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ISSN (E) 2790-9352
ISSN (P) 2790-9344

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ISSN (E) 2790-9352
ISSN (P) 2790-9344

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Aprepitant, When Used with Chemotherapy, Reduces the Risk of Recurrence, Metastasis, And Mortality in Patients with Breast Cancer

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ARTICLE INFO

How to Cite:

Munoz, M. (2026). Aprepitant, When Used with Chemotherapy, Reduces the Risk of Recurrence, Metastasis, And Mortality in Patients with Breast Cancer: Aprepitant in Breast Cancer Outcomes. *Pakistan Journal of Health Sciences*, 7(8), 01-02. <https://doi.org/10.54393/pjhs.v7i8.4537>

The study included a large number of women (n=13,811) who had been treated with chemotherapy and antiemetics for early-stage breast cancer (2008-2020), with follow-up for metastasis and death until 2021. Compared with any other class of antiemetic, researchers determined that the neurokinin-1 receptor (NK-1R) antagonist aprepitant (125 mg on day 1, 80 mg daily on days 2 and 3) proved to significantly improve survival and decreased the risk of metastasis when used in combination with chemotherapy. Triple-negative breast cancer (TNBC) patients had the highest risk reduction, with a rate reduction of 34% for recurrence and 39% for death [1]. In addition, a cohort study of 654 patients showed that aprepitant improved prognosis in chemosensitizer BC patients. Importantly, treatment with the drug was found to be associated with improved overall survival as well as a longer disease-free interval in all three subtypes, such as triple-negative, HR-positive, and HER2-positive BC [2]. These data support the idea that aprepitant enhances the therapeutic effects of standard chemotherapy drugs, which has been previously suggested for the treatment of TNBC [3]. Hence, in this editorial, aprepitant as an NK-1R antagonist is described in terms of the molecular cascades that result in the heightened cellular chemosensitivity, which leads to better antitumor results in BC [3, 4].

There is a growing body of epidemiological evidence highlighting the therapeutic utility of aprepitant as a chemopreventive drug in the treatment of breast BC [1, 2]. Beyond its well-established role in relieving chemotherapy-induced nausea and vomiting (CINV), aprepitant increases the sensitivity of BC cells to cytotoxic agents, while providing multiorgan protection against chemotherapy-induced toxicities, including cardiotoxicity, neurotoxicity, nephrotoxicity, and hepatotoxicity [4]. Standard regimens for BC typically include anthracyclines, taxanes, and cisplatin, the latter being particularly essential in protocols for TNBC. Despite their clinical efficacy, agents such as doxorubicin and cisplatin often lead to chemoresistance, tumor recurrence, and severe systemic toxicity [3]. However, the co-administration of aprepitant with cisplatin or doxorubicin enhances apoptotic pathways and the generation of reactive oxygen species (ROS) specifically in TNBC cells [3]. Furthermore, this combination inhibits the transcription of genes that drive metastasis, inflammation, cell cycle progression, and drug resistance, while protecting functional tissues—for example, against cisplatin-induced cytotoxicity or cisplatin-induced cardiotoxicity [3]. From a mechanistic perspective, these cellular findings offer a plausible explanation for the survival benefits observed in patients with early-stage BC who receive aprepitant in addition to primary chemotherapy. The substance P (SP)/NK-1R signaling axis acts as a key factor in BC pathogenesis [5, 6]. NK-1R expression is ubiquitous in all breast cancer subtypes and is vital for BC cell survival [5]. Elevated plasma levels of SP have been found in clinical cohorts of BC patients, but not in healthy subjects. While SP actively stimulates BC cell proliferation, pharmacological inhibition by NK-1R antagonists, such as L-733,060, L-732,138, and aprepitant, inhibits proliferation and triggers time- and dose-dependent breast cancer cell death [5]. In addition, NK-1R antagonists, such as aprepitant, inhibit neovascularization and exhibit anti-metastatic properties by suppressing the invasion and migration of BC cells [6].

Off-label applications. A clinical trial in HIV-positive patients demonstrated that aprepitant administered at a daily dose of 375 mg for two weeks was safe and well-tolerated. This regimen effectively reduced CD4+ cells expressing PD-1, as well as circulating levels of soluble CD136 and SP [3, 6]. Furthermore, a case study of a lung cancer patient who received palliative radiotherapy combined with compassionate use aprepitant (1140 mg daily for 45 days) showed complete regression of an 8 × 7 cm tumor mass following treatment. Notably, the patient experienced no serious adverse events throughout the course of therapy [3, 6].

In conclusion, epidemiological data indicate that adding aprepitant to chemotherapy regimens for BC—specifically, TNBC—is associated with lower rates of recurrence, distant metastasis, and overall mortality. At the same time, laboratory studies show that combining aprepitant with standard drugs, such as doxorubicin or cisplatin, enhances the elimination of BC cells and offers protection against treatment-related toxicities. Proposed next steps. Phase I: Dose escalation: Evaluate the safety and tolerability of higher doses of aprepitant, beyond standard antiemetic regimens, to achieve therapeutic saturation. Phase II: Clinical evaluation: Evaluate clinical efficacy, overall survival, and recurrence-free survival when administered in combination with systemic chemotherapy in patients with TNBC.

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Original Article

Comparison of Mean Duration of Postoperative Analgesia Following QL2 Block Versus QL3 Block Using Ropivacaine 0.25% In Patients Undergoing Unilateral Inguinal Hernia Repair

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ARTICLE INFO

Keywords:

Ropivacaine, Inguinal Hernia, Regional Anaesthesia, Quadratus Lumborum Block, Analgesia, Visual Analogue Scale

How to Cite:

Ayaz, M., Khan, A., Mahmood, A., Usman, M., Ahmad, Q. A., Iqra, ., Kokab, Q., & Hammad, M. (2026). Comparison of Mean Duration of Postoperative Analgesia Following QL2 Block Versus QL3 Block Using Ropivacaine 0.25% In Patients Undergoing Unilateral Inguinal Hernia Repair: Comparison of Postoperative Analgesia Duration: QL2 vs QL3 Blocks in Inguinal Hernia Repair. Pakistan Journal of Health Sciences, 7(8), 03-08. <https://doi.org/10.54393/pjhs.v7i8.3596>

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ayazm2618@gmail.comReceived Date: 12th November, 20251st Revision Received: 23rd December, 20252nd Revision Received: 2nd March, 20263rd Revision Received: 30th March, 2026Acceptance Date: 7th April, 2026Published Date: 31st August, 2026

ABSTRACT

Effective postoperative pain management after inguinal hernia repair enhances recovery and reduces opioid use. Among quadratus lumborum block variants, evidence remains uncertain as to whether the posterior (QLB-2) or trans-muscular (QLB-3) approach provides superior analgesia. **Objectives:** To compare the mean duration of postoperative analgesia produced by posterior quadratus lumborum block (QLB-2) and trans-muscular quadratus lumborum block (QLB-3) using 0.25% ropivacaine in patients undergoing unilateral inguinal hernia repair. **Methods:** The randomised controlled trial was conducted in the Department of Anaesthesia at Bahawal Victoria Hospital, Bahawalpur, from July to December 2024. Sixty-four male patients aged 18-50 years who underwent unilateral inguinal hernia repair under general anaesthesia were included and randomly divided into two groups of 32 participants each. Group QLB-2 was given the posterior quadratus lumborum block, and Group QLB-3 was given the trans-muscular approach. Twenty millilitres of 0.25% ropivacaine was applied in both groups under ultrasound guidance. The visual analogue scale (VAS) was used to measure postoperative pain, and the duration of analgesia was defined as the time from entering the recovery room to achieving a VAS score >3. **Results:** The mean time to first analgesic request was significantly longer in QLB-3 (457.7 ± 161.3 min) than in QLB-2 (271.8 ± 94.6 min; p<0.001). Rescue analgesia was required in 40.6% of QLB-3 and 62.5% of QLB-2 patients. **Conclusions:** The trans-muscular quadratus lumborum block provided significantly longer and more effective postoperative analgesia than the posterior approach using 0.25% ropivacaine in unilateral inguinal hernia repair.

INTRODUCTION

The ultrasound-guided quadratus lumborum block (QLB) is a developing regional anaesthetic technique that provides consistent postoperative analgesia during abdominal and pelvic surgery. The procedure was originally described by Blanco and involves the placement of local anaesthetic in the fascial plane adjacent to the quadratus lumborum (QL) muscle. As such, it provides both somatic and visceral

analgesia by diffusing into the thoracolumbar space and subsequently blocking the thoracolumbar nerves. Proper management of postoperative pain in inguinal hernia repair is crucial in early mobilisation and reducing the effects of systemic opioid use that may result in complications [1, 2]. Several variants of QLB have been developed, with the primary difference being the targeted plane of anatomy



and the spread pattern. The lateral (QLB-1) and posterior (QLB-2) methods inject anaesthetic along the lateral or posterior of the QL muscle, but the trans-muscular (QLB-3) method injects the needle through the QL into the interfascial space between the QL and psoas major muscles. It is hypothesised that this increased positioning will increase cephalad drug dispersal and produce a more widespread analgesic effect. This deeper placement potentially enhances cephalad drug spread and produces more extensive analgesia [3-5]. Several randomised trials have compared QLB variants. Ahmed *et al.* reported that QLB-3 produced significantly more prolonged analgesia and lower morphine consumption than QLB-2 using 20 mL of 0.25% bupivacaine in unilateral inguinal hernia repair [6]. Bagbanci *et al.* similarly observed lower VAS scores and decreased fentanyl use in QLB-3 recipients [7]. However, most available evidence originates from international populations, with limited evaluation in local surgical settings.

Although these results exist, most evidence is based on international cohorts; no studies have yet directly compared posterior and transmuscular QLB in hernia repair in Pakistan. Ropivacaine 0.25% was used in the current study, as recommended by institutional practice guidelines and supported by previous evidence indicating its effectiveness in achieving long-term sensory blockade with a favourable safety profile. It was hypothesized that the trans-muscular method (QLB-3) would provide a much longer postoperative analgesia period than the posterior method (QLB-2) in local patients. This study aimed to compare the mean time to postoperative analgesia induced by QLB-2 and QLB-3 after administration of 0.25% ropivacaine in patients undergoing unilateral inguinal hernia repair.

METHODS

The randomised controlled trial was conducted in the Department of Anaesthesia at Bahawal Victoria Hospital in Bahawalpur from July to December 2024, vide letter number: 2315/DME/QAMC issued on 14th November 2023 and trial registration number (NCT07200076). The sample size of 64 was calculated with 5% significance and 95% power, based on the mean block durations of 220.1 ± 6 hours (QLB-3) and 12.0 ± 4.8 hours (QLB-2) [6]. All patients were recruited using non-probability consecutive sampling. The random sequence was created by an independent staff member using a lottery system with identical slips of paper. To prevent bias, these slips were kept in sealed, opaque envelopes that were only opened right before the procedure, ensuring the doctors did not know the group assignment beforehand. The inclusion criteria were male patients aged 18-50 years, ASA physical status I-II, and scheduled to undergo unilateral inguinal

hernia repair under general anaesthesia. Strangulated hernia, local infection at the puncture site, hypersensitivity to local anaesthetics, or coagulation abnormality (INR > 1.5) were considered as the exclusion criteria. Of 95 patients assessed, 36 were excluded, and 64 were randomized equally to the QLB-2 and QLB-3 groups; all participants in both groups were included in the final analysis (Figure 1).

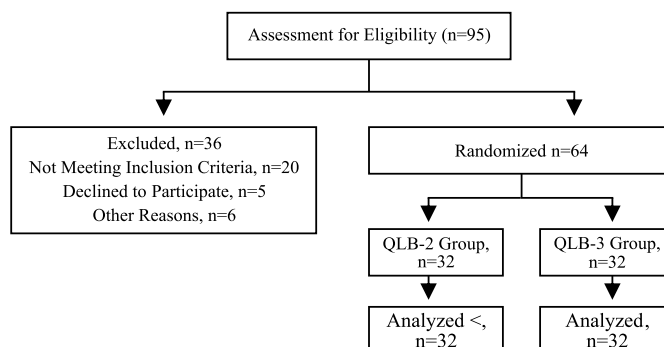


Figure 1: CONSORT Flow Diagram of Patient Enrollment, Randomization, and Analysis

All participants provided written informed consent. Standard premedication of all patients was metoclopramide 10 mg and nalbuphine 0.1mg/kg. Propofol 2 mg/kg and suxamethonium 11.5 mg/kg were used to induce. Nitrous oxide (50% oxygen) was used for anesthesia, supplemented with isoflurane (1-1.5%). Atracurium was used to relax the muscles (0.5mg/kg at the start, 0.1-0.2mg/kg). All blocks were performed by senior anesthesiologists in a sterile setting under ultrasound guidance. To ensure consistency and reduce differences in results, the technique was standardized; every practitioner used the same needle orientation and applied slow, steady injection pressure to achieve a uniform spread of the medicine. In QLB-2, 20 mL of 0.25% ropivacaine was injected into the posterior fascial plane of the QL muscle below the middle thoracolumbar fascia. The needle was placed through the QL, and 20 mL of 0.25% ropivacaine was injected between the QL and the psoas major muscles in QLB-3. Patients were put in a supine position after the block and were extubated after reversal with neostigmine and glycopyrrolate. All patients were monitored indoors and assessed at specific time points (30 minutes, 2, 4, 8, 12, and 24 hours) after surgery. Pain intensity was assessed using the Visual Analogue Scale, a 10-cm horizontal line ranging from 0 (no pain) to 10 (the worst imaginable pain) [6, 7]. The duration of analgesia was defined as the time the patient remained in the recovery room until the VAS reached a set point of 3. To minimize measurement bias, these observations were conducted by an assessor unaware of the block type. Rescue analgesia was defined as the intravenous administration of Tramadol at 1mg/kg immediately after a patient had a VAS score > 3. All the data were processed with SPSS version 26.0.

Quantitative variables (age, BMI, duration of analgesia) were reported as mean $\pm$ SD; qualitative variables (ASA status, necessity to resort to rescue) were reported as frequencies and percentages. The means were compared using an independent-samples t-test after checking the normality assumptions, and the categorical associations were evaluated using a chi-square test with a p-value of 0.05 as the significance level. Post-stratification analyses for age, BMI, and ASA groups were pre-specified in the study protocol to ensure the block's efficacy was consistent across different patient characteristics.

RESULTS

The study included 64 patients, equally divided into two groups (32 patients per group). The mean age was 34.2 ± 9.4 years (range: 18-50), and the mean BMI was 22.54 ± 2.78 kg/m². Among all participants, 35 patients (54.7%) were

classified as ASA physical status I, and 29 patients (45.3%) were classified as ASA II. In the QL2 group, 20 patients (62.5%) required rescue analgesia, while 12 patients (37.5%) remained pain-free without additional medication. In the QL3 group, 13 patients (40.6%) required rescue analgesia, while 19 patients (59.4%) did not. The difference in rescue analgesia requirement between the two groups was not statistically significant ($\chi^2=3.065$, $p=0.080$, Cramér's $V=0.080$). The mean time to the first analgesic request was 457.68 ± 161.27 minutes in the QL3 group and 271.78 ± 94.59 minutes in the QL2 group ($p<0.001$). The mean difference of 185.9 minutes (95% CI: 119.83-251.97) indicated a significantly longer analgesic duration with the trans-muscular approach. The trans-muscular method (QL3) always offered a much longer average time to the first analgesic request than the posterior method (QL2) in all age groups and BMI subgroups (Table 1).

Table 1: Comparison of Mean Time to First Analgesic Request (Minutes) Between QL2 (Posterior) and QL3 (Trans-muscular) Groups According to Age, ASA Grade, and BMI Category

Variables	Categories	QL2 (Posterior)	QL3 (Trans-muscular)	t-test results (t, df, p-value)
Age Group	18-30 years	301.65 $\pm$ 75.43	427.37 $\pm$ 181.20	(t=-2.124, df=20, p=0.046)
	31-40 years	236.33 $\pm$ 62.14	500.84 $\pm$ 173.16	(t=-4.769, df=20, p<0.001)
	41-50 years	277.93 $\pm$ 132.44	443.56 $\pm$ 127.12	(t=-2.853, df=18, p=0.011)
Asa Grade	I	294.25 $\pm$ 102.22	433.37 $\pm$ 146.28	(t=-3.315, df=33, p=0.002)
	II	234.34 $\pm$ 68.72	479.14 $\pm$ 174.99	(t=-4.583, df=27, p<0.001)
BMI Category	Normal weight	270.64 $\pm$ 101.44	434.26 $\pm$ 155.63	(t=-4.5777, df=52, p<0.001)
	Overweight	277.98 $\pm$ 48.98	584.16 $\pm$ 142.93	(t=-4.531, df=8, p=0.002)

Although QL3 tended to require less rescue analgesia, these relationships were statistically significant only in specific patient groups, including those aged 31-40 years and those with ASA I status (Table 2).

Table 2: Association Between Patient Characteristics (Age, ASA Grade, And BMI Category) and the Requirement of Rescue Analgesia in QL2 (Posterior) and QL3 (Trans-muscular) Groups

Variables	Category	Rescue Analgesia	QL2 (Posterior)	QL3 (Trans-muscular)	Chi-square test (χ^2 , df, p-value)
Age Group	18-30 years	No	7 (31.8%)	5 (22.7%)	$\chi^2=0.733$, df=1, p=0.392, Cramér's V=0.392
		Yes	4 (18.2%)	6 (27.3%)	
	31-40 years	No	2 (9.1%)	7 (31.8%)	$\chi^2=4.701$, df=1
		Yes	9 (40.9%)	4 (18.2%)	
	41-50 years	No	3 (15.0%)	7 (35.0%)	$\chi^2=3.200$, df=1, p=0.074, Cramér's
		Yes	7 (35.0%)	3 (15.0%)	
ASA Grade	I	No	10 (28.6%)	10 (28.6%)	$\chi^2=0.972$, df=1
		Yes	10 (28.6%)	5 (14.3%)	
	II	No	2 (6.9%)	9 (31.0%)	$\chi^2=3.932$, df=1
		Yes	10 (34.5%)	8 (27.6%)	
BMI Category	Normal weight	No	10 (18.5%)	16 (29.6%)	$\chi^2=2.670$, df=1, p=0.102, Cramér's V=0.102
		Yes	17 (31.5%)	11 (20.4%)	
	Overweight	No	2 (20.0%)	3 (30.0%)	$\chi^2=0.400$, df=1, p=0.527, Cramér's V=0.527
		Yes	3 (30.0%)	2 (20.0%)	

DISCUSSION

This study demonstrated that the trans-muscular quadratus lumborum block (QL3) provided significantly more prolonged analgesia than the posterior method (QL2) in patients undergoing unilateral inguinal hernia repair with 0.25% ropivacaine. The analgesic time was approximately 3 hours longer with QL3, demonstrating the superiority of the trans-muscular

technique. Although fewer QL3 patients required rescue analgesia, the difference was not statistically significant, consistent with previous research by Ahmed *et al.* and Bagbanci *et al.* [6, 7]. The increased action of QL3 can be explained by the diffusion of the local anaesthetic between the QL and psoas major muscles, which can be extended to the thoracolumbar space and block thoracolumbar nerves T7-L1 [8]. Conversely, the posterior technique primarily focuses on the lateral branches, providing minimal coverage of the viscera. Similar findings have been documented in several abdominal operations [9]. Caparlar *et al.* found superiority of posterior QL3 over posterior TAP block in hernia surgery [10]. Fouad *et al.* compared the transversalis fascia plane (TFP) block with QL3 and found similar pain scores but more frequent rescue needs with TFP [11]. Mostafa *et al.* reported that QL3 provided longer-lasting pain relief than the ilioinguinal-iliohypogastric block [12]. According to a meta-analysis by Korgvee *et al.* (1,557 patients), QL3 increased the time to first rescue by 189 minutes and decreased 24-hour morphine equivalent consumption by 11 mg [1], which is nearly the same as the difference observed in our study. Similar results were reported by Gao *et al.* who found that analgesic requirements were lower with QL3 than with TAP block [13]. Kumar *et al.* compared various variants of QL3 in adult hernia patients and discovered that the trans-muscular (anterior) technique resulted in the lowest 24-hour fentanyl use and pain scores [8]. Paediatric research by El Malla *et al.* and Altinay *et al.* has demonstrated that deeper fascial injections result in longer analgesia and lower pain scores [14, 15]. Abdelbaser *et al.* reported similar effectiveness of the lateral QL3 and TFP blocks in children, indicating that tissue compliance affects the spread [16]. In hip and pelvic surgery, Gutierrez *et al.* demonstrated that QL3 was noninferior to lumbar plexus block for analgesia and associated with fewer motor deficits [17]. In their meta-analysis, Gong *et al.* also reported that QL3 reduced rest pain and opioid use following hip surgery [9]. On the other hand, Brixel *et al.* found that more fentanyl is needed with continuous QL3 than with a constant psoas compartment block, implying that more profound joint surgeries might demand plexus blockade [18]. Hung *et al.* conducted a review of paediatric trials and found that QL3 was the longest time to first rescue in inguinal surgeries among regional blocks [19]. Local evidence from Jadoon *et al.* in Pakistan confirmed that analgesic requirements were lower with QL3 than with TAP block [20]. The superior effect of the trans-muscular quadratus lumborum block Type 3 (QL3) is particularly significant in the local context of Pakistani surgical practice, where early mobilisation is actively encouraged after surgery. Although regional anatomic differences among the Pakistani population may

theoretically alter the distribution of local anaesthetics, the results for all age groups, body mass index, and American Society of Anaesthesiologists (ASA) classification groups have shown that the trans-muscular approach is effective, irrespective of these demographic factors. The analgesic advantage of approximately 3 hours offered by QL3 is incremental, consistent with findings from other meta-analyses in other countries. These studies indicate that the greater the spread of local anaesthetic offered by the technique, the greater the benefit, which is universal and can be easily applied to our clinical setting. The implementation of QL3 into local practice is a reliable approach to enhancing the postoperative recovery and preventing early opioid dependence in our patient population.

