may not predict women's diet quality in this district. A nationally representative analysis from Bangladesh likewise found that maternal education, household wealth, and urban residence were positively linked with higher dietary diversity scores [25], underscoring that economic and educational empowerment are key determinants of maternal diet quality. Food security was relatively high (77.4%), similar to KP in NNS 2018 (70.9%) [7], yet the local diet remained cereal-heavy with low fruit/vegetable and animal-source intake. In Kurram, subsistence agriculture and livestock may buffer availability (10), but national PDHS figures (54.6% food secure) and our HFIAS mean (4.2 ± 5.2;

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comparable to Bangladesh 3.3 ± 4.1) indicate that household access does not translate into diverse diets [14]. This is consistent with recent Pakistani data highlighting that dietary monotony persists even in urban settings despite nominal food security [11]. Consistent with prior work, food security here reflects more than availability, intertwining with education, occupation, wealth, and household structure [10]. The BMI profile, with few underweight but more than one-third overweight/obese, parallels national shifts between NNS 2011 and 2018 (undernutrition ↓; overweight/obesity ↑) and similar KP-NMD patterns [24]. Evidence from Pakistan and Ethiopia also shows substantial overweight among women of reproductive age, plausibly driven by urbanization, poor quality energy-dense foods, and constrained physical activity, while undernutrition persists in poorer/rural groups [26, 27]. Only 13.2% achieved MDD-W ≥5, confirming poor dietary diversity despite apparent household food security; MDD-W is a validated proxy for micronutrient adequacy [28]. Diets were cereal-dominant with low intake of fruits, vegetables, and animal-source foods, patterns seen in Ethiopia [12], though some Ethiopian settings report higher diversity [22], likely reflecting socioeconomic and seasonal differences. By contrast, Rawalpindi reported high diversity (89%) [5], reinforcing the role of education and affluence, notably limited in Kurram [11]. Maternal nutrition knowledge tracks with education and income and likely contributes to these disparities [21]. Stratified analyses highlight inequities: food insecurity and low dietary diversity were concentrated among women with no schooling and in poorer households, a pattern reported in Pakistan and comparable LMICs [10, 13]. The co-occurrence of food insecurity and limited diversity suggests a reinforcing cycle, where constrained resources reduce both access to and utilization of nutrient-dense foods. Collectively, evidence from South Asia underscores that household food insecurity, low income, and limited education jointly restrict maternal dietary diversity and nutritional well-being [14, 25]. Addressing these structural barriers is essential to improving maternal and child nutrition outcomes. Providing district-level evidence from a tribal setting, these findings support targeted counselling (dietary diversity, budget-sensitive food choices) paired with social protection to improve women's diet quality [7, 10]. Programmatically, coupling women's education and counselling with poverty-sensitive food access (cash/in-kind and market facilitation via BISP/health platforms) is likely needed to shift both diet diversity and excess BMI in similar KP–NMD districts [17]. This study benefits from a large, community-based sample, standardized home-visit measurements, and use of validated tools (MDD-W and HFIAS), enhancing internal validity. However, the cross-sectional design limits causal inference. Dietary intake was based on a single 24-hour recall conducted between January and April, so seasonal and recall bias cannot be excluded. BMI during pregnancy may not reflect pre-pregnancy adiposity; MUAC was included as a complementary indicator. Finally, the analysis is primarily bivariate, and residual confounding may remain despite stratified assessment.

CONCLUSIONS

Pregnant women in Upper Kurram face a double burden of malnutrition, with low dietary diversity and excess weight shaped by education and poverty, despite nominal food security. These findings support a shift from food availability to diet quality. We recommend integrating dietary-diversity counselling into routine ANC and LHW contacts, aligned with locally affordable foods, and using this district-level evidence to inform the remodeling of BISP Nashonuma, including diet-quality–sensitive transfers, seasonal top-ups, and routine monitoring of MDD-W and MUAC.

Authors Contribution

Conceptualization: IH, ZUH
Methodology: IH, ZUH, SF
Formal analysis: IH, ZUH, SF
Writing review and editing: IH, AI, MNK, SA, SF, CG, MT, YI

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Association of Low Serum Ferritin Level with Non-Scarring Alopecia in Women from Punjab, Pakistan

Kinza Latif[1*], Zareen Saqib[1], Bushra Bashir[1] and Saira Riaz[1]

[1]Department of Dermatology, Allama Iqbal Memorial Teaching Hospital, Sialkot, Pakistan

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***Corresponding Author:**
Kinza Latif
Department of Dermatology, Allama Iqbal Memorial Teaching Hospital, Sialkot, Pakistan
kinzalatiffarooqi.ki@gmail.com

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ABSTRACT

Hair loss in women is often linked to nutritional deficiencies, especially low serum ferritin. Reduced ferritin may impair hair growth and contribute to non-scarring alopecia, though existing studies show mixed results. **Objectives:** To determine the association between low serum ferritin levels and non-scarring alopecia in women from Punjab, Pakistan. **Methods:** This Case-control study was conducted at the Department of Dermatology, Allam Iqbal Memorial Teaching Hospital, Sialkot, from May 2025 to August 2025. A total of 102 women aged 18–55 years were enrolled, including 51 diagnosed with non-scarring alopecia and 51 age-matched controls with unrelated dermatological conditions. Venous blood samples were analyzed for hemoglobin, ESR, and serum ferritin using ELISA. Serum ferritin <15 ng/mL was categorized as low. Data were analyzed using SPSS v26 and DataTabs. Independent sample t-test compared mean values, chi-square tested categorical associations, and logistic regression determined the predictive value of serum ferritin. **Results:** The mean age of participants was 36.0 ± 10.8 years. Among cases, alopecia areata was most frequent (45.1%), followed by androgenetic alopecia (27.5%) and telogen effluvium (27.5%). Mean ferritin and hemoglobin levels were lower in cases, while ESR was slightly higher. Low ferritin was present in 41.2% of cases versus 19.6% of controls (χ^2 = 5.61, p=0.018). Logistic regression showed low ferritin significantly predicted alopecia (OR=2.87, 95% CI: 1.18–6.98, p=0.02). **Conclusions:** Low serum ferritin is significantly associated with non-scarring alopecia in women. Routine assessment of ferritin may help in identifying iron deficiency as a modifiable factor in patients presenting with hair loss.

INTRODUCTION

Hair loss is a common concern among women and can significantly affect psychological well-being and quality of life [1]. Various conditions under the non-scarring alopecia include telogen effluvium, androgenetic alopecia, and alopecia areata, which can be multifactorial in their causes, including hormonal imbalance, stress, genetics, and nutritional deficiencies [2, 3]. One of the most commonly known nutritional factors that causes diffuse hair loss in women is iron deficiency. Iron is an important constituent of several cellular and metabolic processes that support hair growth [4, 5]. DNA synthesis, energy metabolism, and oxygen transport in the hair follicle bulb are necessary in rapidly dividing cells. Ferritin is a protein that stores iron within a cell and controls the supply of iron to all essential enzymatic processes, including those in the synthesis of keratin. Normal levels of ferritin ensure the metabolic activity of the follicular cells and stimulate the anagen (growth) stage, whereas exhausted reserves may lead to an early transition to the telogen (resting) stage, leading to loss of hair [6, 7]. Serum ferritin is an effective indicator of the total body iron stores, and can be used to identify early iron deficiency before anemia develops. The connection between serum ferritin and various types of hair loss has already been studied in the past, but the results were not always similar. A number of studies have indicated that women who experience non-scarring alopecia have lower levels of ferritin compared to healthy controls, which may indicate that iron deficiency may have a role to play in the

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occurrence of hair loss. It has been suggested by other studies that this association is more pronounced in other conditions like alopecia areata and androgenetic alopecia but less pronounced in telogen effluvium [4, 8].

Although there is a lot of research on the topic globally, there is a dearth of information in South Asia, where iron deficiency and anemia are very high among women of reproductive age. This paper aimed to assess the relationship between low serum ferritin levels and non-scarring alopecia among women in Punjab, Pakistan. Through this relationship, the study will help to answer the question of whether ferritin deficiency is a major factor in the patterns of hair loss in this group of people and whether it will help in supporting the use of early laboratory screening and nutritional correction as part of clinical intervention. This study aimed to determine the association between low serum ferritin levels and non-scarring alopecia in women from Punjab, Pakistan.

METHODS

The case-control study was carried out in the department of dermatology, Allam Iqbal Memorial Teaching Hospital, Sialkot, after receiving the institutional research and ethics committee approval (Ref. No. 30/REC/KMSMC). The study was conducted from 2nd May, 2025 to 20th August, 2025. The WHO sample size calculator was used to determine the minimum sample size of 49 patients in each group (98 in total) with 80% statistical power, 5% significance level, and previously known proportions of low serum ferritin (63% in cases and 38% in controls) [8]. The sample size was adjusted to 51 participants per group to accommodate the potential attrition, non-response, or incomplete investigations, and the total of 102 participants ensured the maintenance of statistical power in the case of minor data loss. Non-probability consecutive sampling was used to enroll the participants. Women aged 18-55 years with non-scarring alopecia that was clinically verified were included in the case group. Conversely, the control group was a group of women who had no history of hair loss or iron deficiency and visited the same dermatology outpatient clinic because of other skin-related problems. To reduce confounding, controls were chosen to be similar to cases in terms of age (±3 years) and socioeconomic background, which was based on household income, education level, and occupation. The same consultant dermatologist (more than five years of experience) examined all the participants to ensure diagnostic consistency and minimize observer variation. The exclusion criteria were congenital or scarring alopecia, hair shaft disorder, acute inflammatory or systemic disease, abnormal thyroid activity, or erythrocyte sedimentation rate (ESR) ≥30 mm/h in the first hour. Postmenopausal women and those women who had taken vitamin B12, folic acid, iron, or multivitamin supplements in the last three months were also excluded. All participants signed informed consent in writing. Each subject was recorded with demographic information, such as age and name. In some cases, the alopecia subtype (androgenetic alopecia, alopecia areata, or telogen effluvium) and Ludwig stage were reported. Each of the participants was sampled by a trained phlebotomist who took 5 mL of venous blood. Of this, 3 ml of it was kept at –20°C to measure serum ferritin, and the rest 2 ml was referred to complete blood count. The enzyme-linked immunosorbent assay (ELISA) was used to determine serum ferritin by means of a sandwich-based Human Ferritin ELISA Kit (DRG Instruments GmbH, Germany) according to the manufacturer. A predesigned proforma was used to record all the information, and serum ferritin of less than 15 ng/mL was considered low. The data were entered and analyzed using SPSS version 26.0 and DataTabs. Numerical variables (age and serum ferritin) were summarized using mean ± standard deviation, whereas categorical variables (alopecia subtype, Ludwig stage and low serum ferritin status) were summarized using frequencies and percentages. The independent sample t-test was used to compare the mean ferritin in cases and controls, and the statistical significance was defined as $p \leq 0.05$. Odds ratios were calculated to determine the association between low serum ferritin and alopecia, with an odds ratio greater than one considered statistically significant.

RESULTS

The mean age of 102 participants was 36.0 ± 10.8 years. Among the cases, alopecia areata was the most frequent subtype, affecting 23 women (45.1%). Androgenetic alopecia and telogen effluvium were observed in 14 women each (27.5% each). In patients with androgenetic alopecia, distribution by Ludwig's classification showed stage I in 8 (57.1%), stage II in 5 (35.7%), and stage III in 1 (7.1%). The mean serum ferritin and hemoglobin levels were lower in cases than in controls, while ESR was slightly higher in cases (Table 1).

Table 1: Comparison of Mean Serum Ferritin, Hemoglobin, and ESR Levels Between Women with Non-Scarring Alopecia (Cases) and Controls

Variables	Cases	Controls	t-test (DF, p-Value)
Serum Ferritin (ng/mL)	20.04 ± 15.17	29.04 ± 14.79	t (100) =-3.03, p=0.003
Serum Hb (g/dL)	12.16 ± 1.51	12.97 ± 1.05	t (100) =-3.14, p=0.002
ESR (mm/hr)	10.10 ± 4.85	9.00 ± 3.20	T (100) =1.36, p=0.178

Low serum ferritin (<15 ng/mL) was more frequent among cases compared with controls (Table 2).

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Table 2: Distribution of Low Serum Ferritin Among Women with Non-Scarring Alopecia (Cases) and Controls With Corresponding Chi-Square Test Results

Low Ferritin	Cases	Controls	Total	χ^2 (DF, p-Value)
No	30 (29.4%)	41 (40.2%)	71 (69.6%)	χ^2=6.80, df=1, p=0.009
Yes	21 (20.6%)	10 (9.8%)	31 (30.4%)	

Low serum ferritin was observed in 30.4% of participants, with the highest proportion in the 36–45 age group (11.8%). No significant association was found between ferritin status and age group (χ^2=3.47, p=0.324) (Table 3).

Table 3: Distribution of Low Serum Ferritin Among Women with Non-Scarring Alopecia According to Age Groups

Age Group (years)	Normal Ferritin (No)	Low Ferritin (Yes)	Total	χ^2 (p-Value)
18–25	15 (14.71%)	9 (8.82%)	24 (23.53%)	χ^2=3.47, p=0.324
26–35	20 (19.61%)	5 (4.90%)	25 (24.51%)	
36–45	19 (18.63%)	12 (11.76%)	31 (30.39%)	
46–55	17 (16.67%)	5 (4.90%)	22 (21.57%)	
Total	71 (69.61%)	31 (30.39%)	102 (100%)	

Similarly, ferritin distribution did not differ significantly across Ludwig stages (χ^2=0.34, p=0.844) (Tables 3 and 4) (Table 4).

Table 4: Distribution of Low Serum Ferritin Among Women with Non-Scarring Alopecia According to Ludwig Stage

Ludwig Stage	Normal Ferritin (No)	Low Ferritin (Yes)	Total	χ^2 (p-Value)
I	6 (5.88%)	2 (1.96%)	8 (7.84%)	χ^2=0.34, p=0.844
II	4 (3.92%)	1 (0.98%)	5 (4.90%)	
III	1 (0.98%)	0 (0.00%)	1 (0.98%)	
Total	11 (10.78%)	3 (2.94%)	14 (13.72%)	

Binary logistic regression analysis revealed a statistically significant association between case status and low serum ferritin (χ^2=5.70, p=0.017). Women in the alopecia group were 2.87 times more likely to have low serum ferritin compared with controls (95% CI: 1.18–6.98, p=0.02) (Table 5).

Table 5: Binary Logistic Regression Analysis Between Case Status and Low Serum Ferritin

Variables	B (Co-efficient)	Standard Error (SE)	z-Value	p-Value	Odds Ratio (Exp(B))	95% Confidence Interval for OR
Constant	-1.41	0.35	4.00	<0.001	0.24	0.12 – 0.49
Label (Case)	1.05	0.45	2.33	0.02	2.87	1.18 – 6.98

DISCUSSIONS

The present study demonstrated a significant association between low serum ferritin and non-scarring alopecia in women. Participants with alopecia had lower ferritin and haemoglobin levels than controls, while erythrocyte sedimentation rate remained comparable. The prevalence of low ferritin (<15 ng/mL) was more than twice as high among cases, and logistic regression confirmed low ferritin as an independent predictor of alopecia (OR = 2.87, 95% CI 1.18–6.98, p=0.02). These findings indicate that iron depletion meaningfully increases the likelihood of hair loss. Iron is important in follicular metabolism and keratin production; low ferritin can cause anagen-telogen imbalance, leading to diffuse shedding. Our findings are consistent with those of Aslam *et al.*, who discovered significantly reduced ferritin in women with alopecia, and Chisti *et al.*, who found the same differences and stronger correlations between alopecia areata and androgenetic alopecia. These regional studies, along with ours, indicate that iron deficiency is a factor in follicular dysfunction among pre-menopausal women and that ferritin testing must be included in preliminary examination [4, 8]. Chen *et al.* conducted a meta-analysis of 23 studies demonstrating that micronutrient deficiencies, especially low vitamin D, are risk factors, whereas Chary and Salechaa et al. found simultaneous deficits in ferritin, vitamin B 12, and vitamin D [9-11]. These results are similar to our conclusion that hair loss is not usually caused by one deficiency; instead, iron deficiency is synergistic with other micronutrient deficiencies. Massive and retrospective studies reinforce this idea. According to Oner and Akdeniz, ferritin deficiency was found in 22 per cent of women versus 9 per cent of men, most often in telogen effluvium, and Abdaljawad *et al.* related low ferritin to more severe and prolonged paediatric alopecia areata. Mohammed *et al.* found ferritin to be one of a range of biochemical correlates of alopecia in both sexes, but Neupane and Kumar found sub-threshold ferritin in female pattern hair loss without statistical significance, demonstrating the sensitivity of different cut-offs to significance [12-15]. These observations are supplemented by studies that focus on methodological improvements. Jasim and Aledan suggested reticulocyte haemoglobin content as a more sensitive measure of iron deficiency in diffuse hair loss, whereas Sulaiman and Qurtas reported trichoscopy as a supplement to biochemical tests. The two methods put forward are that diagnosis can be refined by combining clinical and laboratory markers [16-17]. Saqib *et al.* and Suleri *et al.* studied the deficiency of vitamin D, both in high prevalence and in controls, which supports the multifactoriality of alopecia. The results of Farah *et al.* showed that the reduction of ferritin and haemoglobin was the highest in younger women, which confirms our finding that iron deficiency is especially prevalent before menopause [5, 18, 19]. The lack of homogeneity in the studies is in part due to varying ferritin thresholds. Only 9 percent of female pattern hair loss was found to have ferritin under 15 ng/mL but over 50 percent of patients had ferritin under 70 ng/mL, indicating that ferritin under 15 ng/mL could still be detrimental to hair cycling. Lin *et al.* proposed redefining iron deficiency for hair health as ferritin < 60 ng/mL, noting

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improved regrowth with supplementation, whereas Zhang *et al.* reiterated that ferritin is a sensitive yet context-dependent biomarker that must be interpreted alongside inflammatory markers [6, 20-21]. Regional studies also reinforce the value of ferritin assessment. Joshi *et al.* reported inadequate ferritin in more than three-quarters of Nepali women with alopecia, despite normal haemoglobin, confirming that anaemia alone cannot represent iron status. In contrast, de Queiroz *et al.* observed higher ferritin in alopecia areata, showing that ferritin behavior may vary by subtype or inflammation. Much of this heterogeneity was resolved by the meta-analysis of Treister-Goltzman *et al.* that involved more than 10,029 participants and showed that the pooled mean ferritin difference between women with and without alopecia was -18.5 ng/mL ($p < 0.01$) [1, 22-23]. The data suggest that low ferritin is a reliable correlate of non-scarring alopecia. The differences in studies are mainly due to the variation in the definitions of diagnosis, sample demographics and nutritional baselines. We use our results to generalize this evidence to a Pakistani cohort where iron deficiency is still common among women. Ferritin measurement is a simple, cheap clinical tool that could be used to inform early nutritional intervention. Future studies must combine ferritin with other complementary indices like reticulocyte haemoglobin, vitamin D, and zinc to come up with holistic nutritional profiles of patients who present with diffuse hair loss. There were some limitations of the study. Iron status was determined by serum ferritin alone without any other biochemical measurements of iron metabolism like serum iron, saturation of transferrin or total iron-binding capacity that would have given a more comprehensive picture of iron metabolism. Factors such as dietary intake, menstrual history, and deficiencies of micronutrients (zinc, vitamin D, and vitamin B12) were not taken into account. Longitudinal designs should be employed in future studies to investigate the impact of iron supplementation on hair regrowth among various types of alopecia and a wider nutritional profiling should be undertaken.

CONCLUSIONS

In conclusion, low serum ferritin is significantly correlated with non-scarring alopecia in women. Alopecic patients had lower mean ferritin and hemoglobin levels than the controls, and low ferritin was more prevalent in cases. The low serum ferritin was affirmed as an independent predictor using logistic regression analysis, with the affected women having almost twice the probability of alopecia than those with normal ferritin. These results indicate that ferritin level testing can be used to identify iron deficiency in women with alopecia early and can be used to facilitate the use of appropriate management measures to enhance clinical outcomes.

Authors Contribution

Conceptualization: ZS
Methodology: KL, ZS
Formal analysis: KL, SR
Writing review and editing: BB, SR

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Hypomagnesemia in Diabetic Patients and Its Correlation with Glycemic Control

Abida Pervaiz[1], Sadia Salman[2], Muhammad Zishan Akhter Wali[3], Usman Pasha[4], Amena Moazzam Baig[1], Muhammad Zahid Jamil[3*], and Ismat Ullah[3]

[1]Department of Endocrinology, Jinnah Hospital, Lahore, Pakistan
[2]Department of Medicine, Sir Ganga Ram Hospital, Lahore, Pakistan
[3]Department of Medicine, Jinnah Hospital, Lahore, Pakistan
[4]Department of Biochemistry, University of Health Sciences, Lahore, Pakistan

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***Corresponding Author:**
Muhammad Zahid Jamil
Department of Medicine, Jinnah Hospital, Lahore, Pakistan
zahidjamil173@gmail.com

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ABSTRACT

Diabetes mellitus is a growing pandemic of the modern era with a wide array of complications. Better glycemic control is linked to improved survival and quality of life in diabetes patients. Serum magnesium levels have been postulated to adversely affect glycemic targets. **Objectives:** To determine hypomagnesemia prevalence in diabetic patients and its correlation with glycemic control. **Methods:** This cross-sectional observational study was conducted over six months from January 2025 to June 2025 at the diabetic clinical Jinnah Hospital, Lahore. A total of 174 patients fulfilling the inclusion criteria were enrolled in the study following a non-probability consecutive sampling technique. Informed consent was obtained from the participant. Data were recorded on a predesigned proforma, and analysis was run using SPSS version 25.0 version. **Results:** Out of the total 174 patients, 51 patients had normal magnesium levels, and 123 patients were hypomagnesemic. Poor glycemic control (HbA1C>7.0%) was significantly more prevalent (p=0.001) in hypomagnesemic patients. Although most of the female patients were having low serum magnesium levels (n=77), this gender difference was non-significant (p-value=0.450). Age-wise distribution of hypomagnesemia showed significantly more predilection (p=0.001) for 45 to 60 years age patients. **Conclusions:** The study concluded that hypomagnesemia is significantly linked to poor glycemic control in diabetic patients. Further studies are needed to explore the relationship between serum magnesium and dysglycemia.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia leading to a variety of acute and chronic complications. It has gained major attention of healthcare systems worldwide due to its major impact on cardiovascular and renal diseases [1]. Diabetes burden is growing worldwide, with the highest prevalence in the USA and the Chinese population [2]. Pakistan ranks number three regarding the total number of diabetic patients worldwide [3]. This high incidence of diabetes poses a difficult challenge to the health resources of our country [4]. The morbidity and mortality associated with diabetes have led to the development of a multidisciplinary approach to optimize glycemic management. A diabetes management plan includes a comprehensive patient assessment, followed by lifestyle change and then subsequent pharmacotherapy. Insulin resistance is one of the major pathogenic factors employed in the development of new diabetes as well as poor glycemic control [5]. Various genetic and environmental factors have been implicated in the development of insulin resistance. Serum magnesium, an important electrolyte of the human body, has been proposed as an important factor modulating

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insulin resistance [6]. Previous study reported that higher HbA1C values were significantly associated (p=0.0016) with hypomagnesemia as compared to controls [7]. Prevalence of hypomagnesemia is reported to be around 13 to 47 % in diabetic patients [8]. Previous studies described hypomagnesemia as an independent risk factor (odds ratio 3,64, 1.76–7.52, p=0.001) for albuminuria and inversely related (p<0.001) to glycemic control [9]. A study conducted in Pakistan reported hypomagnesemia in one among 10 diabetes patients, and it was linked (p-value=0.019) with weak glycemic control [10]. Normomagnesimia is essential in maintaining homeostasis of major electrolytes and several other immunomodulation functions [11]. Low magnesium levels occur mostly due to decreased oral intake or poor GI absorption and lead to multiple electrolyte abnormalities like refractory hypokalemia and hypocalcemia [12]. Local studies are insufficient to establish a clear relationship between serum magnesium and glycemic control. Our study was designed to determine the prevalence of hypomagnesemia in diabetes who have poor glycemic control and high insulin requirements. Its objective was to determine the prevalence of hypomagnesemia in patients with diabetes and its comparison with glycemic control.

METHODS

This cross-sectional observational study was conducted over a six-month duration from January 2025 to June 2025 at the diabetic clinic of Jinnah Hospital Lahore, after obtaining approval from the hospital ethical review board (Ref. No. ERB 181/6 16-01-2025/S1 ERB). One hundred and seventy-four patients were included in this study after explaining to them the study purpose and obtaining informed consent. A sample size of 174 was calculated at a 95% confidence interval, 5% margin of error, and an anticipated frequency of hypomagnesemia of 13% [8]. Privacy and anonymity of patient data were ensured. It included patients of type 2 diabetes from 18 to 75 years and both genders with at least two oral antidiabetic drugs. Patients using insulin or GLP1 agonists were also enrolled in the study. The minimal time period of ongoing therapy was at least three months after their last follow-up. Patients with conditions like malabsorption, inflammatory bowel disease, acute gastroenteritis, and stage 3 chronic kidney disease were excluded from the study. Similarly, patients using diuretics or those receiving magnesium supplements didn't qualify inclusion criteria. Patients with poor compliance to treatment or dietary management (as judged by a dietitian) or those with a recent change in therapy were also excluded from the study. Patient demographics and clinical parameters were recorded on a proforma. Five milliliters of blood were withdrawn by nursing staff following aseptic measures and sent to the laboratory immediately for testing. Serum magnesium levels were checked, and a value less than 1.6 mg was labeled as hypomagnesemia, while 1.6 to 2.4 mg/dl was considered as normomagnesemia. HbA1C was also measured on the same sample using the HPLC technique, and a value < 7.0 % was taken as good glycemic control, and > 7.0 % was reviewed as week glycemic control. Patients were called for follow up regarding advice on glycemic management. Data were recorded on proforma for demographic, clinical, and biochemical variables. Data analysis was done using SPSS version 25.0. Demographic variables like age, gender, etc. were charted in the form of means, frequencies and percentages. Hypomagnesemia occurrence was calculated for both genders and various age groups. Glycemic control was also calculated according to the operational definition in all patients. Chi-square test was applied to observe the statistical relation between hypomagnesemia and glycemic control, with a p< 0.05 being considered significant.

RESULTS

This study comprised 174 diabetic patients (62 males and 112 females) who were reviewed for glycemic control and serum magnesium levels. Demographic characteristics of the study population (Table 1).

Table 1: Demographic Characteristics of Study Population

Variables	Category	Frequency (%)
Gender	Male	62 (35.6%)
	Female	112 (64.4%)
Age (years)	30–45	47 (27.0%)
	46–60	82 (47.1%)
	61–75	45 (25.9%)
Body weight (kg)	Mean ± S.D	82.9 ± 13.8
Duration of diabetes (years)	Mean ± S.D	7.9 ± 4.5

Sixty-nine percent (n=120) of patients were using two drugs for their glycemic control, and 31% (n=54) were using three or more drugs. Mean values of baseline laboratory parameters, i.e., serum creatinine, alanine transferase, and LDL cholesterol, were 0.9 mg/dl, 35IU/L, and 93mg/dl, respectively. Good glycemic control (HbA1C<7% as per operational definition) was noted in 26.4% (n=46) patients, while 73.6% patients had HbA1C>7%. Fifty-one patients (29.3%) had normomagnesemia, and one hundred and twenty-three (70.7%) had serum magnesium levels less than 1.6 mg/dl (hypomagnesemia). Cross tabulation was done, which showed a statistically significant relation between glycemic control and serum magnesium levels (p-value 0.001)(Table 2).

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Table 2: Cross-Tabulation of Serum Magnesium Levels and Glycemic Control

Serum Magnesium Status	Good Control (HbA1c<7)	Poor Control (HbA1c>7)	p-Value
Eumagnesemia (≥1.6 mg/dL)	37	14	0.001
Hypomagnesemia (<1.6 mg/dL)	9	114	
Total	46 (26.4%)	128 (73.6%)	

Serum magnesium level was also analyzed for gender distribution (table 2). Although hypomagnesemia was more frequent (68.8%, n=77) in females in our study as compared to males (74.2%, n=46), this difference was statistically insignificant (p=0.450). Hypomagnesemia was also checked in different age groups to assess for any effect of age on hypomagnesemia distribution. Eighty-five percent of hypomagnesemic patients were age between 46 to 60 years, while normomagnesemia was more prevalent (61.7%) in the age group 30 to 45 years. Statistical analysis for age-related distribution of magnesium levels was significant in our study (p=0.001) (Table 3).

Table 3: Serum Magnesium Levels in Different Age Groups (Cross Tabulation)

Age Group (Years)	Eumagnesemia (>1.6 mg/dL)	Hypomagnesemia (<1.6 mg/dL)	p-Value
30–45	29 (61.7%)	18 (38.3%)	0.001
46–60	12 (14.6%)	70 (85.4%)	
61–75	10 (22.2%)	35 (77.8%)	
Total	51 (29.3%)	123 (70.7%)	

DISCUSSIONS

Our study findings denoted an inverse relation between hypomagnesemia and glycemic control. Hypomagnesemia patients' glycemic control was significantly inferior to patients with normomagnesemia. Hypomagnesemia was more prevalent in female diabetes patients and subsequently reflected in their glycemic parameters. Diabetes is a growing pandemic estimated to adversely affect major health systems worldwide in future. It stands as number one cause of end stage renal disease across the globe and also an important contributor to stroke and ischemic heart diseases. Diabetes control is of paramount importance in preventing and delaying its macro- and microvascular complications. A rise in HBA1C above target is strongly linked with diabetic morbidity and mortality and imposes huge burden on health resources of a country. Vigorous efforts have been made to explore underlying factors associated with deranged glycemia. Other comorbidities like hypertension, dyslipidemias, and smoking have proven additive effects on poor cardiovascular outcomes of diabetes and need to be addressed well for overall well-being. Some studies have discussed hypomagnesemia in diabetes patients. Previous study showed hypomagnesemia was 10 times more prevalent in diabetes patients [13]. A systematic analysis conducted by previous researchers showed 32% of patients (n=4192) with diabetes had low serum magnesium levels [14]. Current study findings were quite matching with these studies. Low magnesium trend was noted in female patients in our study which was similar to a study of Hamarshih et al, in which female patients were found to be low (adjusted OR: 2.7, 95%CI: 1.2%-5.8%) in serum magnesium levels [15]. However, when statistical analysis was applied, the gender distribution of hypomagnesemia in our study was not significant. A previous study showed no significant differences in mean serum magnesium levels (2.06 ± 0.49 mg/dl) in diabetic versus nondiabetic individuals (2.22 ± 0.48 mg/dl) [16]. The etiology of hypomagnesemia in diabetic patients is not well explored. It is linked to molecular level changes in insulin secretion and altered cellular response. Drugs may contribute to low serum magnesium levels in diabetes individuals. Other factor which may cause low magnesium levels are renal and GI losses. The relationship between glycemic control and serum magnesium have been explored in a few studies. Serum magnesium alters insulin response as suggested in some studies demonstrating high insulin levels in patients with hypomagnesemia. A study conducted by Morais et al suggested that hypomagnesemia is linked to induce insulin resistance and that magnesium supplementation can improve insulin sensitivity in such patients [17]. Earlier studies showed significantly low (p<0.001) magnesium levels in diabetics as compared to healthy or prediabetic individuals. Furthermore, serum magnesium was negatively linked with glucose (R=-0.58) and HbA1C (R=-0.61) values [18]. Our study findings were in alignment with these results. Some studies also linked hypomagnesemia to the development of early diabetic kidney disease in the form of mild albuminuria. It was observed that hypomagnesemia patients (67.9%) showed more predilections for diabetic complications, especially diabetic kidney disease [19]. Another study by Bherwani *et al.* showed diabetic kidney disease was more prevalent (52%) in patients with decreased (1.40 ± 0.16 mg/dL) magnesium levels, and microalbuminuria was inversely related (r=-0.352, p=0.000) to hypomagnesemia. [20]. Similarly, a study conducted by Shivakumar *et al.* showed sight-threatening diabetic retinopathy was significantly higher (p=0.031) in diabetic patients with hypomagnesemia [21]. Other factors have been postulated to affect glycemic control and thus pose therapeutic challenges in the management of diabetes. There is robust evidence about the pleiotropic effects of vitamin D in glucose metabolism. Abubaker S. *et al.* stated that low vitamin D levels were inversely related (p<0.001) to glycemic targets in the Saudi population (n=370) [22]. Serum zinc levels have been postulated to affect insulin sensitivity (p=0.02), with low zinc levels regarded as contributory to diabetes [23]. A

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comprehensive management of diabetes also takes into account existing cardiovascular risk factors. Dyslipidemias play a key role in the development of the atherosclerosis process and, hence, premature cardiovascular diseases. Strict LDL cholesterol targets are designed to modify this risk factor. Similarly, variability in blood pressure is linked to macrovascular pathologies like stroke, peripheral vascular disease, and myocardial infarction. Optimal blood pressure control in patients with diabetes is recommended to achieve good cardiovascular outcomes. There were certain limitations of our study, is a small sample size, being a single-center study, and a lack of a control group. Multicenter studies with an analytical approach and a large sample size can be very fruitful in establishing a causal relationship between hypomagnesemia and higher HBA1C values

CONCLUSIONS

In conclusion, the study concluded that low serum magnesium level is strongly associated with hyperglycemia in diabetes patients. It may serve as a basis to explore the underlying mechanisms of serum magnesium and glucose metabolism.

Authors Contribution

Conceptualization: AP, SS
Methodology: AP, SS, ZA, UP
Formal analysis: SS, UP
Writing review and editing: AP, SS, AMB, ZJ, IU

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Urinary Vitamin D-Binding Protein as a Diagnostic Marker for Diabetic Nephropathy in Type 2 Diabetic Patients

Nadia Rasheed[1]*, Muhammad Hunain Baghdadi[2], Fauzia Sadiq[3], Sajjad Ul Hassan[4], and Hafiz Muhammad Khalid Mehmood[5]

[1]Department of Medical Lab Technology, NUR International University, Lahore, Pakistan
[2]Department of Medical Laboratory Technology, Superior University, Lahore, Pakistan
[3]Department of Chemical Pathology, Lahore Medical and Dental College, Lahore, Pakistan
[4]Department of Community Medicine, Amna Inayat Medical College, Sheikhupura, Pakistan
[5]Department of Chemical Pathology, University of Health Sciences, Lahore, Pakistan

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***Corresponding Author:**
Nadia Rasheed
Department of Medical Lab Technology, NUR International University, Lahore, Pakistan
naddya24@gmail.com

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ABSTRACT

In T2DM (Type 2 Diabetes Mellitus), the most common microvascular complication is DN (Diabetic Nephropathy). **Objectives:** to explore uVDBP (urinary vitamin D-binding protein) for the detection of DN. **Methods:** This cross-sectional comparative study was conducted in the Chemical Pathology Department, University of Health Sciences, Lahore. The study individuals were mainly categorized into three groups. Group 1 included normoalbuminuric non diabetic control subjects with normal ACR <30mg/g (n=25). Group 2 included normoalbuminuric T2DM patients with normal ACR <30mg/g (n=25). Group 3 comprised microalbuminuric T2DM patients with raised ACR 30 to 299 mg/g (n=25). Spot urine specimens were collected from T2DM patients. The patients were recruited from the Sheik Zayed Hospital Diabetic Clinic, Lahore. Collected data was analyzed by using SPSS version 24.0. Kruskal-Wallis test, Dunn-Bonferroni post-hoc analysis, and Spearman's correlation were applied. **Results:** The findings indicated the Urinary Vitamin D-Binding Protein (uVDBP) level was high in patients with microalbuminuria and normoalbuminuria compared to the control group. Group 3 had the highest median Urinary Vitamin D-Binding Protein (uVDBP) concentration, which was higher than in group 2 and group 1. Among all three groups, there was a statistically significant difference in levels of ACR (Albumin-to-Creatinine Ratio) and urinary Vitamin D-Binding Protein (p value = 0.000). **Conclusions:** In conclusion, the levels of urinary vitamin-D binding protein are significantly increased in T2DM patients having normoalbuminuria and microalbuminuria compared to non-diabetic control subjects. A significant positive correlation was observed between Urinary Vitamin D-Binding Protein (uVDBP) and albumin creatinine ratio.

INTRODUCTION

Diabetes mellitus encompasses a range of metabolic disorders marked by chronic high blood glucose, which arises due to insufficient insulin secretion, impaired insulin action, or both mechanisms combined [1]. T2DM is more prevalent compared to T1DM [2]. Type 2 Diabetes Mellitus (T2DM) is a chronic and progressive metabolic disorder, often asymptomatic in early stages [3]. The resultant chronic hyperglycemia leads to macrovascular and microvascular diabetic complications [4]. Diabetic nephropathy, the most prevalent and severe micro-vascular problem of diabetes mellitus, plays a vital role in enhancing disease and mortality rates seen among patients with diabetes [5]. The prevalence of diabetic nephropathy among diabetics in Pakistan is stated to stand at 27.1 percent [6]. In individuals with diabetes, diabetic nephropathy is an important contributor to end-stage kidney illness [7]. Studies indicate that approximately 30% of diabetic patients develop this condition, placing a significant strain on public healthcare systems [8]. The earliest clinical indicator of diabetic nephropathy is

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microalbuminuria [9]. It is characterized by the emission of albumin 30-300 mg/day in urine, and 30-300 mg/gram in urine creatinine. The gold standard test for the detection of DN in early phases is the detection of micro-albuminuria in 24-hour urine or spot urine. [10]. To enhance the clinical management of diabetes, there is a need for alternative urinary biomarkers capable of detecting diabetic nephropathy at a much earlier stage, ideally, before microalbuminuria becomes evident [11]. Numerous research studies have been carried out to find new biomarkers for DN, which include alpha-1-microglobulin, beta-2-microglobulin, uromodulin, IL-18 (interleukin-18), NGAL (neutrophil gelatinase-associated lipocalin), KIM-1(kidney injury molecule-1), and MCP-1(monocyte chemoattractant protein-1) [12]. The uVDBP biomarker is under investigation for its diagnosis in diabetic nephropathy. VDBP alpha-globulin is synthesized mainly in the liver, with an approximate molecular weight of 58 kDa. It has a serum concentration of 300 to 600 mg/ml. Originally identified as the group-specific element for serum (Gc-globulin), VDBP is recognized for its role in binding roughly 85 percent of 25-hydroxyvitamin-D(25(OH)D) during circulation. It's named VDBP (Vitamin D-binding Protein). Transportation of vitamin D metabolites in the circulation is its primary function. VDBP is filtered through the proximal tubule cells and glomeruli, after which it's reabsorbed via receptor-mediated mechanisms. If this protein is not reabsorbed due to impaired function of the proximal tubules of the glomerulus, it starts appearing in urine [13]. Excretion of VDBP in the urine of T2DM patients has not been evaluated, especially when albuminuria is not present.

This study aimed to evaluate and compare the VDBP level in urine of normoalbuminuric non diabetic control subjects, normoalbuminuric T2DM patients, and microalbuminuric T2DM patients to explore the role of uVDBP in the detection of DN at an early stage.

METHODS

This cross-sectional comparative observational study was conducted in the Chemical Pathology Department, University of Health Sciences, Lahore, and approved by the Ethical Review Committee (Ref. No. UHS/EAPC-22/ERC/18). The study was conducted from February 2023 to July 2023. The sample size was determined using G Power version 3.1 from a one-way ANOVA model because in this study, there was a comparison of urinary Vitamin D-Binding Protein (uVDBP) levels between three independent groups. The main outcome variable for which the sample size was estimated was urinary VDBP concentration. A level of significance (α) of 0.05, power (1-β) of 80%, and an estimated large effect size (Cohen's f=0.40) were used, consistent with differences in uVDBP levels documented in a recent meta-analysis by Chen et al. (2023) [14]. Based on these, a minimum of 25 participants in each group was needed, totaling 75 subjects, which was attained in the current study. For each study participant, informed consent was obtained in written form for participation. Among total of 50 T2DM patients and twenty-five (25) normal controls of either gender were recruited for this study, with age ranges between 40-50 years. Only those patients were recruited whose duration of Diabetes was at least five years. The study individuals were divided into three subgroups. Group 1 comprised of twenty-five (n=25) normoalbuminuric non diabetic control subjects with normal ACR <30mg/g. Group 2 comprised of twenty-five (n=25) normoalbuminuric T2DM patients with normal ACR <30mg/g. Group 3 comprised of twenty-five (n=25) microalbuminuric T2DM patients with raised ACR 30 to 299 mg/g. The main outcome variable of the study was the concentration of urinary VDBP. The secondary outcome measures were albumin-to-creatinine ratio (ACR), age, body mass index (BMI), and disease duration. The individuals suffering from infections, liver diseases, or any chronic disease other than diabetes were excluded from the study. Patients taking hormones and drugs such as vitamin D supplements, hypercalcemic drugs at the time of study, were also excluded from the study. Samples were collected from Sheikh Zayed Hospital Diabetic Clinic, Lahore. Data were collected daily from the Outpatient Department (OPD) of Shaikh Zayed Diabetic Clinic, where the researcher obtained the patients' demographic information through taking patient consent. A convenient sampling technique was used among the diagnosed cases of T2DM from Sheik Zayed Hospital Diabetic Clinic, Lahore. Midstream random urine samples of study individuals were collected in a sterile container from patients. Urine creatinine was measured by the Jaffe kinetic method on the Microlab 300 spectrophotometer (Merck, Germany). Urinary albumin was quantified using the immunoturbidimetric method on the same analyzer (Microlab 300, Merck, Germany). The Albumin-to-Creatinine Ratio (ACR) was calculated by dividing urine albumin concentration (mg) by urine creatinine concentration (g), and expressed in mg/g. Urinary Vitamin D-Binding Protein (uVDBP) was determined using a commercial ELISA kit on the Bio-Rad ELISA Reader Model 410 (Bio-Rad Laboratories, USA), following the manufacturer's instructions. Results were expressed as uVDBP/creatinine ratio to account for variations in urine concentration. Urine analysis reagent strips (Combi10-Medi Test) were used to screen samples for proteinuria, and only those without detectable protein levels were selected for inclusion in the study. By the use of SPSS version 24.0 collected data were analyzed. Qualitative variable like

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gender distribution, was expressed in the form of a percentage, while quantitative variables, such as age, VDBP/Creatinine ratio, and urine creatinine, were presented as Median and IQR. Data normality was checked with the help of the Shapiro-Wilk test. By using an independent Kruskal–Wallis test to compare uVDBP and ACR values among the three groups. Post-hoc pairwise comparisons were performed using the Dunn–Bonferroni test. Spearman's rank correlation coefficient was used to evaluate the association between uVDBP and ACR within each group (p-value ≤0.05 for significant outcomes)

RESULTS

Among all participants, 50 T2DM patients and 25 normal non diabetic controls of either gender were recruited for this study, with an age range between 40-50 years. Only those patients were recruited whose duration of Diabetes was at least five years. The age, gender, and BMI (Body Mass Index) of the patients were noted. In Group 1, the number of male participants was high (62%), trailed by Group 2(58%) and Group 3(48%), also showing statistically non-significant findings after comparison among the three groups (p=0.497). In group 3, the values of interquartile range (IQR) and Median age were detected as high, trailed by groups 2 and 1. The median and interquartile range for BMI (Body Mass Index) were higher in group 3 than in group 1. Conversely, the median and interquartile range of diabetes duration were greater in group 3 than in group 2, and the difference was significant, p=0.000 (Table 1).

Table 1: Demographics of the Study Participants

Demographics		Group 1 (n=25)	Group 2 (N=25)	Group 3 (N=25)	p-Value
Gender	M (%)	16 (62%)	13 (52%)	12 (48%)	0.497a
	F (%)	9 (36%)	12 (48%)	13 (52%)	
Age (years)	Median	42	46	48	0.000*a 0.215b
	IQR	41-46	44-48	46.00-48.50	
BMI kg/m^2	Median	23.70	25.10	25.50	0.663a
	IQR	22.90-25.40	22.70-26.50	23.75-26.60	
Disease Duration (years)	Median	–	6.0	7.00	0.000*a
	IQR	–	5.0-6.5	6.50-8.00	

(a) all groups comparison, (b) group 2 and comparison, (*) showed significancy

Group 3 had the greatest median and interquartile range (Q1–Q3) of ACR at 89 mg/g (75.55–122.50 mg/g), followed by group 2 at 17.50 mg/g (13.30–22.50 mg/g), and group 1 at 8.30 mg/g (6.05–11.50 mg/g) (Table 2).

Table 2: UVDBP (Urinary Vitamin D Binding Protein) and ACR (Albumin Creatinine Ratio) Comparison

Variables	Group1		Group 2		Group 3		p-Value
	Median	IQR (Q1-Q3)	Median	IQR (Q1-Q3)	Median	IQR (Q1-Q3)	
ACR (mg/g)	8.30	(6.05-11.50)	17.50	(13.30-22.50)	89	(75.55-122.50)	0.000*
uVDBP (ng/mg)	98	(73.50-149)	442	(381.50-523)	1056	(905-1215)	0.000*

(*) Denotes statistically significant ≤0.05, IQR= Interquartile range

The comparison by the Independent Kruskal-Wallis test revealed that there was a significant difference among all groups on ACR values, p=0.000 (Figure 1).

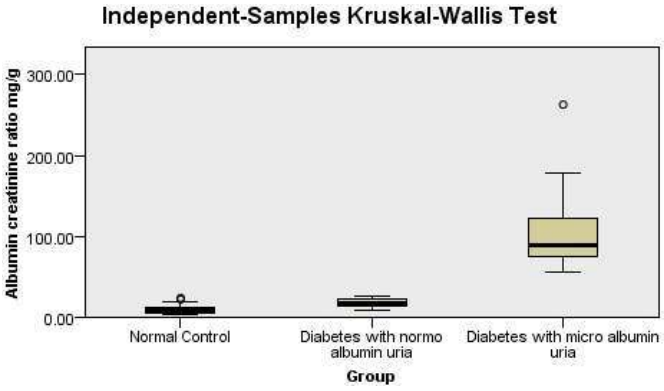

Figure 1: Comparison of ACR Among All Three Groups

Similarly, the comparison of uVDBP levels across the groups using the Independent Kruskal-Wallis test revealed group 3 with the highest median and IQR (Q1-Q3) at 1056ng/mg (905-1215ng/mg), followed by group 2 at 442ng/mg (381.50-523ng/mg), and last group 1 at 98ng/mg (73.50-149ng/mg). This comparison also revealed significant differences among all groups, p=0.000 (Figure 2).

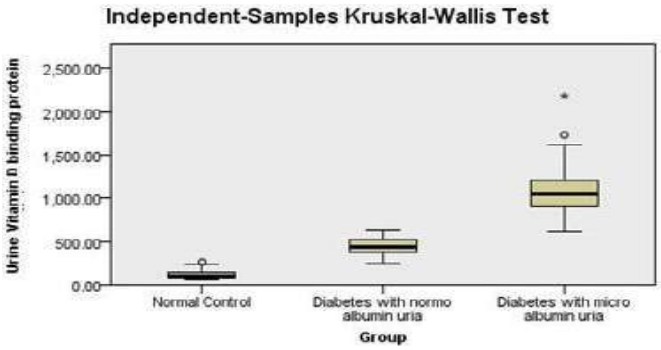

Figure 2: Comparison of uVDBP Levels Among All Three Groups

By using the Dunn-Bonferroni post-hoc test, multiple ACR comparisons within the groups showed that group 1 and 3 had a significant difference with p=0.000, also group 2 and 3 with p=0.000, while there was no statistically significant difference between group 1 and group 2, p=0.567. Similarly, the multiple comparisons within the groups using uVDBP showed a significant difference between groups 1 and 3, and groups 2 and 3 also showed the same results (p = 0.000). Additionally, groups 1 and 2 showed significant differences, with a p=0.000 (Table 3).

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Table 3: ACR and uVDBP Multiple Comparison (n=25 Each Group)

Variables	Groups	Median, IQR(Q1- Q3)	p-Value
ACR (mg/g)	1	8.30 (6.05-11.50)	0.000*a 0.567 b 0.000*c 0.000*d
	2	17.50 (13.30-22.50)	
	3	89 (75.55-122.50)	
uVDBP (ng/mg)	1	98 (73.50-149)	0.0001*a 0.0001*b 0.000*c 0.000*d
	2	442 (381.50-523)	
	3	1056 (905-1215)	

(*) significance of results ≤0.05, (a) all groups comparison, (b) group 1 and 2 comparison, (c) group 1 and 3 comparison, (d) group 2 and 3 comparison

Spearman's rank correlation between urinary VDBP (uVDBP) & albumin-to-creatinine ratio (ACR) levels in group 1 was positive and very strong, with a correlation coefficient (rs) of 0.732, which was statistically significantly high (p=0.000). In group 2, there was a positive moderate correlation with a rs value of 0.427, which was significant, p=0.011. Group 3 showed a highly positive association between two variables, with a rs of 0.879, and this finding was significant, p=0.000 (Table 4).

Table 4: Spearman's Rank Correlation Coefficient Analysis of ACR and uVDBP Levels

Groups	Independent Variables	Correlation Coefficients (r_s)	Dependent variables (uVDBP)
Group 1	ACR	r_s	0.732
		p-value	0.000**
Group 2	ACR	r_s	0.427
		p-value	0.011*
Group 3	ACR	r_s	0.879
		p-value	0.000**

(rs) Correlation coefficient, (+) correlation, 0.7 to 0.9 correlation, strong, 0.4 to 0.6 intermediate correlation, and 0 to 0.3 weak correlation, (**) <0.01 significant correlation, (*) <0.05 significant correlation

DISCUSSIONS

An important finding of the study was that the urinary levels of VDBP were meaningfully amplified in patients with microalbuminuria and normoalbuminuria compared to the control group. As this protein is increased in patients who have a normal ACR ratio, it indicates that proximal tubular damage starts before the glomerular membrane damage in T2DM patients, even before the appearance of microalbumin in urine. This finding defines the function of uVDBP for DN diagnosis at a very early stage. Recently, a meta-analysis has evaluated the role of uVDBP in the diagnosis and monitoring of DN and has concluded that a novel biomarker, uVDBP, is likely to be used for DN diagnosis in the early stage and also could be used for the assessment of the DN severity [15]. Another review study highlighted the role by mean of a potential biomarker for kidney disease early diagnosis. (16) One previous study by Fawzy *et al.* (2018 on the Saudi population also observed similar findings that uVDBP used as an early biomarker to detect DN [16]. Among the previous, Khodeir *et al.* revealed a significant increase in urinary Vitamin D–D-binding protein (VDBP) content in comparison between diabetic patients and healthy controls [17]. Likewise, another topical study on patients with T2DM, grouped according to their albumin-to-creatinine ratio as normoalbuminuric, microalbuminuric, and macroalbuminuric, found a significant increase in the VDBP-to-creatinine ratio in both microalbuminuric and macroalbuminuric patients when compared to non-albuminuric patients [18]. The exact mechanism of increased urinary excretion of VDBP in diabetic nephropathy is not defined. Yet, it is established that proximal tubular epithelial cells possess a multiligand endocytic receptor called megalin, which performs a crucial function of reabsorbing filtered proteins, such as low molecular weight proteins like VDBP, from the glomerular filtrate. Another integral part, cubilin, co-functions with megalin to mediate renal uptake of multiple ligands, including vitamin D-carrying proteins. Renal disease-associated impairment or shedding of the megalin-cubilin complex underlies albuminuria and can partially account for the increased urinary VDBP excretion reported in such patients [19]. Another significant observation made in the contemporary study, the presence of (+) correlation amongst levels of urinary VDBP and ACR in the study groups. A particularly strong relationship was observed in both the normoalbuminuric (group 1) and microalbuminuric (group 3) groups. In support of this finding, a six-year longitudinal study detected a persistent and strong correlation between urinary ACR and VDBP levels at baseline and during the follow-up [20]. The study's limitations include convenience sampling, small sample size, and the cross-sectional design, which prevents assessment of DN progression. Further longitudinal studies with larger sample sizes are recommended.

CONCLUSIONS

In conclusion, the present study indicates that modestly higher urinary VDBP concentrations exist in T2DM patients who have normoalbuminuria or microalbuminuria, compared to non-diabetic controls. A positive, significant correlation between uVDBP and ACR was also found, suggesting the role of uVDBP as an early indicator in diabetic nephropathy.

Authors Contribution

Conceptualization: NR
Methodology: MHB, SUH, HMKM
Formal analysis: MHB, SUH
Writing review and editing: NR, FS, HMKM

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

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Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Thrombolytic Failure with Streptokinase in Acute Myocardial Infarction Using Electrocardiogram Criteria

Maria Farooq[1], Sadaf Abdullah[1*], Hadiqa Khalil[2], Juneda Sarfraz[3], Nisar Ahmed[4] and Hamid Shahzad[1]

[1]Department of Emergency Medicine, Lady Reading Hospital, Peshawar, Pakistan
[2]Department of Medicine, District Headquarter Teaching Hospital, Dera Ismail Khan, Pakistan
[3]Department of Public Health, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan
[4]Department of Cardiology, Poonch Medical College, Rawalakot, Azad Jammu and Kashmir, Pakistan

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Corresponding Author:
Sadaf Abdullah
Department of Emergency Medicine, Lady Reading Hospital, Peshawar, Pakistan
abdullahsadaf2@gmail.com

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ABSTRACT

Streptokinase remains a key thrombolytic agent for ST-elevation myocardial infarction (STEMI) in many low-resource settings. Understanding the rate of thrombolytic failure and its predictors using electrocardiographic criteria is important for optimizing therapeutic strategies. **Objectives:** To determine the rate of thrombolytic failure in acute myocardial infarction using streptokinase, to describe in-hospital outcomes, and to assess associations between baseline clinical and ECG variables and thrombolytic success. **Methods:** This prospective observational study was conducted at Lady Reading Hospital, Peshawar. Ninety-three consecutive adult STEMI patients treated with streptokinase within 12 hours of symptom onset were included. Successful reperfusion was defined as >50% ST-segment resolution at 90 minutes. Demographics, risk factors, MI type, Killip class, symptom-to-door categories, and in-hospital outcomes were recorded. Bleeding events were classified using the TIMI criteria. Data were analyzed using the t-test for continuous variables and the chi-square/Fisher's exact test for categorical variables, with $p < 0.05$ considered significant. **Results:** The thrombolytic success rate was 77.4%. Symptom-to-door categories (<3h, 3–6h, >6h) were not significantly associated with reperfusion success. No baseline risk factors or Killip class independently predicted outcome. In-hospital mortality was 2.2%, TIMI major bleeding was 2.2%, and minor bleeding was 6.5%. Rescue PCI was required in 15.1%. Persistent chest pain, reperfusion arrhythmias, and hemodynamic instability occurred in 16.1%, 17.2%, and 14.0% respectively. **Conclusion:** Streptokinase achieved a high reperfusion rate with low complication rates. Conventional baseline variables did not predict success. Emphasis should remain on early presentation, system-level efficiency, and timely rescue PCI for failures.

INTRODUCTION

ST-elevation myocardial infarction (STEMI) remains a major global cause of cardiovascular morbidity and mortality [1]. Prompt reperfusion therapy, either by primary percutaneous coronary intervention (PCI) or thrombolysis, is vital to restore myocardial perfusion and limit infarct size [2]. In many low- and middle-income countries (LMICs), streptokinase is still widely used due to cost and accessibility, despite newer fibrin-specific agents offering improved profiles [3]. Recent international studies report varying success rates for thrombolytic therapy using streptokinase [4, 5]. For example, a study of 245 STEMI patients in central India found a 73% thrombolysis success rate, significantly higher among patients presenting within 12 hours of symptom onset (OR=3.15, p=0.006) [6]. Similarly, Imad et al. (2025) found that streptokinase administered early (within the first 1.5 to 3 hours) resulted in higher ST-segment resolution in a local Pakistani cohort [7]. A study conducted in Rajkot, India, by Sampat V, et al. (2025) reported approximately 70–76% successful ECG and clinical reperfusion following streptokinase when presentation was within admissible time windows [8]. Local studies in Pakistan affirm that delay in presentation,

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larger infarct territory (anterior MI), and worse clinical status on admission (higher Killip class) are commonly associated with poorer thrombolytic outcomes. However, many published series have conflicting or weak evidence regarding the role of hypertension, diabetes, and other risk factors. Previous studies reported that while risk factors like diabetes and hypertension were more common in failures, their adjusted statistical significance was inconsistent [9, 10]. Despite the accumulation of such data, gaps remain. Many studies focus predominantly on clinical or angiographic endpoints but lack consistent ECG-based reperfusion criteria or standardized follow-up. Additionally, few recent local datasets evaluate both reperfusion success and in-hospital safety outcomes in streptokinase use, explicitly testing baseline clinical and ECG predictors. The present study addresses these gaps by examining thrombolytic failure rates using ST-segment resolution criteria, describing in-hospital outcomes, and assessing baseline predictors in a Pakistani tertiary care setting.

This study aimed to determine the rate of thrombolytic failure in acute myocardial infarction using streptokinase, to describe in-hospital outcomes, and to assess associations between baseline clinical and ECG variables and thrombolytic success.

METHODS

This prospective observational study was conducted in the Department of Emergency Medicine, Lady Reading Hospital, Peshawar, after ethical approval from the Institutional Review Board (Ref. NO. 654/LRH/MTI), over twelve months (February 2023–February 2024). Consecutive sampling was employed to include all eligible patients presenting with acute STEMI during the study period, reflecting real-world emergency practice. This approach minimized selection bias by ensuring that no patient fulfilling the inclusion criteria was excluded based on the investigator's preference. The required sample size was calculated using the OpenEpi sample size calculator, with a 95% confidence level, 5% margin of error, and an anticipated thrombolytic failure rate of around 20–25% based on prior studies [11]. This yielded a final sample size of 93 patients, who were enrolled consecutively during the study period. A post-hoc power analysis was performed. With 93 patients and an observed thrombolytic failure rate of 22.6%, the study had approximately 70% power to detect a medium effect size (odds ratio = 2.0) at a two-sided alpha of 0.05. The study may have been underpowered to detect smaller associations. All adult patients (>18 years) presenting with acute myocardial infarction (AMI) and fulfilling electrocardiographic criteria for ST-segment elevation were eligible for inclusion, provided they received intravenous streptokinase within 12 hours of symptom onset and gave informed consent. Patients with contraindications to thrombolytic therapy, such as active bleeding, recent hemorrhagic stroke, recent major surgery or trauma, or those who underwent primary PCI as the initial reperfusion strategy, were excluded. Patients with incomplete records or missing 90-minute post-thrombolysis ECG data were also excluded. These criteria ensured that the study population consisted of clinically homogenous cases where the effect of streptokinase could be evaluated objectively. Demographic data, cardiovascular risk factors (hypertension, diabetes mellitus, smoking status, family history of IHD), and clinical presentation details were recorded at admission. Symptom-to-door time was carefully noted. Symptom-to-door time was carefully noted. For analysis, it was categorized into <3 hours, 3–6 hours, and >6 hours, reflecting clinically meaningful thresholds used in prior STEMI studies. The Killip class was used to assess the severity of heart failure. According to the participant's medical files they received a standard dose of streptokinase (1.5 million IU) administered intravenously over 60 minutes [2]. A baseline 12-lead ECG was performed before infusion and repeated at 90 minutes post-thrombolysis. ST-segment resolution was measured manually by two independent observers blinded to clinical details to minimize bias. Continuous cardiac monitoring was performed for 24 hours, and patients were observed for reperfusion arrhythmias, persistent chest pain, hemodynamic instability, and bleeding complications. Successful thrombolysis was defined as ≥50% resolution of the maximum ST-segment elevation on a standard 12-lead ECG performed 90 minutes after completion of streptokinase infusion, compared with baseline values. Secondary outcomes included reperfusion arrhythmias, persistent chest pain, hemodynamic instability, rescue PCI, and in-hospital mortality. Bleeding complications were categorized using TIMI criteria as major or minor events. ST-segment resolution was independently assessed by two experienced cardiologists blinded to each other's readings. Inter-observer agreement was calculated using Cohen's kappa statistic, which demonstrated substantial agreement ($\kappa = 0.82$) to ensure reliability. Data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables (age, symptom-to-door time) were assessed for normality and compared using independent-sample t-tests. Categorical variables (gender, hypertension, diabetes, smoking, family history of IHD, type of MI, Killip class, reperfusion arrhythmias, persistent chest pain, hemodynamic instability, rescue PCI, in-hospital mortality) were summarized as frequencies and percentages, and associations with thrombolytic success (ST-resolution >50% vs. <50%) were examined using Chi-

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square or Fisher's exact tests. Multivariate logistic regression was performed to identify independent predictors, with $p < 0.05$ considered statistically significant.

RESULTS

The study included 93 patients with acute myocardial infarction who received streptokinase. The mean age of the cohort was 54.3 ± 10.4 years, with a male predominance (79.6% males vs. 20.4% females). Hypertension was present in 36.6% of patients, diabetes mellitus in 33.3%, and smoking history in 29.0%. A positive family history of ischemic heart disease was reported in 17.2% of cases. These findings indicate that the majority of patients were middle-aged men with conventional cardiovascular risk factors, particularly hypertension and diabetes. Most patients presented with anterior wall MI (68.8%), followed by inferior wall MI (22.6%), and other locations (8.6%). The mean symptom-to-door time was 4.12 ± 1.05 hours, suggesting relatively early hospital presentation. Assessment of clinical status revealed that 69.9% of patients were in Killip Class I, indicating no overt heart failure at presentation. Killip Class II was seen in 15.1%, whereas 15.0% were in Class III–IV, reflecting moderate-to-severe heart failure in a smaller subset of patients. (Table 1).

Table 1: Baseline Demographic, Clinical, and Electrocardiographic Characteristics of Study Population (N=93)

Variables	Category	N (%) / Mean ± SD
Age (years)	–	54.3 ± 10.4
Gender	Male	74 (79.6)
	Female	19 (20.4)
Hypertension	Yes	34 (36.6)
	No	59 (63.4)
Diabetes Mellitus	Yes	31 (33.3)
	No	62 (66.7)
Smoking	Yes	27 (29.0)
	No	66 (71.0)
Family History of IHD	Yes	16 (17.2)
	No	77 (82.8)
Type of MI	Anterior	64 (68.8)
	Inferior	21 (22.6)
	Other	8 (8.6)
Symptom-to-door time (hrs)	-	4.12 ± 1.05
Killip Class	I	65 (69.9)
	II	14 (15.1)
	III	11 (11.8)
	IV	3 (3.2)

Successful reperfusion, defined as >50% ST-segment resolution at 90 minutes, was observed in 72 patients (77.4%), while 21 patients (22.6%) experienced thrombolytic failure. Reperfusion arrhythmias were recorded in 17.2% of patients, whereas 16.1% reported persistent chest pain following thrombolysis. Hemodynamic instability was noted in 14.0% of the study population. Overall, these findings reflect a good thrombolytic response in the majority of patients, with complications limited to a smaller proportion (Table 2).