This is a single-centre study with several methodological limitations. Although the cohort size was sufficient to identify a statistically significant difference in the primary outcome of analgesia duration, it may not have had sufficient power to detect differences in secondary outcomes, including the need for rescue analgesia. The relatively small sample size did not permit the observation of rare adverse events. Possible confounding factors that might influence analgesic time, such as individual surgical factors and surgeon competence, were not controlled. The inclusion of male patients only limits the generalisability of these findings to female populations. Dermatome mapping to accurately define block spread was not done, and the analysis was limited to short-term outcomes.

CONCLUSIONS

In unilateral inguinal hernia repair, trans-muscular QL3 (QL3) provided significantly longer postoperative analgesia than posterior QL3 (QL2) with 0.25% ropivacaine, independent of age, BMI, or ASA status. Its superior analgesic duration and opioid-sparing effect support QL3 as a preferred technique for lower abdominal surgeries.

Authors' Contribution

Conceptualization: MA

Methodology: MA, AM, MH

Formal analysis: MA, AK, MU, QAA, QK

Writing and Drafting: MU, I

Review and Editing: MA, AK, AM, MU, QAA, I, QK, MH

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Determination of Association between Onychoscopy Features and Nail Plate Potassium Hydroxide Test Positivity in Diagnosis of Onychomycosis: A Cross-Sectional Study

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ARTICLE INFO

Keywords:

Onychoscopy, Onychomycosis, Onychoscopic Features, Onycholysis, Jagged Edge, Potassium Hydroxide Microscopy

How to Cite:

Tahir, K., Hanif, S., Shaukat, R., Hamadani, A., Chattha, A. A., Kausar, I., & Nabi, H. (2026). Determination of Association between Onychoscopy Features and Nail Plate Potassium Hydroxide Test Positivity in Diagnosis of Onychomycosis: A Cross-Sectional Study: Onychoscopy Features and Nail Plate Potassium Hydroxide Test Positivity in Onychomycosis. *Pakistan Journal of Health Sciences*, 7(8), 09-14. <https://doi.org/10.54393/pjhs.v7i8.3925>

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ABSTRACT

Onychomycosis is a common chronic fungal infection of the nails, causing significant physical and psychological morbidity. In Pakistan, access to fungal culture and molecular diagnostics is limited, creating a need for non-invasive, rapid, and cost-effective diagnostic tools. **Objectives:** To determine the association between onychoscopic features and KOH positivity in clinically suspected onychomycosis. **Methods:** This cross-sectional observational study was conducted in the Department of Dermatology, Ghurki Trust and Teaching Hospital, Lahore, Pakistan, from 7 August 2025 to 10 January 2026. A total of 52 patients with clinically suspected onychomycosis were enrolled. Each patient underwent onychoscopic examination followed by nail plate potassium hydroxide (KOH) testing for fungal confirmation. Onychoscopic features, including onycholysis, jagged edge with spikes, longitudinal striae, subungual hyperkeratosis, and chromonychia, were documented. Sensitivity, specificity, predictive values, and diagnostic accuracy were calculated for each feature using KOH microscopy as the reference standard. **Results:** KOH test was positive in 82.7% of cases. Onycholysis had the highest sensitivity (86.1%) while jagged edge with spikes demonstrated the highest specificity (88.9%). Onycholysis was significantly associated with KOH positivity ($p=0.026$), and jagged edge with spikes also showed a highly significant association ($p=0.002$). The combination of jagged edge and onycholysis yielded an accuracy of 76.9%. Chromonychia ($p=0.160$) and longitudinal striae ($p=0.716$) showed weaker associations. **Conclusions:** Specific onychoscopic features, particularly jagged edges with spikes and onycholysis, demonstrated a significant association with KOH positivity. However, given variability in sensitivity and specificity, these findings should be interpreted alongside confirmatory testing (culture or PCR, where available) rather than as standalone diagnostic criteria.

INTRODUCTION

Onychomycosis is a chronic fungal infection of the nails with a global prevalence of 2-13% [1-3]. It is characterized by the invasion of pathogenic fungi into the nail unit. The primary causative agents are dermatophytes such as *Trichophyton*, *Epidermophyton*, and *Microsporum*, with *Candida* species contributing a smaller proportion [4, 5]. Predisposing factors include prolonged exposure to humid

environments, impaired immunity, disturbed peripheral circulation, poor hygiene, and compromised nail integrity due to trauma or pre-existing nail disorders [5, 6]. The main clinical subtypes are distal and lateral subungual onychomycosis (DLSO) involving the distal and lateral edges, proximal subungual onychomycosis (PSO) manifesting as white/yellow patches at the nail base,



superficial white onychomycosis presenting as powdery nail surface patches, and total dystrophic onychomycosis (TDO) in which the whole nail is deformed and crumbled [4, 7]. Clinically, onychomycosis manifests with progressive alteration in nail appearance and texture, including brittleness, thickening, discoloration, accumulation of subungual debris, and separation of the nail plate from the underlying nail bed. These changes lead to discomfort, foul odor, pain, functional impairment, and significantly impact the patient's psychological well-being and social interactions [2]. Onychomycosis can be diagnosed using several methods, such as potassium hydroxide (KOH) mount testing, fungal culture, and polymerase chain reaction (PCR) [8-10]. Nail plate KOH test is an inexpensive, rapid method, involving the microscopic examination of nail clippings after treating with KOH solution, which dissolves the nail keratin and preserves the fungal elements [11]. However, KOH testing has limited specificity (38-78%) and relatively high false-negative rates, particularly in early or subtle infections. In contrast, fungal culture is traditionally considered the reference method for confirming the presence of fungal infection but has drawbacks of low sensitivity (31-59%) and requires prolonged incubation time, limiting its utility for immediate diagnosis [12, 13]. PCR is a highly sensitive method, but it is constrained by accessibility due to technical requirements and cost. These limitations highlight the need for more accessible and rapid adjunctive diagnostic approaches. Onychoscopy is a non-invasive diagnostic technique in which a handheld dermoscope (a magnifying device with a built-in light source) is used to examine the nail morphology [14]. The characteristic onychoscopic features include longitudinal striae, jagged edges with spikes, onycholysis, subungual hyperkeratosis, and chromonychia [15]. Onychoscopy helps distinguish different types of onychomycoses as well as differentiate them from other nail disorders [16, 17]. This minimizes the need for unnecessary biopsies while simultaneously optimizing diagnostic accuracy [15, 18]. Accurate and cost-effective diagnostic strategies are essential to prevent misdiagnosis and inappropriate therapy [19, 20].

In resource-limited settings such as Pakistan, confirmatory testing is not routinely available for all patients, which may contribute to inadequate management. Additionally, without laboratory confirmation, treatment failure cannot be reliably differentiated from misdiagnosis. The diagnostic performance of individual onychoscopic features in predicting KOH positivity has not been adequately evaluated in the local population. This study aimed to determine the association between onychoscopic features and nail plate KOH positivity in patients with clinically suspected onychomycosis.

METHODS

This cross-sectional observational study was conducted in the Department of Dermatology, Ghurki Trust Teaching Hospital, Lahore, Pakistan, from 7 August 2025 to 10 January 2026. Ethical approval was obtained from the Institutional Review Board (IRB no: 16981/23 ; dated 9th October 2023). The target population comprised all adult patients presenting with clinically suspected onychomycosis to the Dermatology Outpatient Department during the study period. Sample size of 52 patients was calculated with WHO calculator using the formula $n = Z^2 \times p \times (1 - p) / e^2$, where $Z = 1.96$ for 95% confidence level, $e = 9.4\%$ as margin of error, taken as 0.094, and $p =$ proportion (expressed as a decimal), taken as 0.862 assuming a sensitivity of 86.2% for dermoscopy [2]. Substituting these values: $n = (1.96)^2 \times 0.862 \times (1 - 0.862) / (0.094)^2$, $n = 51.7$, which was rounded up to 52 participants. Non-probability consecutive sampling was employed. Written informed consent was obtained from all participants. Eligible participants were adults older than 18 years of either sex who presented with clinical features suggestive of onychomycosis, such as nail discoloration, onycholysis, or subungual hyperkeratosis. Patients were excluded if they had pre-existing nail disorders such as psoriasis or lichen planus, onychodystrophy secondary to systemic disease, a history of systemic antifungal therapy within the previous 3 months, or if they were pregnant or lactating. All onychoscopic assessments were performed by a single trained observer to ensure consistency, with no blinding. Onychoscopy was performed using a handheld dermoscope (Heine Delta, 10x magnification) in both non-polarized and polarized modes. Onychoscopic features, including onycholysis, jagged edges with spikes, subungual hyperkeratosis, longitudinal striae, chromonychia, and distal irregular termination, were documented as present or absent and photographed. Following this, nail clippings and subungual debris were collected using a nail clipper and probe. The samples were immersed in 20% KOH solution for 24 hours to facilitate the clearing of thick keratinized tissue to ensure thorough keratin dissolution [21]. Microscopic examination was performed at 10x and 40x magnification for the presence of fungal hyphae or spores. The KOH test results were classified as either positive (presence of fungal structures) or negative (absence of fungal structures).

Data were analyzed using SPSS version 20.0. Categorical variables were summarized as frequencies and percentages. The association between onychoscopic features and KOH test positivity was assessed using Fisher's exact test. Estimation of population parameters was performed by calculating 95% confidence intervals using the exact binomial (Clopper-Pearson) method for

sensitivity and specificity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to assess diagnostic performance. Combinations of onychoscopic features were evaluated using AND logic (both features had to be present in a patient to be considered positive). A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 52 patients were included, with a female predominance (80.8%). The KOH test was positive in 43/52 cases (82.7%). KOH positivity was observed in 36/42 females (85.7%) and 7/10 males (70%). The results show the distribution of KOH results according to gender. Columns indicate the number of KOH-positive and KOH-negative cases among females (n=42) and males (n=10) (Figure 1).

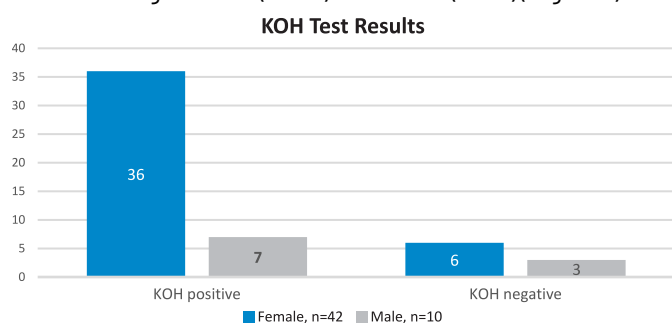


Figure 1: Distribution of KOH Results by Gender

The most common age group was 20 – 30 years. KOH positivity across age groups was 15/17 (88.2%) in 20 – 30 years, 4/6 (66.7%) in 30 – 40 years, 11/15 (73.3%) in 40 – 50 years, 6/6 (100%) in 50 – 60 years, and 7/8 (87.5%) in 60 – 70 years. Distal lateral subungual onychomycosis (DLSO) was the most common clinical subtype, followed by total dystrophic onychomycosis (TDO). KOH positivity varied across clinical subtypes, with 33/37 DLSO cases (89.2%) and 8/11 TDO cases (72.7%) testing positive. Both superficial white onychomycosis (SWO) cases were positive, whereas neither of the two proximal subungual onychomycosis (PSO) cases showed KOH positivity. Demographic and clinical characteristics of study participants are summarized (Table 1).

Table 1: Demographic and Clinical Characteristics of Patients, Including Gender, Age Group (Years), Disease Duration, and Subtype Classification

Parameters	Category	n (%)
Gender	Female	42 (80.8%)
	Male	10 (19.2%)
Age Group (years)	20 – 30	17 (32.7%)
	30 – 40	6 (11.5%)
	40 – 50	15 (28.8%)
	50 – 60	6 (11.5%)
	60 – 70	8 (15.4%)

Disease Duration	<6 Months	14 (26.9%)
	6 – 12 Months	22 (42.3%)
	12 – 24 Months	11 (21.2%)
	>24 Months	5 (9.6%)
Clinical Subtype	Distal and Lateral Subungual Onychomycosis	37 (71.2%)
	Total Dystrophic Onychomycosis	11 (21.2%)
	Proximal Subungual Onychomycosis	2 (3.8%)
	Superficial White Onychomycosis	2 (3.8%)

Among the observed onychoscopic features, onycholysis (76.9%), jagged edge with spikes (67.3%), and chromonychia (55.7%) were the most frequent findings. The findings summarize the frequency distribution of key onychoscopic features stratified by KOH status. Columns show counts of cases with the feature, stratified by KOH status (positive or negative); percentages in parentheses indicate proportion of total sample with that feature (Figure 2).

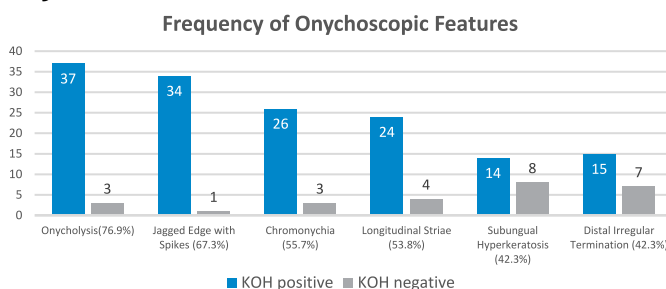
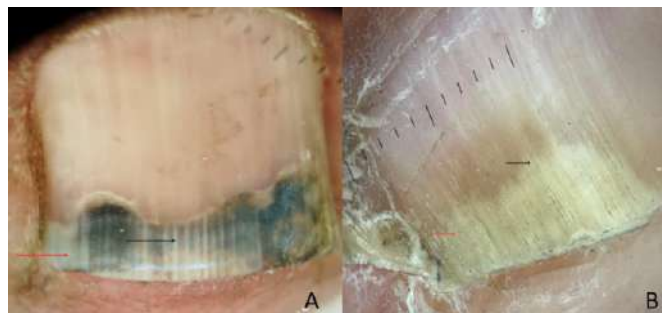


Figure 2: Frequency Distribution and KOH Positivity of Key Onychoscopic Features

Onychoscopic patterns appeared broadly similar across gender and age groups but demonstrated variation across clinical subtypes. DLSO showed higher frequencies of onycholysis (94.6%) and jagged edge with spikes (78.4%), whereas TDO more commonly demonstrated distal irregular termination (90.9%) and subungual hyperkeratosis (72.7%). Interpretation for PSO and SWO was limited due to small case numbers. Representative clinical photographs are provided. (A) Longitudinal striae (black arrow) and distal onycholysis (red arrow). (B) Jagged edges with spikes (black arrow) and distal onycholysis (red arrow). (C) Jagged edges with spikes (black arrow) and distal irregular termination (red arrow). (D) Chromonychia (yellow and black discoloration) (Figure 3).



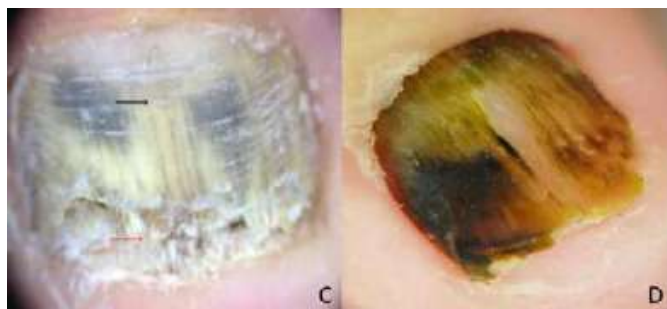


Figure 3: Representative Onychoscopic Images (A-D)

Both onycholysis and jagged edge with spikes demonstrated significant statistical associations with KOH results. Onycholysis showed the highest sensitivity (86.1%), whereas jagged edge with spikes demonstrated the

highest specificity (88.9%) and positive predictive value (97.1%). The features like subungual hyperkeratosis and distal irregular termination also showed statistically significant associations; however, both demonstrated low specificity and modest accuracy. Chromonychia showed moderate diagnostic performance (sensitivity 60.5%, specificity 66.7%) and did not demonstrate a strong association with KOH positivity. Longitudinal striae, although frequently observed, showed limited specificity and no statistically significant association with KOH results. Detailed sensitivity, specificity, positive predictive value, negative predictive value, p-values, and diagnostic accuracy for each feature are presented (Table 2).

Table 2: Sensitivity, Specificity, PPV, NPV, and Diagnostic Accuracy for Each Onychoscopic Feature in Comparison with KOH Positivity

Features	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value %	Negative Predictive Value %	p-value	Diagnostic Accuracy %
Jagged Edge with Spikes	79.1 (63.9–89.9)	88.9 (56.5–98.0)	97.1%	47.0%	0.002	80.7%
Onycholysis	86.1 (72.1–94.7)	66.6 (29.9–92.5)	92.5%	50.0%	0.002	82.6%
Longitudinal Striae	55.8 (40.0–70.4)	55.5 (21.2–86.3)	85.7%	20.8%	0.716	55.7%
Subungual Hyperkeratosis	32.5 (20.2–48.0)	11.1 (0.3–48.2)	63.6%	3.3%	0.002	28.8%
Chromonychia	60.4 (44.4–74.9)	66.6 (29.9–92.5)	89.6%	26.1%	0.160	61.5%
Distal Irregular Termination	34.9 (22.9–49.6)	22.2 (2.8–60.0)	68.2%	6.6%	0.026	32.6%

Legend: CI = Confidence Interval

To evaluate whether combinations of multiple features improved predictive performance, predefined combinations were analyzed. Combinations such as onycholysis with jagged edge, longitudinal striae with jagged edge, and onycholysis with chromonychia were evaluated. Among these, the combination of onycholysis and jagged edge demonstrated the highest diagnostic accuracy (76.9%). The study reports the diagnostic performance of combined onychoscopic features using KOH positivity as the reference standard (Table 3).

Table 3: Diagnostic Accuracy of Combined Onychoscopic Features Using AND Logic

Combinations	Sensitivity %	Specificity %	Diagnostic Accuracy %
Jagged Edge + Onycholysis	74.4%	88.9%	76.9%
Longitudinal Striae + Jagged Edge	44.2%	88.9%	51.9%
Chromonychia + Onycholysis	53.5%	88.9%	59.6%

Legend: AND Logic = Both features have to be present

DISCUSSION

This study evaluated the association between specific onychoscopic features and KOH positivity in patients with suspected onychomycosis. The observed female predominance (80.8%) in our study may partly be related to socioeconomic factors, including frequent wet work and a greater likelihood of seeking medical care for nail-related cosmetic concerns [22]. The high KOH positivity rate

(82.7%) likely reflects the predominance of DLS0, which constituted the majority of cases and demonstrated high positivity (89.2%). The limited number of other subtypes restricts meaningful comparison across clinical patterns. Among individual patterns, jagged edge with spikes demonstrated the highest specificity (88.9%), while onycholysis showed the highest sensitivity (86.1%). Although subungual hyperkeratosis and distal irregular termination showed statistically significant association with KOH positivity, both showed low specificity and modest overall accuracy, limiting their usefulness as standalone predictors. These patterns may reflect non-specific or advanced nail dystrophy rather than definitive fungal infection and should therefore be interpreted cautiously. The combined presence of jagged edge with spikes and onycholysis improved overall accuracy (76.9%), suggesting that clustered feature patterns may enhance predictive association compared with isolated findings. The current study findings align with previously reported diagnostic metrics evaluating individual onychoscopic features. Ma et al. reported high overall sensitivity but limited specificity for onychoscopic diagnosis, reflecting variability in predictive strength across features [2]. Similarly, pooled analysis by Lim et al. demonstrated high specificity for spike patterns and longitudinal striae, supporting our observation that jagged edges with spikes represent one of the most specific individual findings [19].

Minor differences in sensitivity across studies may be attributed to variations in feature definition, inclusion thresholds, and disease severity. Systematic analyses have also highlighted that certain less frequent features may demonstrate very high specificity. Litaïem *et al.* reported extremely high specificity for “ruin appearance”, corresponding to distal irregular termination [17]. While statistically significant in our cohort, this pattern was infrequent, limiting its contribution to overall predictive performance. Regional studies have consistently identified spike patterns and longitudinal streaks as common findings [16, 23]. However, our results emphasize that prevalence does not necessarily equate predictive association. Longitudinal striae were frequently observed in our cohort but did not show statistically significant association with KOH positivity, underscoring the need to distinguish between frequency and diagnostic relevance. Similarly, Iorizzo *et al.* reported onycholysis, chromonychia, and subungual hyperkeratosis as the most frequently observed features in their prospective cohort, supporting our observation that commonly encountered patterns do not necessarily demonstrate the strongest predictive association [7]. Comparative approaches incorporating artificial intelligence and clinician-based assessment have demonstrated diagnostic metrics comparable to onychoscopic evaluation [9]. The high specificity for jagged edges with spikes observed in our analysis suggests that targeted evaluation of well-defined patterns may enhance predictive association as compared with generalized pattern recognition. Overall, the current analysis reinforces that individual features contribute differently to predictive strength and clustered feature assessment may provide a reliable association with KOH-confirmed infection.

This study has several limitations that should be considered when interpreting the findings. It was a single-center study with a relatively small sample size, which may limit the statistical power and generalizability of our findings. Future studies would benefit from a multicenter design and a larger sample size to improve robustness. Incorporating multiple observers with inter-observer reliability testing would further enhance reproducibility in feature recognition. Reliance on KOH as the sole confirmatory test may have limited the diagnostic precision, although KOH microscopy remains widely used in clinical practice. Onychoscopy, while valuable for detecting characteristic patterns of onychomycosis, is limited in its ability to differentiate between fungal species or subtypes. Lack of fungal culture or PCR may have affected diagnostic accuracy. Future studies could benefit from combining onychoscopy with these confirmatory tests to improve accuracy. The absence of long-term

follow-up also limited insights into pattern evolution and its association with treatment outcomes.

CONCLUSIONS

In this study, specific onychoscopic features demonstrated a significant association with KOH-confirmed onychomycosis, with onycholysis showing high sensitivity and jagged edge with spikes showing high specificity. While these findings highlight the predictive relevance of certain patterns, confirmatory testing, such as fungal culture or PCR, where available, remains essential for diagnosis and treatment planning. Further multicenter studies with larger sample sizes are required to validate these associations in broader populations.