Table 2: Thrombolytic Response and Reperfusion Indicators (N=93)

Outcome/Variables	Category	Frequency (%)
ST-Resolution	>50% (Success)	72 (77.4%)
	<50% (Failure)	21 (22.6%)
Reperfusion Arrhythmias	Yes	16 (17.2%)
	No	77 (82.8%)
Persistent Chest Pain	Yes	15 (16.1%)
	No	78 (83.9%)
Hemodynamic Instability	Yes	13 (14.0%)
	No	80 (86.0%)

Chi-square analysis revealed that none of the conventional cardiovascular risk factors—hypertension (χ^2 = 0.028, p = 0.868), diabetes mellitus (χ^2=0.277, p=0.599), smoking (χ^2 =1.312, p=0.252), or family history of IHD (χ^2=0.162, p=0.687) showed a statistically significant association with thrombolytic success. Similarly, type of MI (χ^2=0.063, df=2, p=0.969) and Killip class (χ^2=1.718, df = 3, p=0.633) were not significantly related to ST-segment resolution. Among reperfusion indicators, persistent chest pain showed a non-significant trend toward association (χ^2 =2.591, p=0.107). Rescue PCI requirement (χ^2 =2.247, p=0.134) and in-hospital mortality (χ^2 =0.879, 0.348) were also not significantly different between patients with successful and failed thrombolysis. These findings indicate that none of the studied clinical or electrocardiographic parameters could reliably predict thrombolytic outcome in this cohort (Table 3).

Table 3: Association of Baseline Variables and Outcomes with Thrombolytic Success (N=93)

Variables	ST-Resolution <50% (N=21)	ST-Resolution >50% (N=72)	χ^2 (DF)	p-Value
Risk Factors				
Hypertension (Yes)	8 (23.5%)	26 (76.5%)	0.028 (1)	0.868
Diabetes Mellitus (Yes)	8 (25.8%)	23 (74.2%)	0.277 (1)	0.599
Smoking (Yes)	4 (14.8%)	23 (85.2%)	1.312 (1)	0.252
Family History of IHD (Yes)	3 (18.8%)	13 (81.3%)	0.162 (1)	0.687
Clinical Presentation				
Type of MI – Anterior	14 (21.9%)	50 (78.1%)	0.063 (2)	0.969
Type of MI – Inferior	5 (23.8%)	16 (76.2%)	–	–
Type of MI – Other	2 (25.0%)	6 (75.0%)	–	–
Killip Class I	16 (24.6%)	49 (75.4%)	–	–
Killip Class II	2 (14.3%)	12 (85.7%)	–	–
Killip Class III–IV	3 (20.0%)	11 (80.0%)	1.718 (3)	0.633

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Reperfusion Indicators				
Reperfusion Arrhythmias (Yes)	5 (31.3%)	11 (68.8%)	0.831 (1)	0.362
Persistent Chest Pain (Yes)	1 (6.7%)	14 (93.3%)	2.591 (1)	0.107
Hemodynamic Instability (Yes)	4 (30.8%)	9 (69.2%)	0.580 (1)	0.446
In-Hospital Outcomes				
Rescue PCI (Yes)	1 (7.1%)	13 (92.9%)	2.247 (1)	0.134
Mortality (Yes)	1 (50.0%)	1 (50.0%)	0.879 (1)	0.348

Patients who arrived within 3 hours had the highest success rate (81.8%), while those arriving between 3–6 hours (76.9%) and beyond 6 hours (75.0%) had slightly lower success. However, these differences were not statistically significant (Pearson χ^2=0.146, df=2, p=0.930; Cramer's V=0.040), indicating that, in this cohort, time to presentation did not independently predict reperfusion outcome. None of the clinical factors, hypertension, diabetes mellitus, smoking, Killip class, or symptom-to-door time categories emerged as significant independent predictors. All odds ratios crossed unity, with wide confidence intervals and non-significant p-values. These findings suggest that baseline comorbidities and clinical status did not meaningfully influence the likelihood of achieving successful reperfusion in this study population.

Table 4: Predictors of Thrombolytic Success in STEMI Patients (N=93)

Predictor/ Symptom-to-Door Time	Failure N (%)	Success N (%)	Total	Adjusted OR (95% CI)	p-Value
Hypertension (Yes vs No)	9 (22.5)	31 (77.5)	40	0.87 (0.31–2.43)	0.784
Diabetes Mellitus (Yes vs No)	7 (21.2)	26 (78.8)	33	0.76 (0.27–2.13)	0.604
Smoking (Yes vs No)	5 (16.1)	26 (83.9)	31	2.07 (0.59–7.28)	0.258
Killip Class (≥II vs I)	6 (21.4)	22 (78.6)	28	0.73 (0.23–2.38)	0.606
Symptom-to-Door <3h	2 (18.2)	9 (81.8)	11	Reference	—
Symptom-to-Door 3–6h	18 (23.1)	60 (76.9)	78	1.38 (0.12–16.1)	0.799
Symptom-to-Door >6h	1 (25.0)	3 (75.0)	4	1.67 (0.09–31.1)	0.732

TIMI major bleeding was rare (2.2%), and TIMI minor bleeding occurred in 6.5% of patients. Rescue PCI was required in 15.1% of cases, while in-hospital mortality was low at 2.2%. Overall, these outcomes highlight that streptokinase therapy was generally safe, with a low rate of serious bleeding and favorable short-term survival (Table 5).

Table 5: In-Hospital Outcomes Including TIMI-Defined Bleeding (N=93)

Outcome	Frequency (%)
TIMI Major Bleeding	2 (2.2%)
TIMI Minor Bleeding	6 (6.5%)
Rescue PCI	14 (15.1%)
In-hospital Mortality	2 (2.2%)

The overall in-hospital complication rates were low in this cohort of 93 patients who underwent thrombolysis with streptokinase. Major bleeding occurred in only 2.2% of cases, whereas minor bleeding was observed in 6.5% of patients. The most frequent adverse event was rescuing PCI requirement, seen in 15.1%, reflecting the need for additional intervention in those with suboptimal reperfusion. In-hospital mortality was low, with only 2.2% of patients succumbing during admission. These findings suggest that streptokinase was generally safe and effective in this population, with limited major bleeding and favorable short-term survival.

DISCUSSIONS

The present study of 93 STEMI patients treated with streptokinase showed a 77.4% rate of early ECG reperfusion (ST-segment resolution >50%), with low in-hospital major bleeding (2.2%) and mortality (2.2%). When patients were stratified by symptom-to-door time, no statistically significant difference in thrombolytic success was observed. Although early presenters (<3h) had numerically higher success (81.8%), this effect was not significant, suggesting that in this relatively early-presenting cohort, time-to-door did not independently influence reperfusion outcome. These figures sit within contemporary regional and LMIC experience. Pakistani series commonly report streptokinase success around 69–73%, with acceptable safety; 69–71% success; a large 2025 tertiary-care cohort likewise reported 73% success and higher complications in failed cases [12]. Results comparable to these have also been described in other South Asian centers, with success clustering near 70–76% and clear time-dependence of effect [8]. A key finding of this study was the absence of statistically significant associations between thrombolytic success and conventional baseline factors (hypertension, diabetes, smoking, family history), type of MI, or Killip class. Multivariate logistic regression further confirmed that hypertension, diabetes mellitus, smoking, Killip class, and symptom-to-door categories were not independent predictors of thrombolytic success. All odds ratios crossed unity, and confidence intervals were wide, indicating no significant associations. Some recent literature does report predictors of failed thrombolysis, notably higher Killip class, anterior infarction, and treatment delays. A 5-year analysis from a non-PCI center identified Killip ≥II and tachycardia as independent FT predictors; intriguingly, tenecteplase (vs. streptokinase) carried a higher adjusted odds of FT in that cohort, emphasizing context and selection effects [13]. Other local work underscores time-to-needle as the dominant driver: significantly greater success was observed when streptokinase was administered within 6 hours of symptom onset, while

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demographic risk factors had minimal impact, directionally consistent with the present null associations for age, sex, and comorbidities [10]. The lack of signal for the type of MI (anterior vs. inferior/other) in this study also warrants comment. Anterior STEMI is generally linked with larger infarcts and worse injury profiles (CMR and biomarker data following primary PCI), which could plausibly reduce STR with fibrinolysis; yet that pattern did not emerge here, potentially due to limited sample size or a relatively narrow spectrum of delays and infarct sizes [14]. In addition, STR is an ECG surrogate for tissue reperfusion rather than a direct angiographic endpoint; alignment between STR and angiographic patency is imperfect, which can dilute associations with baseline features. Contemporary data confirm that STR remains clinically useful but not definitive on its own, and that composite reperfusion criteria improve diagnostic accuracy [15]. The safety profile observed here (rare major bleeding, very low in-hospital mortality) is consistent with modern fibrinolysis experience, where systems of care emphasize early presentation and guideline-concordant adjunctive therapy. Bleeding complications were reclassified according to TIMI criteria. TIMI major bleeding was rare (2.2%), minor bleeding occurred in 6.5%, rescue PCI was required in 15.1%, and in-hospital mortality was 2.2%. These findings reinforce the favorable safety profile of streptokinase in this cohort. Registries demonstrate that when pharmacologic reperfusion is selected in non-PCI or delayed-PCI settings, most patients achieve clinical reperfusion with better subsequent survival than failed cases, mirroring the benign in-hospital course in the present cohort [16]. A 2025 PCI-capable series from Pakistan also reported higher complications and mortality when thrombolysis failed, reinforcing the clinical importance of early rescue PCI pathways for non-responders [17]. Several explanations are plausible for why no predictors were statistically significant in this study. First, with 93 patients and very few adverse events the study was underpowered to detect modest effects, particularly across multi-level variables such as Killip class, where expected counts were small. Similar cohorts with several hundred patients have more readily detected independent predictors. Second, there was limited heterogeneity in treatment delay: the mean symptom-to-door time was 4.1 h with relatively narrow dispersion. Studies that demonstrate clear delay effects typically include substantial late-presenter tails. Third, ST-segment resolution (STR) at 90 minutes, while a simple bedside marker, is an imperfect surrogate, as discordance with angiographic patency and microvascular obstruction is recognized; such classification noise reduces power to detect baseline associations [13, 15]. Fourth, potential confounders such as anti-streptokinase antibody titers, adjunctive pharmacotherapy, infarct size, and microvascular dysfunction were not systematically measured and may explain outcome differences in other series [18]. Finally, the study setting likely contributed: regional data suggest streptokinase can be highly effective in early presenters, where baseline risk factors may matter less than timeliness of therapy [19, 20]. Taken together, the pattern of good overall STR success, low adverse events, and absence of significant predictors supports the view that system-level efficiency (symptom-to-needle, door-to-needle time), standardized protocols, and early rescue pathways are the dominant levers in streptokinase-based reperfusion programs, rather than static demographic risk profiles. These findings are consistent with our multivariate regression analysis, where none of the examined baseline characteristics independently predicted success.

CONCLUSIONS

In conclusion, streptokinase achieved high early ECG reperfusion with low in-hospital complications. The absence of significant associations between thrombolytic success and traditional baseline variables likely reflects a combination of limited power, restricted variability in delays, and the imperfect correlation between STR and true tissue-level reperfusion. Programs using streptokinase should prioritize earlier presentation and treatment, systematic 90-minute STR checks, and ready access to rescue PCI for non-responders. Future work should be multicenter and adequately powered; incorporate angiographic or imaging validation of reperfusion; and evaluate additional biological and systems-of-care determinants (antistreptokinase antibodies, adjunct pharmacology, pre-hospital delay reduction).

Authors Contribution

Conceptualization: HK, JS, HS
Methodology: SA, HS
Formal analysis: MF, SA, HK,
Writing review and editing: MF, JS, NA, HS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Assessment of Levels of Disability in Children Following Post-Meningitis Sequelae: A Hospital-Based Cross-Sectional Study

Sajal Rehman Nawaz[1], Sarfraz Ahmad[1], Maida Shabbir[1*], Tayyba Bari[2], Sara Hussain Gardezi[3], Zainab[4], Zobia[5] and Zoha Rehman[6]

[1]Department of Physical Medicine and Rehabilitation, Children's Hospital, University of Child Health Sciences, Lahore, Pakistan
[2]Department of Physical Therapy, Gulab Devi Teaching Hospital, Lahore, Pakistan
[3]Department of Physical Therapy, University of Child Health Sciences, Lahore, Pakistan
[4]Department of Medicine, Mayo Hospital, Lahore, Pakistan
[5]Department of Medicine, Lahore General Hospital, Lahore, Pakistan
[6]Department of Pediatrics, Ordinance Factory Hospital, Wah Cantt., Pakistan

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Corresponding Author:
Maida Shabbir
Department of Physical Medicine and Rehabilitation, Children's Hospital, University of Child Health Sciences, Lahore, Pakistan
imdrmaida@gmail.com

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ABSTRACT

Meningitis is a globally rampant disease, particularly affecting children, and often results in a series of debilitating neuro-physiological and cognitive impairments. These outcomes are collectively classified as post-meningitis sequelae in the pediatric population. **Objectives:** To assess the levels of disability among children following post-meningitis sequelae. **Methods:** A descriptive cross-sectional study was conducted on 144 children (aged 3–10 years) with post-meningitis sequelae at The Children's Hospital, Lahore. Participants were selected using non-probability purposive sampling. Functional outcomes were assessed using a modified Pediatric Glasgow Outcome Scale – Extended (Peds-GOSE). Data were analyzed using SPSS version 26.0. Frequencies and percentages were calculated, and chi-square tests were applied to determine associations between demographic variables and disability levels. **Results:** Out of 144 children, 8% were in a vegetative state (Peds-GOSE 7), 36% had Lower Severe Disability (Peds-GOSE 6), 23% had Upper Severe Disability (Peds-GOSE 5), 17% had Lower Moderate Disability (Peds-GOSE 4), and 6% had Upper Moderate Disability (Peds-GOSE 3). Only 35% showed good recovery (Peds-GOSE 1–2). Overall, 65% experienced unfavorable outcomes (Peds-GOSE 3–7). A statistically significant association was found between age and disability level ($\chi^2 = 63.713$, df = 12, $p<0.001$). **Conclusion:** The majority of children with post-meningitis sequelae demonstrated unfavorable outcomes, with 65.3% falling into moderate to severe disability categories. Lower Severe Disability (25%) was most common, while only 18.8% achieved complete recovery. Younger age was significantly associated with greater disability severity ($p<0.001$), indicating increased vulnerability in early childhood.

INTRODUCTION

Post-viral or bacterial meningitis in children is a concern because of its long-term effects [1, 2]. The prevalence of meningitis is still a threat to public health in the world as children below the age of five years often contract the disease and hence face high morbidity and mortality rates due to the infection [3]. Even after enhanced prevention and treatment, such as conjugate vaccines, there are still long-term disabilities among the survivors, commonly known as post-meningitis sequelae [4]. They are generally wide-ranging neuropsychological and physical sequelae and have major impacts upon the development, quality of life, and overall functioning of children [5]. There is strong evidence that suggests that the survivors of bacterial meningitis often face lifelong disabilities, and likely in 36 percent of cases in children, the result is sustained neurological morbidities [6]. In particular, the literature

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states that the probability of developing chronic health conditions is high, such as cognitive slow development, behavioral symptoms, hearing and sight deficiency, which could be even more evident as the child ages and experiences growing societal and educational challenges [7]. In a recent study in Denmark and the Netherlands, it was identified that children with bacterial meningitis are more prone to show neurodevelopmental impairments and that they increase over time, which supports the necessity of early intervention measures [7]. The sequelae may present differently in other populations, and some of them include partial deafness and motor impairment, among others. These impairments often require intensive rehabilitation and pose challenges to reintegration into traditional education and social systems [6, 8]. As well, some inequalities in the prevalence and recognition of these sequelae in various geographical areas point to the lack of studies that will fill this knowledge gap efficiently. Research concerning the low- and middle-income settings tends to indicate more cases of such disabilities, potentially due to poorer access to the healthcare system and subsequent treatment of these conditions in the event of recovery [9]. Although there is a lot of literature on the subject matter, there are gaps in terms of a comprehensive understanding of the long-term consequences of bacterial meningitis in children. Some reports highlight the importance of conducting more extensive, longitudinal studies that encompass standardized assessment methodologies to be used to investigate the entirety of the consequences of meningitis [10]. The assessment of a variety of studies by means of the meta-analysis suggests that the risk of the long-term health-related quality of life being negatively impacted is rather high, especially in individuals with an adverse outcome in the form of the neurologic and audiologic sequelae after the acute illness [11]. This necessitates urgent attention to the approaches to evaluating the outcomes and the significance of follow-up assessments to detect disabilities that would otherwise remain hidden over the course of a long time [6, 10]. Since post-meningitis sequelae are multidimensional, the combination of pediatricians, neurologists, audiologists, and psychologists is crucial when dealing with children affected by it, as it targets a broader scope of post-meningitic sequelae needing treatment [11]. Moreover, the possible expenses that such consequences could bring are highlighted in recent studies, and policymakers should focus on programs to enhance preventive activities as well as the access to rehabilitation services by the affected children [12]. Accordingly, a suggested cross-sectional research that will be hospital-based aims at systematically evaluating the rates of disability in post-meningitis sequelae children and fills the gaps in the existing body of research, and can consequently assist in establishing specific protocols of medical intervention in clinical practice. Current research highlights the need to identify different types of sequelae, including emotional and cognitive disorders, which can vary dramatically in their ways of appearance in children with different backgrounds, and this may require specialized treatment in dealing with sequelae [13]. The validated scales that will be used to measure these conditions will give a more definitive knowledge of the consequences of meningitis. Despite the high burden of meningitis in the Asian meningitis belt, there is a notable lack of comprehensive data on the levels of disability experienced by children following post-meningitis sequelae in this region. Existing studies often focus on acute management or isolated complications, while detailed functional assessments remain limited. This study aims to fill this critical gap by systematically evaluating the degree of disability using the Pediatric Glasgow Outcome Scale - Extended (Peds GOS-E), a validated tool for assessing neurological and functional outcomes in pediatric populations. Understanding these disability levels is essential for guiding clinical interventions and rehabilitation strategies to improve long-term quality of life for affected children.

This study aimed to assess the levels of disability in children following post-meningitis sequelae.

METHODS

This cross-sectional study was conducted on 144 children at the Department of Physical Medicine and Rehabilitation and the Pediatric Neurology Ward, The Children's Hospital, and the University of Child Health Sciences, Lahore, between June 2024 and January 2025. Ethical clearance was obtained from the ethical committee of The School of Allied Health Sciences, The Children's Hospital, and The University of Child Health Sciences, Lahore (No.700/SAHS). The sample size included 144 children undergoing post meningitis sequelae calculated by the following formula: $n = (Z^2 \times p \times (1 - p) / e^2)$. Where: Z = 1.96 (confidence level), e = 0.05 (margin of error), p = 0.105 (prevalence based on reference [14]. The calculated value (143.3) was rounded up to 144 using the ceiling method. No additional adjustment for non-response was made, as all selected participants were available for inclusion. Non-probability convenience sampling technique was used to collect data. Children ranging from 3 years to 10 years with CSF-diagnosed meningitis were included in the study. Children with a history of meningitis before three years of age were excluded from the study. Patients with encephalitis, cerebral palsy, and developmental delay, and those who were admitted with suspected meningitis attributable to head injury, neurosurgical procedures, or brain abscesses, were not a part of the study. In addition,

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children who died during post- meningitis sequelae were not included in the research assessment. Upon obtaining IRB approval, patients meeting the inclusion criteria were recruited and informed about the study. Informed written consent was obtained from the parents or legal guardians of all participants before data collection. The hospital records provided demographic information such as age, sex, and other pertinent clinical details, which were confirmed using the interviews of the parents/caregivers. The Pediatric Glasgow Outcome Scale-Extended (Peds-GOSE) was used to determine the disability outcomes. The Peds-GOSE categorizes the children into seven ordinal options (scores 1-7) according to their consciousness, independence both at home and out of home, mobility, school performance, behavioral interactions, psychological adjustment, and recovery to the pre-injury functioning. The highest degree of disability was then assigned a score, with a score of 7 representing a vegetative state (no command following), a score of 6 representing dependence in the basic self-care, a score of 5 representing dependence outside of home with aids or use of a wheelchair, a score of 4 representing the inability to resume school or work with reduced role performance, a score of 3 representing social or behavioral problems that limited participation, a score of 2 representing lower good recovery with residual symptoms and functional independence, and a score of 1 representing upper good recovery with complete performance of previous functions As the Peds-GOSE is an ordinal categorical scale, cumulative scoring cannot be used, and every child was put in one of the seven categories. The Peds-GOSE has previously been found to be valid in pediatrics [15]. The data were entered and analyzed using IBM SPSS version 26.0. The categorical variables were illustrated in the form of frequencies and percentages.

RESULTS

A total of 144 Children were included in the study between 3 years of age to 10 years old through a non-probability sampling technique from the Physical Medicine and Rehabilitation Department of the Children's Hospital, Lahore. Since it's a cross-sectional study, the data were recorded at the same time and place. 63 children were between the ages of 3-5, 52 children were between the ages of 6-8, and 29 children were between the ages of 9-10. Among 144 children, 106 were male and 38 were female (Table 1).

Table 1: Demographic Characteristics of Study Participants

Demographics	Frequency (%)
Age	
3–5 Years	63 (43.8%)
6–8 Years	52 (36.1%)
9–10 Years	29 (20.1%)
Total	144 (100%)
Gender	
Male	106 (73.6%)
Female	38 (26.4%)
Total	144 (100%)

Results illustrate the levels of disability assessed through the Peds-GOSE scale; out of 144 children, 132 children were in complete consciousness; however, 12 children were found to be in a vegetative state. Similarly, 48 children out of 144 required assistance for basic ADLs, and 71 children from a sample of 144 required assistance to ambulate freely outside the home. 88 children out of 144 were unable to resume school at the previous capacity, and a predominant number of children, 88 out of 144, suffered from complete withdrawal from any sort of active participation and severe psychological distress. After a thorough evaluation and examination, only 27 children out of 144 returned to normal life, while the remaining children faced incomprehensible impairment due to the sequelae (Table 2).

Table 2: Pediatric Glasgow Outcome Scale-Extended (Peds-GOSE) Assessment Responses

Questions	Response	Frequency (%)	GOSE Score
Consciousness: Is the patient able to obey simple commands or say any words?	Yes	132 (91.7%)	7
	No (Vegetative State)	12 (8.3%)	
Independence inside the home: Can the child perform basic daily life activities, like brushing, eating, and toileting, without any assistance?	Needs No Assistance	96 (66.7%)	6
	Dependent for Basic ADLs	48 (33.3%)	
Independence outside Home: Is the child able to travel without assistance?	Yes	73 (50.7%)	5
	No	71 (49.3%)	
School Performance: Is the child able to resume school at his previous capacity	Yes	88 (61%)	4
	No	56 (39%)	
Social Participation: Is the child able to resume regular social or leisure activities	No	88 (61.1%)	3
	Moderate	6 (4%)	
	Slight	23 (16%)	
	Complete Social Participation	27 (18.8%)	

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Family and Friends: Psychological Irritability	Marked/Constant	88 (61.1%)	2
	Moderate Psychological Discomfort	19 (13.3%)	
	Slight Psychological Discomfort	8 (5.5%)	
	Complete Social Participation	29 (20.1%)	
Return to Normal Life: Are there any problems related to injury that affect daily life?	No	27 (19%)	1
	Yes	117 (81%)	
Total	–	144 (100%)	–

The Pediatric Glasgow Outcome Scale-Extended (Peds-GOSE) was used to classify levels of disability among children with post-meningitis sequelae. The majority of children (65.3%) demonstrated unfavorable outcomes, falling into the moderate to severe disability categories (scores 3–7). The most common category was Lower Severe Disability (score 6), found in 36 children (25.0%), followed by Upper Severe Disability (score 5) in 23 children (16.0%). Only 27 children (18.8%) achieved complete recovery, corresponding to Upper Good Recovery (score 1). This distribution shows that most children continued to experience significant functional limitations after meningitis, with only a small proportion regaining full pre-illness function (Table 3).

Table 3: Levels of Disability Based on Peds-GOSE with 95% Confidence Intervals

Peds-GOSE Score	Level of Disability	Criteria (Summary)	n (%)	95% CI (%)
7	Vegetative State (VS)	No response or only reflexive; unable to follow simple commands	12 (8.3%)	3.8 – 12.8
6	Lower Severe Disability (LSD)	Dependent in basic self-care (feeding, grooming, dressing)	36 (25.0%)	17.7 – 32.3
5	Upper Severe Disability (USD)	Requires mobility aids/wheelchair; dependent outside the home	23 (16.0%)	9.9 – 22.1
4	Lower Moderate Disability (LMD)	Unable to resume school/work; reduced role performance	17 (11.8%)	6.5 – 17.1
3	Upper Moderate Disability (UMD)	Social/behavioral difficulties limiting play or peer interaction	6 (4.2%)	1.0 – 7.4
2	Lower Good Recovery (LGR)	Functional independence achieved, but residual symptoms/ behavioral issues present	23 (16.0%)	9.9 – 22.1
1	Upper Good Recovery (UGR)	Complete recovery to pre-injury level (per caregiver report)	27 (18.8%)	12.3 – 25.3

The association between age groups and the level of disability measured by the Pediatric Glasgow Outcome Scale Extended (Peds-GOSE) was assessed using the chi-square test. The study shows the distribution of Peds-GOSE categories across three age groups (3–5 years, 6–8 years, and 9–10 years) (Table 4).

Table 4: Distribution of Peds-GOSE Disability Categories by Age Group

Peds-GOSE Category	Age 3–5	Age 6–8	Age 9–10	Total
Upper Good Recovery (UGR)	11	5	11	27
Lower Good Recovery (LGR)	11	6	6	23
Upper Moderate Disability (UMD)	6	0	0	6
Lower Moderate Disability (LMD)	0	17	0	17
Upper Severe Disability (USD)	11	12	0	23
Lower Severe Disability (LSD)	18	6	12	36
Vegetative State (VS)	6	6	0	12
Total	63	52	29	144

The chi-square test revealed a statistically significant association between age and disability level ($\chi^2 = 63.713$, df = 12, $p<0.001$), indicating that the distribution of disability severity significantly varies with age among the children studied (Table 5).

Table 5: Chi-Square Test for Association Between Age Group and Peds-GOSE Disability Categories

Statistic	Value	df	p-Value
Pearson Chi-Square	63.713	12	<0.001
Number of Valid Cases	144	–	–

DISCUSSION

The findings of the study provide critical information on the follow-up disability cases in children with post-meningitis sequelae. The number of children assessed was 144 children aged between 3 and 10 years old. The predominance of male participants (73.6%) is notable, as it may relate to variance in independence, social participation, and overall quality of life. This gender disparity in the cases of meningitis reflects itself in a study by Block *et al.* who reported the higher rate of bacterial infection cases in males as compared to females because of the immune response differences [16]. The age distribution of the children in this study indicates that the younger children (3-5 years) comprised the largest proportion of the sampling percentage (43.8%), indicating that the outcome of affected children in that age group tends to have worse implications after getting meningitis. Mohanty *et al.* also highlight this sentiment, citing that younger children with the diagnosis of bacterial meningitis experience much higher risks of developing cognitive impairments and related disorders, with the most emphasis made on the emergence of emotional and behavioral disorders [3]. In keeping with this, the chi-square test conducted in this study (i.e., 63.713, $p<0.001$) has shown a statistically significant relationship between

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age and the level of disability, thus outlining the vulnerabilities of younger children. The distribution of disability levels, as assessed by the Pediatric Glasgow Outcome Scale Extended (Peds-GOSE), shows a concerning trend in the outcome of the recovery outcomes of meningitis. Although 91.7% of participants had intact consciousness, 8.3% were in a vegetative state. This fact aligns with the previous research by Schiess *et al.* where significant proportions of children also showed either severe impairments or altered consciousness after experiencing bacterial meningitis [17]. This important observation illustrates the significant neurological effects reported in the literature, with many survivors experiencing severe impairments in terms of cognitive and communicative skills [8]. Specifically, Garg *et al.* reported that young children (up to 36%) became profoundly disabled due to bacterial meningitis [5]. It was caused by the pathogenic effect of the high-risk pathogens, such as Streptococcus pneumonia [9]. Moreover, the level of psychological distress reported was alarming; 61.1% of children exhibited marked or constant irritability, indicating potential underlying issues that warrant attention. Studies by Schiess *et al.* corroborate these observations, documenting that neurological sequelae can manifest not only as physical disabilities but also as significant psychological distress and behavioral issues [17]. The high rate of social withdrawal (61.1%) and the failure to resume schooling (39%) indicate that these consequences may be disastrous in terms of both their education and development. This observation is reflected in the literature, showing that returning to academic life can be rather problematic with survivors of meningitis unless special assistance is offered to them. Lee *et al.* added that it would delay the development of the children and render them socially withdrawn, which could negatively impact their performance at school and towards their peers [18]. The need for assistance with daily living activities among nearly one-third of the children highlights significant functional limitations caused by post-meningitis sequelae. The evidence provided in one of the meta-analyses carried out by Teixeira *et al.* confirms the validity of this statement, as it reported that pediatric patients who have had bacterial meningitis as their underlying condition have challenges with the ability to complete ADLs and may need a long period to be rehabilitated [9]. Remarkably, almost 61.1% of children in our study could not restart their social lives, which means a serious decrease in their quality of life that corresponds to reported psychosocial burdens in the cohorts of similar patients [17]. A further analysis of the results depicts that the study found 27 children who returned to a normal life after being affected by post-meningitis sequelae. This highlights the long-term economic and social burden associated with post-meningitis sequelae [19]. It is in line with what Francisco *et al.* conclude, which refers to multiple long-term implications that largely include several disabilities that influence the functioning of the child and affect the family significantly [20]. The disabling consequences of meningitis in this research are similar to the conclusions gathered in the literature at a larger scale, and it is clear that more support and rehabilitation among this at-need population is necessary. The chi-square test revealed a statistically significant correlation between age and severity of disability, which also complies with an earlier study by Block *et al.* that proposes that younger children have greater odds of having enduring neurological deficits in the aftermath of meningitis, attributed to the underdeveloped qualities of the brains of the affected children at the crucial phase of development [16]. In summary, some children exhibited recovery, but most of them were at significant risk because they exhibited several disabilities, including psychological, social, and functional areas. The extent of impairment observed in this study highlights the urgent need for improved support systems for children recovering from bacterial meningitis. This is in tandem with recommendations in the literature that support a holistic approach that emphasizes the use of long-term follow-ups and customized rehabilitation strategies [21].

CONCLUSIONS

The majority of children with post-meningitis sequelae demonstrated unfavorable outcomes, with 65.3% falling into moderate to severe disability categories. Lower Severe Disability (25%) was most common, while only 18.8% achieved complete recovery. Younger age was significantly associated with greater disability severity ($p<0.001$), indicating increased vulnerability in early childhood.