Authors' Contribution

Conceptualization: KT

Methodology: KT, SH, RS

Formal analysis: KT, SH, RS, AH, AAC, IK, HN

Writing and Drafting: KT, SH, RS, AH, AAC, IK, HN

Review and Editing: KT, SH, RS, AH, AAC, IK, HN

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Clinical Outcome of Autoinoculation in the Management of Multiple Viral Warts: A Single-Arm Interventional Study

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ARTICLE INFO

Keywords:

Autoinoculation, Human Papilloma Virus, Immunotherapy, Infection, Outcome, Viral Warts

How to Cite:

Huda, N. U., Kausar, S., Hussain, N., Ahmed, I., Yasmin, G., & Hadia, T. (2026). Clinical Outcome of Autoinoculation in the Management of Multiple Viral Warts: A Single-Arm Interventional Study: Clinical Outcome of Autoinoculation in the Management of Multiple Viral Warts. *Pakistan Journal of Health Sciences*, 7(8), 15-21. <https://doi.org/10.54393/pjhs.v7i8.3770>

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Received Date: 31st December, 2025

1st Revision Received: 17th February, 2026

2nd Revision Received: 18th March, 2026

Acceptance Date: 7th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Autoinoculation is a relatively inexpensive immunotherapeutic treatment for viral warts, which is claimed to trigger a specific immune response. **Objective:** To determine the clinical outcome of autoinoculation, in terms of complete, partial, or no response, among patients presented with multiple viral warts. **Methods:** This is a single-arm interventional (quasi-experimental) study, which recruited 60 patients with multiple viral warts through non-probability sampling between March to October 2025. Autoinoculation was done by excision, mincing, and implantation of a donor wart into a pocket made in the subcutaneous area. Follow-ups were made monthly following initiation of treatment, and outcome measured at 12 weeks in terms of complete, partial, or no response. SPSS version 25.0 was used to perform a statistical analysis. Chi-square tests and ordinal logistic regression were used to determine significant associations and to derive adjusted ORs. **Results:** Study results illustrate that 73.3% (n=44) of patients achieved a complete response, 15.0% (n=9) a partial response, and 11.7% (n=7) showed no response. Mean number of warts reduced significantly from 7.7 (pre-treatment) to 1.75 (post-treatment). Stratification analysis revealed a significant association of age with treatment outcome (p=0.031). Patients in the age group 15-30 years showed the highest rate of complete response. No other demographic or clinical factors demonstrated a significant association. **Conclusions:** Autoinoculation is a considerable practicing, safe and effective therapeutic modality in treating various viral warts. Its better results among young patients highlight the critical role of a strong immune system in the implementation of its therapeutic action.

INTRODUCTION

Warts, or verrucae, are benign epidermal lesions caused by the human papillomavirus (HPV), of which over 100 distinct types have been identified [1]. These common infections have a global prevalence of approximately 10%, a figure that rises significantly to 10-20% among school-aged children. Warts can manifest on any part of the body, including the hands, feet, face, and genitals, often leading to social embarrassment, fear of negative appraisal, and a substantially reduced quality of life for affected individuals [2]. This impact is reflected in healthcare-seeking behavior, with warts accounting for consultations in about

2% of adults and 6% of children [3]. Though clinical diagnosis is normally sufficient, some subtypes of warts require confirmation by laboratory studies like histopathology or immunohistochemistry [4, 5]. Several modalities, including salicylic acid, cryotherapy, electrocautery, surgical curettage, and laser therapy, have a wide range of therapeutic effects to deal with viral warts. The ablation of infected epidermal cells is the ultimate goal of most interventions [6]. Nonetheless, a notable drawback is that this local cytotoxicity often does not destroy the latent virus in the neighboring clinically

insignificant cells, and thus, it contributes to the development of therapeutic failure, recalcitrant lesions, and recurrent outbreaks [7, 8]. On the other hand, the use of autoinoculation has been suggested as an ideal modern form of managing multiple and recalcitrant warts. It is characterized by its effectiveness, low cost, less pain, non-invasiveness, and likelihood to heal without scarring compared to conventional treatments [9, 10].

Even though numerous treatment modalities are available, the treatment of warts is complicated, and no single method is universally effective. There is a need to evaluate the efficiency of various treatments, especially in individuals with multiple viral warts. Since autoinoculation is a simple procedure that does not require specialized or costly equipment, this study aimed to measure its impact among the local community in Karachi and explore its potential as a standard therapeutic option.

METHODS

This single-arm interventional (quasi-experimental) study was conducted during March 2025 to October 2025 at the Department of Dermatology of Tertiary Care Hospital, Malir Cantt, Karachi, following approval Institutional Ethical Review Board (IERB) via letter number: 143/2024/Trg/ERC issued on 30th December 2024. The sample size of 60 patients was determined using OpenEpi software, based on a 91.66% complete response rate reported by Ashraf et al., with a 95% confidence interval and 7% margin of error, employing a non-probability consecutive sampling technique. As a non-probability consecutive sampling technique has been used, selection bias can't be excluded [11]. Inclusion criteria encompass patients of either gender, aged 12-65 years, diagnosed with three or more viral warts. Viral warts were diagnosed clinically by the consultant dermatologist if there were benign hyperkeratotic lesions or thrombosed capillary dots caused by HPV on the face, neck, hands, feet, arms, or genitals. If the clinical diagnosis isn't clear, dermoscopy was performed. Exclusion criteria include patients currently or recently (within four weeks) treated for warts, those with an immunocompromised state (malignancies or chronic illness), pregnant or lactating mothers, and those unwilling to participate. All those patients who received immunotherapy within the last 12 weeks were also excluded. Informed consent was taken from all the patients before enrollment. Demographic data (age, marital status, education, job, residence) and clinical details (wart duration, number, size, site, signs/symptoms) were recorded. Wart size was measured using the measuring tape by two observers who were blinded to the study, and the mean of the two measurements was recorded to overcome the interobserver variability. Under local anesthesia and aseptic measures, autoinoculation was

performed. A feasible (easy to approach and excise) wart was selected as a donor wart from any part of the body, preferably the extremities. The volar surface of the forearm or the medial surface of the lower leg was selected as the recipient site, depending upon the preference of the patient. Both donor wart and recipient sites were cleaned with pyodine and local anesthesia (2% lignocaine). The selected warts were excised, cleared, and minced into very small fragments. A subcutaneous pocket was made on the recipient site (forearm or leg, both can be used for any type of warts), and the minced warts were inoculated. Then, the pocket was stitched with Prolene sutures (3.0/4,0). Sterile dressing was applied, and oral or topical prophylactic antibiotics were prescribed for five days to prevent secondary bacterial infection, with follow-ups at 4, 8, and 12 weeks. The procedure may be repeated up to three times for no or partial responses after 4 weeks of follow-up, targeting multiple sites (e.g., face/neck, palmoplantar). Outcomes were assessed at the 12th week after the 1st inoculation. Analysis was conducted using SPSS version 25, calculating means and standard deviations for quantitative variables (age, wart duration, size, number before/after treatment, autoinoculation) and frequencies/percentages for qualitative variables (gender, age groups, marital status, education, job, residence, wart signs/symptoms, site, outcome). Effect modifiers (gender, age, marital status, education, job, residence, wart size/duration/number/site, autoinoculation) were controlled via chi-square stratification, with $p \leq 0.05$ deemed significant. Ordinal logistic regression analysis was done to determine the adjusted odds ratios.

RESULTS

Out of the 60 patients studied, the average age was 38.57 years, with an even distribution between the 30-45 and 46-65 age groups (Table 1).

Table 1: Descriptive Statistics for Demographic Quantitative Variables

Variables (n=60)	Mean $\pm$ ST
Age	38.57 $\pm$ 13.54
Duration of Warts (Months)	17.72 $\pm$ 10.59
Number of Warts (Pre-Treatment)	7.70 $\pm$ 3.95
Number of Warts (Post-Treatment)	1.75 $\pm$ 3.49
Size of Warts (cm)	1.40 $\pm$ 0.62
Number of Inoculations	2.53 $\pm$ 0.50

The sample was slightly male-dominated (55%) and predominantly single (43.3%) in marital status. Education levels and job status were varied, with students comprising the largest occupational group (31.7%). Most patients were urban residents (53.3%) for over a year. The most common site for warts was the feet (25.0%). Before treatment, patients had an average 0%. Clinically, warts had been

present for an average of nearly 18 months, with the majority of patients (61.7%) having them for 7.70 warts, and the majority (63.3%) had more than five warts. The average wart size was 1.40 cm, with 65.0% of patients having warts larger than 1 cm. In terms of characteristics, most warts presented without small grainy growths (60.0%), a rough texture (55.0%), seeds (51.7%), or pain (56.7%) (Table 2).

Table 2: Descriptive Statistics for Clinical Qualitative Variables

Variables	Category	Frequency (%)
Gender	Male	33 (55.0%)
	Female	27 (45.0%)
Age Groups	15-30 years	16 (26.7%)
	31-45 years	22 (36.7%)
	46-65 years	22 (36.7%)
Marital Status	Single	26 (43.3%)
	Married	20 (33.3%)
	Widowed/Divorced	14 (23.3%)
Education	Illiterate	12 (20.0%)
	Primary	10 (16.7%)
	Matriculation	9 (15.0%)
	Intermediate	9 (15.0%)
	Graduate	8 (13.3%)
	Post-Graduate	12 (20.0%)
Job Status	Student	19 (31.7%)
	Unemployed	16 (26.7%)
	Housewife	15 (25.0%)
	Employed	10 (16.7%)
Residence	Urban	32 (53.3%)
	Rural	28 (46.7%)
Duration of Warts	<6 months	12 (20.0%)
	6-12 months	11 (18.3%)
	>12 months	37 (61.7%)
Site of Warts	Feet	15 (25.0%)
	Face & Neck	14 (23.3%)
	Arms	13 (21.7%)
	Hands	10 (16.7%)
	Genitals	8 (13.3%)
Small Grainy Growth	Yes	24 (40.0%)
	No	36 (60.0%)
Feeling Rough to Touch	Yes	27 (45.0%)
	No	33 (55.0%)
Wart Seeds	Yes	29 (48.3%)
	No	31 (51.7%)
Pain or Tenderness	Yes	26 (43.3%)
	No	34 (56.7%)
Number of Warts Group	≤5	22 (36.7%)
	>5	38 (63.3%)
Size of Warts Group	Up to 1 cm	21 (35.0%)
	>1 cm	39 (65.0%)

Pretreatment mean wart count was 7.70 ± 3.95 , which reduced to 1.75 ± 3.49 post-treatment. Paired t-test analysis reported that this difference was statistically

significant (p -value ≤ 0.05). The majority of patients, 44 (73.3%), achieved a complete response to autoinoculation treatment; 9 (15%) of patients experienced a partial response, which means overall efficacy was 53 (88.3%); while a minority, 7 (11.7%), showed no response to the treatment (Figure 1).

Outcome

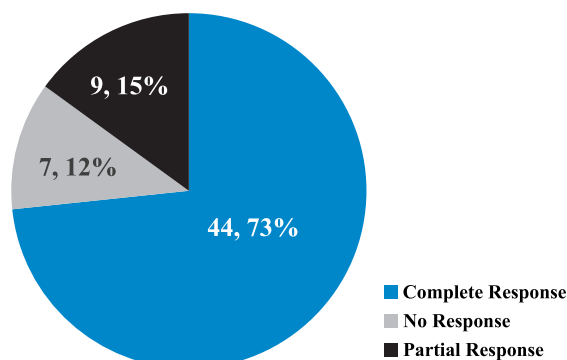


Figure 1: Distribution of Study Outcomes Among Total Study Population

The plantar warts before and after autoinoculation in one of the patients treated have been seen to have a visible reduction and healing of the lesion after the procedure (Figure 2).



Figure 2: Image Showing Autoinoculation Outcome Among Patients With Plantar Warts (A) Before Treatment (B) After Treatment

The before, after, and recovery images of the patients who underwent autoinoculation for plantar warts. These images show the evolution of the treatment and indicate the image of the lesion before the process, the instant post-process state, and the healing process in the recovery process, which is how the autoinoculation therapy was successful (Figure 3).



Figure 3: Image Showing Autoinoculation Outcome (A) Before Treatment (B) After Treatment (Resolution Phase) (C) Recovery

Of all the patient and clinical variables analyzed, only age demonstrated a statistically significant association with treatment outcome ($p=0.031$). Younger patients (15–30 years) showed the highest rate of complete response, whereas the 31–45 age group was disproportionately represented among those with no response to treatment (Table 3).

Table 3: Stratification Analysis of The Study Outcomes

Variables	Categories	Complete Response (n=44)	No Response (n=7)	Partial Response (n=9)	Chi-Square (p-value)
Gender	Male	25 (56.8%)	5 (71.4%)	3 (33.3%)	0.282
	Female	19 (43.2%)	2 (28.6%)	6 (66.7%)	
Age Groups	15–30	15 (34.1%)	0 (0.0%)	1 (11.1%)	0.031
	31–45	13 (29.5%)	6 (85.7%)	3 (33.3%)	
	46–65	16 (36.4%)	1 (14.3%)	5 (55.6%)	
Marital Status	Married	12 (27.3%)	4 (57.1%)	4 (44.4%)	0.267
	Single	21 (47.7%)	3 (42.9%)	2 (22.2%)	
	Widowed/Divorced	11 (25.0%)	0 (0.0%)	3 (33.3%)	
Education	Graduate	5 (11.4%)	1 (14.3%)	2 (22.2%)	0.326
	Illiterate	10 (22.7%)	2 (28.6%)	0 (0.0%)	
	Intermediate	5 (11.4%)	0 (0.0%)	4 (44.4%)	
	Matriculation	6 (13.6%)	2 (28.6%)	1 (11.1%)	
	Post-Graduate	10 (22.7%)	1 (14.3%)	1 (11.1%)	
	Primary	8 (18.2%)	1 (14.3%)	1 (11.1%)	
Job Status	Employed	6 (13.6%)	2 (28.6%)	2 (22.2%)	0.809
	Housewife	12 (27.3%)	1 (14.3%)	2 (22.2%)	
	Student	15 (34.1%)	1 (14.3%)	3 (33.3%)	
	Unemployed	11 (25.0%)	3 (42.9%)	2 (22.2%)	
Residence	Rural	22 (50.0%)	2 (28.6%)	4 (44.4%)	0.567
	Urban	22 (50.0%)	5 (71.4%)	5 (55.6%)	
Duration of Warts	<6 months	10 (22.7%)	1 (14.3%)	1 (11.1%)	0.392
	>12 months	27 (61.4%)	3 (42.9%)	7 (77.8%)	
	6–12 months	7 (15.9%)	3 (42.9%)	1 (11.1%)	
Site of Warts	Arms	9 (20.5%)	2 (28.6%)	2 (22.2%)	0.268
	Face & Neck	13 (29.5%)	0 (0.0%)	1 (11.1%)	
	Feet	10 (22.7%)	1 (14.3%)	4 (44.4%)	
	Genitals	5 (11.4%)	1 (14.3%)	2 (22.2%)	
	Hands	7 (15.9%)	3 (42.9%)	0 (0.0%)	
Number of Warts Group	≤5	19 (43.2%)	1 (14.3%)	2 (22.2%)	0.210
	>5	25 (56.8%)	6 (85.7%)	7 (77.8%)	
Size of Warts Group	Up to 1 cm	15 (34.1%)	3 (42.9%)	3 (33.3%)	0.897
	>1 cm	29 (65.9%)	4 (57.1%)	6 (66.7%)	

Several stratified comparisons were exploratory & no formal adjustment was made, which can increase the risk of type-I error. Ordinal logistic regression analysis showed that age in the range of 15 to 30 years ($AOR=0.002$; $p=0.008$), student status ($AOR=0.015$; $p=0.012$), and living in rural areas ($AOR=0.07$; $p=0.037$) were all significantly associated with complete treatment response, as found in the stratification analysis. No other factors, including gender, wart duration, location, number, or size, had a significant impact on the outcome (Table 4).

Table 4: Ordinal Logistic Regression Analysis of Factors Associated with Treatment Response

Variables	Categories	Adjusted OR	95% CI	p-value
Gender	Female VS Male	1.35	0.18 – 10.21	0.770
Age group (years)	15–30 VS 46–65	0.002	0.000 – 0.19	0.008
	31–45 VS 46–65	0.60	0.08 – 4.55	0.619
Marital status	Married VS Widowed/Divorced	4.87	0.20 – 121.5	0.335
	Single VS Widowed/Divorced	2.95	0.10 – 87.4	0.532
Education	Graduate VS Primary	17.25	0.30 – 987.4	0.168

	Illiterate VS Primary	0.56	0.01 – 45.9	0.797
	Intermediate VS Primary	8.25	0.31 – 219.4	0.207
	Matriculation VS Primary	0.56	0.02 – 17.1	0.739
	Post-graduate VS Primary	0.06	0.001 – 3.35	0.170
Job status	Employed VS Unemployed	2.42	0.15 – 38.5	0.532
	Housewife VS Unemployed	0.57	0.02 – 19.3	0.755
	Student VS Unemployed	0.015	0.001 – 0.40	0.012
Residence	Rural VS Urban	0.07	0.006 – 0.85	0.037
Monthly income	<30k VS 30k–60k	11.19	0.44 – 285.5	0.144
	>60k VS 30k–60k	0.05	0.002 – 1.28	0.070

Duration of warts	<6 months VS 6–12 months	0.15	0.006 – 4.17	0.267
	>12 months VS 6–12 months	0.06	0.003 – 1.13	0.060
Site of warts	Arms VS Hands	10.11	0.24 – 419.5	0.223
	Face & Neck VS Hands	0.02	0.0003 – 1.60	0.081
	Feet VS Hands	2.91	0.05 – 161.7	0.602
	Genitals VS Hands	0.99	0.02 – 47.4	0.995

DISCUSSION

The present study evaluated the efficacy of autoinoculation therapy in patients with multiple viral warts, demonstrating a complete response in 73.3% of cases, a partial response in 15.0%, and no response in 11.7%. The current findings highlight the usefulness of autoinoculation as a highly potent modality in the management of warts, especially in patients who initially present with multiple lesions as well as recalcitrant lesions. The average number of wart burden per patient was significantly decreased after treatment, and most patients only needed two or three inoculations. Notably, there were no clinically significant procedure-related complications reported, and the treatment was well tolerated. Our response rates are in line with the already published studies. Ashraf *et al.* (91.6% complete response rate) articulated a significantly greater rate of clearance in their group compared to Shahid *et al.* (77.1% clearance rate) and agreement with our results [11, 12]. On the same note, Das *et al.* reported a complete clearance rate of 69.5% in their study of 83 patients, which also confirms the effectiveness of this modality [13]. In a randomized controlled trial, Lal *et al.* reported a complete resolution in 62.5% of auto-inoculated patients; it was indicated that this method was better than placebo [14]. However, the present study should be compared with randomized trials with caution because it is a single-arm, non-controlled trial. The therapeutic potential of autoinoculation is supported by recent evidence from Barnwal *et al.* (63.3% complete clearance) and Taneja *et al.* (67% resolution), especially in multiple and recalcitrant lesions [15, 16]. Further research by Narayanan *et al.* on anogenital warts, Swaroop *et al.* with a modified implantation technique, and Chhangte *et al.* in a cohort of patients in North-Eastern India all reported a clearance rate of between 60 and 75 percent, further indicating the reproducibility of the results of the research across the various patient populations and clinical settings [17–19]. These congruent findings indicate that autoinoculation is a minimally invasive and cost-effective method with an effectiveness rate that ranges consistently over 60 percent and, in some cases, up to 90 percent, supporting its presence as a promising therapeutic standard in various viral warts. Above all, it's a safe procedure, as not a single patient reported a significant side effect or secondary infection on follow-up visits. The multivariate ordinal regression analysis indicated that

younger age is a strong predictor of a poor treatment response when adjusted for possible confounders. Additionally, rural residence and student status turned out to be variables that were linked with the increased possibility of a positive outcome. These data indicate that, in addition to immunological factors, sociodemographic factors are also likely to play a role in determining the efficacy of the therapeutic process. Among the clinical and demographic characteristics studied, age was the only variable that was found to have a significant treatment outcome [19]. The highest complete response rates were seen in patients aged 15 to 30 years, and the proportion of non-responders was overrepresented in the 31 to 45-year age bracket. This tendency can be attributed to the fact that younger people have a stronger immune system to resist the infection, which confirms the assumption that immunological competence is one of the primary factors influencing treatment outcomes. Other factors, such as gender, length of warts, size, number, location, education, and house, had no statistically significant influence, which supports the previous argument that host immunity has a more critical influence than demographic or socioeconomic factors [20]. Most of the warts were on the feet, then on the face/neck, and the arms, and this is in line with areas that are usually exposed to trauma or infection. Also, the majority of patients were reported with several warts bigger than 1cm, and this reiterates the recalcitrancy of the disease. Positively, autoinoculation has produced desirable results with these hard-to-treat properties.

The research has a number of strengths, such as a clear methodology, standard outcome measurement, and extensive clinical and demographic stratification. However, limitations should be acknowledged. Although the sample size was sufficient in the context of descriptive analysis, it was relatively small and restricted to one center, which could have impacted the generalizability. Another important limitation is the use of a non-probability consecutive sampling technique for enrollment of patients, which can cause potential selection bias. Furthermore, large confidence intervals and large odds ratios indicate instability of the model as the sample is small, and the outcome distribution is sparse. In addition, the period of follow-up was limited to three months after treatment, which ruled out the possibility of assessing the recurrence in the long term. The findings should be justified by future studies using large and multicenter cohorts with long follow-ups. Last but not least, the lack of a comparator arm makes it impossible to directly compare the efficacy of the treatment with other therapies.

CONCLUSIONS

Autoinoculation proved to be a promising and effective intervention in managing the multiple viral warts due to its

cost-effectiveness, low invasiveness, and better outcome profile, which is especially beneficial in resource-limited settings. However, first-line use should be recommended only after comparative controlled studies. The current study highlights a major role of patient age in determining therapeutic effects, hence the critical role of host immunity in mediating clinical response. Additional research using larger, multicenter, controlled comparative trials with longer follow-up is necessary to support these promising results and strengthen the role of this procedure as one of the standards of care in the dermatological practice.

Authors' Contribution

Conceptualization: NUH, SK

Methodology: NUH, SK, GY

Formal analysis: NUH, NH, IA, TH

Writing and Drafting: NUH, SK, NH

Review and Editing: NUH, SK, NH, IA, GY, TH

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Comparative efficacy of High-Flow Nasal Cannula (HFNC) versus Continuous Positive Airway Pressure (CPAP) in Preventing Bronchopulmonary Dysplasia (BPD) among Preterm Neonates

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ARTICLE INFO

Keywords:

Bronchopulmonary Dysplasia, Preterm Infant, High-Flow Nasal Cannula, Continuous Positive Airway Pressure, Non-Invasive Ventilation, Respiratory Distress Syndrome

How to Cite:

Iqbal, W., Zaman, S., Iqbal, J., Alam, F., Khan, M. K., & Alam, S. S. (2026). Comparative efficacy of High-Flow Nasal Cannula (HFNC) versus Continuous Positive Airway Pressure (CPAP) in Preventing Bronchopulmonary Dysplasia (BPD) among Preterm Neonates: HFNC versus CPAP in Preventing BPD among Preterm Neonates. *Pakistan Journal of Health Sciences*, 7(8), 22-27. <https://doi.org/10.54393/pjhs.v7i8.3991>

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Received Date: 19th February, 2026

1st Revision Received: 18th March, 2026

Acceptance Date: 8th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Bronchopulmonary dysplasia (BPD) remains a major cause of respiratory morbidity in preterm infants requiring respiratory support. Non-invasive ventilation strategies such as nasal continuous positive airway pressure (CPAP) and high-flow nasal cannula (HFNC) are commonly used, but evidence comparing their effectiveness in preventing BPD remains limited, particularly in low- and middle-income settings. **Objectives:** To compare HFNC and CPAP as primary non-invasive respiratory support in preterm neonates <34 weeks' gestation, with BPD at 36 weeks postmenstrual age as the primary outcome. **Methods:** This cohort study was conducted in a tertiary-care neonatal intensive care unit in Peshawar, Pakistan. Preterm neonates <34 weeks who received HFNC or CPAP as initial respiratory support between April 2024 and March 2025 were included. Multivariable logistic regression was performed to identify predictors of BPD. **Results:** A total of 189 neonates were analyzed (HFNC n=95; CPAP n=94). The incidence of BPD was similar between HFNC and CPAP groups (25.3% vs 27.7%; p=0.709). Mortality and major neonatal complications were also comparable. Respiratory modality was not independently associated with BPD (aOR 1.41; 95% CI 0.69-2.90; p=0.348). Intubation was strongly associated with BPD (aOR 19.30; p=0.005), while complete antenatal steroid exposure was protective (aOR 0.24; p=0.016). **Conclusions:** HFNC and CPAP showed similar outcomes in preterm neonates <34 weeks. However, due to the observational design, further prospective studies are needed to confirm these findings.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a major cause of respiratory morbidity in preterm infants requiring respiratory support and oxygen therapy [1]. Despite advances in neonatal care, it remains associated with prolonged hospitalization, recurrent respiratory admissions, and long-term pulmonary and neurodevelopmental complications [2]. Therefore,

contemporary neonatal respiratory strategies increasingly focus on minimizing lung injury by promoting effective gas exchange while reducing volutrauma, barotrauma, and oxygen toxicity [3]. Lung-protective neonatal care largely depends on non-invasive ventilation [4]. Nasal continuous positive airway pressure (CPAP) is the most commonly used first-line respiratory support for preterm neonates



with respiratory distress syndrome (RDS) and helps reduce the need for invasive ventilation [5]. Current guidelines emphasize early non-invasive support and antenatal steroid exposure to reduce the risk of BPD [6, 7]. Heated humidified high-flow nasal cannula (HFNC) has emerged as an alternative non-invasive respiratory modality because of its ease of application, improved patient comfort, and potentially lower rates of nasal trauma related to the interface [8, 9]. However, HFNC generates variable distending airway pressure that depends on flow rate, cannula size, and mouth position, raising uncertainty about whether it provides respiratory support equivalent to CPAP in very preterm infants or those with more severe respiratory distress [10]. Some studies have suggested that HFNC used early after birth may be associated with similar risks of death or BPD compared with CPAP or nasal intermittent positive pressure ventilation, although higher rates of treatment failure have occasionally been reported [11]. Several systematic reviews and meta-analyses have evaluated HFNC compared with CPAP for non-invasive respiratory support in preterm infants. Overall, these pooled analyses have generally demonstrated minimal or no significant difference in BPD risk between the two modalities, although heterogeneity among studies and variations in clinical practice limit the certainty of the available evidence [12]. In particular, many studies have focused on treatment failure or need for intubation rather than BPD as a primary outcome, and relatively few observational cohort studies have specifically examined BPD development in very preterm infants receiving primary non-invasive respiratory support.

Furthermore, there is limited evidence from low- and middle-income countries where neonatal intensive care unit (NICU) resources, patient characteristics, and clinical practice patterns may differ substantially from those reported in large randomized trials conducted in high-income settings. In Pakistan, locally generated evidence comparing HFNC and CPAP in preterm neonates remains scarce, particularly in infants born before 34 weeks' gestation and in studies evaluating BPD as a primary outcome. Therefore, this study aimed to compare the effectiveness of HFNC versus CPAP as primary non-invasive respiratory support in preterm neonates <34 weeks' gestation admitted to a tertiary-care NICU in Pakistan. The primary outcome was bronchopulmonary dysplasia at 36 weeks postmenstrual age, while secondary outcomes included short-term clinical outcomes and major neonatal complications.

METHODS

This cohort study was conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Northwest General Hospital and Research Centre,

Peshawar, Pakistan. The study included preterm neonates admitted between April 2024 and March 2025, and clinical data were retrospectively extracted from NICU medical records. Neonates were followed until discharge or 36 weeks postmenstrual age (PMA) to determine the occurrence of bronchopulmonary dysplasia. Ethical approval for the study was obtained from the Institutional Review Board and Ethical Committee of Alliance Healthcare (Pvt.) Ltd (Reference No. IRB&EC/2024-GH/0278; dated 27th March 2024). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki for research involving human participants (World Medical Association, 2013) [13]. As the study involved retrospective review of routinely collected clinical data, the requirement for individual informed consent was waived, and patient confidentiality was strictly maintained through anonymization of all identifiable information. Sample size estimation was performed using the two-proportion comparison formula: $n = (Z\alpha/2 + Z\beta)^2 \times [p_1(1-p_1) + p_2(1-p_2)] / (p_1 - p_2)^2$, where p_1 represents the expected incidence of bronchopulmonary dysplasia in the CPAP group, and p_2 represents the expected incidence in the HFNC group. Based on previously published neonatal respiratory support studies reporting BPD rates ranging between 20–30% among preterm infants receiving non-invasive ventilation, an expected incidence of 30% in the CPAP group and 15% in the HFNC group [5] was assumed with a 95% confidence level and 80% statistical power. The minimum calculated sample size was approximately 180 neonates. A total of 189 neonates were ultimately included in the final analysis after applying the eligibility criteria. Eligible participants included preterm neonates with gestational age <34 weeks who required non-invasive respiratory support shortly after birth and received either HFNC or CPAP as the initial respiratory modality. Neonates with major congenital anomalies, chromosomal abnormalities, significant congenital heart disease other than patent ductus arteriosus, those requiring immediate invasive ventilation after birth, transfers within 24 hours of admission, or incomplete clinical records were excluded. Respiratory support was provided according to standard NICU clinical protocols. HFNC therapy was delivered using heated and humidified blended oxygen via nasal cannula, typically initiated at flow rates between 4–6 L/min and adjusted according to gestational age, oxygen saturation, and clinical response. CPAP support was delivered through nasal prongs with initial pressures generally ranging between 5–7 cmH₂O, with adjustments based on oxygen requirement, work of breathing, and arterial blood gas findings. Standard neonatal supportive care included thermoregulation, nutritional support, caffeine therapy for

apnea of prematurity, and surfactant administration when clinically indicated. The choice of respiratory modality (HFNC or CPAP) was determined by treating neonatologists based on clinical judgment and unit practice rather than random allocation. To reduce potential confounding by indication, important clinical variables, including gestational age, birth weight, antenatal steroid exposure, surfactant therapy, baseline FiO_2 requirement, sepsis, and patent ductus arteriosus, were included as covariates in the multivariable regression model. Escalation to invasive mechanical ventilation was considered in cases of treatment failure, including persistent or worsening respiratory distress, sustained oxygen requirement greater than 60%, recurrent apnea despite caffeine therapy, severe respiratory acidosis ($\text{pH} < 7.20$ with elevated PaCO_2), or hemodynamic instability. Clinical data were collected retrospectively using a structured data extraction form that included maternal characteristics, perinatal factors, neonatal baseline characteristics, respiratory support parameters, early clinical course, complications, and outcomes. Bronchopulmonary dysplasia was defined as oxygen dependence at 36 weeks postmenstrual age according to commonly used clinical definitions in neonatal research. Physiologic oxygen reduction testing and NICHD severity grading were not routinely performed in the study unit. A total of 204 NICU records were initially screened for eligibility. After a detailed review, 15 records were excluded due to incomplete or contradictory clinical documentation, resulting in a final sample of 189 neonates included in the analysis. Data quality was ensured by cross-checking extracted information with both electronic medical records and nursing charts. Double-entry verification was performed to minimize transcription errors.

Statistical analysis was conducted using IBM SPSS Statistics version 26.0. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables were expressed as mean $\pm$ standard deviation and compared using the independent-samples t-test. In contrast, non-normally distributed variables were presented as median with interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and analyzed using the Chi-square test or Fisher's exact test, as appropriate. Multivariable binary logistic regression analysis was performed to identify independent predictors of bronchopulmonary dysplasia at 36 weeks PMA. Variables considered clinically relevant or demonstrating a p-value < 0.200 in univariable analysis were included in the multivariable model. Results were reported as adjusted odds ratios (aOR) with 95% confidence intervals. Model adequacy was evaluated using

the Hosmer-Lemeshow goodness-of-fit test. Multicollinearity among predictor variables was assessed using variance inflation factors (VIF). Model discrimination was further assessed using the area under the receiver operating characteristic (ROC) curve and overall classification accuracy. A p-value ≤ 0.050 was considered statistically significant.

RESULTS

A total of 204 NICU records were screened, of which 15 records were excluded due to incomplete or contradictory documentation, leaving 189 preterm neonates included in the final analysis (HFNC $n=95$; CPAP $n=94$). Baseline maternal and neonatal characteristics were largely comparable between the HFNC and CPAP groups. There was no significant difference in maternal age, antenatal care status, PROM, maternal comorbidities, gestational age, birth weight, Apgar scores, sex distribution, or surfactant administration between groups. However, a significantly higher proportion of mothers in the HFNC group received a complete course of antenatal steroids compared with the CPAP group (69.5% vs 54.3%; $p=0.036^*$). Other maternal and neonatal variables were similar between the two groups, suggesting overall baseline comparability (Table 1).

Table 1: Baseline Maternal and Neonatal Characteristics

Variables	HFNC (n=95), Mean $\pm$ SD / n (%)	CPAP (n=94), Mean $\pm$ SD / n (%)	p-value
Maternal Age (years)	28.52 $\pm$ 4.60	29.24 $\pm$ 4.78	0.292
Booked Antenatal Care	74 (77.9%)	65 (69.1%)	0.173
Complete Antenatal Steroids	66 (69.5%)	51 (54.3%)	0.036*
PROM	18 (18.9%)	27 (28.7%)	0.115
Hypertension/Preeclampsia	16 (16.8%)	21 (22.3%)	0.341
Maternal Diabetes	11 (11.6%)	15 (16.0%)	0.382
Gestational Age (Weeks)	29.63 $\pm$ 2.28	29.18 $\pm$ 2.34	0.186
Birth Weight (g)	1273.85 $\pm$ 284.09	1199.47 $\pm$ 327.99	0.097
Male Sex	52 (54.7%)	46 (48.9%)	0.425
SGA/IUGR	15 (15.8%)	12 (12.8%)	0.553
Surfactant Given	55 (57.9%)	52 (55.3%)	0.721

*Indicates statistically significant difference at $p \leq 0.050$

The respiratory support characteristics were similar between the two study groups. There were no significant differences in FiO_2 at initiation, peak FiO_2 within the first 72 hours, duration of non-invasive ventilation, total oxygen therapy duration, or age at initiation of respiratory support. Clinical outcomes were also comparable between the groups. Bronchopulmonary dysplasia at 36 weeks PMA occurred in 24 (25.3%) neonates in the HFNC group and 26 (27.7%) in the CPAP group ($p=0.709$). Mortality before discharge, NICU length of stay, and discharge weight were also similar between groups (Table 2).

Table 2: Respiratory Support Characteristics and Clinical Outcomes

Variables	HFNC (n=95)	CPAP (n=94)	p-value
FiO ₂ at Initiation, Median (IQR)	0.42 (0.16)	0.44 (0.15)	0.975
Peak FiO ₂ within 72 h	0.59 (0.19%)	0.59 (0.25%)	0.553
Total NIV Duration (Days), Median (IQR)	11 (7)	11.5 (8)	0.209
Total Oxygen Duration (Days)	23 (18%)	23 (22.3%)	0.832
Age At Start of Support (Hours)	2.1 (1.9%)	2.3 (1.9%)	0.783
Intubation at Any Time, n (%)	15 (15.8%)	16 (17.0%)	0.819
BPD at 36 Weeks PMA, n (%)	24 (25.3%)	26 (27.7%)	0.709
Mortality Before Discharge, n (%)	9 (9.5%)	8 (8.5%)	0.817
Length of NICU Stay (days)	37 (22%)	39 (25%)	0.690
Discharge Weight (g)	2002 ± 373	1919 ± 481	0.187

The frequency of major neonatal complications did not differ significantly between the two respiratory support modalities. Rates of pneumothorax, nasal trauma, feeding intolerance, necrotizing enterocolitis, severe intraventricular hemorrhage, and retinopathy of prematurity requiring treatment were similar between the HFNC and CPAP groups (Table 3).

Table 3: Neonatal Complications

Complications	HFNC (n=95), n (%)	CPAP (n=94), n (%)	p-value
Pneumothorax	6 (6.3%)	3 (3.2%)	0.497
Nasal trauma	11 (11.6%)	14 (14.9%)	0.501
Feeding intolerance	20 (21.1%)	20 (21.3%)	0.970
NEC (Bell ≥ II)	5 (5.3%)	5 (5.3%)	1.000
Severe IVH	4 (4.2%)	8 (8.5%)	0.250
ROP requiring treatment	6 (6.3%)	7 (7.4%)	0.782

The multivariable logistic regression model demonstrated adequate fit according to the Hosmer–Lemeshow goodness-of-fit test, and no significant multicollinearity was observed among predictor variables. Multivariable logistic regression analysis was performed to identify independent predictors of bronchopulmonary dysplasia. After adjustment for relevant clinical covariates, respiratory modality (HFNC vs CPAP) was not independently associated with BPD (aOR 1.41, 95% CI 0.69–2.90; p=0.348). However, intubation at any time during NICU stay emerged as a strong independent predictor of BPD (aOR 19.30, 95% CI 2.42–154.04; p=0.005*). Conversely, absence of antenatal steroid exposure was associated with significantly higher odds of BPD compared with complete steroid exposure (aOR 0.24, 95% CI 0.07–0.76; p=0.016*) (Table 4).

Table 4: Multivariable Predictors of Bronchopulmonary Dysplasia

Variables	Adjusted OR (95% CI)	p-value
HFNC vs CPAP	1.41 (0.69–2.90)	0.348
Partial vs Complete Steroids	0.40 (0.16–1.05)	0.063
None vs Complete Steroids	0.24 (0.07–0.76)	0.016*

Gestational Age	1.09 (0.93–1.27)	0.289
Birth Weight	0.999 (0.998–1.000)	0.155
Surfactant Therapy	1.16 (0.57–2.36)	0.686
Baseline FiO ₂	0.92 (0.02–37.10)	0.964
Intubation (Any)	19.30 (2.42–154.04)	0.005*
Sepsis	0.54 (0.23–1.25)	0.151
PDA	1.25 (0.57–2.78)	0.577

*Indicates statistically significant difference at p ≤ 0.050

DISCUSSION

The present study compared high-flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP) as primary non-invasive respiratory support in preterm neonates <34 weeks' gestation. The results demonstrated no significant difference in bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age between the two groups, and respiratory modality was not independently associated with BPD after multivariable adjustment. These findings are consistent with previous systematic reviews evaluating HFNC compared with CPAP in preterm infants. A Cochrane review reported that HFNC likely results in little or no difference in death or BPD compared with CPAP, although treatment failure may occur slightly more frequently in certain populations [6]. Similarly, a systematic review published in 2021 found no statistically significant difference in BPD risk between HFNC and CPAP [12], and a recent meta-analysis focusing on BPD prevention also concluded that neither modality demonstrated clear superiority [14]. Together, these findings suggest that the choice between HFNC and CPAP alone may not be a major determinant of BPD risk when other aspects of respiratory management are optimized. Although the respiratory modality itself was not associated with BPD in our adjusted model, intubation at any time during NICU stay emerged as a strong independent predictor of BPD. This finding is biologically plausible and consistent with previous literature demonstrating that exposure to invasive mechanical ventilation contributes to lung injury through volutrauma, barotrauma, and oxidative stress. International neonatal respiratory guidelines, therefore, emphasize early and effective non-invasive respiratory support strategies aimed at minimizing invasive ventilation whenever possible [15]. The current study findings reinforce the importance of preventing escalation to mechanical ventilation as a key strategy in reducing the risk of BPD. The study also observed a protective association of complete antenatal steroid exposure, which is biologically plausible because antenatal corticosteroids promote fetal lung maturation and improve early pulmonary adaptation [14–16]. Although there was a higher proportion of complete steroid exposure in the HFNC group at baseline, adjustment in the multivariable model confirmed that respiratory modality itself was not

independently associated with BPD. Major neonatal complications were similar between HFNC and CPAP, including pneumothorax, necrotizing enterocolitis, severe intraventricular hemorrhage, and retinopathy of prematurity, consistent with previously reported safety profiles for both modalities [17, 18]. Some studies have suggested that HFNC may result in lower rates of nasal trauma because of the less intrusive interface; however, treatment failure rates may be slightly higher in certain populations, emphasizing the need for careful patient selection and clear escalation criteria [19, 20]. The sample size calculation assumed BPD incidences of 30% in the CPAP group and 15% in the HFNC group based on earlier neonatal studies reporting BPD rates of approximately 20–30%. However, more recent meta-analyses suggest that the true difference between modalities may be smaller, which should be considered when interpreting the findings.

This study has several limitations. This cohort design limits causal inference, and respiratory modality selection was based on clinician judgment, introducing potential confounding by indication. In addition, the study was conducted at a single tertiary-care NICU, which may limit generalizability. Physiologic oxygen reduction testing and standardized NICHD BPD severity grading were also not routinely performed. Future multicenter prospective studies and randomized controlled trials are needed to further evaluate the comparative effectiveness of HFNC and CPAP in preventing bronchopulmonary dysplasia.

CONCLUSIONS

In preterm neonates <34 weeks' gestation, HFNC and CPAP were associated with similar rates of bronchopulmonary dysplasia, mortality, and major neonatal complications. Respiratory modality was not independently associated with BPD, whereas intubation increased BPD risk, and complete antenatal steroid exposure appeared protective. Because this was an observational study with clinician-driven modality selection, the findings should be interpreted as demonstrating association rather than equivalence between HFNC and CPAP. Further prospective research is required to confirm these results.

Authors' Contribution

Conceptualization: WI

Methodology: SZ, MKK

Formal analysis: JI, SSA

Writing and Drafting: WI, SZ, JI, FA, MKK, SSA

Review and Editing: WI, SZ, JI, FA, MKK, SSA

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Digital Literacy in Medical Education: Strengths, Gaps, and the Way Forward

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ARTICLE INFO

Keywords:

Digital Literacy, Medical Education, Artificial Intelligence, Cybersecurity, Undergraduate Healthcare Curriculum

How to Cite:

Shamim, H., Waheed, N., Azher, Z., Karim, H., Abid, F., & Iqbal, S. (2026). Digital Literacy in Medical Education: Strengths, Gaps, and the Way Forward: Digital Literacy in Medical Education. *Pakistan Journal of Health Sciences*, 7(8), 28-33. <https://doi.org/10.54393/pjhs.v7i8.3721>

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Received Date: 13th December, 2025

1st Revision Received: 10th January, 2026

2nd Revision Received: 20th January, 2026

Acceptance Date: 25th February, 2026

Published Date: 31st August, 2026

ABSTRACT

Digital transformation of healthcare has transformed clinical practice, medical education, and professional competencies around the world. Digital literacy includes technological skills, ethical use, artificial intelligence (AI), and cybersecurity. It is now regarded as a safe, effective, and future-ready healthcare practice. Despite increased exposure to digital tools, evidence reveals that healthcare students may lack structured capabilities in new digital domains.

Objectives: To evaluate the level of digital literacy among undergraduate medical and dental students and identify domain-specific strengths and gaps, particularly in emerging areas such as artificial intelligence and cybersecurity. **Methods:** An analytical cross-sectional study was conducted using a validated 24-item self-report instrument. The survey measured seven domains of digital literacy using a 5-point Likert scale. A total of 304 MBBS and BDS students participated. Data were analyzed using SPSS v26, applying descriptive statistics, t-tests, and Spearman's correlation. **Results:** Among the participants, 77.6% were MBBS students and 22.4% were from BDS, with 60.9% females and 39.1% males. No significant gender-based differences were found in any digital literacy domain. First-year students scored significantly higher in the digital security domain than second-year students ($p=0.002$). Overall, students demonstrated moderate digital literacy, with comparatively lower scores in AI and cybersecurity domains. **Conclusions:** While digital literacy is generally consistent across gender and academic levels, low competency in AI and cybersecurity signals an urgent need for targeted curricular interventions. Integrating digital literacy, especially AI and data security, into undergraduate curricula is essential for preparing future-ready healthcare professionals.