Authors Contribution

Conceptualization: SRN
Methodology: SRN, Z[2]
Formal analysis: SHG, Z[1]
Writing review and editing: SA, MS, TB, ZR

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

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A Comparative Study of Platelet-Rich Plasma and Normal Saline Dressings in the Treatment of Chronic Wounds

Shahid Hussain[1*] and Asiya Shabbir[1]

[1]Department of Surgery, Bahawal Victoria Hospital, Bahawalpur, Pakistan

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***Corresponding Author:**
Shahid Hussain
Department of Surgery, Bahawal Victoria Hospital, Bahawalpur, Pakistan
ssc.bwp@gmail.com

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ABSTRACT

Chronic wounds pose a major challenge in clinical practice, often requiring advanced interventions. Platelet-rich plasma (PRP) dressings, by releasing growth factors, have emerged as a promising alternative to conventional approaches. **Objectives:** To compare the efficacy of PRP versus normal saline (NS) dressings in promoting wound healing. **Methods:** This randomized controlled trial was conducted at the Department of Surgery, Bahawal Victoria Hospital, Bahawalpur, from April to October 2024. A total of 156 patients with chronic wounds were randomized into PRP (n = 78) or NS (n = 78) groups. Baseline characteristics were recorded, and patients were followed for six weeks. Healing outcomes were analyzed using Chi-square and t-tests, with significance set at p≤0.05. **Results:** The PRP group achieved significantly higher healing (91.0%) compared to the NS group (66.7%) (p=0.000). Subgroup analysis revealed greater efficacy of PRP in older patients, female, immobile individuals, and those with long-standing wounds. PRP also showed superior results in diabetic (p=0.007) and pressure ulcers (p=0.004), though not in venous ulcers (p=0.477). **Conclusions:** PRP enhances chronic wound healing compared to saline dressings, with particular benefits in high-risk patient groups. It is a safe and effective therapeutic option.

INTRODUCTION

Chronic wounds remain a persistent challenge in clinical practice, not only delaying healing but also contributing to increased morbidity, disability, and healthcare costs. These wounds are typically defined as those that fail to progress through the orderly and timely phases of repair, and their persistence is often linked to factors such as local ischemia, infection, diabetes mellitus, or vascular insufficiency [1]. Because they rarely follow the expected biological cascade of hemostasis, inflammation, proliferation, and remodeling, they tend to remain in a chronic inflammatory state, further impairing tissue regeneration [2]. Traditional wound care strategies, including saline dressings, have been widely employed. While these methods help maintain wound moisture and prevent desiccation, their role in stimulating cellular and molecular repair is limited, often resulting in slow recovery and recurrent infections [3]. Hence, there has been increasing interest in therapeutic interventions that can actively promote wound healing by supplying essential biological cues. Among these, Platelet-Rich Plasma (PRP) has emerged as a promising modality. PRP is an autologous concentration of platelets suspended in plasma, enriched with growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β), all of which are crucial mediators of wound repair [4, 5]. These molecules

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enhance angiogenesis, collagen synthesis, fibroblast migration, and epithelialization, while simultaneously modulating inflammation [6]. In this way, PRP is capable of creating a microenvironment more favorable for tissue regeneration compared to conventional dressings. Accumulating evidence from randomized controlled trials and meta-analyses has demonstrated that PRP accelerates wound closure, increases the rate of complete healing, and reduces complication rates when compared to saline dressings [7, 8]. Its effectiveness has been particularly well documented in diabetic foot ulcers, where PRP use resulted in faster granulation tissue formation, substantial reduction in wound size, and shorter overall treatment duration [9, 10]. Moreover, studies have reported reduced infection rates and improved patient quality of life without introducing additional adverse effects [11]. Importantly, although the preparation of PRP was initially considered complex, recent technical advances have simplified the procedure, making it inexpensive, reproducible, and feasible in routine clinical settings [12]. Given these advantages, PRP has become increasingly relevant in the search for effective strategies to manage chronic wounds. However, despite growing evidence in favor of PRP, there remains a need for context-specific data, particularly in resource-constrained healthcare systems where cost and feasibility strongly influence clinical decision-making.

This study aims to compare PRP dressings with normal saline dressings in patients with chronic wounds, with a primary focus on healing outcomes, to provide evidence that may guide future wound care practices.

METHODS

This randomized controlled trial (RCT registry No. NCT06849232) was conducted in the Department of Surgery at Bahawal Victoria Hospital, Bahawalpur, over six months from April 17, 2024, to October 16, 2024. Ethical approval was granted under letter number 2381/DME/QAMC/Bahawalpur, and written informed consent was obtained from all participants before enrollment. The trial was reported in accordance with the CONSORT 2010 guidelines. Patients were recruited using a non-probability consecutive sampling technique. The trial aimed to compare the effectiveness of platelet-rich plasma (PRP) dressings with normal saline (NS) dressings in the treatment of chronic wounds. A previous study by Orban *et al.* reported a healing rate of 86.1% with PRP dressings compared to 63.9% with NS dressings [13]. Using these proportions, with 90% power and a 5% level of significance, the sample size for each group was calculated using the formula for comparing two proportions: $n = [(Z_{1-}\alpha/_2 + Z_{1-}\beta)^2 \times (P_1(1 - P_1) + P_2(1 - P_2))] \div (P_1 - P_2)^2$. Where $Z_{1-a}/_2 = 1.96$ and $Z_{1-\beta} = 1.28$, $P_1 = 0.861$, and $P_2 = 0.639$. The calculated sample size was 78 patients per group, giving a total of 156 patients. This calculation followed the method described by Lwanga *et al.* [14]. Patients aged 18–60 years of either gender were included if they had a chronic wound persisting for at least six weeks and measuring at least 2 × 2 cm. Exclusion criteria were wounds of less than six weeks' duration, prior treatment with PRP dressings, known hypersensitivity to PRP, or burn injuries (confirmed by review of medical records). Baseline characteristics, including age, gender, HbA1C levels, mobility status (ambulatory or bed-bound), history of prolonged standing, wound duration, and wound type (diabetic, pressure, or venous), were documented. This information was obtained from patients' hospital records and files, including laboratory reports (for HbA1C), clinicians' notes, and direct history-taking at the time of enrollment. Eligible patients were recruited consecutively until the required sample size was reached, using a non-probability consecutive sampling approach. This method ensured that every patient meeting the inclusion criteria during the study period was considered for enrollment. After enrollment, participants were randomly allocated to either the PRP or NS dressing group using simple randomization (lottery method). To maintain allocation concealment, sequentially numbered, sealed, opaque envelopes were prepared by an independent researcher not involved in recruitment or assessment. Each envelope contained the group assignment generated by computer-assisted random numbers and was opened sequentially only after the patient was enrolled. No stratification or block randomization was applied, as baseline characteristics were comparable between groups. Because the PRP procedure was visible, neither the participants nor the treating surgeons could be blinded, making this an open-label trial. However, outcome assessment was performed by independent evaluators blinded to group allocation. These assessors were not involved in treatment administration and relied on standardized clinical parameters and serial wound photographs. PRP was prepared by the hematology department following a standardized two-step centrifugation technique. For each patient, 20 ml of venous blood was drawn under aseptic conditions into tubes containing acid-citrate-dextrose (ACD) as an anticoagulant. The first centrifugation ("soft spin") was performed at 1500 rpm for 10 minutes to separate red blood cells from plasma and the buffy coat. The upper plasma and buffy coat layers were carefully aspirated into a sterile tube and subjected to a second centrifugation ("hard spin") at 3000 rpm for 10 minutes. This yielded three layers: platelet-poor plasma (PPP) at the top, a middle buffy coat containing concentrated platelets, and red cells at the bottom. The upper PPP was discarded, and the platelet-

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rich fraction was collected. The final PRP contained a platelet concentration approximately 4–5 times higher than baseline counts, which was confirmed using hematology analyzers. The PRP was used immediately after preparation to preserve platelet activity. Patients in Group A received PRP dressings. Wounds were cleaned with NS, followed by injection of autologous PRP into the wound margins twice weekly, and then covered with sterile gauze. Patients in Group B received normal saline (NS) dressings, which represent the standard wound care practice in our hospital setting. As such, the NS group served as the positive control group, allowing comparison of PRP against an established conventional treatment rather than a placebo or no treatment. Patients were followed weekly for six weeks to monitor healing progress. At each visit, wound healing was evaluated by independent blinded assessors using three complementary approaches applied concurrently: (1) Visual inspection of the wound bed for epithelialization, granulation tissue formation, and reduction in exudate; (2) Serial standardized wound photographs taken under identical lighting and distance to allow week-to-week comparison; and (3) The Pressure Ulcer Scale for Healing (PUSH) version 3.0, developed by the National Pressure Ulcer Advisory Panel [15]. The PUSH tool quantifies three wound characteristics: surface area, exudate amount, and tissue type—each scored and summed to yield a total score from 0 to 17, where lower scores indicate better healing and a score of 0 represents complete epithelialization. The three assessments were interpreted together: when both clinical and photographic evaluation confirmed full epithelialization with absence of exudate or granulation tissue and the PUSH total score was 0, the wound was classified as healed; otherwise, it was considered not healed. These combined criteria were used to document weekly progress and determine healing status at six weeks. The primary outcome of the study was complete wound closure (PUSH = 0) by week six. Data were analyzed using SPSS version 22. Quantitative variables (age, HbA1C levels, wound duration) were expressed as mean ± standard deviation (SD). The normality of continuous variables (age, HbA1C, wound duration) was assessed using the Shapiro–Wilk test. As the data were normally distributed, results are expressed as mean ± SD. Within-group (pre- vs post-treatment) comparisons were made using McNemar's test for paired categorical variables (e.g., healed vs not healed at baseline and at week six) and the paired t-test for continuous variables such as PUSH total scores. Between-group comparisons were performed using the Chi-square test (or Fisher's exact test where applicable) for categorical variables and the independent t-test for continuous variables. In subgroup analyses, potential confounders, including diabetes status, glycemic control (HbA1C), mobility, and comorbidities, were adjusted for using multivariate logistic regression to assess the independent effect of PRP. The model's calibration was verified using the Hosmer–Lemeshow goodness-of-fit test. A p-value≤0.05 was considered statistically significant. The CONSORT flow diagram of participant enrollment, allocation, follow-up, and analysis was shown (Figure 1).

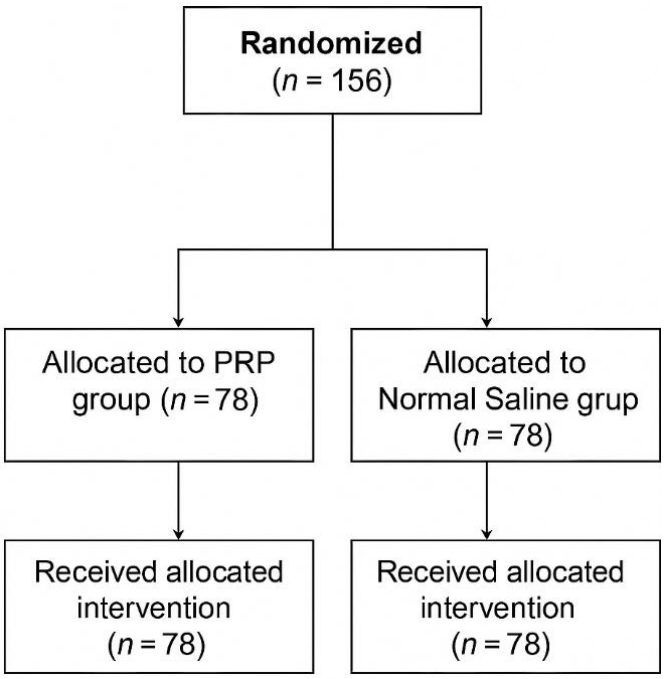

Figure 1: CONSORT Flow Diagram of Participant Enrollment, Allocation, Follow-Up, and Analysis

RESULTS

A total of 156 patients were included in this study. The mean age of participants was 38.67 ± 11.92 years, with an average HbA1C level of 6.92 ± 0.87%. The mean duration of the wound was 29.97 ± 12.93 weeks. The study compares the overall healing outcomes between the two groups of patients treated with PRP dressing and those treated with normal saline dressing. In the PRP group, 71 (91.0%) patients achieved complete wound healing, whereas 7 (9.0%) did not heal. In the normal saline group, 52 (66.7%) patients achieved healing, while 26 (33.3%) failed to heal. The difference between the two groups was statistically significant (p=0.000), demonstrating the superior efficacy of PRP dressing over saline dressing in promoting wound healing (Table 1).

Table 1: Comparison of Healing Outcomes Between PRP Dressing and Normal Saline Dressing

Group	Not Healed	Healed	p-Value
PRP Dressing	7 (9.0%)	71 (91.0%)	<0.001*
Normal Saline Dressing	26 (33.3%)	52 (66.7%)	

*=p<0.05 considered statistically significant.

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The study provides a subgroup analysis comparing healing outcomes between PRP and saline dressings. Among patients aged 18–40 years, PRP resulted in significantly higher healing rates (38 (86.4%)) compared to saline (26 (66.7%)) (p=0.033). Similarly, in the 41–60 years age group, PRP achieved 33 (97.1%) healing compared to 26 (66.7%) with saline (p=0.001). These findings indicate that PRP was effective in both younger and older patients, with a particularly notable benefit in older individuals. For wounds of shorter duration (6–12 weeks), PRP demonstrated 100% healing, while saline achieved 70.0% (p=0.041), suggesting that PRP may be more effective in newly formed wounds. For moderately chronic wounds (13–24 weeks), the difference between PRP (66.7%) and saline (84.6%) was not statistically significant (0.274). In long-duration wounds (25–36 weeks), PRP healed 90.5% compared to 69.2% with saline, although this difference did not reach statistical significance (p=0.077). However, for very long-duration wounds (37–51 weeks), PRP achieved 100% healing, whereas saline healed only 55.2% (p=0.000), demonstrating a clear benefit of PRP in managing chronic wounds of extended duration. In terms of gender, males showed high healing rates in both groups, with PRP achieving 33 (91.7%) compared to 29 (85.3%) in the saline group, a difference that was not statistically significant (p=0.402). In female, however, PRP was significantly more effective, achieving 38 (90.5%) healing versus 23 (52.3%) in the saline group (p = 0.000), suggesting that PRP may be particularly beneficial for female patients. Among ambulatory patients, PRP healed 40 (90.9%) compared to 24 (70.6%) with saline (p=0.020), showing a significant improvement in mobile individuals. Similarly, in bed-bound patients, PRP healed 31 (91.2%) compared to 28 (63.6%) in the saline group (p=0.005), highlighting the effectiveness of PRP even in immobile patients. Patients with a history of prolonged standing experienced significantly better outcomes with PRP (41 (91.1%)) than with saline (21 (55.3%)) (p=0.000). Among those without prolonged standing, the difference between PRP (30 (90.9%)) and saline (31 (77.5%)) was not statistically significant (p=0.124). In terms of wound types, PRP was particularly effective for diabetic wounds, achieving 22 (95.7%) healing compared to 18 (64.3%) with saline (p=0.007). Similarly, PRP outperformed saline in pressure ulcers, with 29 (90.6%) healing versus 15 (57.7%) (p=0.004). For venous ulcers, PRP healed 20 (87.0%), compared to 19 (79.2%) in the saline group, but this difference was not statistically significant (p=0.477) (Table 2).

Table 2: Comparison of Healing Outcomes by Different Variables Between PRP and Normal Saline Dressing

Variables	Subgroup	PRP Healed, n (%)	PRP Not Healed, n (%)	Saline Healed, n (%)	Saline Not Healed, n (%)	p-Value
Age	18–40 Years	38 (86.4%)	6 (13.6%)	26 (66.7%)	13 (33.3%)	0.033*
	41–60 Years	33 (97.1%)	1 (2.9%)	26 (66.7%)	13 (33.3%)	0.001*
Wound Duration	6–12 Weeks	12 (100%)	0 (0.0%)	7 (70.0%)	3 (30.0%)	0.041*
	13–24 Weeks	10 (66.7%)	5 (33.3%)	11 (84.6%)	2 (15.4%)	0.274
	25–36 Weeks	19 (90.5%)	2 (9.5%)	18 (69.2%)	8 (30.8%)	0.077
	37–51 Weeks	30 (100%)	0 (0.0%)	16 (55.2%)	13 (44.8%)	0.000*
Gender	Male	33 (91.7%)	3 (8.3%)	29 (85.3%)	5 (14.7%)	0.402
	Female	38 (90.5%)	4 (9.5%)	23 (52.3%)	21 (47.7%)	0.000*
Mobility Status	Ambulatory	40 (90.9%)	4 (9.1%)	24 (70.6%)	10 (29.4%)	0.020*
	Bed Bound	31 (91.2%)	3 (8.8%)	28 (63.6%)	16 (36.4%)	0.005*
Standing History	Yes	41 (91.1%)	4 (8.9%)	21 (55.3%)	17 (44.7%)	0.000*
	No	30 (90.9%)	3 (9.1%)	31 (77.5%)	9 (22.5%)	0.124
Type of Chronic Wound	Diabetic	22 (95.7%)	1 (4.3%)	18 (64.3%)	10 (35.7%)	0.007*
	Pressure	29 (90.6%)	3 (9.4%)	15 (57.7%)	11 (42.3%)	0.004*
	Venous	20 (87.0%)	3 (13.0%)	19 (79.2%)	5 (20.8%)	0.477

*=p<0.05 considered statistically significant.

After adjusting for potential confounding factors, including age, HbA1C, gender, mobility status, wound duration, and wound type, PRP remained a strong independent predictor of wound healing. Patients treated with PRP dressings were more than five times as likely to achieve complete healing compared to those treated with normal saline dressings (Adjusted OR=5.53, 95% CI: 2.11–14.49, p=0.000). In addition, female patients had significantly higher odds of healing compared to males (Adjusted OR=3.59, 95% CI: 1.32–9.77, p=0.012). Other variables, including age group, HbA1C level, mobility status, wound duration, and wound type, were not statistically significant independent predictors in the adjusted model. The overall model demonstrated good calibration (Hosmer–Lemeshow test p=0.962) and explained approximately 25% of the variance in wound healing outcomes (Nagelkerke R^2 = 0.253) (Table 3).

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Table 3: Multivariate Logistic Regression for Predictors of Wound Healing

Variable	Adjusted OR	95% CI	p-Value
Group (PRP vs Saline)	5.53	2.11–14.49	<0.001*
Gender (Female vs Male)	3.59	1.32–9.77	0.012*
Age (41–60 vs 18–40)	0.61	0.25–1.49	0.274
HbA1C (Continuous)	0.79	0.47–1.33	0.383
Mobility (Bed-bound vs Ambulatory)	1.75	0.70–4.34	0.228
Wound Duration (Ref = 37–51 Weeks)	—	—	0.829
6–12 Weeks	1.52	0.35–6.64	0.579
13–24 Weeks	0.75	0.22–2.55	0.644
25–36 Weeks	0.80	0.27–2.38	0.685
Wound Type (Ref = Venous)	—	—	0.466
Diabetic	0.84	0.26–2.74	0.774
Pressure	0.52	0.16–1.65	0.266

*=p<0.05 considered statistically significant.

Within-group analysis using McNemar's test demonstrated a statistically significant improvement in healing status from baseline to week six in both treatment groups (p<0.001 for each). All patients were unhealed at baseline, but by week six, 91.0% in the PRP group and 66.7% in the normal saline group achieved complete wound closure. This indicates that while both interventions facilitated significant within-group improvement, the magnitude of healing was markedly greater in the PRP group, reflecting its superior wound-healing potential compared with conventional saline dressings (Table 4).

Table 4: Within-Group Comparison of Healing Status (Pre- vs Post-Treatment) by McNemar's Test

Group		Healing Status at Week 6	Healing Status at Baseline	Improved, n (%)	McNemar's p-Value
PRP Dressing (n=78)	Not Healed	78 (100%)	7 (9.0%)	71 (91.0%)	<0.001 *
	Healed	0 (0%)	71 (91.0%)		
Normal Saline Dressing (n=78)	Not Healed	78 (100%)	26 (33.3%)	52 (66.7%)	<0.001 *
	Healed	0 (0%)	52 (66.7%)		

Test: McNemar's test for paired categorical data (pre- vs post-treatment). *=p<0.05 considered statistically significant.

DISCUSSIONS

This study demonstrated the superiority of Platelet-Rich Plasma (PRP) dressing over Normal Saline (NS) dressing in promoting wound healing, as evidenced by significantly higher healing rates in the PRP group. These findings align with the broader literature on PRP in wound management, which has shown promising outcomes in diverse clinical settings. In our study, 71 (91.0%) patients in the PRP group achieved wound healing compared to 52 (66.7%) in the NS group (p=0.000). These results are consistent with the study by Orban *et al.*, which reported an 86.1% healing rate with PRP compared to 63.9% in the conventional dressing group, highlighting PRP's effectiveness in accelerating wound closure [13]. Subgroup analyses further supported PRP's benefits across different patient profiles. In younger patients (18–40 years), healing was achieved in 86.4% with PRP versus 66.7% with NS (p=0.033). Among older patients (41–60 years), PRP demonstrated an even greater advantage, with 97.1% healing compared to 66.7% in the NS group (p=0.001), consistent with Fibrini *et al.* [16]. PRP also showed superior outcomes in long-standing wounds (37–51 weeks), achieving 100% healing compared to 55.2% with NS (p=0.000), underscoring its potential in managing difficult chronic wounds, as also supported by Orban *et al.* [13]. Gender-specific analysis revealed that PRP was particularly effective in female, with 90.5% healing compared to 52.3% with NS (p=0.000). In males, however, healing rates were high in both groups with no significant difference. These findings mirror El-Mabood *et al.* [17], who reported greater improvements in female patients. Patients with a history of prolonged standing also benefited significantly from PRP, with 91.1% healing versus 55.3% with NS (p=0.000), in line with Syafira *et al.* [18]. When analyzed by wound type, PRP was especially effective for diabetic wounds (95.7% vs. 64.3%, p=0.007) and pressure ulcers (90.6% vs. 57.7%, p=0.004), echoing the findings of Elsaid *et al.* and Peng *et al.* respectively [19, 20]. However, for venous ulcers, healing rates did not differ significantly (87.0% vs. 79.2%, p = 0.477), consistent with Li *et al.* who noted variable outcomes in this subgroup [2]. Importantly, the results of our multivariate logistic regression analysis confirmed that PRP is an independent predictor of wound healing, even after adjusting for age, HbA1C, gender, mobility, wound duration, and wound type. Patients treated with PRP had 5.5 times higher odds of healing compared to NS (Adjusted OR = 5.53, 95% CI: 2.11–14.49, p=0.000). Female gender also emerged as an independent predictor of higher healing rates (Adjusted OR = 3.59, 95% CI: 1.32–9.77, p=0.012), while other variables were not statistically significant. These findings reinforce that PRP's superiority is not simply due to imbalances in patient characteristics but represents a genuine therapeutic effect. No adverse effects were observed in patients treated with PRP, supporting its safety profile. This is consistent with meta-analyses by Li *et al.* and Suthar *et al.* which concluded that PRP is safe and does not increase the risk of infection or complications [2, 21]. Finally, it should be acknowledged that our study recorded healing status at six weeks but did not capture the exact week of wound closure. As a result, time-to-complete healing could not be analyzed. Future trials incorporating detailed weekly healing data and survival analyses are warranted to provide stronger evidence of PRP's superiority in accelerating wound closure.

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CONCLUSIONS

This randomized controlled trial demonstrated that platelet-rich plasma (PRP) dressings significantly improved healing outcomes in chronic wounds compared with normal saline dressings. At six weeks, 91.0% of patients in the PRP group achieved complete wound healing compared to 66.7% in the saline group (p=0.000). Subgroup analyses showed PRP to be particularly effective in older patients, females, bed-bound individuals, and those with long-standing wounds. PRP also enhanced healing in diabetic and pressure ulcers, though no significant advantage was observed in venous ulcers. Importantly, multivariate analysis confirmed that PRP was an independent predictor of wound healing, even after adjusting for potential confounders.

Authors Contribution

Conceptualization: SH
Methodology: SH, AS
Formal analysis: SH
Writing review and editing: AS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Underlying Causes of Short Stature in Children Aged 4 to 16 Years Presenting at the Endocrine Clinic of a Tertiary Care Hospital in Pakistan

Fizzah Naz[1], Wasif Ahmed Khan[1], Muzna Arif[1], Annayah Usman[1], Muhammad Farrukh Qazi[1], Imran Nisar[1], and Khadija Nuzhat Humayun[1*]

[1]Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan

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***Corresponding Author:**
Khadija Nuzhat Humayun
Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan
khadija.humayun@aku.edu

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ABSTRACT

Short stature is a frequent pediatric presentation that may arise from normal growth variants or underlying pathological conditions. In Pakistan, its burden is heightened by malnutrition, infections, and delayed healthcare-seeking behaviors. Identifying the underlying causes is crucial for timely intervention and better outcomes. **Objectives:** To determine the underlying causes of short stature in children aged 4–16 years presenting at the Endocrine Clinic of a Tertiary Care Hospital in Pakistan. **Methods:** This descriptive cross-sectional study was conducted at the Pediatric Endocrinology Clinic, Aga Khan University Hospital, Karachi, from March 2023 to March 2024. All children aged 4–16 years with short stature, defined as height <-2 SD for age and sex or below the 3rd centile, were enrolled. Participants were evaluated for normal variants (familial short stature and constitutional delay of growth and puberty) and pathological causes (endocrine and non-endocrine). **Results:** Among 384 children, 128 (33.3%) had normal variants, most commonly familial short stature (70.3%). Pathological short stature was found in 256 (66.7%) children, with endocrine disorders predominating (60.9%), mainly growth hormone deficiency, hypothyroidism, panhypopituitarism, and hypogonadism. Non-endocrine causes included rickets, celiac disease, and genetic syndromes. No significant gender differences were observed in the distribution of short stature types. **Conclusions:** Pathological conditions were the leading cause of short stature, accounting for two-thirds of cases, with endocrine disorders being the most frequent contributors. These findings underscore the importance of timely endocrine evaluation in children presenting with growth concerns.

INTRODUCTION

Short stature, a prevalent issue in the paediatric population of developing countries, is defined as a height more than 2 standard deviations (SD) below the mean for age and sex, or below the 3rd percentile on standardized growth charts, in accordance with international pediatric endocrinology guidelines [1-3]. According to the United Nations Children's Fund (UNICEF) report, globally, 23.2% of children under five were stunted in 2024, amounting to 150.2 million affected children [4]. Short stature can result from various underlying etiologies, including genetic, endocrine, nutritional, and systemic disorders. Understanding the causes of short stature is crucial for appropriate diagnosis, management, and timely intervention [5-7]. In Pakistan, where malnutrition and infectious diseases are common, short stature is prevalent and represents a manifestation of several underlying diseases rather than a condition itself [7, 8]. Various studies have shown variations in the magnitude of different causes. Studies have identified several common factors in Pakistan contributing to short stature in children [2, 9]. These include familial short

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stature (FSS), hypothyroidism, growth hormone deficiency (GHD), insulin-dependent diabetes mellitus (IDDM), and constitutional delayed growth and maturation (CDGM). Despite the availability of studies at the national and international levels, there is a need to continuously monitor the specific etiological factors contributing to short stature in Pakistani children. We hypothesize that nutritional and endocrine causes, particularly hypothyroidism and growth hormone deficiency, along with familial short stature, account for the majority of cases.

This study aims to analyze the etiological spectrum of short stature in children aged 4 to 16 years presenting at a Tertiary Care Endocrine clinic in Pakistan.

METHODS

This cross-sectional study was conducted at the Endocrinology Clinic of Aga Khan University Hospital, Karachi, Pakistan, from March 2023 to March 2024. Ethical approval was granted by the Institutional Review Board of the Aga Khan University Hospital (Ref. No. 2023-8357-24166). Consecutive sampling was used to recruit all eligible children with short stature during the study period. As the study involved a retrospective review of medical records without direct patient contact, informed consent was not required. Patient confidentiality and anonymity were strictly maintained. The sample size was estimated for a descriptive cross-sectional study using the single-population proportion formula, assuming a prevalence of 50% (to maximize variance), 95% confidence level, and 5% margin of error. This yielded a minimum required sample size of 384 children. Our study included 384 cases, thereby fulfilling this requirement. The formula applied was: $n = (Z^2 \times p(1-p)) / d^2$, where n = required sample size, Z = standard normal deviate at 95% confidence level (1.96), p = expected prevalence (0.50), and d = margin of error (0.05) [10]. The inclusion criteria were children aged 4 to 16 years presenting with short stature. While children with missing information regarding short stature were excluded, all eligible cases meeting the inclusion criteria during the study period were included. Short stature was defined as a height more than 2 standard deviations (SD) below the mean for age and sex, or below the 3rd percentile on standardized growth charts, in accordance with international pediatric endocrinology guidelines [1-3]. A pre-structured proforma was used to collect all the data. Data were extracted from patient records, which included baseline characteristics, clinical histories, physical examination findings, growth measurements, and results of diagnostic tests. Information regarding variant (normal/abnormal), sub-categories of normal variant such as familial short stature and constitutional delay of growth and puberty (CDGP), pathological short stature, endocrine and non-endocrine causes, and idiopathic short stature were observed. Pubertal development was assessed using the Tanner staging system, based on clinical examination of breast development in girls and genital development in boys, supplemented by pubic hair assessment. Examinations were performed by trained pediatric endocrinologists to ensure reliability. For analytical purposes, participants were stratified into three groups: Group 1: Tanner Stage 1 (prepubertal); Group 2: Tanner Stage 2 (early pubertal); Group 3: Tanner Stages 3–5 (mid to late pubertal). This classification allowed comparison of etiologies of short stature across different phases of pubertal maturation [11]. Recorded heights measured by healthcare professionals using a stadiometer and plotted on WHO growth charts were noted. Parental heights mentioned in the medical records were used to calculate mid-parental height. Normal variant short stature included familial short stature (parental height <3rd percentile, with consistent mid-parental height prediction) and constitutional delay of growth and puberty (delayed bone age with expected pubertal catch-up). Pathological short stature included endocrine causes (e.g., GHD, hypothyroidism) and non-endocrine causes (e.g., celiac disease, renal insufficiency, systemic disorders). Statistical analysis was performed using RStudio (version 4.4.0). Quantitative variables were summarized as mean ± SD, while categorical variables were presented as frequencies and percentages. Associations between categorical variables were assessed using Chi-square or Fisher's exact tests, as appropriate. Test statistics (χ^2 values, degrees of freedom, and corresponding p-values) are reported in the tables. A p-value of ≤0.05 was considered statistically significant.