INTRODUCTION

The rapid digitalization of the health sector has led to significant advances across medical training, diagnostic accuracy, disease surveillance, and treatment regimens [1]. This development has tremendously contributed to the quality of patient care as it has enhanced medical infrastructure, improved the quality of diagnosis, treatment outcome, and automation of follow-ups. It is also transforming clinical practice systems [2]. The implications of this transformation are the most poignant

in the sphere of education and training of medical students. Digital possibly has upended the knowledge acquisition process, collaboration, and outreach to the up-and-coming technologies by medical students [3]. This evolution highlights the significance of digital literacy and training the future healthcare providers to manage the needs of clinical practice. The development of digital healthcare has brought significant changes in methods of teaching, the learning process, diagnostic quality, and

management of patients [2]. These evolutions have not only optimized clinical workflows but have also resulted in more accurate diagnoses, treatments, and patient follow-ups [4]. Online platforms are recently becoming a good source of learning that allows students to use resources, perform in virtual simulations, and be involved in the most advanced types of medical equipment [4]. This digital transition will require that students have good digital capabilities to stay motivated and useful in a system that is increasingly becoming more tech-oriented [5]. Integrating digital literacy into medical education is becoming a reality in Pakistan. An example is the introduction by the National University of Medical Science (NUMS) of special computer skills as part of its current undergraduate MBBS curriculum. Such an initiative also provides students with the crucial competencies that will be useful in their future profession, such as the utilization of medical software, which makes them ready to succeed in a digitalized healthcare space [6]. Nevertheless, a study carried out reveals that even at the time, much can still be done to enhance digital literacy among healthcare students. De La HOZ *et al.* underlined the necessity to conduct undergraduate programs to train digital and scientific skills, dedicated to e-Health literacy [7]. Although there is increased application of digital tools in learning and in social life, most of the students do not tune into some of the basic competencies that they need to utilize these tools properly [1]. To illustrate, there is research done in Canada, which found that even first-year university students who owned their personal computers and smartphones were not very familiar with them, but only operated basic operations [6]. This underscores a very important disparity between the current and actualized need in digital proficiency. ChatGPT and other tools that are artificial intelligence (AI) based are highly useful in medical education as they can aid cognitive skills that include recalling, interpreting, applying, analyzing, evaluating, and creating [8].

Nevertheless, the idea of AI integration should be approached with precautions to prevent any threats to sensitive patient information and ethical and legal issues related to this practice. This study aims to assess the level of digital literacy among health professions students at our institution and to identify gaps requiring curricular improvement. The findings will inform targeted curriculum development to enhance digital competence and support the effective integration of digital tools into contemporary clinical practice.

METHODS

An analytical cross-sectional study design was used to determine the level of digital literacy among undergraduate students at Lahore Medical College and Institute of

Dentistry, Lahore, Pakistan. The population of interest was all the registered students of the MBBS and BDS programs at Lahore Medical College and the Institute of Dentistry. The study was conducted from March to June 2024 after receiving ethical clearance from the institutional review board (Case#901/ERC/CMH/LMC; dated 15th March 2023). Taking part in the study was voluntary, and informed consent was received digitally from all participants. Anonymity and confidentiality of information were assured. Students who were enrolled in the MBBS or BDS courses and used the internet were included in the study. Those students who didn't use the internet, academically detained or repeating a year, and those who declined participation were excluded. The sample size was calculated using the standard formula for estimating a proportion in a cross-sectional study: $n = Z^2 \times p \times (1 - p) / d^2$ and found to be a required minimum of 278 participants. The study was completed by a total of 304 students, more than required. A non-probability convenience sampling approach was utilized to have a representative sample from various academic years and programs. The data were gathered via a self-report, pre-tested, reliable, and validated instrument consisting of 24 items [2]. Before the main study, a pilot testing phase was carried out to evaluate the questionnaire's validity and reliability. Thirty undergraduate medical and dentistry students (15 from each group) took part in the validation procedure; however, they were excluded from the final sample. Cronbach's alpha was used to assess internal consistency reliability (α -value is 0.785). The tool was meant to evaluate digital literacy over seven different dimensions, like Software and multimedia, Hardware, Network and communication/collaboration, Ethics, Security, Artificial intelligence, Interest, and knowledge. Part A aimed to obtain demographic information such as gender, academic program, and level of study. Part B: Each of the items had a rating over a 5-point Likert scale from "Strongly Disagree" (1) through "Strongly Agree" (5). The participants self-administered the questionnaire. Quantitative data were analyzed with SPSS version 26. Descriptive statistics such as means, standard deviations (SD), medians, interquartile ranges (IQR), frequencies, and percentages were utilized to describe demographic attributes and digital literacy scores. Each of the domain scores was calculated by averaging the responses to corresponding items, and a total digital literacy score was calculated by taking the mean of all the domain scores. A 95% confidence level was used for statistical analysis, and results were considered statistically significant at a p-value of less than 0.05, in accordance with standard biomedical research conventions. Along with p-values, effect sizes were calculated using Cohen's d to assess the practical

significance of differences between gender and academic-year groups. The comparisons were conducted across predefined digital literacy domains; no formal adjustment for multiple comparisons was applied. The analyses were exploratory in nature and guided by prior literature. To support meaningful interpretation, effect sizes (Cohen's *d*) were reported alongside *p*-values. In addition to *p*-values, effect sizes were calculated using Cohen's *d* to assess the magnitude and practical significance of differences between groups. Effect sizes were interpreted as small ($d=0.2$), moderate ($d=0.5$), and large ($d=0.8$), in accordance with standard conventions. Before performing independent samples *t*-tests, assumptions of normality and homogeneity of variances were assessed. Normality of digital literacy scores was evaluated using the Shapiro-Wilk test, while equality of variances was examined using Levene's test. As assumptions were met, parametric independent samples *t*-tests were applied for gender- and academic-year comparisons.

RESULTS

Data screening demonstrated that the assumptions required for parametric testing were satisfied. The data analysis showed that the overall digital literacy scores were approximately normally distributed ($p>0.05$). Minor deviations observed in some subdomains were acceptable given the sample size, supporting the use of parametric tests for group comparisons. A total of 345 students participated in the study; 249 (72.1%) were enrolled in the MBBS program, while 96 (27.8%) were from the BDS program. 149 (43.18%) of the participants were female, and 196 (56.8%) were male. Assumption testing confirmed that digital literacy scores were approximately normally distributed and that homogeneity of variances was satisfied across comparison groups (Shapiro-Wilk and Levene's tests, all $p>0.05$), supporting the use of independent sample *t*-tests (Table 1).

Table 1: Distribution of Participants by Academic Year ($n=345$)

Academic Years	Programs	Frequency (%)
1 st Year	MBBS	55 (15.9%)
2 nd Year	MBBS	62 (18.9%)
3 rd Year	MBBS	48 (13.9%)
4 th Year	MBBS	45 (13.0%)
Final Year	MBBS	39 (11.3%)
1 st Year	BDS	24 (7.0%)
2 nd Year	BDS	21 (6.1%)
3 rd Year	BDS	28 (8.1%)
Final Year	BDS	23 (6.6%)
Total	BDS	345 (100%)

Assessment of data distribution showed that the overall digital literacy score was approximately normally distributed. Shapiro-Wilk tests conducted for each digital

literacy domain revealed no significant deviation from normality (all p -values >0.05). Visual inspection of histograms and Q-Q plots further supported the assumption of normal distribution. Therefore, parametric statistical tests were considered appropriate for subsequent analyses. The descriptive statistics (mean $\pm$ SD) of digital literacy components among male and female students indicate no statistically significant differences between genders ($p>0.05$) (Table 2).

Table 2: Mean Scores of the Studied Digital Variables According to Total and Academic Level

Components	Male ($n=196$), Mean $\pm$ SD	Female ($n=149$), Mean $\pm$ SD
Software & Multimedia	3.85 $\pm$ 0.58	4.02 $\pm$ 0.54
Hardware	3.72 $\pm$ 0.60	3.89 $\pm$ 0.57
Network	3.66 $\pm$ 0.64	3.78 $\pm$ 0.59
Ethics	3.94 $\pm$ 0.55	4.10 $\pm$ 0.52
Security	3.58 $\pm$ 0.63	3.80 $\pm$ 0.58
Artificial Intelligence	3.49 $\pm$ 0.69	3.70 $\pm$ 0.62
Interest & Knowledge	3.80 $\pm$ 0.61	3.95 $\pm$ 0.57

The primary inferential analysis for gender-based differences in digital literacy components, conducted using independent samples *t*-tests, indicated no statistically significant differences between male and female students across any domain (all $p>0.05$) (Table 3).

Table 3: Analysis of Year of Gender-Based Difference in Digital Literacy Components

Component	t-value	p-value
Software & Multimedia	-0.18	0.86
Hardware	-0.47	0.64
Network	0.69	0.49
Ethics	0.68	0.50
Security	0.69	0.49
AI	0.36	0.72
Interest & Knowledge	-1.48	0.14

Although minor differences in mean scores were observed between genders (Table 2), these differences were not statistically significant based on inferential analysis (Table 3). For gender-based comparisons, effect size analysis revealed small Cohen's *d* values across all digital literacy domains ($d<0.20$), indicating negligible practical differences between male and female students despite minor variations in mean scores. These findings support the absence of meaningful gender-based differences in digital literacy competencies. Although a statistically significant difference was observed in the digital security domain between first- and second-year students ($p=0.002$), the associated effect size was small (Cohen's $d=0.28$), suggesting limited practical significance. No other academic-year comparisons demonstrated meaningful effect sizes. Students in their first and second years did not

substantially differ in many digital literacy components, according to a follow-up t-test analysis, depending on the research year (Table 4).

Table 4: Analysis of Year of Study-Based Difference in Digital Literacy Components

Component	1 st Year (n=79), Mean $\pm$ SD	2 nd Year (n=83), Mean $\pm$ SD	p-value
Software & Multimedia	3.78 $\pm$ 0.60	3.89 $\pm$ 0.56	0.153
Hardware	3.71 $\pm$ 0.63	3.75 $\pm$ 0.59	0.628
Network	3.60 $\pm$ 0.67	3.68 $\pm$ 0.61	0.421
Ethics	3.96 $\pm$ 0.58	4.05 $\pm$ 0.53	0.229
Security	3.59 $\pm$ 0.66	3.67 $\pm$ 0.60	0.387
Artificial Intelligence	3.52 $\pm$ 0.72	3.60 $\pm$ 0.66	0.439
Interest & Knowledge	3.83 $\pm$ 0.64	3.91 $\pm$ 0.58	0.398

Overall, first-year students demonstrated significantly higher perceived knowledge of digital security than second-year students. These findings suggest that while digital literacy competencies are relatively consistent across demographics, certain areas, such as security, may require targeted interventions based on academic level.

DISCUSSION

The current research examined the level of digital literacy of undergraduate students who are studying health professions. Since the demand for technology in healthcare is rising, the paper provides relevant information on the combination of the preparedness of aspiring medical practitioners to work productively within a digital environment. Analyzing the results, it becomes clear that despite relatively modest and steadily distributed levels of digital literacy among students across gender and academic years, there are several areas, such as cybersecurity and artificial intelligence (AI), which require a significant amount of attention to be paid to them within the undergraduate curriculum [9]. The small effect sizes observed across gender and academic-year comparisons indicate that differences in digital literacy, while occasionally statistically significant, are unlikely to be educationally meaningful, emphasizing the need for institution-wide rather than subgroup-specific interventions. The results of the study are the absence of any statistically significant differences in the scores of digital literacies between male and female students in both categories that were checked [10]. The finding applies to similar studies conducted in other countries, such as those that found that gender bore no discernible influence on the level of digital proficiency among Turkish health care students [2]. This follows results obtained in Bangladesh, where authors highlighted the importance of curriculum adjustments to improve the weaker aspects of learning, such as ethics and AI, whilst maintaining gender equity, and observed positive results in that they were unable to detect gender disparities when measured in seven digital areas

[11]. Once it can be seen as the same availability of digital devices, internet, and platforms between the two genders in the Pakistani education system of medicine, and specifically in CMH LMC and IOD [12]. In another similar study performed in King Edward Medical University utilizing the Digital Health Literacy Instrument (DHLI), there were also sufficient scores in operational skills as well as privacy protection, with inadequacies that occurred in assessing the reliability and relevance of data. These results justify why the medical students in Pakistan are required to have more organized interventions to enhance their critical digital skills [13]. Except for digital security, where first-year students scored noticeably higher than second-year students, there was no statistically significant difference in digital literacy between first- and second-year students in most categories [14]. This finding defies logic and poses significant queries. It might represent a recent focus on cybersecurity in orientation sessions or beginning computer courses taken by young professionals, which is bolstered by recent curriculum modifications implemented by organizations such as NUMS and UHS. On the other hand, it could indicate a decrease in the focus on digital ethics and safety beyond the first phases of medical education, indicating the necessity of ongoing curriculum-wide reinforcement [15]. The students reported mild proficiency in the areas of network and collaboration, hardware understanding, and software and multimedia usage. These outcomes are in line with research by Sriram et al. which found that junior physicians thought they were somewhat proficient in fundamental digital abilities but had trouble using them in clinical situations. This highlights a global trend: despite students' growing exposure to technology in social and academic settings, their capacity to effectively use it for academic, clinical, and collaborative objectives is still lacking [16]. In recent studies, the low to moderate results in the AI domain indicate a deficiency in structured AI teaching. Many researchers emphasized the need for foundational AI education among medical students; if students are aware of AI's presence in modern medicine, their actual understanding of AI applications, limitations, and ethical implications remains superficial [17, 18]. This area requires immediate attention due to the exponential rise of AI in diagnostics, decision support systems, and instructional tools. Institutional efforts toward equity have been successful; the lack of gender inequalities also shows that interventions can be broadly implemented without requiring gender-specific customization [19]. In the meantime, subpar results in AI and cybersecurity highlight deficiencies in teacher knowledge or structured curriculum content [20]. Integrating digital literacy into professional training is crucial for lowering inequities and enhancing healthcare

procedures, as emphasized in a recent scoping review. Literature also suggests the effectiveness of interactive teaching strategies, gamification, and curriculum mapping in improving digital health literacy among future healthcare professionals. These innovative methods can bridge the gap between theoretical knowledge and real-world application [12, 21]. Beyond academic competence, digital literacy plays a transformative role in achieving health equity. By equipping students with digital skills, institutions can help reduce disparities in healthcare access and empower future professionals to deliver more equitable and inclusive care [22]. Modules on cybersecurity awareness, data protection regulations, and AI applications in medicine should be given top priority by curriculum writers through interactive workshops or interdisciplinary partnerships [9].

This study has certain limitations. This cross-sectional design, based on a self-administered questionnaire, precludes inferring causal and/or temporal relationships between digital literacy and the variables being assessed, and self-reported responses may be subject to social desirability bias and recall bias, thereby possibly leading participants to overestimate or underestimate their actual skills, especially in newer fields like AI and Cybersecurity; in addition, the data was collected from a single institution (Lahore Medical College and Institute of Dentistry, Lahore) using non-probability convenience sampling, which may hamper the generalizability of the findings to other institutions and areas within Pakistan where curricular exposure to digital tools or technology infrastructure might vary. Digital competency ought to be required as a fundamental undergraduate accomplishment by regulatory organizations such as PM and DC. These competencies will be further reinforced by faculty training programs that incorporate digital resources into instruction.

CONCLUSIONS

Undergraduate students have a modest level of digital literacy in most disciplines. However, significant deficiencies in cybersecurity and artificial intelligence skills point to important areas for curriculum improvement. To prepare skilled and future-ready healthcare practitioners, undergraduate programs must incorporate structured digital literacy training, with a special emphasis on AI, data security, and ethical digital practice.

Authors' Contribution

Conceptualization: HS, SI

Methodology: HS, ZA, SI

Formal analysis: ZA, HK, FA, NW

Writing and Drafting: HS, HK, NW

Review and Editing: HS, NW, ZA, HK, FA, SI

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Prevalence of Eosinophilia in Chronic Obstructive Pulmonary Disease Exacerbation

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ARTICLE INFO

Keywords:

Chronic Obstructive Pulmonary Disease, Diabetes Mellitus, Eosinophilia, Hypertension, Smoking

How to Cite:

Ali, K., Kaleemullah, ., Mushir, A., Kumar, R., Hussain, M., & Akhtar, S. (2026). Prevalence of Eosinophilia in Chronic Obstructive Pulmonary Disease Exacerbation: Eosinophilia in Chronic Obstructive Pulmonary Disease Exacerbation. Pakistan Journal of Health Sciences, 7(8), 34-39. <https://doi.org/10.54393/pjhs.v7i8.3859>

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality worldwide. **Objectives:** To determine the prevalence of eosinophilia in COPD exacerbation, and to evaluate its association with exacerbation severity. **Methods:** This cross-sectional study was conducted at the Department of Pulmonology, Indus Hospital and Health Network, Karachi, Pakistan, during April 2024 to September 2024. A total of 141 diagnosed cases of COPD patients were analyzed. Eosinophilia was labeled as a blood eosinophil count $\geq 2\%$. Stratification analysis was performed to observe the effects of effect modifiers on the prevalence of eosinophilia, applying Chi-square or Fisher's exact test, taking $p < 0.050$ as statistically significant. **Results:** In a total of 141 patients, 101 (71.6%) were males, and the median age was 62.0 (52.0-71.0) years. Monthly family income was classified as low in 80 (56.7%) patients. Smoking status was 'never smoked' in 65 (46.1%), 'ex-smoker' in 61 (43.3%), and 'current smoker' in 15 (10.6%) patients. Hypertension and diabetes mellitus were reported in 92 (65.2%) and 73 (51.8%) patients. Eosinophilia was identified in 58 (41.1%) patients. Smoking status differed significantly with respect to the prevalence of eosinophilia ($p = 0.024$). Severity of COPD exacerbation differed by eosinophilia status, as increasing severity was significantly associated with eosinophilia ($p < 0.001$). **Conclusions:** Blood eosinophilia was frequently observed among patients admitted with COPD exacerbation and showed a significant association with smoking status and exacerbation severity.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality worldwide. Around 250 million people are estimated to suffer from COPD annually, whereas 5% of total annual deaths are attributed to COPD [1]. COPD is the 4th leading cause of mortality and is projected to rise as the 3rd leading cause of death in 2050 [2, 3]. Population-based evidence from South Asia indicates a substantial prevalence of spirometry-defined COPD, with a pooled estimate of 8.0-11.1% [4]. In Pakistan, community-level estimates remain heterogeneous, yet regional epidemiological data reported a COPD prevalence of 2.1% among adults aged over 40 years [5]. Eosinophilic inflammation is anticipated in COPD, and contemporary

literature exhibits that eosinophils may reflect therapeutic effects and phenotypes of COPD [6]. With recent developments, the role of controlling blood eosinophilia in COPD management has increased, and COPD with increased eosinophilia is also used as a biomarker of exacerbations [7, 8]. Significant variability in blood eosinophil levels has been shown throughout the course of COPD. In 25%-40% of COPD exacerbations, the eosinophilic phenotype is present [9]. Smoking is one of the primary determinants of COPD progression and exacerbation risk, and prior cohort data suggest that the relationship between blood eosinophils and exacerbations may vary by smoking status, indicating potential effect

modification [10]. Diabetes and hypertension are highly prevalent comorbidities in COPD and have been linked with higher exacerbation-related healthcare use and worse inpatient outcomes, which is clinically relevant because systemic corticosteroids used during exacerbations can worsen glycaemic control and cardiometabolic instability [11]. Evaluating smoking status and cardiometabolic comorbidity alongside eosinophil measurements can refine the interpretation of eosinophilic phenotypes during acute exacerbations and inform risk stratification and treatment decisions.

The prevalence of eosinophilic COPD exacerbation in Asian populations has only been briefly studied. Not much recent data from Pakistan is available about the evaluation of eosinophilia in newly diagnosed COPD patients. This study aims to determine the prevalence of blood eosinophilia among patients with acute exacerbation of COPD, and to evaluate its association with exacerbation severity.

METHODS

This cross-sectional study was performed at the Department of Pulmonology, Indus Hospital and Health Network, Karachi, Pakistan, during April 2024 to September 2024. A sample size of 141 was calculated through the online Open Epi sample size calculator, taking the anticipated proportion of eosinophilia in COPD as 15.6% [12], with 95% confidence level and 6% margin of error. Non-probability, consecutive sampling technique was adopted. Inclusion criteria were patients of any gender, aged 40-80 years, and diagnosed with COPD according to GOLD, as clinical history and spirometry showed persistent airflow limitation with a ratio of FEV1 / FVC < 0.70 pre- and post-bronchodilator [13]. Patients with a history of asthma and bronchiectasis, on long-term oral steroid use, or diagnosed with tuberculosis were excluded. This study was commenced after approval from the Institutional Review Board (IHHN_IRB_2024_03_002; dated 29th March 2024). Written informed consent was obtained from each participant or caregiver. Information like age, gender, monthly family income, and smoking status was collected from the patients. Weight and height were recorded at enrolment, and body mass index (BMI) was calculated as weight (kg) divided by height (m²). Venous blood was drawn under aseptic technique, and 2-3 mL was collected in an EDTA tube, gently inverted, transported promptly to the laboratory, and analyzed for CBC with differential on an automated hematology analyzer, and eosinophilia was defined as $\geq 2\%$ eosinophils [12]. Diabetes mellitus was defined as a prior documented diagnosis or use of glucose-lowering medication, or random plasma glucose ≥ 200 mg/dL at presentation. Hypertension was defined as a prior documented diagnosis or use of antihypertensive medication, or systolic blood pressure ≥ 140 mmHg and or

diastolic blood pressure ≥ 90 mmHg on presentation (measured after 5 minutes rest, repeated if elevated). Monthly family income was recorded in Pakistani Rupees per month and categorized into low ($\leq 55,000$), middle (55,001-80,000), and high ($> 80,000$) [14]. COPD exacerbation severity was categorized according to guideline-based event definitions as mild when managed with short-acting bronchodilators alone, moderate when requiring systemic corticosteroids and or antibiotics, and severe when requiring emergency department visit or hospital admission [13]. All information was recorded into a pre-designed proforma by the researchers themselves.

Statistical analyses were performed using IBM-SPSS Statistics, version 26.0. All continuous variables like age, height, weight, body mass index (BMI), and eosinophil count were assessed by the Shapiro-Wilk test to check for normality assumption and represented as mean and standard deviation (SD), or median and inter-quartile range (IQR). Frequency and percentage were computed for all categorical variables, such as gender, smoking status, hypertension, diabetic mellitus, monthly family income status, education status, COPD severity, and eosinophilia (yes/ no). Stratification analysis was performed to observe the effects of effect modifiers like age, BMI, gender, smoking status, hypertension, diabetic mellitus, monthly family income, education status, and COPD severity on the prevalence of eosinophilia. After stratification, the chi-square or Fisher exact test was used to observe the effect of effect modifiers on the outcome (eosinophilia), and odds ratios (OR) with 95% confidence interval (CI) were calculated, taking $p < 0.050$ as statistically significant.