RESULTS

The study included 384 children with a mean age of 10.0 ± 3.5 years, with almost equal distribution between children aged 4–10 years (50.3%) and those older than 10 years (49.7%). Gender distribution was also balanced (51.8% females vs. 48.2% males). The majority were term births (95.3%) and had appropriate birth weight (88.0%). A positive family history of short stature was reported in 40.6% of cases, most commonly maternal (31.5%) and less frequently paternal (18.0%). Most participants were prepubertal or in early puberty, with only 20.8% reaching mid to late pubertal stages (Table 1)

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Table 1: General Characteristics of the Population

Characteristics	Overall N=384	Group 1 N=158	Group 2 N=146	Group 3 N=80
	N (%)			
Age, Years				
4-10 Years	193 (50.3%)	128 (81%)	62 (42.5%)	3 (3.8)
>10 Years	191 (49.7%)	30 (19%)	84 (57.5%)	77 (96.3)
Gender				
Male	185 (48.2%)	74 (46.8%)	79 (54.1%)	32 (40%)
Female	199 (51.8%)	84 (53.2%)	67 (45.9%)	48 (60%)
Gestational age at Birth				
Preterm	18 (4.7%)	9 (5.7%)	8 (5.5%)	1 (1.3%)
Term	366 (95.3%)	149 (94.3%)	138 (94.5%)	79 (98.8%)
Low Birth Weight (<2.5kg)	46 (12%)	23 (14.6%)	17 (11.6%)	6 (7.5%)
Family history of short stature	156 (40.6%)	62 (39.2%)	59 (40.4%)	35 (43.8%)
Mother's history of short stature	121 (31.5%)	48 (30.4%)	47 (32.2%)	26 (32.5%)
Father's history of short stature	69 (18%)	26 (16.5%)	25 (17.1%)	18 (22.5%)
Maternal family's history of short stature	36 (9.4%)	18 (11.4%)	13 (8.9%)	5 (6.3%)
Paternal family's history of short stature	29 (7.6%)	13 (8.2%)	9 (6.2%)	7 (8.8%)
Sibling's history of short stature	30 (7.8%)	14 (8.9%)	10 (6.8%)	6 (7.5%)
Maternal history of delayed puberty	23 (6%)	6 (3.8%)	10 (6.8%)	7 (8.8%)
Paternal history of delayed puberty	26 (6.8%)	11 (7%)	10 (6.8%)	5 (6.3%)

Group 1 = children at Tanner Stage 1 (prepubertal); Group 2 = children at Tanner Stage 2 (early pubertal); Group 3 = children at Tanner Stages 3–5 (mid to late pubertal).

Among the participants, 128 (33.3%) exhibited normal variant short stature, which includes non-pathological growth delays such as familial short stature affecting 90 (70.3%) and CDGP 38 (29.7%). In contrast, a significant proportion, 256 (66.7%), were diagnosed with pathological short stature. Of the 256 children with pathological short stature, endocrine causes were the most frequent, observed in 156 cases (60.9%), while non-endocrine causes accounted for 90 cases (35.2%), with a small subset showing combined etiologies (3.9%). These findings highlight that endocrine disorders represent the leading contributors to pathological short stature in this population (Table 2).

Table 2: Categories of Causes of Short Stature among the Study Population, Stratified by Gender

Characteristics	Overall N=384	Male N=185	Female N=199	p-Value
	N (%)			
Normal variant, N=128	128 (33.3%)	61 (33%)	67 (33.7%)	0.885
Familial Short Stature (FSS)	90 (70.3%)	40 (65.6%)	50 (74.6%)	0.263
Constitutional delay in growth and puberty (CDGP)	38 (29.7%)	21 (34.4%)	17 (25.4%)	0.354
Pathological ShortStature, N=256	256 (66.7%)	123 (66.5%)	133 (66.8%)	0.942
Endocrine	156 (60.9%)	78 (63.4%)	78 (58.6%)	0.435
Non-endocrine	90 (35.2%)	38 (30.9%)	52 (39.1%)	0.17
Both Endocrine and Non-endocrine	10 (3.9%)	7 (5.7%)	3 (2.3%)	0.185
Groups				
Group 1	158 (41.1%)	74 (40%)	84 (42.2%)	0.116
Group 2	146 (38%)	79 (42.7%)	67 (33.7%)	
Group 3	80 (20.8%)	32 (17.3%)	48 (24.1%)	

Chi-square or Fisher's exact test applied as appropriate: normal variants (χ^2=0.021, df=1, p=0.885); familial short stature vs. CDGP (χ^2=1.254, df=1, p=0.260); pathological subcategories (χ^2=0.005, df=1, p=0.942).

Within endocrine causes, growth hormone deficiency was the most frequent diagnosis, followed by panhypopituitarism and hypothyroidism. Non-endocrine causes included rickets, chronic systemic diseases, and syndromic conditions, while a small subset had combined etiologies. Gender differences across these subcategories were not statistically significant (Table 3).

Table 3: Subcategories of Causes of Short Stature Among the Study Population, Stratified by Gender

Characteristics	Overall N=384	Male N=185	Female N=199	p-Value
	N (%)			
Normal variant, N=128	128 (33.3%)	61 (33%)	67 (33.7%)	0.885
Familial Short Stature (FSS)	90 (70.3%)	40 (65.6%)	50 (74.6%)	0.263
Constitutional delay in growth and puberty (CDGP)	38 (29.7%)	21 (34.4%)	17 (25.4%)	0.354
Pathological Short Stature, N=256	256 (66.7%)	123 (66.5%)	133 (66.8%)	0.942
Endocrine, N=156	156 (60.9%)	78 (63.4%)	78 (58.6%)	0.435
Growth Hormone Deficiency/Resistance	118 (75.6%)	61 (78.2)	57 (73.1%)	0.748
Hypothyroidism	2 (1.3%)	0 (0.0%)	2 (2.6%)	0.217
Panhypopituitarism (GHD and Hypothyroidism)	20 (12.8%)	9 (11.5%)	11 (14.1%)	0.807
Diabetes Mellitus	2 (1.3%)	2 (2.6%)	0 (0.0%)	0.155
Hypogonadism	6 (3.8%)	3 (3.8%)	3 (3.8%)	0.604

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Growth Hormone Deficiency & Hypogonadism	1(0.6%)	1(1.3%)	0(0.0%)	0.316
Post Chemotherapy/ Radiotherapy in childhood malignancy	1(0.6%)	1(1.3%)	0(0.0%)	0.316
Others	6(3.8%)	1(1.3%)	5(6.4%)	0.086
Non-endocrine, N=90	90(35.2%)	38(30.9%)	52(39.1)	0.17
Dysmorphic Syndrome, N=11	11(12%)	4(11%)	7(13%)	0.675
Down Syndrome	1(9%)	1(25%)	0(0%)	0.165
Turner Syndrome	5(45%)	0(0%)	5(71%)	0.022
Others	5(45%)	3(75%)	2(29%)	0.137
Rickets	35(39%)	17(45%)	18(35%)	0.331
Skeletal Dysplasia	2(2%)	1(3%)	1(2%)	0.822
Chronic Systemic Disease, N=36	36(40%)	13(34%)	23(44%)	0.078
Celiac Disease	14(39%)	3(23%)	11(48%)	0.403
Malnutrition/Malabsorption	12(33%)	6(46%)	6(26%)	0.107
Chronic Liver Disease	2(5%)	1(8%)	1(4%)	0.486
Malignancies	2(5%)	1(8%)	1(4%)	0.486
Chronic Anemia	2(5%)	1(8%)	1(4%)	0.486
Chronic Infections	2(5%)	1(8%)	1(4%)	0.486
Others	10(28%)	3(23%)	7(30%)	0.901
IUGR	6(7%)	3(8%)	3(6%)	0.69
Both Endocrine and Non-endocrine, N=10	10(3.9%)	7(5.7%)	3(2.3%)	0.185
Growth Hormone Deficiency & Rickets	5(50%)	4(57%)	1(33%)	0.569
Growth Hormone Deficiency & Chronic Systemic Disease	2(20%)	2(29%)	0(0%)	0.467
Growth Hormone Deficiency, Rickets & Chronic Systemic Disease	1(10%)	0(0%)	1(33%)	0.373
Post Chemotherapy/ Radiotherapy & Chronic Systemic Disease	1(10%)	1(14%)	0(0%)	0.467
Growth Hormone Deficiency & Intra-uterine growth retardation	1(10%)	0(0%)	1(33%)	0.373
Groups				
Group 1	158(41.1)	74(40)	84(42.2)	0.116
Group 2	146(38)	79(42.7)	67(33.7)	
Group 3	80(20.8)	32(17.3)	48(24.1)	

Chi-square or Fisher's exact test applied as appropriate: endocrine vs. non-endocrine causes (χ^2=0.61, df=1, p=0.435); chronic systemic disease subtypes (χ^2=3.105, df=1, p=0.078); dysmorphic syndromes (χ^2=0.176, df=1, p = 0.675)."

DISCUSSION

Pathological causes accounted for two-thirds of cases, underscoring the predominance of endocrine and systemic disorders in this tertiary care cohort. This contrasts with community-based studies from Pakistan, where normal variants are more frequent, but is consistent with findings from referral centers in Pakistan and Egypt. These differences likely reflect referral bias, availability of diagnostic facilities, and healthcare-seeking behaviors. Normal variants comprised one-third of cases (33.3%), comparable to previous Pakistani reports, where normal growth variations were seen in 38.35% of cases, and familial short stature was observed in 11.0% [12, 13]. However, our prevalence of familial short stature was lower than in previous studies, which may reflect differences in referral populations or diagnostic thresholds. Endocrine causes, particularly growth hormone deficiency and hypothyroidism, were more frequent in our cohort and other tertiary-based studies [14, 15]. This difference likely reflects referral bias, since our study was conducted in a tertiary endocrine clinic where suspected hormonal cases are preferentially directed. Improved diagnostic availability and physician awareness may also contribute, a pattern consistent with other hospital-based reports. Interestingly, a retrospective study found that 69% of short stature cases were attributed to growth hormone deficiency, which is substantially higher than what was observed in our population and underscores the variability in growth hormone deficiency prevalence across different clinical settings [13, 14]. Celiac disease contributed to 3.6% of cases, consistent with other regional estimates (3–6%), underscoring its role as an underdiagnosed yet important etiology of growth failure. The mean age at presentation (10 years) suggests delayed recognition of growth concerns compared with an Indian cohort, where the mean age was 12 years [15, 16]. This highlights the importance of improving parental and physician awareness to facilitate earlier referral and intervention. Recent advances emphasize the role of genetic evaluation, including chromosomal microarray and next-generation sequencing, which provide diagnostic yields of up to 30–40% in children with idiopathic or syndromic short stature [17-20]. Studies have identified novel variants in growth plate and GH–IGF axis genes, improving etiological precision and guiding personalized management [21, 22]. Although genetic testing was not undertaken in our cohort, future incorporation of such tools could substantially enhance diagnostic accuracy. The current study has both strengths and limitations. Strengths include the robust sample size (n=384) and detailed categorization of short stature, which enhance the validity of the findings. The inclusion of gender-based analysis also provides insights into differences between male and female children, relevant for personalized medical approaches. Limitations include its single-center, retrospective design, absence of a control group of children with normal stature, and limited biochemical or genetic evaluation, which restricts generalizability and causal inference. Since only children with short stature were included, the findings mainly describe etiological distribution within this subgroup and do not fully capture determinants of growth in the general

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pediatric population. Future research should incorporate appropriate control groups, multicenter prospective cohorts, and long-term follow-up. Advanced diagnostic tools, such as genetic profiling and detailed hormonal assays, could further refine etiological identification and improve management strategies. By addressing these areas, future research can significantly strengthen our understanding of short stature in children and improve management strategies.

CONCLUSIONS

Approximately one-third of cases of short stature in this cohort were attributable to normal growth variations, including familial short stature and constitutional delay of growth and puberty (CDGP), while two-thirds were pathological. Among the pathological causes, endocrine disorders particularly growth hormone deficiency and hypothyroidism were the most frequent contributors. These findings confirm that the etiological spectrum of short stature in Pakistani children is dominated by endocrine conditions. They underscore the importance of timely recognition, and comprehensive medical assessment of children with growth disturbances, with particular attention to endocrine evaluation, to facilitate early diagnosis, targeted management, and improved growth outcomes.

Authors Contribution

Conceptualization: FN, IN, KNH
Methodology: MA, IN, KNH
Formal analysis: AU, MFQ
Writing review and editing: FN, MA, IN, KNH

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

Conflicts of Interest

All the authors declare no conflict of interest.

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The Efficacy of Self Help Cognitive Behavior Therapy in Managing Psychological Distress in Pregnant Women

Saba Naz[1*] and Uzma Ali[1]

[1]Institute of Clinical Psychology, University of Karachi, Karachi, Pakistan

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***Corresponding Author:**
Saba Naz
Institute of Clinical Psychology, University of Karachi, Karachi, Pakistan
sabanaz2515@gmail.com

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ABSTRACT

During pregnancy, stress, anxiety, and depressive symptoms are common and may negatively affect both the woman's and the fetus's health. Self-help CBT has emerged as an effective and accessible intervention to alleviate these symptoms in pregnant women. **Objectives:** To evaluate the efficacy of self-help CBT in managing psychological distress (depression, anxiety, and stress) in pregnant women. **Methods:** An experimental study was conducted from July 2023 to November 2024 in Karachi, Pakistan. 40 pregnant women, aged 20 to 35 (28.03 ± 4.83), were recruited purposively from various maternity clinics and hospitals in Karachi. Demographic Form, followed by DASS-42, was administered. Two groups, the Intervention and the Control Group, had formed non-randomly. A brief explanation was provided regarding the use of the culturally adapted CBT-based self-help manual for the Intervention Group. Following that, participants practiced them alone for eight weeks. Meanwhile, no intervention was provided to the Control Group for a similar time period. Afterwards, the DASS was given to both groups to re-evaluate the difference. Statistical analysis was done using SPSS version 22.0. **Results:** Statistically significant improvement in stress and anxiety symptoms (p=0.003; p=0.035, respectively) was found in the Intervention Group. Within-group analyses revealed large reductions in stress and anxiety among the Intervention Group (p<0.001), while no significant differences were found in the Control Group (p=0.162). **Conclusions:** Self-help CBT appears to be an effective approach for promoting mental health during pregnancy without necessitating professional consultation.

INTRODUCTION

Pregnancy is a transformative period, marked by profound biopsychosocial changes from conception to birth. These changes can influence a woman's well-being, making it enjoyable or challenging, depending on various factors, including early marriage, first-time pregnancy, hormonal fluctuations, pregnancy symptoms (e.g., nausea, vomiting, fatigue, back pain), and prolonged worries. Prenatal stress significantly impacts the neurodevelopment of offspring [1]. Elevated cortisol levels, a hormone responsive to stress during pregnancy, may result in preterm delivery, lower birth weight, and developmental delays associated with intellectual and behavioral issues [2]. Physical health issues, past trauma, and internalizing problems (e.g., depression and anxiety) are leading risk factors for prenatal and postnatal stress [3]. Depression and anxiety are among the leading causes of disability, contributing to the global burden of disease [4]. Women are more vulnerable to experiencing depression during pregnancy [5]. In Pakistan, 37.1% of multigravida and 32.9% of primigravida reported mild depression during transition to motherhood [6]. Despite the high prevalence of perinatal mental health concerns, they remain unrecognized. Social stigma, poor mental health literacy, limited service availability, financial barriers, and cultural beliefs that emotional distress is a normal part of pregnancy all contribute to this neglect. As a result, many expectant mothers do not receive adequate

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psychological assistance, which raises concerns for the health of the mother and the unborn child. These challenges highlight the need for accessible, stigma-free, and culturally sensitive psychological support. Self-help CBT is an evidence-based intervention, effective in reducing depression, anxiety, and stress, particularly for those who are unable to seek professional help. In Pakistan, culturally adapted CBT has been effective in reducing secondary traumatic stress [7] and maternal depression among immigrant Pakistani women [8].

Despite the growing global recognition, prenatal self-help CBT remains underutilized in Pakistan. This study aimed to evaluate the efficacy of self-help CBT in managing stress, anxiety, and depression during pregnancy in Pakistan by giving the critical need for low-cost, culturally appropriate, and scalable therapies.

METHODS

The quasi-experimental study was carried out from July 2023 to November 2024 at various maternity clinics and hospitals in Karachi City. Initially, the approval was taken from the Advanced Studies and Research Board, University of Karachi. Ethical approval was secured from the Ethical Review Board of the Institute of Clinical Psychology (Ref. No: ICP-1(101)/7356). Written informed consent was taken from all participants before their inclusion in the study. This study was retrospectively registered at https://doi.org/10.17605/OSF.IO/AG2YJ, included forty pregnant women in their first trimester, aged 20-35 years (28.03 ± 4.83). They were proficient in the Urdu language, had at least matriculation, belonged to one of four socio-economic classes (lower-middle, middle, upper-middle, and upper), and resided with their husband in a nuclear or joint family system. Participants reported no history of serious physical or psychological illness. The baseline assessment through a demographic form and the Depression, Anxiety, and Stress Scale, DASS-42 [9], a self-report instrument translated into Urdu, was employed. This scale comprises 42 items, was designed to assess three negative emotional states (anxiety, depression, and stress), and occurred within the past year. The adaptation involved a forward–backward translation procedure and expert panel review to ensure cultural equivalence was translated and validated for the Pakistani population. DASS (Urdu version), used in local studies, has demonstrated an excellent reliability (e.g., Anxiety Scale: α=0.91, Depression Scale: α=0.94, Stress α=0.93, and Total DASS: α=0.97). In the current study, internal consistency is also good (Stress α=0.76, Anxiety = 0.78, Depression α=0.89, and total DASS α=0.87). Participants exhibiting mild to moderate stress, anxiety, and depression were allocated non-randomly through alternate assignment into two groups: The Control and Intervention Group (i.e., the first participant to the Intervention Group, the second to the Control Group, and so on). The Intervention Group was presented with the culturally-adapted CBT-based self-help manual "Khushi aur Khatoon" [10], intended to address mild to moderate levels of stress, concomitant depression, and anxiety. The intervention consisted of an eight-week training program in which participants used a single manual independently. Meanwhile, the Control Group did not receive any psychological intervention. After eight weeks, participants from the Intervention and Control Groups were re-approached for post-intervention assessment by DASS to evaluate the discrepancy. According to ethical guidelines, the Control Group, displaying 'mild to moderate' levels of depression, anxiety, and stress based on post-assessment results, was provided with self-help CBT. Data analysis was done by applying descriptive statistics to appraise participants' demographic and independent and paired t-tests compared pre- and post-intervention effectiveness, using SPSS version 22.0.

RESULTS

Statistical Package for Social Sciences (SPSS version 22.0) was used to analyze the descriptive statistics of 40 participants, with a mean age of 28.03 years. T-tests for independent and paired samples were performed to evaluate treatment effectiveness between and within groups. The age of participants ranged from 21 to 35, with a mean age of 28.03 and a standard deviation of 4.83 (Table 1).

Table 1: Mean and Standard Deviation of Age of Participants (n=40)

Group	n	Min	Max	Mean ± SD
Age	40	21	35	28.03 ± 4.83

M: Mean; SD: Standard Deviation

Socio-demographic characteristics of the Intervention and Control Groups are presented (Table 2).

Table 2: Socio-Demographic Characteristics of Intervention and Control Group n=40

Variables	Category	Frequency (%)		
		Total (n=40)	Intervention Group (n=20)	Control Group (n= 20)
Education	Matriculation	12 (30%)	07 (35%)	05 (25%)
	Intermediate	07 (17.5%)	06 (30%)	01 (05%)
	Graduation	10 (25%)	04 (20%)	06 (30%)
	Masters	11 (27.5%)	03 (15%)	08 (40%)
Profession	Working	08 (20%)	02 (10%)	06 (30%)
	House wife	32 (80%)	18 (90%)	14 (70%)
Socioeconomic Status	Lower-middle	10 (25%)	06 (30%)	04 (20%)
	Middle	21 (52.5%)	12 (60%)	09 (45%)
	Upper-middle	06 (7.5%)	02 (10%)	04 (20%)
	Upper	03 (15%)	–	03 (15%)
Family System	Nuclear	10 (25%)	03 (15%)	07 (35%)
	Joint	30 (75%)	17 (85%)	13 (65%)

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Number of Pregnancies	One	20 (50%)	14 (70%)	06 (30%)
	Two	06 (15%)	02 (10%)	04 (20%)
	Three	06 (15%)	01 (05%)	05 (25%)
	Four	06 (15%)	03 (15%)	03 (15%)
	Five	01 (2.5%)	–	01 (05%)
	Nine	01 (2.5%)	–	01 (05%)
Miscarriages	Yes	09 (22.5%)	02 (10%)	07 (35%)
	No	31 (77.5%)	18 (90%)	13 (65%)

The reliability analysis of the DASS-42 Urdu version demonstrated high internal consistency across all subscales. The Cronbach's alpha values of the present study indicate 0.89 for Depression, 0.78 for Anxiety, and 0.76 for Stress, with the overall scale showing a strong reliability coefficient of 0.87 (Table 3).

Table 3: Internal Consistency of the DASS-42 Scales

Scale	No. of Items	Cronbach's Alpha
Depression	14	0.89
Anxiety	14	0.78
Stress	14	0.76
Total DASS	42	0.87

Results showed a statistically significant difference in post-test stress scores: Intervention Group (10.40 ± 6.28) versus Control Group (17.35 ± 7.56), t (38) = -3.15, p=0.003, with a large effect size (Cohen's d = 1.00). Results indicated a statistically significant difference in anxiety between the groups, t (38) = -2.18, p = 0.035. Participants in the Intervention Group (3.90 ± 3.17) showed little anxiety compared to the Control Group (6.35 ± 3.88), with a large effect size (d=0.69). Results indicated no significant difference in depression between the Intervention and Control Group, t (38) = -1.42, p=0.162, d = 0.45. However, the Intervention Group (3.75 ± 4.45) exhibited a low level of depression compared to the Control Group (5.75 ± 4.44), indicating a trivial difference between the groups (Table 4).

Table 4: Between-Group Comparison for Stress Scores, Anxiety Scores, and Depression Scores (Independent Samples T-Test, n=40)

Group	n	Mean ± SD	T	df	Sig.	d
Stress Scores						
Intervention Group	20	10.40 ± 6.28	-3.15	38	0.003	1.00
Control Group	20	17.35 ± 7.56				
Anxiety Scores						
Intervention Group	20	3.90 ± 3.17	-2.18	38	0.035	0.69
Control Group	20	6.35 ± 3.88				
Depression Scores						
Intervention Group	20	3.75 ± 4.45	-1.42	38	0.162	0.45
Control Group	20	5.75 ± 4.44				

p<0.05; result is statistically significant

Results highlighted a substantial decrease in stress of the Intervention Group from pre-test (20.10± 6.98) to post-test (10.40 ± 6.28), t (19) = 6.87, p<0.001, Cohen's d = 1.54. Conversely, the Control Group showed an insignificant difference in stress across pre-test (15.70 ± 4.99) and post-test (17.35± 7.56), t (19) = -1.25, p=0.225, d = 0.28. Findings showed an improvement in anxiety in the Intervention Group from pre-test (8.70 ± 4.98) to post-test (3.90 ± 3.17), t (19) = 4.73, p<0.001, Cohen's d =1.54. While the Control Group showed no significant difference in anxiety between pre-test (6.90 ± 5.58) and post-test (6.35 ± 3.88), t (19) = 0.54, p=0.59, d = 0.12. Results showed a substantial decline in depression of the Intervention Group from pre-test (9.60 ± 8.36) to post-test (3.75 ± 4.45), t (19) = 5.38, p=0.001, d=1.20, and Control Group pre-test (9.00 ± 8.10) and post-test (5.75 ± 4.41), t (19) = 2.59, p=0.018, d=0.58 (Table 5).

Table 5: Within-Group Comparison for Stress Scores, Anxiety Scores, and Depression Scores (Paired Sample T-Test, n=40)

Group	Condition	Mean ± SD	T	df	Sig.	d
Stress Scores						
Intervention Group	Pre-Test	20.10 ± 6.98	6.87	19	<0.001	1.54
	Post-Test	10.40 ± 6.28				
Control Group	Pre-Test	15.70 ± 4.99	-1.25	19	0.225	0.28
	Post-Test	17.35 ± 7.56				
Anxiety Scores						
Intervention Group	Pre-Test	8.70 ± 4.98	4.73	19	<0.001	1.54
	Post-Test	3.90 ± 3.17				
Control Group	Pre-Test	6.90 ± 5.58	0.54	19	0.59	0.12
	Post-Test	6.35 ± 3.88				
Depression Scores						
Intervention Group	Pre-Test	9.60 ± 8.36	5.38	19	0.001	1.20
	Post-Test	3.75 ± 4.45				
Control Group	Pre-Test	9.00 ± 8.10	2.59	19	0.018	0.58
	Post-Test	5.75 ± 4.41				

DISCUSSIONS

The current study focused on evaluating the efficacy of self-help CBT for managing psychological distress (stress, anxiety, and depression) in pregnant women. Specifically, it tested three hypotheses related to the reduction of (1) depression, (2) anxiety, and (3) stress. In Pakistan, culturally adapted self-help CBT is an effective treatment in improving self-esteem, social anxiety [11], social functioning in secondary school adolescents, as well as reducing depression, anxiety [12], and PTSD symptoms among female victims of domestic violence [13]. However, limited studies have been done in pregnant women in Pakistan, and still, people are unaware of the emotional and mental well-being of pregnant women. Thus, this study applied the self-help CBT to pregnant women experiencing psychological distress, aiming to prevent serious psychopathology in both the women and their offspring later in life. The first hypothesis proposed that self-help CBT would significantly reduce stress in pregnant women. The comparison of post-intervention stress scores

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between groups was statistically significant ($p<0.05$). Findings revealed a greater reduction in stress scores in the Intervention Group ($p<0.001$), signifying the impact of self-help CBT in reducing stress. These results are consistent with recent studies showing the efficacy of CBT in perinatal populations. In Pakistan, pregnant women who experienced stress related to their unborn child's health and development, family conflicts, and financial limitations reported reduced stress levels and improved interpersonal relationships following a CBT-based intervention [14]. The second hypothesis stated a significant reduction in anxiety in pregnant women who used self-help CBT compared to the Control Group. Post-test anxiety scores between the groups indicated a statistically significant difference ($p<0.05$), and within the Intervention Group, showed a considerable decline in anxiety ($p<0.001$). In contrast, the Control Group revealed no significant change ($p>0.5$), demonstrating the effectiveness of self-help CBT in decreasing anxiety symptoms. These findings align with previous studies conducted in Pakistan, indicating that both guided self-help CBT and CBT delivered by non-specialists significantly lowered anxiety symptoms [15, 16]. The third hypothesis proposed that self-help CBT would significantly reduce depression in pregnant women. In post-test depression scores between groups indicated a statistically insignificant difference ($p>0.05$). Within-group t-test revealed a substantial reduction in depression scores from pre-test to post-test in both the Intervention and Control Groups. Although both groups showed improvement over time, the Intervention Group ($p=0.001$) worked better at reducing depressive symptoms than the Control Group ($p=0.018$). This improvement may be attributed to placebo effects, natural remission, or uncontrolled factors such as increased social connectedness [17, 18], hope, improved physical health, or the mere passage of time. The large effect size in the Intervention Group showed the treatment efficacy and therapeutic potential. These results align with recent research demonstrating that CBT reduces depressive symptoms in pregnant women [19]. Another study proved that self-study and practice of CBT books lowered depressive symptoms more than antidepressant medication alone [20]. Present findings also support an expanding corpus of studies emphasizing the efficacy of CBT for pregnant women with depression, anxiety, and stress [21]. Nonetheless, not all formats yield identical results. Systematic review found that brief, unguided online CBT was less successful in mitigating prenatal depression, with a higher dropout rate, suggesting that the delivery method and degree of support may affect therapy outcomes [22]. This study supports the hypothesis that self-help CBT enhances individuals' ability to restructure maladaptive thoughts and reduce psychological distress. Self-administered programs enable users to progress at their own pace, fostering a sense of autonomy and increasing therapeutic engagement [23]. Moreover, in the contemporary era characterized by time constraints and a preference for home-based services following the COVID-19 pandemic, various forms of therapeutic interventions have emerged as alternatives to traditional services, as proven by recent research. For example, online CBT improved prenatal distress, stress reactivity, and psychological resilience [24]. These findings coincide with the current study's findings and emphasize the rising demands of self-directed, adaptable, and scalable therapies for targeting psychological challenges in real-world settings, especially in Pakistan, where professional services remain underused, stigma around mental health persists, and emotional and behavioral challenges in pregnant women are often overlooked. Thus, facilitating access to self-help CBT in this culture would be a better and more easily accessible option for those who are unable or unwilling to seek professional aid [10].

CONCLUSIONS

This study highlighted the efficacy of self-help CBT in alleviating stress and anxiety; however, it didn't yield a significant difference in depressive symptoms. These results underscore the need for further interventions that explicitly address prenatal depression while also serving as a foundation for creating accessible interventions that can be incorporated into prenatal care in Pakistan. These findings should be interpreted cautiously due to certain limitations, including reliance on self-reported data, small sample size, non-randomized group assignment and absence of blinding.

Authors Contribution

Conceptualization: SN, UA
Methodology: SN, UA
Formal analysis: SN
Writing review and editing: UA

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

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Frequency of Hypothyroidism and Subclinical Hypothyroidism in Females with Secondary Infertility Presenting at a Tertiary Care Hospital

Hafiz Mouhammad Mouzam Ali[1], Aneela Nadeem[2], Faryal Sadaqat[3,4], Amna Batool[5], Sadia Chaudhary[6,7], Mahpara Shaukat[8] and Hafiz Muhammad Zeeshan Raza[9*]

[1]Department of Obstetrics and Gynaecology, Lahore General Hospital, Lahore, Pakistan
[2]Department of Obstetrics and Gynaecology, Hayat Memorial Hospital, Lahore, Pakistan
[3]Department of Obstetrics and Gynaecology, Combined Military Hospital, Hyderabad, Pakistan
[4]Department of Obstetrics and Gynaecology, Combined Military Hospital, Rawalpindi, Pakistan
[5]Department of Obstetrics and Gynaecology, Kalsoom Social Security Hospital, Okara, Pakistan
[6]Department of Obstetrics and Gynaecology, Iqra Medical Complex, Lahore, Pakistan
[7]Department of Obstetrics and Gynaecology, Rahbar Medical and Dental College, Lahore, Pakistan
[8]Department of Obstetrics and Gynaecology, Sahiwal Medical College, Sahiwal, Pakistan
[9]Department of Biosciences, Comsats University Islamabad, Sahiwal, Pakistan

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***Corresponding Author:**
Hafiz Muhammad Zeeshan Raza
Department of Biosciences, Comsats University of Islamabad, Sahiwal, Pakistan
hafizraza26@gmail.com

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ABSTRACT

Hypothyroidism, particularly subclinical hypothyroidism (SCH), is a frequent endocrine disorder linked to reproductive dysfunction, including secondary infertility. In Pakistan, where infertility rates are rising, understanding the prevalence and impact of thyroid dysfunction among women with secondary infertility is critical for improving fertility management. **Objectives:** To investigate the correlation between secondary infertility and subclinical hypothyroidism among Pakistani women. **Methods:** A cross-sectional descriptive study was conducted on 130 women aged 20–40 years presenting with secondary infertility at a tertiary care hospital in Pakistan. Participants underwent clinical assessment, including measurement of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels. SCH was defined as TSH between 4.5 and 20 mIU/L with normal FT3 and FT4. Data on demographic variables, parity, and duration of infertility were collected. Statistical analysis involved chi-square tests to examine associations between hypothyroidism and demographic/clinical factors. **Results:** Hypothyroidism was identified in 28.5% of participants, comprising 20.8% with subclinical and 7.7% with overt hypothyroidism. The highest prevalence of subclinical hypothyroidism was observed among women aged 31–40 years (28.6%) and those with BMI ≥25 kg/m^2 (21.1%). However, it revealed no statistically significant associations between hypothyroidism and age (p=0.256), BMI (p=0.827), parity (p=1.000), or duration of infertility (p=1.000). **Conclusions:** Thyroid dysfunction, particularly subclinical hypothyroidism, is highly prevalent in women with secondary infertility, despite the absence of significant associations with common demographic or reproductive variables. These findings support routine thyroid screening as an essential component of infertility assessment.

INTRODUCTION

Family and children are seen in Pakistan as the pillars of society; procreation has great social and cultural value linked to them [1]. Economic development and social stability depend critically on the idea of children. According to recent studies, couples in Pakistan seem to be increasingly infertile; the prevalence rates range from 12% to 18% and show a continuous increase over the years [2]. While rates of infertility in the Western world have stayed

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constant, Pakistan has seen rising worries about reproductive health, especially among women suffering secondary infertility, in which case conception does not follow a past successful pregnancy [3]. A common yet subtle endocrinological condition, hypothyroidism, affects reproductive health greatly. In women who manage to conceive, it disrupts things like delayed puberty, menstrual irregularities, anovulatory cycles, infertility, and a higher chance of pregnancy loss [4]. The milder type of the disorder, subclinical hypothyroidism (SCH), is defined by modestly raised thyroid-stimulating hormone (TSH) levels ranging from 4.5 to 20 mIU/L, with normal free triiodothyronine and free thyroxine levels [5]. Affecting ovarian function and the release of sex hormone-binding globulin (SHBG), prolactin, and gonadotropin-releasing hormone (GnRH), recent investigations have shown that SCH is tightly linked with reproductive failure, therefore influencing menstrual cycles [6]. Furthermore, connected to ovulatory dysfunction and maybe causing infertility in women is SCH. With some studies showing its frequency as high as 14% among infertile women, compared to only 2-4% in the general population, subclinical hypothyroidism is thought to be a major cause of fertility issues in Pakistan, where the incidence of infertility is rising [7]. Research on women with high TSH levels has indicated that they often have longer periods of infertility and reduced conception rates than those with normal thyroid function, therefore stressing the need for recognizing and treating thyroid dysfunctions as part of infertility treatment [8]. The study hypothesize that subclinical hypothyroidism is prevalent in women with secondary infertility. The purpose of this study is to investigate the correlation between secondary infertility and subclinical hypothyroidism. The results might have major effects on fertility treatment strategies and enhance the Pakistani population's reproductive health outcomes.

This study aimed to ascertain among women presenting with infertility the requirement of regular screening of thyroid function, especially for SCH.

METHODS

This cross-sectional descriptive design allowed data collection from June to August 2025, providing a snapshot of the prevalence of thyroid dysfunction in this specific population. The study was approved by the review board of the Lahore General Hospital, Lahore, with reference number 2025/ERC/40. All participants had been informed about the reasons for the study, what they could gain from it, and the possible risks and gave consent. The investigators kept the participants' information private throughout the study. Women in the study were aged 20 to 40 and had secondary infertility, successfully reaching the infertility clinic of the tertiary care hospital in Lahore. If a couple experiences infertility after already having a child, that is called secondary infertility, and usually it means there aren't any other clear reasons for infertility [9]. The study excluded women with initial difficulty getting pregnant, those with suspected thyroid disorders at the start and women with reproductive system abnormalities. The sample size of 130 was calculated using the formula $n = Z^2 \times P(1-P) / d^2$, assuming a prevalence (P) of 14% for subclinical hypothyroidism, 95% confidence level ($Z = 1.96$), and 5% margin of error ($d = 0.05$) [7]. To have enough power in the statistical analysis for the study, 130 infertile women were chosen based on the 14% prevalence of subclinical hypothyroidism in this group. Self-developed systematic questionnaire was used, besides clinical evaluations, to obtain the data. During their tests, the participants' medical history and physical examination concentrated on whether they had periods, whether they were pregnant before and if they had any health concerns. Blood samples were collected for thyroid function testing, including TSH, FT3, and FT4, using enzyme-linked immunosorbent assay (ELISA) kits (TSH: Human TSH ELISA Kit, DRG Instruments GmbH, Germany; FT3: Free Triiodothyronine ELISA Kit, Calbiotech Inc., USA; FT4: Free Thyroxine ELISA Kit, Monobind Inc., USA). Subclinical hypothyroidism (SCH) was defined as a TSH level between 4.5 and 20 mIU/L with normal FT3 and FT4 concentrations. Both descriptive and inferential types of statistics were used to look at the data. In the study, researchers used frequencies and percentages to see how many people had subclinical hypothyroidism. To study the impact of hypothyroidism on several socio-demographic parameters, a chi-square test was performed, whereas logistic regression analysis was used to evaluate any hazardous effects of thyroid dysfunction on infertility. SPSS version 25.0 was used to analyze all the data, and the significance level chosen was $p<0.05$.

RESULTS

A total of 130 women with secondary infertility were included in the study. Among women aged 31–40 years, subclinical hypothyroidism was notably higher (28.6%) compared to younger women (13.4%), despite a lower rate of overt hypothyroidism (3.2% vs. 6.0%). Similarly, women with a BMI ≥25 kg/m^2 exhibited a slightly higher prevalence of both overt (8.4%) and subclinical hypothyroidism (21.1%) compared to those with lower BMI, though the difference was not statistically significant ($p=0.827$). The distribution across parity and infertility duration showed similar trends, with subclinical hypothyroidism consistently more prevalent than overt forms in all subgroups (Table 1).

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Table 1: Prevalence of Hypothyroidism by Demographic and Clinical Variables

Variables	Total (n)	Overt Hypothyroidism n (%)	Subclinical Hypothyroidism n (%)	Total Hypothyroidism n (%)	p-Value (Chi-square)
Age					
18–30 Years	67	4 (6.0%)	9 (13.4%)	13 (19.4%)	0.256
31–40 Years	63	2 (3.2%)	18 (28.6%)	20 (31.3%)	
BMI					
<25 kg/m^2	35	2 (5.7%)	7 (20.0%)	9 (25.7%)	0.827
≥25 kg/m^2	95	8 (8.4%)	20 (21.1%)	28 (29.5%)	
Parity					
Primipara	51	4 (7.8%)	10 (19.6%)	14 (27.5%)	1.000
Multipara	79	6 (7.6%)	17 (21.5%)	23 (29.1%)	
Infertility Duration					
1–3 Years	73	5 (6.8%)	16 (21.9%)	21 (28.8%)	1.000
>3 Years	57	5 (8.8%)	11 (19.3%)	16 (28.2%)	

This study presents a comprehensive overview of thyroid hormone levels measured via ELISA and the distribution of thyroid status within the study population of 130 women with secondary infertility. Euthyroid women constituted the majority (71.5%), with all thyroid parameters within normal ranges. Subclinical hypothyroidism (20.8%) was defined by elevated TSH (mean 7.8 mIU/L) alongside normal FT3 and FT4 levels, while overt hypothyroidism (7.7%) showed more pronounced TSH elevation (mean 15.6 mIU/L) and reduced peripheral hormones (FT3 and FT4), consistent with classic biochemical hypothyroidism. These results highlight that nearly 1 in 3 women in this infertile population had some form of thyroid dysfunction, with subclinical hypothyroidism being the most common form, underlining the importance of thyroid screening even in the absence of overt symptoms (Table 2).

Table 2: Thyroid Hormone Levels (ELISA) and Distribution of Thyroid Status in Study Population (n=130)

Thyroid Status	n (%)	TSH (mIU/L)	Ft3 (pg/mL)	Ft4 (ng/dL)
Euthyroid	93 (71.5%)	2.1 ± 0.9	3.3 ± 0.5	1.2 ± 0.2
Subclinical Hypothyroid	27 (20.8%)	7.8 ± 2.3	3.1 ± 0.4	1.1 ± 0.2
Overt Hypothyroid	10 (7.7%)	15.6 ± 3.8	2.2 ± 0.5	0.7 ± 0.3

Findings summarize the results of chi-square analyses assessing the association between hypothyroidism and demographic/clinical variables. No statistically significant associations were found between hypothyroidism and age group ($\chi^2 = 1.291$, p=0.256), BMI ($\chi^2 = 0.047$, p=0.827), parity ($\chi^2 = 0.002$, p=1.000), or duration of infertility ($\chi^2 = 0.001$, p=1.000). These results suggest that in this sample population, thyroid dysfunction—whether overt or subclinical occurs relatively independently of these common reproductive and metabolic indicators. This further underscores the clinical value of routine thyroid screening in all women with secondary infertility, regardless of their age, weight, or infertility history (Table 3).

Table 3: Chi-Square Test Results for Association with Hypothyroidism

Variables	Chi-Square Value (χ^2)	Degrees of Freedom (df)	p-Value
Age Group (18–30 vs 31–40)	1.291	1	0.256
BMI Group (<25 vs ≥25 kg/m^2)	0.047	1	0.827
Parity (Primipara vs Multipara)	0.002	1	1.000
Duration of Infertility (1–3 vs >3 Years)	0.001	1	1.000

Results present the logistic regression model analyzing potential predictors of hypothyroidism. None of the variables, like age, BMI, parity, or duration of infertility, demonstrated statistically significant associations with the outcome. Women aged 31–40 had an odds ratio (OR) of 1.89 (95% CI: 0.85–4.21, p=0.117), suggesting a trend toward increased risk, although not reaching significance. Similarly, elevated BMI (OR=1.21, p=0.640), multiparity (OR=1.08, p=0.851), and longer infertility duration (OR=0.97, p=0.942) did not significantly impact hypothyroidism risk (Table 4).

Table 4: Binary Logistic Regression Analysis of Factors Associated with Hypothyroidism

Predictor	Odds Ratio (OR)	95% Confidence Interval (CI)	p-Value
Age (31–40 vs 18–30)	1.89	0.85 – 4.21	0.117
BMI (≥25 vs <25)	1.21	0.54 – 2.71	0.640
Parity (Multipara vs Primipara)	1.08	0.48 – 2.46	0.851
Duration (>3 vs 1–3 Years)	0.97	0.43 – 2.18	0.942

DISCUSSIONS

This study shows that among women presenting at a tertiary care hospital in Pakistan with secondary infertility [10], 28.5% hypothyroidism, including 20.8% subclinical hypothyroid and 7.7% overt hypothyroid is rather common. This frequency is in line with results of comparable studies conducted throughout the world, where hypothyroidism is recognized as a frequent endocrine condition among infertile women [11]. Routine thyroid monitoring is therefore even more important in the management of infertility, as several studies have shown a prevalence of hypothyroidism in infertile populations between 24% and 28%. Particularly, subclinical hypothyroidism, which affects ovarian function, ovulation, and early pregnancy maintenance, hypothyroidism has been identified as a major contributing cause to low fertility [12]. Despite the great frequency of hypothyroidism noted in our study, no statistically significant correlations were detected between hypothyroidism and age, body mass index (BMI), parity, or length of infertility. This implies that, in this group, hypothyroidism may not be particularly influenced by these factors, even if it is still a major determinant of reproductive dysfunction. Previous research has revealed

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different relationships between hypothyroidism and these variables; some suggest that rising age and BMI could help to explain thyroid malfunction. Our results, however, refuted these links, which would indicate the complexity of thyroid diseases and their multifaceted influence on reproductive health [13]. Women between the ages of 31 and 40 had more hypothyroidism (31.3%) than those between the ages of 18 and 30 (19.4%). Although this variation might seem clinically important, statistical investigation revealed no notable correlation between age and hypothyroidism. This result is consistent with some other research indicating that although advancing age increases risk, thyroid malfunction can develop in women of different age ranges. Our study's lack of statistical significance could be ascribed to other confounding elements not taken into consideration or sample size [14]. Although earlier studies have indicated a possible link between obesity and thyroid malfunction, especially subclinical hypothyroidism, our analysis revealed no appreciable correlation between BMI and hypothyroidism. Though this difference was not statistically significant, women with a BMI greater than 25 kg/m2 had a somewhat higher prevalence of hypothyroidism (29.5%) than those with a BMI of less than 25 kg/m^2 (25.7%). The absence of a robust correlation could suggest that thyroid malfunction in infertile women could be independent of BMI, or that other underlying factors (e.g., genetic predispositions or environmental factors) may play a more major role in thyroid health [15]. Likewise, there was no appreciable association between hypothyroidism and parity (primipara vs. multipara) or infertile length of time. These results align with certain research demonstrating hypothyroidism as a risk factor for infertility independent of past pregnancies or duration of infertility [16]. Longer periods of infertility, however, have been linked in some studies to increased prevalence of thyroid dysfunction since the cumulative impact of hormonal abnormalities may aggravate over time [17]. The absence of correlation in our study could reflect the rather homogeneous character of the population, or it could imply that thyroid dysfunction has a similar influence over different infertility durations [18]. The great frequency of hypothyroidism shown in this study highlights the need to add thyroid screening to the infertility treatment for women with secondary infertility. Early identification of thyroid dysfunction, especially subclinical hypothyroidism, may direct suitable therapy and enhance fertility results [19]. In women with thyroid insufficiency, thyroid hormone replacement therapy has been demonstrated to enhance ovulatory ability and conception rates. Thus, prompt management may help women with hypothyroidism who are experiencing infertility to have either spontaneous conception or assisted reproductive technology more successfully [19, 20].

CONCLUSIONS

This study revealed a high prevalence of thyroid dysfunction among women with secondary infertility, with 28.5% found to have hypothyroidism, including 20.8% with subclinical hypothyroidism and 7.7% with overt hypothyroidism. Subclinical hypothyroidism emerged as the predominant thyroid abnormality, often occurring without overt clinical symptoms, thus posing a hidden barrier to conception. These findings highlight the critical importance of incorporating routine thyroid function testing into infertility evaluations for early detection and appropriate management of thyroid dysfunction.

Authors Contribution

Conceptualization: HMMA
Methodology: AN, AB, SC, MS
Formal analysis: HMZR
Writing review and editing: AN, FS, AB, SC, MS

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

Conflicts of Interest

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Spectrum of Autoimmune Diseases in Children with Celiac Disease: A Single Center Cross-Sectional Study from A Tertiary Childcare Facility of South Punjab, Pakistan

Sundus Irshad[1*], Irum Aslam[1], Abu Talib[1], Ghazi Khosa[1], Aslam Sheikh[1] and Saima Zahid[1]

[1]Department of Pediatrics Gastroenterology, Hepatology and Nutrition, The Children's Hospital and The Institute of Child Health, Multan, Pakistan

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***Corresponding Author:**
Sundus Irshad
Department of Pediatrics Gastroenterology, Hepatology and Nutrition, The Children's Hospital and The Institute of Child Health, Multan, Pakistan
drsundusirshad@gmail.com

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ABSTRACT

Celiac disease (CD), an autoimmune disorder triggered by gluten ingestion, is increasingly recognized for its association with a higher prevalence of other autoimmune conditions in children, underscoring the need for more exploration. **Objectives:** To evaluate the spectrum of autoimmune diseases (AIDs) in children with CD. **Methods:** This cross-sectional study was performed at the Department of Gastroenterology, Hepatology and Nutrition, The Children's Hospital and The Institute of Child Health, Multan, Pakistan, from September 2023 to December 2024. Children aged between 1-12 years and having CD were analyzed. The presence of AIDs was explored utilizing physical and clinical examination, along with relevant laboratory and radiographic studies. **Results:** In a total of 167 children with CD, 95 (56.9%) were male. The mean age was 6.01 ± 3.31 years. The most frequent presenting complaints were abdominal pain, diarrhea, and weight loss, noted in 70 (41.9%), 65 (38.9%), and 53 (31.7%) children, respectively. AIDs were diagnosed in 38 (22.8%) children, while the most common AIDs were autoimmune thyroiditis, type-1 diabetes mellitus (T1DM), asthma, and autoimmune hepatitis, found in 11 (6.6%), 7 (4.2%), 4 (2.4%), and 4 (2.4%) children, respectively. Low monthly family income (p=0.013), or severe CD type (p=0.010), were found to have a significant association with AIDs. **Conclusions:** Children with CD have a high prevalence of associated AIDs, with autoimmune thyroiditis, T1DM, asthma, and autoimmune hepatitis being the most commonly observed conditions. The severity of CD appears to be a contributing factor to the development of AIDs.

INTRODUCTION

Celiac disease (CD) is a common autoimmune disorder triggered by the ingestion of gluten proteins found in wheat, barley, and rye [1]. CD is marked by the presence of anti-transglutaminase autoantibodies and damage to the intestinal villi. In children with other autoimmune diseases (AIDs), such as type 1 diabetes mellitus (T1DM), or thyroiditis, screening frequently uncovers previously undiagnosed CD, affecting approximately 5% to 10% of these pediatric patients [2, 3]. The prevalence of AIDs is significantly higher in children with CD [4, 5]. The interplay between CD and other autoimmune disorders appears to be bidirectional, with studies indicating an increased prevalence of AIDs in CD patients. However, the relationship remains largely associative rather than causal, as no definitive mechanistic link has been established. Prolonged gluten exposure in pediatric CD patients has been suggested as a potential contributor to the development of additional AIDs, though it remains unclear

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whether gluten directly triggers these conditions or if underlying genetic and immunological factors predispose CD patients to autoimmunity [6]. Contemporary epidemiological evidence has indicated a significant rise in the prevalence of AIDs among CD patients [7]. Ventura et al. analyzing 909 patients of CD reported a 34% prevalence of AIDs, and proposed that prolonged gluten exposure may have contributed to factors influencing AIDs [8]. A study from Finland by Viljamaa et al. evaluating 703 CD patients revealed the prevalence of AIDs as 31%, while a French study analyzing 924 patients reported that to be 19.3% [9, 10]. These findings suggest a strong association, but they do not establish a direct causal relationship. Several potential mechanisms have been proposed to explain the coexistence of CD and AIDs, including shared genetic predisposition (such as HLA-DQ2 and HLA-DQ8 alleles), environmental triggers, dysregulated immune responses, impaired intestinal barrier function, and increased intestinal permeability. While these mechanisms support an immunopathological overlap, further research is needed to determine whether CD actively drives the onset of other AIDs or if both conditions arise independently due to common risk factors. Despite the well-documented association between CD and AIDs, there is a significant lack of regional data from South Punjab, Pakistan, where CD remains underdiagnosed and often presents late with complications. Most studies on this relationship come from Western populations, limiting their applicability to South Asian children due to genetic, environmental, and dietary differences. There are no region-specific screening guidelines for AIDs in CD patients, making it unclear which AIDs are most prevalent locally. The role of prolonged gluten exposure in AID development also remains debated, with limited pediatric-specific data exploring whether early diagnosis and strict dietary adherence influence AID risk. Given the increasing recognition of AIDs in CD, this study aims to address these gaps by determining the spectrum and prevalence of AIDs in children with CD, providing critical insights for early screening, targeted management, and localized clinical guidelines.

This study aims to evaluate the spectrum of AIDs in children with CD.

METHODS

This cross-sectional study was conducted at the Department of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital, and The Institute of Child Health, Multan, Pakistan, from September 2023 to December 2024. Children of either gender, aged between 1-12 years, and having CD were included. A sample size of 167 was calculated based on an estimated 19.3% prevalence of AIDs in CD, as reported in a French study [10]. This estimate was selected due to the lack of region-specific data from South Punjab, Pakistan, and was considered relevant based on available international literature. A 6% margin of error was chosen to balance statistical precision with feasibility, ensuring adequate power to detect a meaningful prevalence estimate within the constraints of a single-center study. This approach allows for a robust yet practical sample size while maintaining a 95% confidence level for reliable estimates. The sample size was calculated using the online Open EPI sample size calculator. Children with acute on chronic liver disease (ALT > 40 IU/L), irrespective of the cause, were excluded. Children diagnosed with intestinal tuberculosis were also excluded. The CD was confirmed through small intestinal biopsy exhibiting mucosal alterations as per "Modified March Criteria" that involved partial to complete villous atrophy, crypt elongation with or without a rise in intraepithelial lymphocytes [11]. Approval for this study was obtained from the Institutional Ethical Committee (IEC) (letter number: ERC/2023/1644) of The Children's Hospital and The Institute of Child Health, Multan, Pakistan. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant institutional guidelines for research involving human subjects. Written informed consent was obtained from parents or legal guardians of all participating children before data collection. Participant confidentiality was ensured by anonymizing all data, using unique identification codes instead of personal identifiers, and restricting access to study records to authorized personnel only. Non-probability, consecutive sampling technique was utilized. Gender, age, residential status, family history of CD or AIDs, along with related gastrointestinal (GI) symptoms, were documented. The CD was labeled as mild to moderate between type 2 to 3a, while it was named severe if above type 3b to 4 [12]. Anemia was designated as hemoglobin below 11 g/dl [13]. Monthly family income was termed high if above PKR 65,000, middle if between 35,000 to 65,000, or low if below 35,000 [14]. The diagnosis of AIDs was made utilizing physical and clinical examination along with relevant laboratory and radiographic studies. Data were analyzed using IBM-SPSS Statistics, version 26.0. For age, the mean and standard deviation were calculated. Frequency and percentages were shown for gender, residence, socio-economic status, CD staging, family history of CD or AIDs, GI-related symptoms, and AIDs. Comparison of categorical data was made using the chi-square test, considering $p<0.05$ as significant.

RESULTS

In a total of 167 children with CD, 95 (56.9%) were male and 72 (43.1%) female. The mean age was 6.01 ± 3.31 years,

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ranging between 1 to 12 years. The residential status of 107 (64.1%) children was rural. The monthly family income was low in 95 (56.9%) children. The CD stage evaluation revealed that 116 children belonged to mild to moderate disease. Family history of CD and AIDs was reported in 24 (14.4%) and 63 (37.7%) children, respectively. The most frequent presenting complaints were abdominal pain, diarrhea, and weight loss, noted in 70 (41.9%), 65 (38.9%), and 53 (31.7%) children, respectively (Table 1).

Table 1: Demographics and Clinical Characteristics (n=167)

Characteristics		n (%)
Gender	Male	95 (56.9%)
	Female	72 (43.1%)
Age (Years)	1-5	91 (54.5%)
	6-12	76 (45.5%)
Residence	Urban	60 (35.9%)
	Rural	107 (64.1%)
Monthly Family Income	Low	95 (56.9%)
	Middle	49 (29.3%)
	High	23 (13.8%)
Celiac Disease Staging	Mild to Moderate	116 (69.5%)
	Severe	51 (30.5%)
Family History of Celiac Disease		24 (14.4%)
Family History of Autoimmune Disease		63 (37.7%)
Anemia		31 (18.6%)
Frequency of Presenting Symptoms/Complaints	Abdominal pain	70 (41.9%)
	Diarrhea	65 (38.9%)
	Weight loss	53 (31.7%)
	Nausea and/or Vomiting	45 (26.9%)
	Reflux	39 (23.4%)
	Constipation	26 (15.6%)
	Dyspepsia	26 (15.6%)
	Joint Pain	24 (14.4%)
	Fever	21 (12.6%)

AIDs were diagnosed in 38 (22.8%) children with CD, while the most common autoimmune diseases were autoimmune thyroiditis, T1DM, asthma, and autoimmune hepatitis, found in 11 (6.6%), 7 (4.2%), 4 (2.4%), and 4 (2.4%) children, respectively. Findings are showing the details about the types of AIDs diagnosed among children with CD (Figure 1).

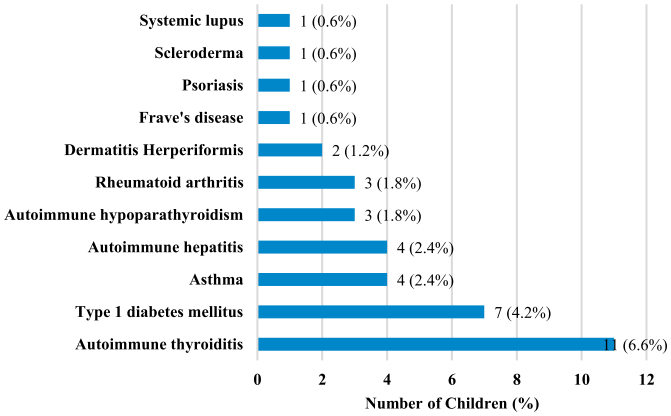

Figure 1: Types of Autoimmune Diseases Noted among Children with Celiac Disease (n=167)

No association of presence of AIDs was found with gender (p=0.886), age (p=0.081), residential status (p=0.198), family history of CD (0.195), or family history of AIDs (0.898). Low monthly family income (p=0.013), or severe CD type (p=0.010) were found to have a significant association with AIDs (Table 2).

Table 2: Association of Autoimmune Diseases with Demographic and Clinical Characteristics of Children with Celiac Disease (n=167)

Characteristics		Autoimmune disease		p-Value
		Yes (n=38)	No (n=129)	
Gender	Male	22 (57.9%)	73 (56.6%)	0.886
	Female	16 (42.1%)	56 (43.4%)	
Age (Years)	1-5	16 (42.1%)	75 (58.1%)	0.081
	6-12	22 (57.9%)	54 (41.9%)	
Residence	Urban	17 (44.7%)	43 (33.3%)	0.198
	Rural	21 (55.3%)	86 (66.7%)	
Monthly Family Income	Low	22 (57.9%)	73 (56.6%)	0.013
	Middle	6 (15.8%)	43 (33.3%)	
	High	10 (26.3%)	13 (10.1%)	
Celiac Disease Staging	Mild to Moderate	20 (52.6%)	96 (74.4%)	0.010
	Severe	18 (47.4%)	33 (25.6%)	
Family History of Celiac Disease		3 (7.9%)	21 (16.3%)	0.195
Family History of Autoimmune Disease		14 (36.8%)	49 (38.0%)	0.898
Anemia		8 (21.1%)	23 (17.8%)	0.653
Frequency of Presenting Symptoms/ Complaints	Abdominal pain	15 (39.5%)	55 (42.6%)	0.728
	Diarrhea	12 (31.6%)	53 (41.1%)	0.291
	Weight loss	12 (31.6%)	41 (31.8%)	0.981
	Nausea and/ Vomiting	14 (36.8%)	31 (24.0%)	0.118
	Reflux	8 (21.1%)	31 (24.0%)	0.703
	Constipation	10 (26.3%)	16 (12.4%)	0.038
	Dyspepsia	4 (10.5%)	22 (17.1%)	0.329
	Joint Pain	11 (28.9%)	13 (10.1%)	0.004
	Fever	6 (15.8%)	15 (11.6%)	0.496

DISCUSSION

In the present study, 22.8% children with CD had some kinds of AIDs, which means that nearly 1 in 5 children with

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CD are exposed to other AIDs as well. Literature highlights some reports from Europe indicating a co-occurrence of CD with other autoimmune conditions. Contemporary data have consistently shown a distinct pattern exhibiting high prevalence rates of various AIDs in CD in comparison to controls [15-18]. As the risk of diverse AIDs is increasing worldwide, it is also anticipated to rise among CD patients as well [19]. The underlying cause for these associations could be the shared pathogenic autoimmune mechanisms or genetic defects in the same responsible genes. A study from Turkey analyzing patients with CD revealed that 31.3% patients had AIDs [12]. In a recently published study by Hajaj *et al.* from Morocco, analyzing 60 children with CD, found that 13% children had associated AIDs [20]. Khan *et al.* showed that 5% of CD patients after 5 years had de novo AIDs diagnosis versus 1.3% controls (p=0.01) [21]. A hallmark of active CD is the presence of anti-transglutaminase antibodies, which often disappear when the patient adheres to a gluten-free diet. The underlying mechanisms linking CD and AIDs remain multifactorial, involving shared genetic predisposition (HLA-DQ2/DQ8), immune dysregulation, environmental triggers, and impaired intestinal barrier function. While molecular mimicry has been proposed as a mechanism where infectious agents trigger autoimmunity through cross-reactivity with self-antigens, other potential contributors include chronic immune activation due to gut permeability, persistent systemic inflammation, and dysbiosis-driven immune modulation [22]. Further research is required to elucidate these pathways and their role in AID development in CD patients. In this study, autoimmune thyroiditis, T1DM, autoimmune hepatitis, and asthma were the most frequent AIDs. Kayar and Dertli documented that autoimmune thyroiditis, asthma, and T1DM were the most common AIDs among patients with CD [12]. Hajaj *et al.* found T1DM to be the most common AID among children with CD [20]. Cosnes *et al.* from France reported T1DM, autoimmune thyroiditis, and psoriasis to be the most frequent autoimmune diseases in patients with CD [10]. Dermatitis herpetiforms is considered to be the most common dermatological disorder in CD, and we found that it was found in 1.2% children with CD in this study [23]. A range of hepatobiliary disorders has been documented in individuals with CD. The first recognition of liver changes in CD patients and subsequent studies have confirmed these findings, showing that abnormal liver enzyme tests are present in 9-25% CD cases [24-26]. Mild liver enzyme abnormalities are frequently seen in individuals with CD and tend to improve or normalize when the patient adheres to a strict gluten-free diet. In cases where CD is accompanied by autoimmune liver diseases, the liver's histological findings are typically indicative of the specific liver condition involved, such as autoimmune hepatitis or primary biliary cholangitis, each with distinct pathological features [27]. This association underscores the importance of considering CD in the differential diagnosis of unexplained liver enzyme elevations, as timely diagnosis and dietary management can lead to significant improvements in liver function. While some studies suggest that a gluten-free diet may reduce the risk or severity of AIDs, particularly autoimmune thyroiditis and autoimmune hepatitis, the impact of dietary adherence on long-term AID prevalence remains controversial [28, 29]. Further studies are needed to establish whether strict gluten avoidance can prevent or mitigate AID onset in pediatric CD patients. The present study is the first one from the region showing the details of AIDs among children and may pave the way towards further research.

CONCLUSIONS

Children with CD have a high prevalence of associated AIDs, with autoimmune thyroiditis, T1DM, asthma, and autoimmune hepatitis being the most commonly observed conditions. The severity of CD appears to be a contributing factor to the development of AIDs. Future studies should focus on the long-term impact of CD severity and early intervention strategies to mitigate the risk of autoimmune comorbidities.

Authors Contribution

Conceptualization: AT
Methodology: SI, IA, GK, AS, SZ
Formal analysis: GK, AS, SZ
Writing review and editing: SI, AT

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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The Early Dental Visit: Timing, Rationale, and Road Blocks

Amira Shahid[1*], Maliha Muneer[2], Mehwish Munawar[3], Maleeha Khurram[4], Sarosh Iqbal[5] and Nida Khan[6]

[1]Department of Operative Dentistry, University Medical and Dental College, Faisalabad, Pakistan
[2]Department of Operative Dentistry, Punjab Medical College Dental Institute, Faisalabad Medical University, Faisalabad, Pakistan
[3]Department of Operative Dentistry, Azra Naheed Dental College, Superior University, Lahore, Pakistan
[4]Department of Dental Materials, University Medical and Dental College, Faisalabad, Pakistan
[5]Department of Oral Biology, University Medical and Dental College, Faisalabad, Pakistan
[6]Department of Community Dentistry, University Medical and Dental College, Faisalabad, Pakistan

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Corresponding Author:
Amira Shahid
Department of Operative Dentistry, University Medical and Dental College, Faisalabad, Pakistan
amira.shahid19@gmail.com

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ABSTRACT

A child's first dental visit at the first tooth eruption or at one year of age has the potential to prevent early disease treatment and modify the child's dental behavior. **Objectives:** To assess the knowledge of parents about age, reasons, and hurdles to first dental visits of children. **Methods:** This cross-sectional questionnaire-based study was carried out at the outpatient department at Madina Teaching Hospital, Faisalabad, in a period of six months from February 2023 to July 2023. The parents of children<1 to 15 years meeting the inclusion criteria and who gave verbal consent were included in the study. **Results:** A total of 180 children (104 male, 76 female) enrolled in the study. Only 8.9 % (n=16) of parents were aware of the recommended time for the first dental visit of children. Most parents (46.7%, n=84) believed that children should visit a dentist at the time of a dental problem. Common reasons for the first dental visit were dental caries (50.6%, n=91) and dental pain (22.2%, n=40). Parents reported having time constraints (16.7%, n=30), believing primary teeth unimportant (13.3%, n=24) child cooperation problems (13.3%, n=24) as hurdles to early dental visits. **Conclusions:** Most participants were unaware of recommendations, and some had misbeliefs that led to a delay in the first dental visit of children. Efforts should be made to educate the local population about the proposed time and importance of the first dental visit of children.