RESULTS

In a total of 141 patients, 101 (71.6%) were males, and 40 (28.4%) were females. The median age was 62.0 (52.0-71.0) years. There were 94 (66.7) patients who had a BMI between 18.5 and 24.9 kg/m². Monthly family income status was classified as low in 80 (56.7%) patients. Smoking status was 'never smoked' in 65 (46.1%), 'ex-smoker' in 61 (43.3%), and 'current smoker' in 15 (10.6%) patients. Hypertension and diabetes mellitus were reported in 92 (65.2%) and 73 (51.8%) patients, respectively. The study shows details about the characteristics of patients studied (Table 1).

Table 1: Characteristics of Patients (n=141)

Characteristics		Frequency (%)
Gender	Male	101 (71.6%)
	Female	40 (28.43%)
Age Groups (years)	40 to 50	17 (12.1%)
	51 to 60	45 (31.9%)
	61 to 70	46 (32.6%)
	71 to 80	33 (23.4%)

BMI (kg/m ²)	<18.5	8 (5.7%)
	18.5 to 24.9	94 (66.7%)
	25.0 to 29.9	22 (15.6%)
	≥30.0	17 (12.1%)
Monthly Family Income	Low	80 (56.7%)
	Middle	49 (34.8%)
	High	12 (8.5%)
Education	Illiterate	58 (41.1%)
	Primary-Secondary	30 (21.3%)
	Matriculation	36 (25.5%)
	Intermediate	11 (7.8%)
	Graduation or above	6 (4.3%)
Smoking	Never Smoked	65 (46.1%)
	Ex-smoker	61 (43.3%)
	Current Smoker	15 (10.6%)
Hypertension	—	92 (65.2%)
Diabetes Mellitus	—	73 (51.8%)

Eosinophilia was identified in 58 (41.1%) patients with COPD exacerbation, while 83 (58.9%) had no eosinophilia. Eosinophilia prevalence did not differ with respect to gender ($p=0.437$), age groups ($p=0.518$), BMI ($p=0.181$), monthly family income ($p=0.167$), education status ($p=0.615$), hypertension ($p=0.209$), and diabetes mellitus ($p=0.499$). Smoking status differed significantly with respect to the prevalence of eosinophilia prevalence ($p=0.024$), as the current smoking status was recorded in 10 (17.2%) patients with eosinophilia, and 5 (6.0%) without eosinophilia, with OR of 4.5 (95% CI 1.4 to 14.9) compared with never-smokers, and ex-smokers were 28 (48.3%) among eosinophilia patients, and 33 (39.8%) in the non-eosinophilia group, with OR 1.9 (95% CI 0.9 to 4.0). The details about the association of eosinophilia with various demographic and clinical characteristics of patients are shown (Table 2).

Table 2: Association of Eosinophilia with Various Demographic and Clinical Characteristics (n=141)

Characteristics		Eosinophilia		95% CI	p-value
		Yes (n=58)	No (n=83)		
Gender	Male	39 (67.2%)	62 (74.7%)	Reference	0.512
	Female	19 (32.8%)	21 (25.3%)	1.4 (0.7-3.0)	
Age Groups (years)	40 to 50	7 (12.1%)	10 (12.0%)	Reference	0.518
	51 to 60	21 (36.2%)	24 (28.9%)	1.3 (0.4-3.9)	
	61 to 70	20 (34.5%)	26 (31.3%)	1.1 (0.4-3.4)	
	71 to 80	10 (17.2%)	23 (27.7%)	0.6 (0.2-2.1)	
BMI (kg/m ²)	<18.5	2 (3.4%)	6 (7.2%)	0.5 (0.1-2.4)	0.181
	18.5 to 24.9	40 (69.0%)	54 (65.1%)	Reference	
	25.0 to 29.9	6 (10.3%)	16 (19.3%)	0.5 (0.2-1.4)	
	≥30.0	10 (17.2%)	7 (8.4%)	1.9 (0.7-5.5)	
Monthly Family Income	Low	38 (65.5%)	42 (50.6%)	Reference	0.167
	Middle	15 (25.9%)	34 (41.0%)	0.5 (0.2-1.0)	
	High	5 (8.6%)	7 (8.4%)	0.8 (0.2-2.7)	
Education	Illiterate	26 (44.8%)	32 (38.6%)	Reference	0.615
	Primary-Secondary	14 (24.1%)	16 (19.3%)	1.1 (0.5-2.6)	
	Matriculation	11 (19.0%)	25 (30.1%)	0.5 (0.2-1.3)	
	Intermediate	4 (6.9%)	7 (8.4%)	0.7 (0.2-2.7)	
	Graduation or above	3 (5.2%)	3 (3.6%)	1.2 (0.2-6.6)	
Smoking	Never Smoked	20 (34.5%)	45 (54.2%)	Reference	0.024
	Ex-smoker	28 (48.3%)	33 (39.8%)	1.9 (0.9-4.0)	
	Current Smoker	10 (17.2%)	5 (6.0%)	4.5 (1.4-14.9)	
Hypertension	—	44 (75.9%)	48 (57.8%)	2.3 (1.1-4.8)	0.209
Diabetes Mellitus	—	32 (55.2%)	41 (49.4%)	1.3 (0.6-2.5)	0.499

Severity of COPD exacerbation differed by eosinophilia status, as increasing severity was significantly associated with eosinophilia ($p<0.001$) (Figure 1).

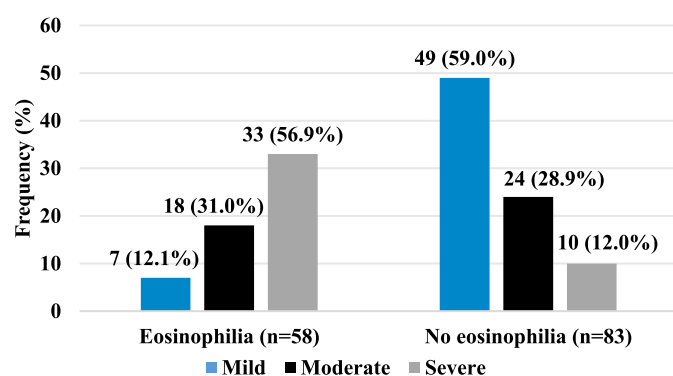


Figure 1: Association of Prevalence of Eosinophilia with Respect to Severity of COPD Exacerbation (n=141)

DISCUSSION

Blood eosinophilia was identified in 41.1% patients presenting with COPD exacerbation. This prevalence sits close to estimates reported by Hasegawa and Camargo Jr., where eosinophilia based on the same $\geq 2\%$ threshold was observed in 40% of hospitalized COPD patients with exacerbation, supporting the view that a relative eosinophil cut-off identifies a substantial eosinophilic phenotype in COPD patients [15]. Javed *et al.* in a local study from Faisalabad, found eosinophilia in 39.3% patients with acute exacerbation of COPD [16]. These estimates from different centers suggest that eosinophilia is frequently encountered during COPD exacerbations [17]. Ahmad *et al.* reported eosinophilia in 23.7% COPD patients [17]. The absence of a statistically significant difference in eosinophilia prevalence across age strata, or gender distribution in the present study, is consistent with reports that eosinophilic status is not primarily driven by age alone. A study from Saudi Arabia examined eosinophilic COPD and found no meaningful differences between eosinophilic and non-eosinophilic groups in age or gender distribution [18]. Kiani *et al.* described higher pack-year exposure and pulmonary hypertension prevalence with higher eosinophils at diagnosis, yet ICU admission, invasive ventilation requirement, and mortality during exacerbations were not clearly separated by eosinophil status, indicating that eosinophilia may not map neatly onto various indices or all markers of physiological compromise [19]. Monthly family income and educational attainment were also not associated with eosinophilia in the present study. Smoking status showed a significant association with eosinophilia, as current smoking was recorded in 17.2% patients with eosinophilia, and 6.0% without eosinophilia, corresponding to an OR of 4.5 (95% CI 1.4 to 14.9). Ex-smokers comprised 48.3% in the eosinophilia patients, and 39.8% in the non-eosinophilia patients, with an OR of 1.9 (95% CI 0.9 to 4.0). This relationship may reflect several mechanisms, as active smoking can promote airway epithelial injury and

dysregulated immune signaling, and may interact with corticosteroid exposure and infection patterns that shape blood eosinophil proportions during acute illness [20]. The present results indicate that smoking cessation counselling remains central not only for exacerbation prevention but also because smoking may be linked to inflammatory profiles that influence acute management decisions. Exacerbation severity differed by eosinophilia status in the present study, with increasing severity significantly associated with eosinophilia ($p < 0.001$). This observation is clinically important because it suggests that eosinophilic inflammation may cluster among greater acute care requirements, reinforcing the role of eosinophils as a marker of exacerbation phenotype rather than baseline demographics [21]. The link is consistent with longitudinal evidence that eosinophil elevation predicts future exacerbation burden. Vedel-Krogh *et al.* reported that higher baseline blood eosinophils were associated with increased incidence rate ratios for both severe and moderate exacerbations, indicating that eosinophil-driven inflammation is connected to subsequent exacerbation trajectories [22]. Chan *et al.* observed that eosinophil proportions $\geq 2\%$ were associated with higher exacerbation frequency over the subsequent 12 months and conferred an adjusted odds ratio of 2.98 for exacerbation risk [23]. Juthong and Kaenmuang found higher annual exacerbation rates and higher admission frequency in eosinophilic COPD defined by ≥ 300 cells/ μL , with admission burden differences aligning with the concept that eosinophilia tracks higher healthcare utilization [24]. These findings provide a possible mechanistic and prognostic context in which the present severity association is plausible, especially in an inpatient cohort enriched for clinically significant events.

The study was conducted at a single center with non-probability consecutive sampling, which may limit generalizability across different healthcare settings and referral patterns. Eosinophilia was defined using a proportional cut-off of $\geq 2\%$ rather than absolute eosinophil count thresholds, which complicates direct comparison with cohorts using absolute definitions. Pack-years and recency of smoking were not captured, which restricts quantified response assessment. The present analysis did not quantify treatment outcomes.

CONCLUSIONS

It was concluded that the blood eosinophilia was frequently observed among patients admitted with COPD exacerbation and showed a significant association with smoking status and exacerbation severity.

Authors' Contribution

Conceptualization: K

Methodology: AM, RK, MH, SA

Formal analysis: AM

Writing and Drafting: KA, K

Review and Editing: KA, K, AM, RK, MH, SA

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Knowledge, Skills, and Attitudes of Recent Medical Graduates Regarding the Management of Poisoning Cases

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ARTICLE INFO

Keywords:

Poisoning, Emergency Management, Medical Graduates, Competence, Toxicology Education

How to Cite:

Manzoor, S., Iqbal, Z., Safdar, M., Abbas, N., Zafar, A., & Asif, M. (2026). Knowledge, Skills, and Attitudes of Recent Medical Graduates Regarding the Management of Poisoning Cases: Recent Medical Graduates Regarding the Management of Poisoning Cases. *Pakistan Journal of Health Sciences*, 7(8), 40-44. <https://doi.org/10.54393/pjhs.v7i8.3883>

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sincerwithu@gmail.comReceived Date: 26th January, 20261st Revision Received: 3rd March, 20262nd Revision Received: 24th March, 20263rd Revision Received: 9th April, 2026Acceptance Date: 11th April, 2026Published Date: 31st August, 2026

ABSTRACT

Poisoning remains a major cause of emergency department visits and preventable mortality, particularly in low- and middle-income countries. Newly graduated medical officers are frequently the first responders in poisoning emergencies. **Objectives:** To evaluate the knowledge, skills, and attitudes of recent medical graduates regarding the diagnosis, management, and medico-legal responsibilities associated with poisoning cases. **Methods:** An analytical cross-sectional study was conducted among 201 recent MBBS graduates working in tertiary care teaching hospitals in Lahore, Pakistan. A structured, pilot-tested questionnaire assessed knowledge using multiple-choice and scenario-based questions, skills through structured clinical scenarios, and attitudes using Likert-scale items. Data were analyzed using SPSS version 26.0. Independent t-tests, chi-square tests, Pearson correlation, and multiple linear regression were applied. A p-value ≤ 0.050 was considered statistically significant.

Results: Graduates who completed an emergency department rotation demonstrated significantly higher knowledge scores than those without such training. Greater exposure to poisoning cases was associated with improved practical skills, and a moderate positive correlation was observed between the number of poisoning cases managed and overall competence. Emergency rotation and clinical exposure independently predicted competence after adjustment for demographic variables. Major competence gaps were identified in toxidrome recognition, decontamination sequencing, airway protection, corrosive poisoning management, and medico-legal documentation. **Conclusions:** Recent medical graduates possess moderate theoretical knowledge but demonstrate important deficiencies in practical and medico-legal competencies. Structured emergency rotations and simulation-based toxicology training are essential to improve preparedness for poisoning management.

INTRODUCTION

Poisoning remains a significant global public health concern and contributes substantially to morbidity and mortality worldwide. According to the World Health Organization, acute poisoning accounts for hundreds of thousands of deaths annually, with the greatest burden occurring in low- and middle-income countries where access to antidotes, regulatory oversight of toxic substances, and trained emergency care providers is often limited [1, 2]. In South Asia, including Pakistan, poisoning is

a frequent cause of emergency department presentations and preventable deaths [3, 4]. Commonly encountered agents include pesticides, pharmaceuticals, corrosive substances, and household chemicals. These exposures are often intentional or accidental and require prompt recognition and management in emergency settings [3, 5]. Delays in airway stabilization, decontamination, or antidote administration may result in severe complications or death [5, 6]. Recent medical graduates, particularly house



officers, are often the first physicians responsible for the initial evaluation and management of poisoning cases. Effective care requires early identification of toxidromes, stabilization of airway, breathing, and circulation, appropriate decontamination measures, timely antidote administration, and vigilant monitoring for complications [6, 7]. However, multiple studies have demonstrated that junior doctors frequently lack adequate practical experience and confidence in managing poisoning emergencies during early clinical practice [6–8]. In addition to clinical management, poisoning cases carry important medico-legal responsibilities, including documentation, evidence preservation, and legal reporting. Newly graduated doctors often report insufficient training and limited confidence in fulfilling these obligations [8–10]. Evidence suggests that structured emergency medicine exposure and focused toxicology education improve clinical competence and professional confidence among junior physicians [9, 11]. Despite inclusion of toxicology in undergraduate curricula, hands-on exposure and formal medico-legal training remain limited in many medical institutions in Pakistan [10, 12].

Given the frontline role of recent graduates in emergency care, evaluating their knowledge, skills, and attitudes toward poisoning management is essential to identify deficiencies and guide educational reform. This study aimed to assess these competencies and determine factors associated with preparedness for poisoning emergencies. This study aims to assess the knowledge, skills, and attitudes of recent medical graduates regarding the diagnosis, management, and medico-legal responsibilities related to poisoning cases.

METHODS

An analytical cross-sectional study was conducted in tertiary care teaching hospitals in Lahore, Pakistan, from 16 December 2025 to 16 January 2026. Ethical approval was obtained from the Ethical Review Committee of Ameer-ud-Din Medical College / PGMI, Lahore General Hospital, Lahore, Pakistan (Approval No. AMC/PGMI/LGH/Article/Research No/2025/ERC/73; dated 4th December 2025). Written informed consent was obtained from all participants. The study included 201 recent MBBS graduates who had completed their degree within the previous two years and were working in clinical departments. Sample size was calculated using Cochran's formula, and non-probability convenience sampling was employed. Sample size was calculated as $n = Z^2 * p * (1-p) / d^2$, where $Z = 1.96$ (Z-value for 95% confidence level), $p = 0.5$ (Estimated proportion), $d = 0.05$ (Margin of error), and $n = 300$ (Population size). Finite Population Correction: $n_{adj} = n / 1 + (n-1)/N$. The final sample size was 200 participants. Data were collected using a structured questionnaire.

Knowledge and skills assessment were based on structured multiple-choice questions and scenario-based evaluations, adapted from previous studies on junior doctors' toxicology competence. Attitudes were measured using a Likert-scale questionnaire validated in similar populations. Knowledge was assessed through multiple-choice and scenario-based questions covering poisoning types, toxidrome recognition, decontamination principles, and antidote use. Skills were evaluated using structured clinical scenarios assessing airway management, antidote administration, corrosive poisoning handling, and medico-legal procedures. Skills assessment was scenario-based and not purely self-reported. Attitudes were measured using Likert-scale items evaluating ethical responsibility, reporting behavior, and professional confidence. The questionnaire was pilot-tested on 20 recent graduates not included in the final analysis, and internal consistency was acceptable (Cronbach's alpha = 0.78).

Data were analyzed using SPSS version 26.0. Descriptive statistics were expressed as mean $\pm$ standard deviation or frequency (%). Independent t-tests, chi-square tests, Pearson correlation, and multiple linear regression were applied. A p-value ≤ 0.050 was considered statistically significant.

RESULTS

The sample size was 201, and all participants responded. Males constituted 88 (44%) of the sample, while 113 (56%) were females. The mean age of the respondents was 25 ± 1.2 years. Regarding institutional background, 119 (59%) graduates were from government medical colleges and 82 (41%) were from private institutions. During their in-house employment, 127 (63%) participants had completed a formal emergency department rotation, whereas 74 (37%) had not (Table 1).

Table 1: Demographic Characteristics of Participants

Characteristics	n (%) / Mean $\pm$ SD
Gender	
Male	88 (44%)
Female	113 (56%)
Age (years)	25 ± 1.2
Type of Institution	
Government	119 (59%)
Private	82 (41%)
Emergency Rotation Completed	
Yes	127 (63%)
No	74 (37%)

The mean knowledge score was 19 ± 4 out of 30, indicating a relatively low level of conceptual understanding. Graduates who had completed an emergency rotation achieved significantly higher knowledge scores (20.5 ± 3.7) than those who had not (15.8 ± 4.0) ($t = 6.41$, $p = 0.001$). Domain-

wise analysis revealed good knowledge of common types of poisoning (73%) and indications for antidotes such as atropine and naloxone (69%). However, deficits were observed in the identification of toxidromes (41%), contraindications of gastric lavage and activated charcoal (37%), and monitoring for complications (34%) (Table 2).

Table 2: Knowledge, Skills, and Attitude Scores of Participants

Parameters	Mean $\pm$ SD / n (%)	Significant Findings
Knowledge Score (Out of 30)	19 $\pm$ 4	Higher with emergency rotation: 20.5 $\pm$ 3.7 vs 15.8 $\pm$ 4.0 (p=0.001)
Knowledge Domains (% Correct)	—	Common poisoning: 73%; Antidotes: 69%; Toxidromes: 41%; Contraindications: 37%; Monitoring: 34%
Skills Score (Out of 25)	17.2 $\pm$ 4.5	Higher with >5 poisoning cases: 19.2 $\pm$ 3.8 vs 14.7 $\pm$ 4.6 (p=0.003)
Skills Gaps (% Correct)	—	Airway protection: 47%; Corrosive ingestion: 38%; Decontamination sequence: 40%; Medico-legal documentation: 40%
Attitude Score (Out of 40)	29 $\pm$ 5	Government: 29.0 $\pm$ 4.5 vs Private: 24.2 $\pm$ 5.0 (p=0.020); 71% support reporting; 50% confident in documentation

The mean skills score was 17.2 $\pm$ 4.5 out of 25. Participants who managed more than five poisoning cases during training demonstrated significantly higher skills scores (19.2 $\pm$ 3.8) than those with low or no exposure (14.7 $\pm$ 4.6) (p=0.003). Major competence gaps were observed in airway protection of unconscious patients (47%), care of corrosive ingestion (38%), sequencing of decontamination procedures (40%), and medico-legal documentation and sample preservation (40%). The overall attitude score was 29 $\pm$ 5 out of 40, reflecting a generally favorable professional attitude. Government graduates had significantly higher attitude scores (29.0 $\pm$ 4.5) than private graduates (24.2 $\pm$ 5.0) (p=0.002). Although 71% of participants believed that poisoning cases should always be documented as medico-legal cases, only 50% expressed confidence in accurately completing medico-legal documentation. Chi-square analysis demonstrated a significant association between emergency rotation completion and adequate knowledge levels ($\chi^2 = 11.8$, p=0.001), as well as between exposure to poisoning cases and skills adequacy ($\chi^2 = 9.6$, p=0.002). Pearson correlation analysis revealed a moderate positive relationship between the number of poisoning cases managed and overall competence (r = 0.41, p<0.001). Multiple regression analysis further showed that emergency rotation was a significant predictor of competence ($\beta = 0.38$, p=0.001) (Table 3).

Table 3: Association Between Training Factors and Competence

Factor Assessed	Statistical Test	Test Value	Significance
Emergency rotation and Knowledge adequacy	Chi-square	$\chi^2 (1) = 11.8$	p=0.001
Exposure to poisoning cases and Skills adequacy	Chi-square	$\chi^2 (1) = 9.6$	p=0.002
Number of poisoning cases and Overall competence	Pearson correlation	r = 0.41	p<0.001
Emergency rotation (predictor of competence)	Multiple regression	$\beta = 0.38$	p=0.001

After controlling demographic variables (age, gender, type of institution, and year of graduation), a multiple linear regression analysis was performed to determine if training-related characteristics independently predicted total competence. 22% of the competence variance was explained by the entire model, which was statistically significant (p<0.001) ($R^2 = 0.22$, adjusted $R^2 = 0.20$). Overall competency was found to be significantly predicted by emergency rotation ($\beta = 0.38$, p=0.001, 95% CI: 0.15–0.61). There was also a strong positive correlation between exposure to poisoning cases ($\beta = 0.24$, p=0.012, 95% CI: 0.05–0.43). A statistically significant independent effect was not shown by any of the demographic variables. Independent samples t-tests revealed significant differences in knowledge, skills, and attitude scores between groups based on training exposure and institutional background (Table 4).

Table 4: Independent Samples t-Test Results

Comparisons	Group 1, (Mean $\pm$ SD)	Group 2, (Mean $\pm$ SD)	t-value	p-value	Interpretation
Knowledge Score	Emergency rotation: 20.5 $\pm$ 3.7	No rotation: 15.8 $\pm$ 4.0	6.41	0.001	Significant
Skills Score	>5 Cases: 19.2 $\pm$ 3.8	≤ 5 cases: 14.7 $\pm$ 4.6	—	0.003	Significant
Attitude Score	Government: 29.0 $\pm$ 4.5	Private: 24.2 $\pm$ 5.0	—	0.002	Significant

Scatter plot showing the positive linear relationship between the number of poisoning cases managed and overall competence score, with the regression line indicating increasing competence with greater clinical exposure (r = 0.41, p<0.001) (Figure 1).

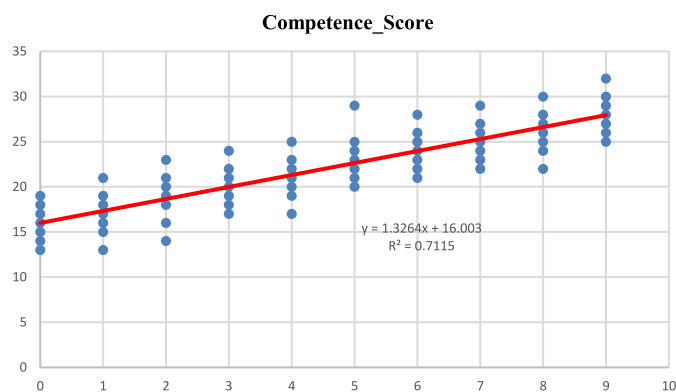


Figure 1: Positive Linear Relationship Between the Number of Poisoning Cases Managed and Overall Competence Score

DISCUSSION

This study evaluated the preparedness of recent medical graduates in managing poisoning cases and identified training-related factors influencing overall competence. Although theoretical knowledge was moderate, significant gaps were identified in practical skills and medico-legal readiness. Graduates who completed Department of Emergency rotations demonstrated superior knowledge, supporting previous findings that structured emergency exposure enhances understanding of poisoning management [13, 14]. Clinical exposure was a strong determinant of skills competence, with increased case experience correlating positively with overall competence. Similar associations between experiential learning and improved emergency care performance have been reported in comparable healthcare settings [15, 16]. Despite reasonable awareness of common poisons and antidotes, deficiencies in toxidrome recognition, airway protection, and decontamination protocols were evident. These findings mirror earlier studies demonstrating inadequate practical training in toxicology among junior doctors [14–17]. Medico-legal documentation emerged as one of the weakest competence domains, consistent with previous reports of limited medico-legal awareness and confidence among early-career physicians [18]. Attitudes toward professional responsibility were generally positive, particularly among graduates from government institutions, possibly reflecting greater exposure to emergency and medico-legal cases. However, positive attitudes alone did not translate into adequate competence, reinforcing the need for structured, skills-based training [16–18]. Regression analysis confirmed that emergency rotation completion and poisoning case exposure independently predicted competence, regardless of demographic factors. These findings align with evidence demonstrating that supervised emergency training and targeted educational interventions significantly improve preparedness among junior

physicians [19, 20].

This study has several limitations. Convenience sampling may limit generalizability, and skills were assessed through structured scenarios rather than direct bedside observation. Self-reported exposure to poisoning cases may introduce recall bias. Future multicenter studies incorporating objective structured clinical examinations and longitudinal follow-up are recommended.

CONCLUSIONS

Recent medical graduates demonstrate moderate theoretical knowledge of poisoning management but exhibit important deficiencies in practical skills and medico-legal readiness. Structured emergency department rotations, simulation-based toxicology training, and formal medico-legal education should be integrated into medical curricula to enhance preparedness and improve patient outcomes.

Authors' Contribution

Conceptualization: SM

Methodology: SM, MA

Formal analysis: NA, AZ

Writing and Drafting: ZI, MS

Review and Editing: SM, ZI, MS, NA, AZ, MA

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Comparative Evaluation of the WHO Labour Care Guide and Modified Partograph in Cesarean Section Frequency, Delivery Outcomes, and Maternal Stress in Tertiary Care Hospitals in Hyderabad

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ARTICLE INFO

Keywords:

Labour, Obstetrics, Parturition, Partograph, Cesarean Section, Pregnancy Outcomes, Maternal Stress

How to Cite:

Bano, S., Parveen, F., Mustafa, P., Aslam, A., Zia, A. S., & Paras, . (2026). Comparative Evaluation of the WHO Labour Care Guide and Modified Partograph in Cesarean Section Frequency, Delivery Outcomes, and Maternal Stress in Tertiary Care Hospitals in Hyderabad : WHO Labour Care Guide and Modified Partograph in Cesarean Section and Maternal Stress. Pakistan Journal of Health Sciences, 7(8), 45-51. <https://doi.org/10.54393/pjhs.v7i8.4040>

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Received Date: 24th February, 2026

1st Revision Received: 13th March, 2026

2nd Revision Received: 25th March, 2026

Acceptance Date: 11th April, 2026

Published Date: 31st August, 2026

ABSTRACT

The global rise in cesarean section (CS) rates has raised concerns due to associated maternal and neonatal risks, increased healthcare costs, and psychological stress. To address this issue, the World Health Organization introduced the Labour Care Guide (LCG) as an updated, evidence-based tool for monitoring labour and improving childbirth outcomes. **Objectives:** To compare the frequency of cesarean sections among women managed using the WHO Labour Care Guide (LCG) and those managed with the Modified Partograph in tertiary care hospitals of Hyderabad, Sindh. **Methods:** A comparative cross-sectional study was conducted at Liaquat University Hospital and Khidmat-e-Khalq Foundation Hospital over four months. A total of 430 pregnant women were enrolled, with 215 participants in each group. Maternal stress levels were assessed using the Perceived Stress Scale (PSS). Data were analyzed using SPSS version 26.0, and the Chi-square test was applied to compare categorical variables. **Results:** Women managed with the LCG had a significantly lower CS rate compared with those monitored using the Modified Partograph (40 vs. 65; $p=0.02$). The LCG group also demonstrated improved neonatal outcomes, including higher birth weights and better Apgar scores. Additionally, maternal stress levels were significantly lower and satisfaction with care was higher among women in the LCG group ($p<0.050$). **Conclusions:** The WHO Labour Care Guide appears to be more effective than the Modified Partograph in reducing cesarean section rates and improving maternal and neonatal outcomes while lowering maternal stress during labour.

INTRODUCTION

Cesarean sections (CS) have been on the rise globally, with the worldwide average CS rate increasing from 12% in 2000 to 21% in 2015 and projected to reach nearly 29% by 2030 if current trends continue [1]. Increased risks of infections (3 to 15%), hemorrhage (up to 10), anesthesia-related complications (up to 7), and a long recovery process in resource-limited settings may worsen the situation further

in women undergoing CS [2]. Furthermore, the following CSs are more likely to lead to uterine rupture, abnormal placentation, and an increased risk of repeat CS, which also hurts healthcare systems. The high CS rates are associated with the rise of healthcare expenses in terms of prolonged hospital stays, the use of more resources, and the necessity to provide more specialized care during the

surgery and after it [3]. This economic burden has the potential of redirecting funds to other important services to maternal and child health, hence affecting the quality of care in general [4-6]. Another important issue that depends on the mode of delivery is pregnancy outcomes. Vaginal birth takes shorter to heal, has fewer infections and immediate mother-infant bonding, which is healthy for the health and development of the newborn baby in the long term as compared to C Section [7, 8]. In addition, the mental health of CS mothers is also becoming an increasing concern [9]. Research has found that women who deliver through CS are likely to develop more postpartum depression, anxiety, and stress than those who deliver through the vagina. The psychological consequences of an unexpected or emergency CS may also be especially significant and may also add to the failure, loss of control, and trauma [10]. To overcome these problems, the conventional partograph and the new WHO Labour Care Guide (LCG) tools have been created. Partograph is a graph tool that is applied to track the progress of labor and determine whether there are deviations in norms, so that the interventions may be timely. Yet, it has not been used regularly and has not had many effects on the decrease of the unnecessary CS [11]. The WHO Labour Care Guide (LCG) seeks to enhance labour management through a more holistic and evidence-based method of monitoring labour [12]. The LCG focuses on personalized care, ongoing labor, and evidence-based intervention, which will help to decrease unnecessary CS and enhance delivery outcomes. Comparing the effectiveness of the LCG with the traditional partograph, the given study aims at identifying the possible advantages of LCG in terms of decreasing the rate of CS and improving both maternal and neonatal conditions, including maternal mental health [13]. According to the last report of Pakistan Demographic and Health Survey (PDHS), the rate of C-Section deliveries is soaring, with the authority noting a change in 2012-13, where the rates stood at 14%. In 2017-18, the rates have improved to 22%. This excessive use puts an enormous and avoidable burden on the health system of the country, which otherwise consumes limited resources in other areas of priority. It is also known to drive up the cost of delivering care that affects poorer families in disproportionately large measures [14, 15].

The study is specifically timely and relevant in that it can guide the policy and practice, making childbirth practices and health outcomes in mothers and babies safer to protect health and well-being worldwide. This study aimed to offer evidence on the need to implement the LCG to encourage safer birth practices and improve the maternal and neonatal health of women in Pakistan by intervening with both physical and mental health outcomes.

METHODS

A comparative cross-sectional study was conducted at Liaquat University Hospital and Khidmat e Khalq Foundation Hospital, Hyderabad, in the time frame of four months from 11-10-2025 to 10-02-2026, after the approval of the research proposal by the research ethics committee of LUMHS, Jamshoro (NO. LUMHS/REC-1147; dated 10th October 2025). A non-probability consecutive sampling method was used. The sample size was calculated by the equation $n = [(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times (p_1(1-p_1) + p_2(1-p_2))] / (p_1 - p_2)^2$ based on comparison of cesarean section rates between the WHO Labour Care Guide and Modified Partograph groups. Assuming a cesarean section rate of 30% in the Modified Partograph group and 18% in the WHO Labour Care Guide group, with a 95% confidence level and 80% power [13], the required sample size was calculated as 195 participants per group. After adjusting for a 10% anticipated dropout rate, a total of 430 participants (215 per group) were included in the study. Groups: Intervention Group: Labour monitored using the WHO Labour Care Guidelines and Control Group: Labour monitored using the Modified Partograph. Inclusion Criteria consisted of pregnant women aged 18 to 35 years, primigravida and multigravida women admitting with spontaneous labour in the active phase, live Singleton pregnancy with cephalic presentation, having normal vital signs, and vaginal birth was anticipated. Exclusion criteria were defined for patients with induced labour, pregnant women admitted in the 2nd stage of labour, women with any pregnancy-related complications, antenatal women with medical disorders like Diabetes mellitus/Hypertension/Anemia/Heart diseases/Autoimmune diseases, and women with preterm labour, premature rupture of membranes, or contracted pelvis were excluded from the study. Written informed consent from the pregnant woman or her attendant was obtained after providing them with clear and concise information about the study's purpose, procedures, risks, and benefits. Participants were assured of the confidentiality of their data. The participants have the autonomy to leave the study or not to answer any question. The questions were asked of the participants in their local language so they could easily understand and answer. Whereas, for assessing the stress levels in participants during labour and delivery, the Perceived Stress Scale (PSS) was employed. The Perceived Stress Scale (PSS-10) is a widely used instrument for measuring perceived psychological stress. It consists of 10 items rated on a 5-point Likert scale (0 = never to 4 = very often). After reversing the scores of positively worded items (items 4, 5, 7, and 8), the responses are summed to obtain the total stress score. The minimum possible score was 0, and the maximum possible score is 40, with higher scores

indicating greater perceived stress. Generally, scores were interpreted as low stress (0-13), moderate stress (14-26), and high stress (27-40) [16]. Regarding reliability, recent studies have reported strong internal consistency, with Cronbach's alpha values typically exceeding 0.70, indicating acceptable to high reliability. In terms of validity, the PSS has shown strong construct validity, commonly supporting a two-factor structure (perceived helplessness and perceived self-efficacy), confirmed through confirmatory factor analysis [17]. Additionally, the scale demonstrates good convergent validity, with significant associations with related psychological constructs such as anxiety and depression. Recent validation studies conducted in diverse populations (e.g., Iran, Peru, Bangladesh) further confirm that the PSS is a psychometrically sound and culturally adaptable tool for measuring perceived stress [18].

SPSS version 26.0 was used for data analysis. Qualitative variables, such as mode of delivery, were presented as frequencies and percentages. Quantitative variables, including duration of labor, birth weight, and Apgar scores, were expressed as mean and standard deviation. Normality of quantitative variables was assessed using the Shapiro-Wilk test. Chi-square test was applied for comparing categorical variables between groups (LCG vs. Modified Partograph), and the independent sample t-test was used for normally distributed continuous variables. A p-value of less than 0.050 was considered statistically significant.

RESULTS

The study presents the socio-demographic characteristics of the participants. The majority of women in both groups were aged 18-25 years (36.0%), followed by 26-30 years (34.9%). Most participants had secondary level education (58.1%). Regarding marriage duration, 45.3% had been married for 3-5 years. Approximately 43.0% had one to two children, and 61.6% reported previous labour experience. In addition, this study provides a comparison of the maternal health outcomes and the cases of complications such as hemorrhage, infection, and high blood pressure. The LCG Group had fewer cases of complications, 20 cases of hemorrhage, 10 of infections, and 15 of high blood pressure. On the contrary, it was the Modified Partograph Group that exhibited more complication rates, especially hemorrhage (30 cases) and infection (20 cases). A greater share of women in the two groups did not have complications, with 170 in the LCG Group and 155 in the Modified Partograph Group. This study also presents fetal health outcomes where the average birth weight (3.3 kg), Apgar score at 1 minute (8.5), and Apgar score at 5 minutes (9.0) were slightly higher in the LCG Group than in the Modified Partograph Group, which had lower values of the above outcomes. The LCG Group

had lower NICU admissions, too (5 cases), than the Modified Partograph Group (8 cases) (Table 1).

Table 1: Demographic Information of Participants and Maternal and Fetal Health Outcomes

Variables	LCG Group, n (%)	Modified Partograph Group, n (%)	Total, n (%)
Age Group			
18-25	80 (37.2%)	75 (34.9%)	155 (36.0%)
26-30	70 (32.6%)	80 (37.2%)	150 (34.9%)
31-35	65 (30.2%)	60 (27.9%)	125 (29.1%)
Educational Level			
No Formal Education	15 (7.0%)	10 (4.7%)	25 (5.8%)
Primary	40 (18.6%)	50 (23.3%)	90 (20.9%)
Secondary	120 (55.8%)	130 (60.5%)	250 (58.1%)
Tertiary	40 (18.6%)	25 (11.6%)	65 (15.1%)
Marriage Duration			
≤2 Years	60 (27.9%)	55 (25.6%)	115 (26.7%)
3-5 Years	95 (44.2%)	100 (46.5%)	195 (45.3%)
>5 Years	60 (27.9%)	60 (27.9%)	120 (27.9%)
Parity (Number of Children)			
0 (Primigravida)	85 (39.5%)	80 (37.2%)	165 (38.4%)
1-2	90 (41.9%)	95 (44.2%)	185 (43.0%)
≥3	40 (18.6%)	40 (18.6%)	80 (18.6%)
Previous Labour Experience			
Yes	130 (60.5%)	135 (62.8%)	265 (61.6%)
No	85 (39.5%)	80 (37.2%)	165 (38.4%)
Maternal Health Outcomes			
Hemorrhage	20 (9.3%)	30 (14.0%)	50 (11.6%)
Infection	10 (4.7%)	20 (9.3%)	30 (7.0%)
High Blood Pressure	15 (7.0%)	10 (4.7%)	25 (5.8%)
None	170 (79.1%)	155 (72.1%)	325 (75.6%)
Fetal Health Outcomes			
Birth Weight (kg)	3.3	3.1	3.2
Apgar Score (1 min)	8.5	8.0	8.3
Apgar Score (5 min)	9.0	8.7	8.9
NICU Admissions	5	8	13

(The results present the results of the Shapiro-Wilk test for assessing the normality of continuous study variables, including birth weight, Apgar scores, and duration of labour, in both the WHO Labour Care Guide (LCG) and Modified Partograph groups. All variables had p-values greater than 0.050, indicating that the data were normally distributed. This finding justified the use of parametric tests (e.g., independent t-test) for comparing the mean values of these variables between the two groups in subsequent analyses (Table 2).

Table 2: Shapiro-Wilk Test for Normality

Variables	Shapiro-Wilk Test	p-value
Birth Weight (LCG)	0.989	0.114
Birth Weight (Modified Partograph)	0.994	0.507
Apgar Score (LCG)	0.995	0.707
Apgar Score (Modified Partograph)	0.995	0.667

Duration of Labor (LCG)	0.994	0.589
Duration of Labor (Modified Partograph)	0.995	0.749

*Note: $p \leq 0.050$ indicates statistical significance. No variables reached significance in this test

To determine the impact of LCG and the Modified Partograph on the proportion of cesarean section cases, the frequency of CS delivery using the two methods was compared using a chi-square test to determine the differences in the proportions. The findings show that the rate of cesarean section in the LCG group was significantly lower than that of the Modified Partograph group ($p < 0.050$), indicating that the LCG is more effective in preventing unnecessary cesarean sections. The t-test of continuous variables results of the LCG Group and the Modified Partograph Group are provided. The LCG Group was much taller with respect to birth weight (3.3 kg vs. 3.1 kg, $p = 0.004$) and the labor length (10.2 hrs vs. 12.0 hrs, $p = 0.010$). Moreover, the LCG Group was at a higher Apgar score at 1 minute (8.5 vs. 8.0, $p = 0.003$). These variations denote that LCG Group had better maternal and fetal outcomes (Table 3).

Table 3: Cesarean Section Rates

Variables	LCG Group, n (%) / Mean ± SD	Modified Partograph Group, n (%) / Mean ± SD	p-value
Mode of Delivery			
Vaginal Delivery	175 (81.4%)	150 (69.8%)	0.020*
Caesarean Section	40 (18.6%)	65 (30.2%)	
T-Test for Continuous Variables			
Birth Weight (kg)	3.3 ± 0.5	3.1 ± 0.6	0.041*
Duration of Labor (hrs)	10.2 ± 3.5	12.0 ± 4.1	0.013*
Apgar Score (1 min)	8.5 ± 1.2	8.0 ± 1.1	0.031*

*Note: $p \leq 0.050$ indicates statistical significance

The results show satisfaction with care delivery by the participants in the LCG Group and in the Modified Partograph Group. Greater satisfaction levels were reported in the LCG Group; higher percentages of participants indicated that they were Very Satisfied (60 vs. 30) and satisfied (100 vs. 80) in the LCG Group than in the Modified Partograph Group. On the other hand, more participants of the Modified Partograph Group were not satisfied (Very Dissatisfied (20 vs. 10) and Dissatisfied (25 vs. 15). The p-value of 0.02 shows that the difference in satisfaction between the two groups was statistically significant, with the LCG Group winning (Table 4).

Table 4: Participants' Satisfaction with Care during Delivery

Satisfaction	LCG Group, n (%)	Modified Partograph Group, n (%)	p-value
Very Dissatisfied	10 (4.7%)	20 (9.3%)	0.021*
Dissatisfied	15 (7.0%)	25 (11.6%)	
Neutral	30 (14.0%)	40 (18.6%)	
Satisfied	100 (46.5%)	80 (37.2%)	
Very Satisfied	60 (27.9%)	30 (14.0%)	

*Note: $p \leq 0.005$ indicates statistical significance

The study shows the mode of delivery (Vaginal vs. Cesarean) results of the Chi-square test between the two groups. The Chi-square statistic value has the value of 0.45 and 1 degree of freedom, and the p-value of 0.502, which was above the level of significance of 0.050. This implies that no substantial disparity can be established in terms of mode of delivery between the LCG Group and the Modified Partograph Group, which implies that the distribution of Vaginal and Cesarean deliveries was the same in both groups. The duration of labor significantly varies between the two groups ($p < 0.050$), as the LCG Group has a lower duration of labor. The difference between the Apgar score at 1 minute between the two groups is statistically significant ($p < 0.050$), with the LCG Group doing better. The difference in birth weight between the LCG Group and the Modified Partograph Group ($p < 0.050$) statistically differed, with the LCG Group reporting higher birth weight (Table 5).