INTRODUCTION

All parents should know that a child should visit for first dental checkup at an early age. According to the American Academy of Pediatric Dentistry, European Academy of Pediatric Dentistry and Canadian Dental Association recommendations, the first dental visit of a child should be made when the first primary tooth erupts and at least at 12 months of age. Early dental visit should include a clinical oral examination, individualized caries risk assessment, cleaning teeth, assessing fluoride exposure and proper feeding practice, counseling for age-related injury prevention, treatment or referral of any oral disease, assessing oral-facial growth and recommending an interval for periodic reevaluation. It is generally observed that children visit the dentist primarily for a dental problem. This delays early recognition of dental diseases or abnormalities, increasing disease severity, needing complex treatments, and decreasing prevention opportunities. An early dental visit is considered the first step towards preventive dental care and developing oral care habits for children that last a lifetime. The prevention includes educating the parents about children correct oral hygiene, appropriate diet guidance, early detection and

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intervention for reversal of disease like incipient caries, and prevention of dental traumatic injuries. Other benefits of early and regular dental visits include monitoring dentofacial growth and development, detecting unusual teeth alignment with their timely handling with less invasive procedures in less time, visits and costs [1, 2]. Dental caries is the most common disease globally, affecting almost every country in the world, and according to the WHO, its reported prevalence in children is 60-90%.[3] Early childhood caries increases risk of caries in permanent teeth, if remain untreated may lead to complex symptoms like pain, abscess, cellulitis, bone loss and orthodontic complications. This may need complex invasive procedures, longer appointments, difficulty eating, missed schools, increasing economic burden on the resources of the families [3]. This is one of the leading cause of tooth loss, edentulism and functional disability, affect the food intake and general health. Although caries is well known burden on state health system and economy yet it is preventable. Early dental visits are opportunities to educate parents especially mothers in improving their attitude towards oral care and other preventive measures for their children [4]. Early life dental visit and interventions help prevent caries and other oral problems thus improve child dental health [5]. Thus, children may reach their adulthood with healthy permanent teeth, better oral care habits, improved quality of life, wellbeing and confidence for rest of the life. Overall, at community level, it may also reduce overall burden of the disease at health care system of a country. Early and regular dental checkups help in development of child trust, increasing comfort to dental procedures. Early visits enable children to familiarize with dental environment at an early age and this help them reducing anxiety and fear to dental treatment and improve children future behavior at dental visits [6]. Despite recommendations the studies have shown that parents do not bring their child for dental visit at recommended age but only when a problem or symptom of a disease occur. According to previous studies the majority of the children had their first dental visit between 3-10 years. The common reasons for delayed visits included parents believing that it was not necessary or child would not cooperate to dental procedure, lack of awareness, economic or transport problems or dental fear of parents [4, 7, 8]. There are multiple studies conducted in different parts of the world about the evaluation of knowledge of parents about children age at first dental visit, reasons and its importance. Such studies are very few among the local population [2, 4, 5]. This would provide a primary information regarding parents' awareness and guide dental practitioners and community health workers for future pediatric preventive dental work for long-term oral health and wellbeing of the children. This would also decrease oral disease burden at health resource that may then be utilized for other diseases in a better way.

This study aims to assess the knowledge of parents about age, reasons, and hurdles to children's first dental visit in a sub-population in Pakistan.

METHODS

This cross-sectional study was conducted in parents of children aged <1 to 12 years, visiting the dental outpatient department at Madina teaching hospital, Faisalabad, during a period of six months from February 2023 to July 2023. The ethical approval was taken from the Institutional Review Board of The University of Lahore Faisalabad (Ref. No. TUF/IRB/155/2023). The estimated sample size was 180 using the open epi sample size calculator, with a prevalence 21%, a confidence level of 95% and a margin of error 6%. The data was collected using a non-probability purposive sampling technique. The parents were informed regarding the aims and objectives of the study. The parents who visited for the first time and gave verbal consent to participate voluntarily were included in the study. The parents of children with systemic disease and mental or physical disability among parents or children were excluded from the study. The response to the questionnaire was recorded by them and returned at the same appointment. At the end of the appointment, the parents were educated about the recommended age for the first dental checkup age of their children and their importance. The questionnaire was made based on a previous study, content validated by Alshahrani et al [9]. It contained demographic questions, including name, gender, age, and relationship with the child. There were three questions. The first was enquiring their opinion of the ideal age for the first dental visit. The second question asked them the reasons for the first dental visit of their child. The third question was knowing the hurdles parents feel prevent them from taking their child for an early dental check-up. The questionnaire was pilot tested on parents of children with their first dental visit at the dental outpatient department, and final modifications were made by an expert judgment. The parents who were unable to read and write in English or the local language, a trained dental surgeon helped them understand the question and record the response. After the data collection, IBM.SPSS version 22.0 for Windows was used for data analysis. Mean and standard deviation were reported for quantitative variables. Frequency and percentage were expressed as frequency and percentage.

RESULTS

In this study, 180 participants were enrolled. The age of first visit ranges from 0-14years (Mean 8.54, SD 3.14). There

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were more boys who visited the dental hospital than girls in the study group (Table 1).

Table 1: Gender distribution in the study group (N=184)

Gender	n (%)
Male	104 (57.8%)
Female	76 (42.2%)
Total	180 (100.0%)

Out of 180 participants of the study, 8.9 % (n=16) of parents were aware of the recommended time for the first dental visit of the children. Most (46.7%, n=84) parents believe that children should be taken to the dentist only when a problem arises. Some (23.3%, n=42) participants believe the ideal age for the first dental visit should be 5 to 8 years (Table 2).

Table 2: Opinion Of Participants Regarding Ideal Age for First Dental Visit

Frequency of Dental Visits	n (%)
At one year	16 (8.9%)
2–4 years	24 (13.3%)
5–8 years	42 (23.3%)
More than 8 years	14 (7.8%)
Only when a dental problem arises	84 (46.7%)
Total	180 (100%)

The most common reason (50.6%, n=91) for the first dental visit was caries or cavity in a tooth. Other frequent reasons include pain (22.2%, n=40) and uneven teeth/ malocclusion (8.3%, n=15). Only (3.3%, n=6) of the children visited for a routine dental checkup. Patients with cleft palate or lip (1.1%, n=2) also had their first dental visit (Referred for making PNAM appliance) within the first years of life (Table 3).

Table 3: Reasons for First Dental Check-Up Among BSN Students (N=180)

Reason for First Dental Check-Up	n (%)
Routine check-up	6 (3.3%)
Caries	91 (50.6%)
Pain or sensitivity	40 (22.2%)
Swelling or abscess	3 (1.7%)
Mobile teeth	5 (2.8%)
Uneven teeth or malocclusion	15 (8.3%)
Extraction of primary teeth	6 (3.3%)
Trauma to teeth	8 (4.4%)
Stain, discolored teeth, or bad breath	1 (0.6%)
Missing or extra teeth	3 (1.7%)
Cleft palate or lip	2 (1.1%)
Total	180 (100.0%)

Response of the participants to the question about hurdles to early dental visits, most participants 41.1% were able to take their children to dentists whenever required. Some participants had personal problems like time constraints 16.7%, lack of transport 5% and financial problems 1.7%. Some participants 13.3% believe primary teeth are not important, and 13.3% believe their child will not cooperate dental procedure. 7.2% parents had dental fear and 1.7% visited a medical practitioner for dental problems (Table 4).

Table 4: Response About Hurdles to Early Dental Visits

Reason for Not Visiting the Dentist	n (%)
I can take my child to the dentist when required	74 (41.1%)
I am busy, I have no time	30 (16.7%)
Lack of appointment or transport	9 (5.0%)
Unnecessary, as primary teeth are not important and fall off	24 (13.3%)
A child may be uncooperative with dental treatment	24 (13.3%)
I usually visit a medical physician	3 (1.7%)
I am afraid of dentists	13 (7.2%)
Dental treatments are costly, and I cannot pay	3 (1.7%)
Total	180 (100.0%)

DISCUSSION

In the current research, the proportion of the participants who were aware that the first dental visit of a child should be at the age of one year was 8.9. Participants had less awareness as compared to other local studies, where 39.5% of parents were aware of this recommendation [10]. Similar results were observed in a Saudi population (6.6%) and a Saudi study (0.5%) [7, 11]. In India, children attended the dentist; one year old had 3.8% of the entire population visiting the dentist, and Poland and Bangkok recorded 11.5% and 2.42, respectively [12-14]. In America, 13 percent of caregivers had their children visiting the dentist at the age of one year [15]. Preventive visits in early stages have been found to reduce caries rates in the mouth and also decrease the occurrence of operative or emergency dental procedures [16-17]. A mere 3.3% of respondents answered that the initial visit to the dentist was to have a check-up. Indians had 0.2 percent of children attending routine check-ups, and Bangkok had 2.6% of males and 4.4% of females doing the same. In China, children were first being attended to preventatively, 12.1%, and on dental grounds, 34.4% [16]. A proportion of parents in developed nations were more attentive to preventive visits, with 83 percent in the United States, 47.4 percent in Poland, 23.1 percent in Turkey, and 36.6 percent in Bangkok mentioning preventive visits as the primary reason [13, 15, 18]. The most common cause of the visit to a dentist in the current research was dental caries (50.6%), which is consistent with the local results that indicate a prevalence of 65.7% [10]. The caries rate of the dental is estimated at 56.62% nationally [19]. Comparatively, Saudi and Turkish studies showed an outcome of dental caries as the cause of the first dental visit in 32.8% and 15.6% children, respectively [7, 18], but another Turkish study showed 33.5% and 29.5% respectively [20]. Dental caries has been a significant

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problem among all ages throughout the world. In Bangkok and Indian studies, caries was reported as the reason of the first visit in 33.4 and 47% of cases, respectively [6,12,14]. Other frequent reasons to visit the dentist in the given study included dental pain (22.2%), uneven teeth/malocclusion (8.3%), and dental trauma (4.4%). The same was also observed in Saudi Arabia, Bangkok, and Turkey, where 31.7, 33.4 and 36.4 percent of the first visits were attributed to pain, respectively. In Poland, the trauma to teeth accounted for 19.7% of the first visit. Concerning obstacles to visiting the dentist at an early age, 41.1 percent of the participants said that they can bring their children when they need them. Some of the reported hurdles were economic (1.7%), lack of transport (5%), and a misconception that primary teeth are inconsequential (13.3%). A further 13.3% felt that their child could not cooperate, and 7.2% said they had dental fear. Similar obstacles were cited in Saudi Arabia, Bangkok, and Australia, such as beliefs that primary teeth are insignificant, children are too young or uncooperative, and dental fear among parents [7, 13, 14, 21]. Insensitivity is the most common cause of late detection of the first dental visit. Stereotypes concerning the minor importance of primary teeth, dependence on medical professionals in case of dental problems, and fear of dentists on the part of parents are some of the variables that can be altered. Pediatric dental prevention should be included in the health policy and community-level education of dental workers and professionals in order to establish the idea of early and frequent dental check-ups and enhance oral health results. In our research, the data were gathered among a limited number of respondents in a local hospital. This would be a very minimal percentage of the people. In order to confirm the findings above, the follow-up proposed survey will consist of a large sample size across several private and public centers. Survey questions only contained several reasons, yet there are several demographics, social, and economic variables that should be evaluated to comprehend how the patient's knowledge influences their early visits to a dentist and children. Subsequent research ought to comprise various demographic variables and the connection between them and the population awareness.

CONCLUSIONS

Most of the participants of the study were unaware of the recommended time of first dental check-up; some reported misbeliefs that resulted in severe delay till a dental problem arises. Every effort should be made by dental practitioners, community health workers, and policy makers to educate the local population.

Authors Contribution

Conceptualization: AS, MM[1]
Methodology: AS, MM[2]
Formal analysis: MM[2]
Writing review and editing: AS, MM[1], MK, SI, NK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Urinary Tract Infections in Protein-Calorie Malnutrition Children in Mardan Medical Complex

Shah Khalid[1], Ansar Hussain[2*], Kiramtulllah[1], Hamza Sardar[3], Abdul Basit Khan[4] and Rizwana Kalsoom[5]

[1]Department of Pediatrics, Mardan Medical Complex, Mardan, Pakistan
[2]Department of Pediatrics, Hayatabad Medical Complex, Peshawar, Pakistan
[3]Department of Pediatrics, Khyber Hospital, Mardan, Pakistan
[4]Department of General Surgery, Mardan Medical Complex, Mardan, Pakistan
[5]Department of Biochemistry, Gomal Medical College, Dera Ismail Khan, Pakistan

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Corresponding Author:
Ansar Hussain
Department of Pediatrics, Hayatabad Medical Complex, Peshawar, Pakistan
ansar14f@gmail.com

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ABSTRACT

Protein-calorie malnutrition (PCM) remains a significant cause of morbidity and mortality in low- and middle-income countries, where it often coexists with infections such as urinary tract infections (UTIs). Malnourished children are immunologically vulnerable, and UTIs further complicate their clinical course. **Objectives:** To determine the frequency of UTIs and associated risk factors among children with PCM admitted to a tertiary care hospital in Mardan, Pakistan. **Methods:** This descriptive cross-sectional study was conducted in the Department of Pediatrics, Mardan Medical Complex, from August 2024 to January 2025. A total of 123 children aged 6 months to 12 years with PCM were included. Demographic, clinical, and laboratory data were collected using a structured proforma. Urinary investigations included microscopy, dipstick nitrite test, and culture. Associations between UTI and clinical-demographic variables were analyzed using the Chi-square test, with effect size reported by Cramer's V. **Results:** The prevalence of UTI was 48.0%. Significant associations were observed with age <24 months ($p<0.001$, V=0.642), rural residence ($p=0.035$, V=0.190), severe acute malnutrition ($p=0.015$, V=0.219), and edema ($p=0.017$, V=0.216). Escherichia coli (30.1%) was the most common pathogen isolated. Most children improved with treatment (89.4%), though complications such as sepsis (10.6%) and acute kidney injury (6.5%) were reported. **Conclusions:** UTIs are common among malnourished children, particularly those under 2 years, severely malnourished, or from rural areas. Early screening and targeted interventions may reduce morbidity and improve outcomes.

INTRODUCTION

Protein-calorie malnutrition (PCM) is a major public health problem and one of the leading contributors to childhood morbidity and mortality worldwide [1]. Malnutrition compromises immune defenses, increasing vulnerability to infections and prolonging recovery from common illnesses [2]. Among these infections, UTI is particularly concerning, as it may cause renal scarring, chronic kidney disease, and impaired growth in children [3]. International evidence has consistently highlighted a strong association between malnutrition and UTI. A multicenter study from Sub-Saharan Africa reported that nearly one-third of hospitalized children with severe malnutrition had concurrent UTIs [4]. Similarly, research from South Asia has shown UTI prevalence rates ranging from 20% to 35% in malnourished children, with Escherichia coli identified as the predominant pathogen [5, 6]. Rising antimicrobial resistance further complicates management in these settings [7]. In Pakistan, the burden of malnutrition remains alarmingly high. The National Nutrition Survey (2019) documented stunting in 40.2% and wasting in 17.7%

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of children under five years [8]. Local hospital-based studies have confirmed that infections such as pneumonia, diarrhea, and UTI frequently complicate PCM, but most of these studies are either outdated or limited to small cohorts from urban centers [9, 10]. Evidence from Khyber Pakhtunkhwa is particularly scarce, despite its large rural population, where poverty and limited healthcare access heighten risks. Although global literature recognizes UTI as a frequent comorbidity in malnourished children, little is known about how demographic (e.g., age, sex, residence) and clinical characteristics (e.g., severity of malnutrition, edema) influence UTI risk in Pakistan. This knowledge gap hampers the development of effective screening strategies tailored to high-risk subgroups. By addressing this gap, the findings aim to generate locally relevant evidence that can guide early diagnosis, timely management, and context-specific preventive strategies for malnourished children in Pakistan.

This study aimed to determine the frequency of UTI in children admitted with PCM at Mardan Medical Complex and to evaluate demographic and clinical factors associated with UTI.

METHODS

This descriptive cross-sectional study was conducted in the Department of Pediatrics, Mardan Medical Complex, a tertiary care hospital affiliated with Bacha Khan Medical College, Mardan, Pakistan. Ethical approval for this study was granted by the Institutional Review Board of Bacha Khan Medical College, Mardan (Ref. No. 404/BKMC). The study was carried out over a period of six months, from August 2024 to January 2025. The study was conducted in accordance with institutional and CPSP guidelines for postgraduate research. Written informed consent was obtained from the parents or guardians of all participating children before enrollment. The hospital caters to both urban and rural populations. For this study, children residing within Mardan city and its municipal limits were classified as urban, while those from surrounding tehsils and villages, including Takht Bhai, Katlang, and Rustam, were considered rural. The sample size was calculated using the single proportion formula: $n = (Z^2 \times p \times (1 - p)) / d^2$. For a 95% confidence level, Z was taken as 1.96. The expected prevalence of UTI among malnourished children was assumed to be 30% (p=0.30), based on previously published studies [11], with a margin of error of 8% (d=0.08). Substituting these values, the required sample size was estimated to be 126. However, due to the availability of eligible cases during the study period, a total of 123 children fulfilling the inclusion criteria were recruited. This reduction represented only a 2.4% decrease from the planned sample size, minimally affecting statistical precision, with the achieved margin of error widening from 8.0% to 8.2%, which does not compromise the validity of the findings. Children aged between 6 months and 12 years, admitted with a clinical diagnosis of PCM confirmed by anthropometric assessment, were included in the study. Severity of malnutrition was defined using WHO criteria: moderate acute malnutrition (MAM) as a weight-for-height Z-score between –2 and –3 SD or MUAC 11.5–12.4 cm, and severe acute malnutrition (SAM) as a weight-for-height Z-score < –3 SD, MUAC <11.5 cm, or the presence of bilateral pitting edema. Z-scores were calculated using the WHO Anthro software for standardization. Children with known chronic kidney disease, congenital urinary tract anomalies, recent antibiotic use (within two weeks), or incomplete clinical records were excluded from the study. Anthropometric measurements were performed by a single trained pediatric resident using calibrated instruments to minimize inter-observer variability. Data were collected using a structured proforma by trained pediatric residents under faculty supervision. Demographic details, including age, sex, residence, and parental education, were recorded at admission. Clinical characteristics such as PCM severity, MUAC, edema, fever, history of previous UTI, diarrhea, and pneumonia were documented after thorough clinical evaluation. Laboratory investigations included urine microscopy for pyuria, dipstick for nitrites, urine culture for bacteriuria, and pathogen identification. For UTI diagnosis, pyuria was defined as ≥5 white blood cells per high-power field (WBC/HPF), significant bacteriuria as $\geq 10^5$ colony-forming units (CFU)/mL on urine culture, and nitrite positivity on dipstick as supportive evidence. Urine was collected according to hospital SOPs: clean-catch midstream specimens for toilet-trained children and sterile catheterization when indicated in non–non-toilet-trained. Bag specimens were not used for culture-based diagnosis; if used for initial screening, confirmatory clean-catch or catheter samples were required. Clinical outcomes such as length of hospital stay, sepsis, acute kidney injury, electrolyte imbalance, and discharge status were also noted. Sepsis was defined using pediatric Sepsis-3 criteria, and acute kidney injury was classified according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines to ensure reproducibility. To ensure reliability and validity, standardized WHO criteria were used for the classification of malnutrition, while all laboratory tests were performed in the hospital's diagnostic laboratory following standard operating procedures [12]. Internal validity was strengthened by using uniform definitions for outcome variables and by double-checking data entries for accuracy. Data were entered and analyzed using SPSS version 26.0. Descriptive statistics were applied to summarize demographic variables, including age, sex,

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residence, and parental education, as well as clinical characteristics such as severity of PCM, MUAC category, presence of edema, fever, history of previous UTI, diarrhea, and pneumonia. Urinary findings, including pyuria, nitrite test, bacteriuria, culture results, and pathogens isolated, were presented separately. Clinical outcomes, such as length of hospital stay, complications, and discharge status, were described in table 5. Inferential analysis included Chi-square tests and Cramer's V for effect sizes. In addition, multivariable logistic regression was performed to adjust for potential confounders (age, sex, residence, PCM severity, edema, fever, and diarrhea) when evaluating associations with UTI. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among 123 malnourished children, most were aged 24–59 months (39.8%), followed by <12 months (24.4%), 12–23 months (20.3%), and ≥60 months (15.4%). Males slightly outnumbered females (52.0% vs. 48.0%). Over half were from rural areas (52.8%), and nearly half of parents had no formal education (47.2%), reflecting the influence of rural background and low parental education on PCM prevalence. Among the malnourished children, the distribution of severity was nearly equal, with MAM observed in 50.4% and SAM in 49.6%. MUAC revealed that 42.3% had values between 11.5 and 12.4 cm, while 35.8% were severely malnourished with MUAC <11.5 cm. Oedema, a clinical marker of severe malnutrition, was present in 39.8% of the children. Fever was the most common presenting feature, reported in 72.4%, followed by diarrhea (41.5%) and pneumonia (26.8%). A history of previous UTI was noted in 22.8% of participants, suggesting recurrence in a subset of cases. Collectively, these findings highlight the burden of comorbidities and infections that often complicate malnutrition in children (Table 1).

Table 1: Demographic and Clinical Characteristics of Children with PCM (N=123)

Variables	N (%)
Age group (months)	
<12	30 (24.4%)
12–23	25 (20.3%)
24–59	49 (39.8%)
≥60	19 (15.4%)
Sex	
Female	59 (48.0%)
Male	64 (52.0%)
Residence	
Rural	65 (52.8%)
Urban	58 (47.2%)
Parental education	
None	58 (47.2%)
Primary–Secondary	47 (38.2%)
Higher	18 (14.6%)
PCM severity	
MAM	62 (50.4%)
SAM	61 (49.6%)
MUAC category (cm)	
<11.5	44 (35.8%)
11.5–12.4	52 (42.3%)
≥12.5	27 (22.0%)
Oedema	
Yes	49 (39.8%)
No	74 (60.2%)
Fever	
Yes	89 (72.4%)
No	34 (27.6%)
History of previous UTI	
Yes	28 (22.8%)
No	95 (77.2%)
Diarrhea	
Yes	51 (41.5%)
No	72 (58.5%)
Pneumonia	
Yes	33 (26.8%)
No	90 (73.2%)

Laboratory evaluation revealed urinary abnormalities in a significant proportion of children. Pyuria was present in 56.1%, while bacteriuria was documented in 55.3%. Urine nitrite was positive in nearly half of the cases (48.8%). Culture positivity was observed in 44.7% of children, confirming UTI as a frequent complication among malnourished children. Among the pathogens, E. coli was the predominant isolate (30.1%), followed by Klebsiella (8.9%), Proteus (4.9%), and Pseudomonas (0.8%). No organism was detected in 55.3% of cultures, likely reflecting either prior antibiotic use or non-bacterial causes. These results confirm that Gram-negative bacilli, particularly E. coli, remain the most common etiological agents of UTI in malnourished children (Table 2).

Table 2: Urinary Findings and Culture Results of Malnourished Children (N=123)

Variables	N (%)
Pyuria (WBC/HPF)	
Yes	69 (56.1%)
No	54 (43.9%)
Urine Nitrite	
Positive	60 (48.8%)
Negative	63 (51.2%)
Bacteriuria	
Yes	68 (55.3%)
No	55 (44.7%)
Culture Result	
Positive	55 (44.7%)

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Negative	68 (55.3%)
Pathogen Isolated	
E. coli	37 (30.1%)
Klebsiella	11 (8.9%)
Proteus	6 (4.9%)
Pseudomonas	1 (0.8%)
None	68 (55.3%)

Significant associations were observed between UTI status and several clinical-demographic variables. Children under 24 months had a markedly higher prevalence of UTI (83.6%) compared to older children (19.1%, χ^2=50.7, p<0.001, Cramer's V=0.642), indicating age as the strongest predictor. Residence also played a role, with rural children more affected (56.9% vs. 37.9%, χ^2=4.43, p=0.035, V=0.190). Similarly, SAM cases had higher UTI rates (59.0%) compared to MAM (37.1%, χ^2=5.92, p=0.015, V=0.219). The presence of oedema was also significantly linked with UTI (61.2% vs. 39.2%, χ^2=5.73, p=0.017, V=0.216). In contrast, sex, fever, and diarrhea did not show significant associations. These findings reinforce that younger age, severe malnutrition, oedema, and rural residence are key risk factors for UTI among malnourished children (Table 3).

Table 3: Association of UTI with Demographic and Clinical Variables (N=123)

Variable	UTI Present N (%)	UTI Absent N (%)	χ^2 (DF=1)	p-Value	Cramer's V
Age <24 Months	46 (83.6%)	9 (16.4%)	50.7	<0.001*	0.642
Sex (Male)	33 (51.6%)	31 (48.4%)	0.69	0.406	–
Residence (Rural)	37 (56.9%)	28 (43.1%)	4.43	0.035*	0.190
Severe Pcm (SAM)	36 (59.0%)	25 (41.0%)	5.92	0.015*	0.219
Oedema Present	30 (61.2%)	19 (38.8%)	5.73	0.017*	0.216
Fever Present	46 (51.7%)	43 (48.3%)	1.78	0.182	–
Diarrhea Present	26 (51.0%)	25 (49.0%)	0.32	0.573	–

In multivariable logistic regression analysis (Table 5), age remained the strongest independent predictor of UTI. Compared to children aged 24–59 months, those aged 12–23 months had more than 200-fold higher odds of UTI (aOR 222.2, 95% CI 15.1–3266.5, p < 0.001), while children aged ≥60 months also showed significantly elevated odds (aOR 444.4, 95% CI 22.8–8672.6, p < 0.001). Estimates for the <12-month group were unstable due to quasi-complete separation but consistently indicated a very high risk. Diarrhea was an additional independent predictor (aOR 4.72, 95% CI 1.01–22.1, p = 0.049). In contrast, sex, residence, PCM severity, oedema, and fever did not retain statistical significance after adjustment. The final model demonstrated good calibration (Hosmer–Lemeshow χ^2=1.04, p=0.998), explained 79% of the variance (Nagelkerke R^2 = 0.792), and correctly classified 90.2% of cases (Table 4).

Table 4: Multivariable Logistic Regression for Predictors of UTI in Children with PCM (N=123)

Variables	Adjusted Odds Ratio (aOR)	95% CI for aOR	p-Value
<12 months	Estimation unstable*	–	0.997
12–23 months	222.2	15.1 – 3266.5	<0.001
≥60 months	444.4	22.8 – 8672.6	<0.001
Sex (ref: Male)	2.10	0.52 – 8.57	0.301
Residence (ref: Urban)	0.52	0.13 – 2.11	0.360
PCM severity (ref: MAM)	1.35	0.31 – 5.81	0.688
Oedema (ref: No)	1.14	0.30 – 4.41	0.846
Fever (ref: No)	5.66	0.93 – 34.64	0.061
Diarrhea (ref: No)	4.72	1.01 – 22.06	0.049

Model statistics: Omnibus χ^2 (9) =110.8, p<0.001; Nagelkerke R^2=0.792; Hosmer–Lemeshow χ^2 (8) =1.04, p=0.998; overall classification accuracy=90.2%. *Estimation for the <12 months group was unstable due to quasi-complete separation (very high UTI prevalence in this subgroup).

Nearly half of the children (48.0%) had hospital stays of 6–10 days, while 34.1% stayed ≤5 days and 17.9% >10 days. Complications were infrequent, with sepsis (10.6%), acute kidney injury (6.5%), and electrolyte imbalance (11.4%) observed; most children (over 85%) had no major complications. Outcomes were generally favorable, with 89.4% improving, though a minority were referred (4.9%), left against advice (2.4%), or died (3.3%), indicating that a subset remained at risk of adverse outcomes (Table 5).

Table 5: Clinical Outcomes of Children with PCM (N=123)

Outcome	N (%)
Length of Stay	
≤5 days	42 (34.1%)
6–10 days	59 (48.0%)
>10 days	22 (17.9%)
Sepsis	
No	110 (89.4%)
Yes	13 (10.6%)
Acute Kidney Injury	
No	115 (93.5%)
Yes	8 (6.5%)
Electrolyte Imbalance	
No	109 (88.6%)
Yes	14 (11.4%)
Discharge Status	
Improved	110 (89.4%)
Referred	6 (4.9%)
LAMA	3 (2.4%)
Death	4 (3.3%)

The clustered bar chart illustrates the relationship between UTI presence and key risk factors, including age, residence, severity of malnutrition, and presence of oedema. The chart demonstrates that younger children (<24 months) were significantly more prone to UTI, with 83.6% testing positive compared to only 19.1% in those

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aged ≥24 months. Similarly, residence showed a notable disparity, as 56.9% of rural children had UTI compared to 37.9% of urban children. Nutritional status also influenced outcomes: SAM was strongly associated with UTI (59.0%) compared to MAM (37.1%). Furthermore, oedema-positive children exhibited a higher UTI prevalence (61.2%) than those without oedema(39.2%)(Figure 1).

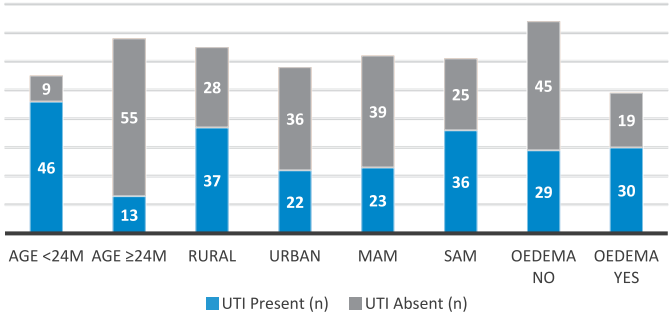

Figure 1: Distribution of UTI Status by Demographic and Clinical Factors among Malnourished Children(N=123)

DISCUSSIONS

This study found a high burden of urinary abnormalities among malnourished children, with culture-confirmed UTI in 44.7% and E. coli as the leading pathogen (30.1%). The organism pattern aligns with recent pediatric series and reviews in South Asia and sub-Saharan Africa, where E. coli dominates, followed by Klebsiella and Proteus among under-fives [12]. In severely malnourished populations, similar spectra have been reported, and gram-negative predominance is consistently linked to mucosal and innate immune compromise in wasting/SAM [13]. Pakistani datasets outside strictly malnourished cohorts also show E. coli leading and provide contemporary susceptibility context for empirical choices. [14] Age emerged as the strongest correlate: children <24 months carried markedly higher odds of UTI (χ^2=50.7; Cramer's V=0.642). The age-gradient mirrors large observational series and meta-analyses showing peak UTI incidence in the youngest age groups and substantial recurrence in early childhood [15]. The finding was clinically relevant in malnourished settings because nonspecific febrile presentations are common and urinalysis may be falsely negative; recent pediatric studies caution that reliance on single screening tests can miss cases in under-twos [12]. Nutritional severity also tracked with infection: SAM and oedema were significantly associated with UTI. These results are congruent with studies in SAM cohorts demonstrating higher UTI prevalence than in MAM or non-malnourished peers, and with multicountry work describing broad infection vulnerability (including UTI) among children admitted for SAM [16]. Recent scoping reviews and immunologic analyses reinforce biologic plausibility that protein-energy deficiency impairs barrier function, complement activity, and phagocytic killing, predisposing to gram-negative bacteremia and urosepsis. [17] Current WHO guidance on wasting underscores proactive infection screening and standardized treatment pathways in SAM, which supports the systematic urine testing approach used here [18]. A place-of-residence effect was observed: rural children had a greater UTI burden than their urban counterparts. Similar rural disadvantages have been described in recent pediatric UTI work from low- and middle-income settings, with proposed contributors including delayed care-seeking, water and sanitation constraints, and higher rates of over-the-counter/unsupervised antibiotic exposure [19, 20]. These contextual drivers matter for antimicrobial stewardship and may partly explain culture-negative pyuria when prior antibiotics are used before hospital presentation. Fever and diarrhea were frequent but not independently associated with UTI in this dataset, echoing reports that clinical features alone have limited predictive value in young or malnourished children and cannot replace laboratory testing [21]. Length of stay clustered around 6–10 days and most children improved, comparable to contemporary pediatric UTI series where early diagnosis and targeted therapy reduce complications [22]. Nonetheless, measurable rates of sepsis (10.6%) and electrolyte imbalance (11.4%) highlight the ongoing risk envelope in malnutrition and the need for standardized inpatient bundles recommended in the 2023 WHO guideline [23]. Antimicrobial susceptibility testing was not systematically performed in this study, which limits the ability to make definitive empirical therapy recommendations. While existing Pakistani pediatric datasets show E. coli as highly prevalent, resistance rates vary by province and healthcare setting. For this reason, it is recommended that future studies in malnourished populations incorporate standardized urine culture with susceptibility profiling. This will allow empirical regimens to be tailored more reliably, reduce inappropriate antibiotic use, and improve outcomes. The generalizability of these findings must be interpreted cautiously. This was a single-center study with a modest sample size, conducted in Mardan Medical Complex, a tertiary referral hospital serving both rural and urban catchments in Khyber Pakhtunkhwa. While the prevalence and predictors identified here are consistent with regional and international data, they may not fully represent malnourished children in other Pakistani provinces where healthcare access, referral patterns, and pathogen ecology differ. Larger multicenter studies across diverse Pakistani regions are therefore essential to validate these results and provide nationally representative estimates. Taken together, the data reinforce three operational points: (1) routine urine testing is justified in all hospitalized malnourished children, particularly under-twos; (2)

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empirical therapy should primarily cover E. coli and other Enterobacterales while awaiting culture, but definitive recommendations require ongoing local susceptibility surveillance; and (3) rural outreach and stewardship interventions (safe water, timely referral, rational antibiotic use) are likely to reduce missed infections and resistance pressure.

CONCLUSIONS

This study demonstrated a high frequency of urinary tract infection among children with protein-calorie malnutrition admitted to a tertiary hospital in Mardan. The strongest independent predictor was younger age (<24 months), while diarrhea also remained significant after adjustment. Severe malnutrition, oedema, and rural residence showed crude associations but did not retain significance in multivariable analysis. E. coli was the predominant pathogen isolated. These findings support the integration of routine urine screening in the clinical care pathway for malnourished children, particularly the youngest age groups, and highlight the need for context-specific empirical therapy guided by local antimicrobial susceptibility data.

Authors Contribution

Conceptualization: KU
Methodology: HS, ABK
Formal analysis: AH, RK
Writing review and editing: SK, KU, HS, ABK, RK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Impact of Ghutka and Mawa Use on Oral Health in a Sub-Urban Population of Karachi

Vijay Kumar Khatri[1*], Hafsa Munir[2], Tooba Mahmud Gauhar[3], Khalid Iqbal[4], Devi Kumari[5] and Roop Kumar[6]

[1]Department of ENT, Al-Tibri Medical College and Hospital, Karachi, Pakistan
[2]Department of Nephrology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan
[3]Department of General Surgery, Al-Tibri Medical College and Hospital, Karachi, Pakistan
[4]Atia General Hospital, Malir, Karachi, Pakistan
[5]Department of Anatomy, Al-Tibri Medical College and Hospital, Karachi, Pakistan
[6]Jinnah Postgraduate Medical Center, Karachi, Pakistan

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***Corresponding Author:**
Vijay Kumar Khatri
Department of ENT, Al-Tibri Medical College and Hospital, Karachi, Pakistan
doctor_vijay@hotmail.co.uk

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ABSTRACT

Ghutka and Mawa are smokeless tobacco products mostly used in South Asia. They have areca nut, tobacco, lime, catechu, paraffin wax, and flavoring materials. These mixtures are highly addictive and cancer-causing, related to oral submucous fibrosis, leukoplakia, and mouth cancers. Still, awareness of their harmful effects remains very low among users. **Objectives:** To observe oral findings and clinical patterns in Ghutka and Mawa users visiting ENT clinics. **Methods:** This cross-sectional research was done in Al-Tibri Medical College and Hospital, Karachi, from January to June 2025. One hundred patients who used Ghutka or Mawa for at least six months were selected by purposive sampling. Oral history and a detailed mouth examination were done. Data was entered and analyzed in SPSS using the Chi-square test, with a significance level $p \leq 0.05$. **Results:** Out of 100 users, dental issues were most common (73%), then trismus (44%), pain (40%), and chewing trouble (21%). The majority were addicted for 6–20 years, while 11 had more than 20 years of use. Ulcers were found in 58 Mawa and 53 Ghutka users; growths in 35 and 29 respectively. Longer use had more severe lesions, with malignant signs mostly after 10 years ($p < 0.05$). **Conclusions:** Ghutka and Mawa are strongly connected with ulcers, dental and jaw problems, and precancerous growths. Long-term use increases damage. Awareness, early detection, and strict public control are urgently required.

INTRODUCTION

Ghutka and Mawa are smokeless tobacco products that are commonly used in the Indian subcontinent and also among some immigrant groups living abroad. They usually have areca nut, slaked lime, catechu, paraffin wax, tobacco, and different flavoring agents that can be sweet or spicy, mixed in a powder or small grain-like form [1-2]. When people chew them, the mixture quickly mixes with saliva and causes a reddish-brown color on the teeth and inside of the mouth. With continued use, these stains become permanent and often come with changes in the mouth lining. Use of smokeless tobacco in various forms like betel quid, paan, naswar, and areca nut has been prevalent for centuries in South Asian culture [3]. However, Ghutka and Mawa became more popular during the last two decades because of their cheap cost, ready availability in small sachets, and lack of awareness regarding their harmful effects [4]. The method of intake is simply a pinch placed between the cheek and gum, slowly sucked and chewed, very similar to other forms of tobacco chewing. But unlike traditional forms, Ghutka/Mawa is highly addictive and strongly carcinogenic [5]. Several studies have confirmed the association of Ghutka and Mawa with multiple oral and

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pharyngeal diseases. These include dental caries, gingival recession, oral ulcers, leukoplakia, oral submucous fibrosis, and malignancies of the oral cavity and pharynx [6-7]. The International Agency for Research on Cancer (IARC) classifies areca nut and smokeless tobacco products as Group 1 carcinogens, with a well-documented role in squamous cell carcinoma of the oral cavity [8]. In Pakistan and India, oral cancers are among the most common malignancies, with strong epidemiological links to Ghutka and Mawa consumption [9-10]. The burden is increasing especially in younger age groups, which makes the problem even more alarming for clinicians working in ENT and oral surgery units.

METHODS

This cross-sectional observational study was conducted in the outpatient department of Al-Tibri Medical College and Hospital, Karachi. The study duration was six months, from January 2025 to June 2025. Ethical approval was obtained from the Institutional Review Board (Ref. No. IREC/ATMC/16(02-2024)/01) of Al-Tibri Medical College and Hospital. Written informed consent was taken from every patient before participation. A total of 100 patients were enrolled by non-probability purposive sampling. Sample size was calculated using Cochran's formula for proportions, $n = \frac{Z^2 \cdot p \cdot q}{e^2}$ where n is the required sample size, Z is 1.96 at 95% confidence level, p is the expected prevalence of oral lesions in Ghutka/Mawa users from earlier studies, q = 1-p, and e (margin of error) was taken as 0.05. The minimum sample size came to around 96, but we included 100 patients to make the results more reliable. Patients above 18 years, with a history of Ghutka/Mawa use for at least six months and presenting with oral complaints, were included. Patients with other forms of tobacco use, systemic illnesses causing oral lesions, or those who refused consent were excluded. Data collection was done by taking a short history mainly regarding Ghutka/Mawa consumption habits like duration, frequency, and any combinations. After that, a detailed oral cavity examination was carried out by the investigator, and findings were noted in a structured Performa. In a few patients, although they came for other medical problems, they themselves talked about the Ghutka habit when examined. Data were entered and analyzed using SPSS version 22.0. Descriptive statistics were applied for demographic and clinical variables. Association between Ghutka/Mawa use and oral cavity findings and duration was checked using the Chi-square test, and a p-value ≤0.05 was taken as significant. Data collection was done by taking a short history mainly regarding Ghutka/Mawa consumption habits like duration, frequency, and any combinations. The data collection instrument was a self-designed, structured Performa. To ensure content validity, a panel of three senior ENT specialists and a dental public health expert reviewed it. They had their say in order to enhance the simplicity fand understandability of items. To determine the reliability and feasibility of the Performa, 10 patients (excluding the main study) were piloted on it. The pilot demonstrated the steady knowledge and use of the Performa, and it was not necessary to make any significant change. After that, a detailed oral cavity examination was carried out by the investigator, and findings were noted in this structured Performa.

RESULTS

Out of 100 patients examined, dental problems were the most common complaint (73 cases), followed by trismus (44), pain (40), and chewing difficulty (21). The majority of patients had addiction for 6–20 years, while 11 patients used it for more than 20 years (Table 1).

Table 1: Frequencies of Different Complaints Among Patients and Duration of Addiction

Category	Subcategory	Frequency (n)
Complaints	Chewing	21
	Trismus	44
	Dental Issue	73
	Pain	40
Duration of Addition	Less than 5 years	25
	6-10 years	30
	11-20 years	34
	More than 20 years	11

Ghutka and Mawa showed the highest association with oral lesions. Ulcers were seen in 58 Mawa and 53 Ghutka users, growths in 35 and 29, respectively, while dental issues were frequent in both groups. Other products like niswar, tobacco, pan, and smoking also showed a significant relation, though less frequent. Chi-Square test was applied; level of significance was <0.05 (Table 2).

Table 2: Association of Material of Addiction with Examination Findings

Substances	N	Ulcer (N)	Growth (N)	Dental Issue (N)	p-Value
Gutka	53	35	12	25	0.037
Mawa	58	29	22	15	0.016
Pan	8	2	1	5	0.049
Niswar	10	1	0	0	0.001
Tobacco	15	10	2	3	0.001
Smoking	13	2	1	11	0.001
Supari	15	0	0	15	0.001
Manpuri	1	1	0	0	0.001

With longer duration of use, more severe findings were noted. Less than 5 years of habit showed mostly ulcers and dental issues, while patients with more than 10 years of use had a higher frequency of growths, some suspicious of malignancy. The relation between duration and oral

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findings was statistically significant. Chi-Square test was applied; level of significance was <0.05 (Table 3).

Table 3: Association of Examination Findings with the Duration of Addiction

Duration of Habit	N	Ulcer (N)	Growth (N)	Dental Issue (N)	p-Value
Less than 5 years	25	2	00	22	0.001
6-10 years	30	11	01	18	0.027
11-20 years	34	13	05	16	0.041
More than 20 years	11	6	4	1	0.001

DISCUSSION

The patients who took Ghutka and Mawa in our study had oral complaints that ranged from stains in the teeth and mucosa to actual ulcers and fibrotic alterations. These results can be compared to the previous research in Pakistan and India, the long-term smokeless tobacco use has been reported to induce oral submucous fibrosis, leukoplakia, and even squamous cell carcinoma [11-12]. This mechanism is established, and the alkaloids of the areca nut and tobacco are carcinogens; slaked lime increases the penetration of these carcinogens into the mucosa [13]. Among the notable findings was the fact that a good number of patients were not quite aware of the deleterious consequences of Ghutka/Mawa. This lack of awareness and the low cost render it a significant social health concern, particularly among the low socio-economic populations. These patterns have been recorded in the research of Karachi and other South Asian cities where awareness level regarding the risk of oral cancer is low, and the consumption has been high [14,15]. The results of this paper corroborate the evidence of Ghutka/Mawa being an addictive substance. Admitted patients stated that they could not quit the habit even knowing about the stains and frequent oral ulcers. This addiction is congruent with the pharmacological impact of arecoline (areca nut) and nicotine (tobacco) that are associated with the development of dependence [16]. The addition of paraffin wax and flavoring substances can also be seen as increasing the likability of the product amongst younger users, thus the popularity of adolescents as new consumers can be reported more often [17]. As an ENT, these habits are not restricted to the pathology of the oral cavity. They also diffuse to pharynx and larynx. Past researches have revealed an association with cancers of the oropharynx, trismus secondary to submucous fibrosis and chronic pharyngitis [18-19]. Most of our patients came with irrelevant ENT issues, but when we examined them, we noticed lesions that were clearly a result of Ghutka use. The rising rate of oral cancer cases in Pakistan is also another problem. As Virani *et al.* and other reports have demonstrated many times over, oral cavity cancers are one of the leading cancers in both men and women, and they are primarily associated with the use of smokeless tobacco [20]. This is also supported by our findings and indicates that urgent measures to have been taken in the area of public health. It can be reduced through simple measures such as awareness campaigns, preventing sales around schools and ensuring close scrutiny of sachet manufacturing, primarily among the youth. Our study has several strengths, including the fact that it is limited by a small sample, and it was conducted in a single center. Nevertheless, the findings are not in vain as they reflect a clinical trend that ENT doctors have to deal with on a daily basis. The use of Ghutka and Mawa has a close relationship with oral and throat issues. Even when other complaints are presented to the ENT specialists, they must remain alert to observe early mucosal changes to provide early advice and referrals. Moreover, the non-probability sampling in one hospital OPD has some bias in that the study as well may not reflect the entire community of Ghutka and Mawa users as they may be symptom-free, or are not visiting hospitals. Catching of Ghutka and Mawa related lesions at an early stage should be conducted by regularly examining the mouth in ENT and dental clinics. The dangers of these products should be demonstrated through awareness campaigns, mostly among the younger people. This habit can be prevented with the assistance of schools and community programs. The laws which regulate the selling of Ghutka and Mawa need to be tough and a total ban implemented to check this growing health hazard.

CONCLUSIONS

Our study shows that Ghutka and Mawa use is highly linked with many mouth problems like ulcers, bad teeth, trismus, and some doubtful growths. The severity was more in patients who were using them for long years, mostly above 10 years. Most of the users had very little awareness and visited ENT OPD very late, where we found hidden mouth lesions during a normal checkup. Early finding and good counseling to patients are very important to stop further damage. Public health knowledge and strong control on selling are needed to reduce this bad and growing habit.

Authors Contribution

Conceptualization: VKK
Methodology: VKK, HM
Formal analysis: TMG
Writing review and editing: KI, DK, RK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of Efficacy of Intravenous Dexmedetomidine Versus Intravenous Lidocaine for Attenuation of Stress Response to Laryngoscopy and Endotracheal Intubation in Patients Undergoing General Anesthesia for Elective Surgeries

Yashal Syed[1*], Sheikh Ziarat Ali[1], Mehtab Tipu Chaudhry[1], Samra Ahmad[1], Aqsa Iram[2] and Tahira Nemat[2]

[1]Department of Anesthesia, Sir Ganga Ram Hospital, Lahore, Pakistan
[2]Department of Anesthesia, Fatima Jinnah Medical University, Lahore, Pakistan

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***Corresponding Author:**
Yashal Syed
Department of Anesthesia, Sir Ganga Ram Hospital, Lahore, Pakistan
yashal.syed23@gmail.com

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ABSTRACT

Sympathetic stimulation by laryngoscopy and endotracheal intubation raises blood pressure and heart rate, increases the risk of myocardial ischemia, and increases bleeding. **Objectives:** To evaluate how intravenous dexmedetomidine and lidocaine affect the laryngoscopy stress response. **Methods:** This quasi-experimental research was conducted at Sir Ganga Ram Hospital, Lahore. After receiving ethical approval from Fatima Jinnah Medical University's ERC, July 2022 to August 2023 was set as the timeframe. Consecutive sampling was used to select a total of 136 ASA I–II patients, between the ages of 20 and 40 years, and undergoing elective surgeries. They were divided evenly into two groups. Group D was given IV dexmedetomidine (1 µg/kg over 10 min), and Group L was given IV lidocaine (1.5 mg/kg) before laryngoscopy. Baseline, immediately after intubation, and 1-, 3-, and 5-minute intervals, the hemodynamic parameters (MAP and HR) were recorded. Efficacy was assessed by the total cumulative rise in MAP and HR. SPSS version 26.0 was used for the data analysis. **Results:** The HR and MAP after the intubation were significantly lower for dexmedetomidine compared to lidocaine at all time points ($p<0.001$). The average increases in HR (11.40 ± 2.97 vs. 20.43 ± 6.95 bpm) and MAP (6.99 ± 3.35 vs. 14.19±4.10 mmHg) were lower than those treated with dexmedetomidine. **Conclusions:** Elevation of HR and MAP in all subgroups was lower in those dexmedetomidine than lidocaine. The two drugs demonstrated comparability in safety, although dexmedetomidine was highly effective with haemodynamic stability without additional risk.

INTRODUCTION

Over the past four to five decades, improvements in anesthetic services have dramatically reduced morbidity and mortality among patients undergoing surgery. This drop in mortality is largely the result of more anesthesia providers and the development of safe anesthetic techniques [1]. Securing the airway with endotracheal intubation via direct laryngoscopy remains the gold standard; however, it may have some detrimental effects [2]. Laryngoscopy followed by endotracheal intubation causes sympathetic stimulation via the pharyngeal plexus, resulting in activation of the cardioaccelerator sympathetic outflow from the T1 to T4 segments of the spinal cord and an elevation in circulating catecholamines secreted by the adrenal medulla [3, 4]. This sympathetic stimulation results in positive inotropic, chronotropic, and dromotropic effects. In cardiovascular disease, this rise in BP and HR may lead to ischemic heart injury [5]. Further, it may lead to increased surgical hemorrhage and poor

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visualization of the surgical field. To minimize these detrimental effects, the stress associated with laryngoscopy and intubation should be attenuated [6]. Various studies have stated different methods like prophylactic use of beta blockers, inducing deeper planes of anesthesia, and administration of opioids to minimize the stress response to laryngoscopy [7]. With a short half-life and a higher affinity for alpha-2 receptors, dexmedetomidine is a centrally acting alpha-2 adrenergic agonist. In the spinal cord and central nervous system (CNS), postsynaptic activation of α2 receptors reduces sympathetic activity, which lowers blood pressure and heart rate [8, 9]. According to one study, MAP decreased by about 9% following the administration of dexmedetomidine in comparison to baseline [10]. In patients undergoing laparoscopic cholecystectomy, intravenous dexmedetomidine was found to be more effective in reducing the hemodynamic response. Conversely, lidocaine showed mixed time-related effects on blood pressure and heart rate by continuously inhibiting heart rate arising and keeping systolic and diastolic blood pressure steady and constant [11]. It is indicated that when administered in conjunction, lidocaine and propofol were not inferior in reducing the hemodynamic response to endotracheal intubation and laryngoscopy, and had fewer side effects [12]. It is important to establish whether these two agents are relatively effective in their operation, bearing in mind the clinical significance of dealing effectively with the stress reactions in such a procedure. Available data is still not clear on the comparative efficacy of intravenous lidocaine and dexmedetomidine in the perioperative setting of minimizing the hemodynamic response to laryngoscopy and intubation. This debate will be tackled to achieve better patient outcomes in elective surgery and make significant contributions to anesthetic practice. This research will determine the effect of intravenous dexmedetomidine and Lidocaine on stress response to the laryngoscopy.

METHODS

This quasi-experimental study was conducted in 1 year, that is, between July 2022 and August 2023, in the Sir Ganga Ram Hospital, Lahore, after receiving the approval of the Institute review board of Fatima Jinnah Medical University, Lahore. 136 patients were included in the study via a non-probability consecutive sampling method based on the nature of the intervention applied. The sample size was calculated based on an expected mean difference of 4.9 mmHg in mean arterial pressure (MAP) between the dexmedetomidine group (88.30 ± 10.24) and the Lidocaine group (93.20 ± 10.10), measured 5 minutes post-laryngoscopy and intubation [8]. The study enrolled patients aged 20–40 years of both genders, classified as ASA physical status I or II, scheduled for elective surgery, and who had given informed consent. Exclusion criteria included anticipated or documented difficult intubation, allergy to the study drugs, Mallampati class III or IV airway, uncontrolled hypertension, diabetes mellitus, body mass index (BMI) above 30 kg/m^2, obstetric cases, laryngoscopy lasting more than 15 seconds, or use of beta-blockers. Standardized operational definitions were applied: the stress response was described as transient hemodynamic changes during laryngoscopy and intubation, reflected by elevations in HR and BP. Attenuation of stress response was defined as the difference in MAP and HR from baseline to peak values, assessed immediately after intubation and at 1, 3, and 5 minutes. Efficacy was measured as a lower cumulative change in MAP and HR from baseline across the observation period. Hypotension was defined as MAP <60 mmHg, and bradycardia as HR <50 bpm when associated with hypotension. Based on the anesthetic plan selected by the attending anesthesiologist, patients were split equally into two groups. In Group D, dexmedetomidine (1 µg/kg diluted in 100 mL normal saline) was administered intravenously over 10 minutes, finishing five minutes before induction. Group L was given intravenous lidocaine (1.5 mg/kg) three minutes before intubation and laryngoscopy. Upon arrival in the operating room, patients were monitored using standard equipment (pulse oximetry, non-invasive blood pressure, ECG), and baseline MAP and HR were recorded using a cardiac monitor (model: BSM-2301K). Induction was carried out using IV propofol (1.5–2 mg/kg) followed by atracurium (0.5 mg/kg), and patients were ventilated with 1 MAC isoflurane in 100% oxygen for 3 minutes. Laryngoscopy and endotracheal intubation were performed by the same anesthesiologist for all cases, with confirmation of tube placement through end-tidal CO_2. No surgical stimuli were applied during the 5-minute study period post-intubation MAP and HR, among other hemodynamic parameters, were measured right after intubation and then at 1, 3, and 5 minutes. Phenylephrine (0.5–1 µg/kg) was used to treat hypotension, and atropine (0.01 mg/kg) was used to treat bradycardia. Labetalol (1–2 mg) was used to control tachycardia and hypertension. A structured proforma was used to record demographic and intraoperative variables, including age, gender, BMI, ASA grade, and surgery type. SPSS version 26.0 was used to analyze the data. For both qualitative and quantitative variables, descriptive statistics were computed. The study used a t-test to compare hemodynamic changes and a chi-square test to compare side effects, with a p-value of less than 0.05 indicating statistical significance.

RESULTS

The mean age of participants in Group D was 33.85⁻ 5.51 years and 34.43 ± 4.53 in Group L. There was also a similarity

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in gender distribution, where Group D had 61.8% and Group L had 54.4% males. The average BMI was almost similar in both groups, which was 26.91 +3.93 in Group D and 26.78 +4.11 in Group L. The Majority of the participants in both groups were classified as overweight (64.7% in Group D and 69.1 in Group L), and a smaller proportion of participants were found to have normal BMI. Group D and L had 55.9% and 58.8% patients with ASA I and the rest had ASA II respectively (Table 1).

Table 1: Demographics and Clinical Characteristics of Patients

Characteristics	Group D (N=68)	Group L (N=68)
Age (years)	33.85 ± 5.51	34.43 ± 4.53
20–30 years	22 (32.4%)	20 (29.4%)
31–45 years	46 (67.6%)	48 (70.6%)
Gender		
Male	42 (61.8%)	37 (54.4%)
Female	26 (38.2%)	31 (45.6%)
BMI (kg/m^2)	26.91 ± 3.93	26.78 ± 4.11
Normal weight	24 (35.3%)	21 (30.9%)
Overweight	44 (64.7%)	47 (69.1%)
ASA Status		
ASA I	38 (55.9%)	40 (58.8%)
ASA II	30 (44.1%)	28 (41.2%)

At baseline, both groups showed similar HR (84.99 ± 2.95 vs. 85.43 ± 3.02 bpm) and MAP (92.93 ± 4.08 vs. 93.59 ± 3.55 mmHg; p > 0.05). Following intubation, Group D always exhibited much lower values of HR and MAP at all time points, including the values immediately following intubation (HR: 96.38 4.48 vs. 105.85 7.09bpm; MAP: 99.91 5.65 vs.107.78 5.88mmHg p<0.001). The same trend followed at 1, 3 and 5 minutes. The mean change from baseline in HR (11.40 ± 2.97 vs. 20.43 ± 6.95 bpm) and MAP (6.99 ± 3.35 vs. 14.19 ± 4.10 mmHg) was also significantly lower in Group D (p<0.001), indicating superior attenuation of the hemodynamic response by Dexmedetomidine (Table 2).

Table 2: Comparison of Hemodynamic Changes Between the Study Groups

Intervals	Parameters	Group D	Group L	p-Value
Baseline	HR	84.99 ± 2.95	85.43 ± 3.02	0.391
	MAP	92.93 ± 4.08	93.59 ± 3.55	0.314
Immediately after Intubation	HR	96.38 ± 4.48	105.85 ± 7.09	0.000
	MAP	99.91 ± 5.65	107.78 ± 5.88	0.000
1 Minute Post Intubation	HR	94.00 ± 5.69	103.53 ± 7.34	0.000
	MAP	98.25 ± 5.80	105.24 ± 6.27	0.000
3 Minutes Post Intubation	HR	89.47 ± 4.95	97.54 ± 7.52	0.000
	MAP	94.94 ± 5.73	99.51 ± 6.40	0.000
5 Minutes Post Intubation	HR	86.21 ± 4.76	92.04 ± 7.08	0.000
	MAP	91.88 ± 5.26	96.26 ± 5.92	0.000
Change from Baseline	Δ HR	11.40 ± 2.97	20.43 ± 6.95	0.000
	Δ MAP	6.99 ± 3.35	14.19 ± 4.10	0.000

The incidence of adverse events was low in both groups. Hypotension and bradycardia each occurred in 1 patient (1.5%) in both groups. Arrhythmias were reported in 1 patient (1.5%) in Group D and none in Group L. No cases of allergic reactions were reported. These findings suggest that both Dexmedetomidine and Lidocaine were well-tolerated, with a similar and minimal side effect profile (Table 3).

Table 3: Comparison of Side Effects Among Study Groups

Side Effect	Yes/No	Study Groups		p-Value
		Group D	Group L	
Hypotension	Yes	1 (1.5)	1 (1.5)	1.000
	No	67 (98.5%)	67 (98.5%)	
Bradycardia	Yes	1 (1.5)	1 (1.5)	1.000
	No	67 (98.5%)	67 (98.5%)	
Arrhythmias	Yes	1 (1.5)	0 (0.0)	1.000
	No	67 (98.5%)	68 (100.0%)	
Allergy	Yes	0 (0.0%)	0 (0.0%)	1.000
	No	68 (100%)	68 (100%)	

DISCUSSION

Anesthetic care primarily aims to manage the physiological stress response during surgery, especially in elective procedures. Intravenous lidocaine has long been administered to suppress sympathetic stimulation caused by laryngoscopy and intubation; however, its brief duration of action often limits its effectiveness throughout the peri-intubation period. Dexmedetomidine, which is 2 2-adrenergic agonist, provides a more stable sympathetic blockade as well as regulation of hemodynamic variables, but is still compared with lidocaine [8, 9]. This study compared dexmedetomidine and lidocaine for controlling intubation-induced stress. Participants (mean age 34.14, 58.1% male) had a mean BMI of 26.85. Most were low-risk, classified as ASA I/II (57.4%/42.6%) and Mallampati I/II (56.6%/43.4%), reflecting a typical elective surgery demographic. These attributes are consistent with anesthetic population profiles reported in the past [13, 14]. There was no significant difference between baseline heart rate (HR) and mean arterial pressure (MAP) between the groups (p= 0.391 and p= 0.314, respectively). Patients undergoing lidocaine intubation exhibited a great deal more HR and MAP values at every time point (p<0.001). Conversely, dexmedetomidine was consistently associated with lower values of HR and MAP, which confirms the better suppressive effects of dexmedetomidine on tachycardic and hypertensive emissions after laryngoscopy and intubation, which has also been confirmed by previous studies [15-18]. The increase in HR with dexmedetomidine was 11.40 + 2.97bpm and 20.43 + 6.95bpm with lidocaine (p<0.001). On the same note, MAP rose significantly by 14.19 +4.10 mmHg in the

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lidocaine group (p<0.001). The subgroup analyses were conducted using age, sex, BMI, and ASA categories and indicated that dexmedetomidine provided better hemodynamic control in all the categories. In cases of combination with propofol or dexmedetomidine, the prior research also reported successful hemodynamic stability in the case of lidocaine [12]. It was noted in the past that dexmedetomidine at the level of 1 µg/kg gave the best results and no significant benefit at lower dosages compared to lidocaine [17, 19]. The two groups had similar and rare adverse events. Hypotension and bradycardia were found in 1.5 percent and 1.5 percent respectively, and arrhythmias were observed in 1.5 percent of cases in the dexmedetomidine group and zero percent in the lidocaine group. There were no allergic reactions (p=1.000). The results are in agreement with the past studies that have also recorded these safety profiles [16, 19]. A more recent meta-analysis also determined no general difference in sympathetic response rate between dexmedetomidine and lidocaine, but dexmedetomidine was linked with a little higher rate of bradycardia and sedation [20]. The major strength of this study is that anesthetic protocol was standardized, and using regular monitoring methods improved the reliability of assessment of the hemodynamics. Besides, the results have practical implications on the local clinical population. However, as a single-center study with a small sample size, it cannot be generalized well. Multicenter studies using larger sample sizes should be granted in the future to corroborate these findings and determine the relationship between these findings and long-term hemodynamic stability and postoperative recovery. Also, the quantification of biochemical stress indices including plasma catecholamines and serum cortisol can also be used to further explain the physiological stress response in various anesthetic procedures.

CONCLUSIONS

Despite a little increase in mean arterial pressure and heart rate, dexmedetomidine was proved better than lidocaine in reducing hemodynamics during laryngoscopy and intubation. Its effectiveness was also consistent and was supported by such variables as age, gender, BMI, and ASA score. Also, the side effects were similar in both drugs, and this points out the advantage of dexmedetomidine in maintaining hemodynamic stability without increasing risk.

Authors Contribution

Conceptualization: YS
Methodology: YS, SA
Formal analysis: YS, SA
Writing review and editing: YS, SA, MTC, SA, AT, TN

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Conflicts of Interest

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