Table 5: Chi-square Test for Mode of Delivery

Variables	Chi-square Statistic, t-value	Degrees of Freedom (df)	p-value
Mode of Delivery (Vaginal vs. Cesarean)	0.45	1	0.502
Independent Sample t-test for Duration of Labor			
Duration of Labor	-4.11	428	0.005**
Apgar Score (1 min)	3.46	428	0.006**
Birth Weight	3.23	428	0.001**

*Note: ** $p \leq 0.050$ indicates statistical significance

DISCUSSION

The increasing incidence of cesarean sections (CS) in the world has brought up serious issues of maternal and neonatal health consequences [19]. The global rise in CS rates, which were 12% in 2000 and are projected to reach 29% by 2030, has not only had an impact on physical health but also introduced socioeconomic implications in the healthcare systems. The non-medical influences on the practice of CS in most countries are on the rise, especially in Pakistan, where they are being inspired by maternal wishes, perceived convenience, and financial gains within healthcare facilities [20]. Psychological stress experienced by women especially following emergency or unplanned deliveries of CS adds to the risks involved in this procedure, such as infections, hemorrhage, and lengthy recovery periods context, the research aimed at assessing the usefulness of the WHO Labor Care Guide (LCG) in the reduction of CS occurrence and the health outcomes of both mothers and their newborns relative to the Modified Partograph, which is widely used as a labor progress monitoring tool [21-23]. The research found that the LCG was more effective in decreasing the frequency of cesarean sections by a significant margin, with $p < 0.050$. The results can be compared to previous sources that

highlight that the LCG facilitates personalized care, sustained support, and evidence-based interventions that proactively minimize unnecessary CS. The result conforms to the WHO recommendation that the CS rates should not be above 10-15 because above this level, there are high chances of maternal and neonatal morbidity. Prioritizing a more individualized approach to labor management, the LCG is most likely to promote timely interventions as well as prevent needless surgical interventions [24]. Although a valuable instrument for tracking labor progress, the Modified Partograph has been demonstrated to be inconsistently used and has a restricted influence in minimizing CS rates [25]. The LCG subsequently mitigates these shortcomings by including continuous labor support and care plans tailored to each individual, that has the potential to lead to maternal and fetal outcomes. As this research suggests, the LCG Group was less likely to have CS than the Modified Partograph group (40 vs. 65, $p=0.020$), and this may be because more extensive labor monitoring could provide more favorable results when the delivery process is concerned. The LCG Group had fewer complications (hemorrhage and infection) in terms of maternal outcomes than the Modified Partograph Group. In particular, postpartum hemorrhage was much lower in the LCG Group (20 vs. 30, $p<0.050$), which is one of the most important factors to enhance maternal health. Furthermore, the fetal outcome was also better with the LCG Group (babies born with a better birth weight of 3.3 kg compared to 3.1 kg) with a higher Apgar score at 1 minute (8.5 vs. 8.0) and 5 minutes (9.0 vs. 8.7) [26]. The LCG Group had fewer admissions to the NICU (5 vs. 8), which also confirms the idea that the LCG makes the process of providing adequate neonatal care easier, and the babies are born in the best possible circumstances. This is significant, since vaginal births are associated with superior immediate infant outcomes when compared to a cesarean section, which has been frequently linked with infant lateness to breastfeeding and reduced instant mother-infant attachment. The research also determined the level of maternal stress during childbirth, which has been associated with poor health conditions in both the mother and the infant. Measures of stress during labor were done by use of the Perceived Stress Scale (PSS) [27]. The LCG Group expressed lower levels of stress than the Modified Partograph Group, and the high levels of stress were significantly reduced (65 vs. 55, $p<0.050$). This indicates that the emphasis of constant help and personalized care by the LCG can minimize stress and anxiety during labor, that are beneficial to both the health of the mother and the baby [16]. Another variable taken into consideration in the research was satisfaction with care. The level of satisfaction in the LCG Group was also much

greater, as the percentage of participants who stated that they were "Very Satisfied" (60 vs. 30, $p<0.050$) with the treatment they obtained during labor. This finding confirms the hypothesis that the individual approach and ongoing assistance are major elements contributing to the improvement of patient experience in childbirth. The results are in line with the studies that have shown that the more satisfied mothers are, the greater their chances of achieving good mental health results, such as reduced post-partum depression and anxiety levels. The findings of this study suggest that the use of the WHO Labour Care Guide can support improved monitoring and decision-making during labour compared with the Modified WHO Partograph. Healthcare institutions should consider integrating the Labour Care Guide into routine intrapartum care and provide appropriate training for healthcare providers to ensure its effective implementation. This may help improve the quality of maternal care and potentially enhance maternal and neonatal outcomes during labour.

This study was conducted in a single tertiary hospital, limiting generalizability, and did not fully assess factors like socioeconomic status, nutrition, or antenatal care. Reliance on accurate documentation for the WHO Labour Care Guide and Modified Partograph may introduce observer bias, and long-term maternal and neonatal outcomes were not evaluated. Future studies should be conducted in multiple healthcare settings with larger and more diverse populations to improve the generalizability of the findings. Further research should also include additional maternal and socioeconomic factors and assess long-term maternal and neonatal outcomes to better evaluate the effectiveness of the WHO Labour Care Guide compared with the Modified WHO Partograph. Regular training of healthcare providers on the correct use of these monitoring tools is also recommended.

CONCLUSIONS

To sum up, the LCG is a more suitable instrument in the control of labor, and its advantages are substantial regarding the decreasing number of unnecessary cesarean sections and enhancement of maternal and fetal outcomes. The study supports the use of the LCG in the clinical setting to simplify the labor process, reduce unnecessary surgical operations, and enhance the quality of the service provided to mothers and their children. The findings indicate the importance of applying evidence-based beliefs in improving births and maternal health, especially in low-resource settings, as is the case in Pakistan.

Authors' Contribution

Conceptualization: SB

Methodology: SB, FP

Formal analysis: SB

Writing and Drafting: PM, AA, ASZ, P

Review and Editing: SB, FP, PM, AA, ASZ, P

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Effect of Infiltration in Temporomandibular Joint with Triamcinolone Acetonide for Pain Relief in Internal Derangement

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ARTICLE INFO

Keywords:

Orofacial Pain, Triamcinolone Acetonide, Internal Derangement, Temporomandibular Joint, Pain Management, Intra-Articular Injection

How to Cite:

Tufail, I., Akhtar, U. B., Farooq, A., Tariq, S., & Zubair, S. (2026). Effect of Infiltration in Temporomandibular Joint with Triamcinolone Acetonide for Pain Relief in Internal Derangement: Infiltration in Temporomandibular Joint with Triamcinolone Acetonide for Pain Relief. *Pakistan Journal of Health Sciences*, 7(8), 52-57. <https://doi.org/10.54393/pjhs.v7i8.3894>

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ABSTRACT

Orofacial pains are frequently caused by disorders of the temporomandibular joint (TMJ), which are often associated with masticatory difficulties, joint noises, and limited mouth opening. Despite the availability of several treatment options, a standardized management approach has yet to be developed. Intra-articular infiltration with Triamcinolone acetonide has been explored as a minimally invasive intervention for local symptomatic relief; clinical evidence regarding its effectiveness remains variable. **Objective:** To evaluate the effect of intra-articular triamcinolone acetonide injection on pain reduction in patients with TMJ internal derangement. **Methods:** A single-arm interventional pre-post study was performed on 71 patients with symptomatic TMJ internal derangement. Each patient received a local injection of 40mg/ml Kenacort (triamcinolone acetonide) under standard aseptic outpatient settings. The Wong-Baker FACES[®] Pain Rating Scale was employed to assess pain both before and one month following the intervention. **Results:** Among the 71 patients who reported pre-intervention pain, the mean pain score decreased from 6.085 to 2.423, and this change was statistically significant on paired t-testing ($t=17.905$, $p<0.001$). Improved joint sounds and jaw mobility were observed along with a statistically significant decrease in pain scores ($p\leq 0.050$). **Conclusion:** Intra-articular triamcinolone acetonide injection demonstrated a significant reduction in TMJ-related pain for short-term relief in this outpatient cohort.

INTRODUCTION

The temporo-mandibular joint (TMJ) is a point of connection between the mandible and the skull. The temporomandibular joint (TMJ) is a special synovial joint that enables intricate motions necessary for speaking, eating, chewing, and maintaining correct jaw alignment [1]. For both sliding and hinge-link movement the surrounding ligaments, cartilage, and muscles work together to coordinate its architecture. Malfunctioning of this sensitive system can cause pain, joint sounds, chewing

difficulties, restricted range of motion, and even jaw locking. Temporomandibular disorders (TMD) are common among people, which have a significant impact on day-to-day life [1]. Recent studies suggest that symptoms occur most frequently in adults aged between 20 and 40 years, with women being more affected roughly in a ratio of 9:1 [2]. This disparity is mostly caused by hormonal influences, particularly estrogen, along with malocclusion and parafunctional habits such as bruxism. The breakage of



articular cartilage occurs in the type of TMJ osteoarthritis (OA), which is defined as a degenerative disease of the jaw joint (unilateral disease), accompanied by architectural changes in the bone and ineffective degeneration of the synovial tissues, causing pain and/or dysfunction of functional movements of the jaw. OA may also be the first joint disease of the jaw, unlike rheumatoid arthritis, when the TMJ is often the last joint affected [2, 3]. Patho physiologically, OA involves increased degradation of the extracellular matrix (ECM) through matrix metalloproteinases (MMPs) and ADAMTS enzymes, which results in reduced ECM production and chondrocyte death, further leading to progressive cartilage loss [3]. There can be many symptoms for this condition, including: pain during jaw movement, clicking or grinding noises within the joint, deviation on opening, restricted mouth opening, and, in some cases, persistent joint stiffness [3]. There are so many ways to treat TMD, and a few examples include the most conservative treatments like physiotherapy, oral medications, and occlusal splints, to more focused treatments such as injections directly into the joint or surgical methods. About 10 years ago, botulinum toxin was investigated in some cases, but its use surpasses the expenses and contraindications [4]. Corticosteroid injections are a more reasonable method for potentially reducing pain and inflammation in the joints that are affected [5]. Triamcinolone acetonide is a synthetic glucocorticoid; it is a corticosteroid with anti-inflammatory and immunosuppressive properties [5]. Triamcinolone inhibits phospholipase A2 in the membrane, thereby inhibiting the pathway that produces pro-inflammatory mediators such as prostaglandins and leukotrienes. The combination of these two reduces swelling, limits vascular permeability, and alleviates pain. Additionally, it reduces the activity of specific immune cells that can regulate the process of persistent inflammation occurring within the joint [5]. Some studies have used Triamcinolone acetonide either standalone or in combination for relieving TMD-associated pain symptoms [6, 7]. Corticosteroids' efficacy, in pain reduction and inflammation control, has been well established in managing the inflammatory symptoms associated with larger joints (i.e., knee, shoulder) [5]. In contrast, the role of corticosteroids is less clear in the treatment of TMDs. Whereas with TMJ therapy, the extent of documented evidence supporting the use of corticosteroids and the position of corticosteroids as a single agent has not been widely explored [4]. This is, in part, due to the pooled data comparing the effect of triamcinolone with agents such as hyaluronic acid [7].

The lack of focused evidence makes it challenging to evaluate corticosteroids' clinical effectiveness as a standalone standard intervention for addressing pain

associated with TMD. This study aims to demonstrate the clinical effectiveness of intra-articular injection of triamcinolone acetonide in the role of an outpatient, stand-alone type of treatment for pain relief in patients with internal derangement.

METHODS

This single-arm interventional pre-post study was conducted for one year from November 2023 to September 2024 at the Department of Oral and Maxillofacial Surgery OPD, Sharif Medical and Dental College, Lahore, after ethical approval from the Sharif Medical Research Center (Ref. No. SMDC/SMRC/317-23; dated 13th November 2023). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. A sample size of 71 participants was calculated using the WHO sample size calculator, assuming a 95% confidence level, 10% precision, and an anticipated treatment response proportion of 75% with triamcinolone acetonide [8]. Participants were recruited consecutively using non-probability sampling from patients presenting with clinical features suggestive of temporomandibular disorders (TMD). Diagnosis of temporomandibular disorders was established by a specialist using accepted clinical diagnostic criteria based on the International Classification of Headache Disorders guidelines of the International Headache Society [8]. The assessment incorporated both patient-reported symptoms and objective clinical findings. Typical presentations included recurrent pain localized to the jaw, face, or temporal region that was exacerbated by jaw movement or mastication. Radiographic imaging was performed when clinically indicated to confirm internal derangement and to exclude alternative pathologies. Only patients fulfilling the diagnostic criteria and having symptoms attributable to internal derangement were considered eligible for intra-articular triamcinolone acetonide infiltration. Adults aged 18–80 years with pain on temporomandibular joint (TMJ) palpation, functional limitation, and symptoms consistent with internal derangement were included, while those with prior TMJ injections, hypersensitivity to corticosteroids, active infection, dermatologic lesions at the injection site, pregnancy or lactation, history of maxillofacial trauma or TMJ surgery, bleeding disorders, anticoagulant use, uncontrolled systemic disease, or inability to comply with follow-up were excluded. Baseline assessment included demographic and clinical characteristics such as age, sex, duration, and laterality of symptoms, prior conservative treatment, and baseline functional status. Clinical examination comprised TMJ palpation, measurement of maximal mouth opening, documentation of joint sounds, and pain assessment using the Wong-Baker FACES® Pain Rating Scale (0–10) [9]. Under aseptic conditions and

following auriculotemporal nerve block and joint lavage with isotonic saline, intra-articular injection of triamcinolone acetonide (1 mL containing 40 mg/mL) was administered by an experienced consultant oral and maxillofacial surgeon. Post-procedure care included cold compression, supervised manual jaw mobilization, and instruction in passive stretching exercises to improve mouth opening. The primary outcome was change in pain intensity from baseline to one-month follow-up, with a reduction of at least 2 points considered clinically meaningful. Secondary outcomes included change in maximal mouth opening, presence of joint sounds, and patient-reported functional improvement in mastication and daily activities. Participants were monitored for immediate and delayed adverse events, including facial nerve weakness, swelling, infection, hematoma, or steroid-related complications. Compliance with post-procedure instructions and follow-up attendance were documented, and losses to follow-up were accounted for in the analysis. Data were analyzed using SPSS version 24.0. Continuous variables were summarized as mean $\pm$ standard deviation depending on data distribution assessed by the Shapiro-Wilk test. Pre- and post-intervention comparisons were performed using a paired t-test. A p-value ≤ 0.050 was considered statistically significant.

RESULTS

A total of 71 patients with temporomandibular joint internal derangement were included in the final analysis. Pain was the presenting symptom in all participants. Associated clinical features included joint clicking in 53 (74.6%) patients and restricted mouth opening in 9 (12.7%) patients. The study population consisted predominantly of females (76.1%). Most participants were aged between 40 and 60 years (52.1%). Most patients reported unilateral symptoms (69.0%) and had a history of prior conservative treatment (64.8%), such as analgesics, physiotherapy, or occlusal splints. Baseline clinical assessment demonstrated limitation of mouth opening (12.7%) (Table 1).

Table 1: Baseline Clinical Assessment

Variables	n (%)
Gender	
Female	54 (76.1%)
Male	17 (23.9%)
Others	
20-40	12 (16.9%)
40-60	37 (52.1%)
60-80	22 (31.0%)
Age Group (Years)	
Joint Clicking	53 (74.6%)
Restricted Mouth Opening	9 (12.7%)
Prior Conservative Treatment	46 (64.8%)

Unilateral Symptoms	49 (69.0%)
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At baseline, patients experienced a substantial degree of discomfort, with a mean pain score of 6.09 ± 2.25 , indicating predominantly moderate to severe pain. At one-month follow-up after intra-articular triamcinolone acetonide injection, the mean pain score significantly decreased to 2.42 ± 1.62 , corresponding to mild pain intensity. The mean reduction in pain score was 3.67 points, which exceeded the predefined threshold for clinically meaningful improvement. Paired comparison demonstrated a statistically significant reduction in pain intensity ($t = 17.905$, $p < 0.001$) (Table 2).

Table 2: Comparison of Pain Scores (Wong-Baker FACES Scale) Pre- and Post-Intervention

Variables	Mean $\pm$ SD	Mean Difference	t-value	p-value
Pre-Treatment Pain Score	6.09 ± 2.25	3.67	17.905	<0.001
Post-Treatment Pain Score	2.42 ± 1.62			

The proportion of patients with restricted mouth opening decreased from 12.7% at baseline to 4.2% at one-month follow-up, indicating improved mandibular mobility. Similarly, joint clicking showed partial resolution, decreasing from 74.6% to 43.7%, suggesting a reduction in intra-articular mechanical dysfunction (Table 3).

Table 3: Secondary Functional Outcomes After Intra-Articular Triamcinolone Injection (n=71)

Outcome Variables	Baseline, n (%)	1-Month Follow-Up, n (%)	Improvement, (%)
Restricted Mouth Opening	9 (12.7%)	3 (4.2%)	66.7%
Joint Clicking	53 (74.6%)	31 (43.7%)	41.5%
Pain on Palpation	71 (100%)	22 (31.0%)	69.0%
Functional Limitation During Mastication	58 (81.7%)	19 (26.8%)	67.2%
Difficulty in Speaking	34 (47.9%)	10 (14.1%)	70.6%

Only a small proportion of patients experienced minor transient adverse events, including short-term post-injection discomfort (9.9%) and mild facial swelling (4.2%), which resolved without additional treatment. Temporary facial nerve weakness was observed in one patient and recovered spontaneously. Importantly, no cases of infection, hematoma formation, systemic steroid-related complications, or serious procedure-related adverse events were reported during the follow-up period (Table 4).

Table 4: Safety and Adverse Events Following Procedure (n=71)

Adverse Events	n (%)
Transient Post-Injection Discomfort	7 (9.9%)
Mild Facial Swelling	3 (4.2%)
Temporary Facial Nerve Weakness	1 (1.4%)
Hematoma at Injection Site	0 (0%)
Infection	0 (0%)

Steroid-Related Systemic Effects	0 (0%)
Procedure-Related Serious Complication	0 (0%)

DISCUSSION

TMDs cover a wide range of heterogeneous clinical conditions involving TMJ, associated musculature, and supporting structures [10, 11]. Patients with TMDs mostly suffer from pain as the primary symptom of the disorder, frequently along with joint sounds and occasionally restriction in mouth opening. Findings of this study are in accordance with these established clinical patterns, as all of the enrolled patients in the present study presented with a lesser number of reported joints clicking and limitation in mouth opening. This frequency of symptoms was not unexpected, as studies have already reported that pain is the primary reason for patients seeking medical help in comparison to functional limitations like restricted mouth opening. These secondary symptoms usually develop later in the course of the disease [12]. The uneven distribution of symptoms observed during this study among the enrolled patients holds clinical significance and implications for interpretations. As discussed earlier, we observed pain in all the patients, while a smaller fraction reported joint sounds or restricted mouth opening, which limited the ability to draw robust conclusions regarding these secondary outcomes. Symptom variability is a common challenge in TMJ research, as it tends to complicate the study design as well as the analyses. From a demographic point of view, our results are in accordance with the previously reported findings in the literature. TMD has been observed to be higher in females, particularly in reproductive years. This can be associated with the potential role of hormonal influences, especially estrogen, affecting joint physiology and pain perception [13]. Although this study did not perform sex stratified analysis, the background clarifies the predominance and frequency of pain in our patient population. The variability of the treatment response in the study could potentially be attributed to gender distribution. This study divided patients into three age brackets: 20–40, 40–60, and 60–80 years to better reflect how TMJ internal derangement tends to present and evolve. Individuals between 20 and 40 years commonly represent the peak age for disc displacement and inflammatory TMJ pain, where synovial inflammation is often a dominant feature. Those in the 40–60-year range frequently fall into a transitional stage, where persistent internal derangement may coexist with early degenerative changes. In contrast, patients aged 60–80 years are more likely to demonstrate predominantly degenerative joint alterations [14, 15]. This framework is clinically useful when considering both prognosis and expected response to intra-articular therapies. The current study's most notable finding of the study was the

pain reduction observed in patients post intervention, as the mean pain score dropped from 6.09 ± 2.25 at baseline to 2.42 ± 1.62 at one-month follow-up. This was a change that was highly statistically significant. This change was clearly reflected in the patients, as the majority reported mild or no pain after the treatment. This degree of improvement is impactful not only from a clinical standpoint, but it is also translated into tangible benefits in daily activities, i.e., of chewing, speaking, or even sleep quality [11]. The current study results are in accordance with the previously reported studies in the literature, suggesting that pain is not only the most predominant symptom in TMD but also responds to targeted intra-articular interventions [16–20]. The findings of this study need cautious interpretation as the benefits of the intervention were not uniform for all the patients enrolled. Some patients continued to report mild to moderate pain at the follow-up. Considering TMD being a multifactorial condition, this variability of the response was not surprising for us, as the treatment response is also influenced by a wide range of factors, e.g., disease chronicity, underlying joint pathology, parafunctional habits such as bruxism, occlusal factors, and even psychosocial stressors [2]. Lack of baseline data on these variables has posed a limit on the predictors of response in this study. This heterogeneity of response can be interpreted as ineffectiveness of a single intervention as a universal treatment in all patients. The literature reports a degree of variability in intra-articular therapies for TMDs in terms of intervention protocols and effectiveness. Multiple studies have used corticosteroids in combination with other agents, for instance, hyaluronic acid, to address both degeneration and inflammation. However, some systematic reviews have highlighted the heterogeneity of the study design, patient selection, and outcome parameters, thus reporting mixed conclusions [21, 22]. Patient safety is an important consideration in administering intra-articular corticosteroids in patients. The study did not find any major adverse event in our patients for the entire duration of the study. The relatively short duration of the follow-up can be a limitation of this study, particularly regarding long-term safety. Some evidence exists for adverse effects on joint cartilage over time due to frequent administration of corticosteroid injections [22]. This highlights a cautious approach in patient enrolment for long-term and/or repeated interventions. Although we observed a decline in the pain scores after intervention, one-third of the patients still experienced moderate discomfort. This can be interpreted as a variable response to the treatment. Kacker *et al.* reported an effective short-term use of intra-articular corticosteroids in pain relief. Yet they emphasized combination therapies as a potential for long-term

alternatives [23].

The current study acknowledges some of the limitations of our study. The lack of a control group is the most important limitation, as it hinders the ability to correlate the improvement observed during the span of the study with the intervention. The relatively short follow-up is another limitation, as it does not allow for the long-term efficacy and durability of the intervention. In addition to these, the lack of baseline patient characteristics data, i.e., duration and severity of symptoms, laterality, prior treatments, and comorbidities, thus restricts our ability to perform more accurate analyses for the identification of the factors influencing the efficacy of the treatment. Lastly, the improvement in joint sounds and jaw mobility, although observed, was not measured in a standardized manner, thus limiting the strength of conclusions perceived regarding functional improvements. Regardless of the discussed limitations, the present study offers insights into the role of corticosteroid injections as a minimally invasive option for pain management and relief in TMD internal derangement, especially for an outpatient setting. This study clearly demonstrates the effectiveness of the reported intervention for an effective short term for a significant section of patients in the short term. Based on current study findings, the study recommends more detailed studies in this area, focusing on randomized controlled trials with longer follow-ups, administering corticosteroids alone or in combination with alternative treatment options, along with arthrocentesis, as such would be more valuable for long-term pain management, but will also strengthen the evidence base and help the patients.

CONCLUSIONS

This present study shows that infiltration with triamcinolone acetonide provides a statistically significant reduction in pain intensity in patients with TMD. The results support the clinical utility of triamcinolone acetonide in TMD pain relief and are a promising therapeutic choice. Future studies with longer-term follow-up involving larger cohorts would help validate these findings and establish safety and efficacy profiles for this procedure, given the extended follow-up times.

Authors' Contribution

Conceptualization: IT

Methodology: IT

Formal analysis: AF, SZ

Writing and Drafting: IT, UBA, AF, ST, SZ

Review and Editing: IT, UBA, AF, ST, SZ

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Comparative Efficacy of Microneedling with and without Topical Vitamin D3 in Localized *Alopecia areata*

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ARTICLE INFO

Keywords:

Alopecia areata, Microneedling, Vitamin D3, Severity of Alopecia Tool, Severity of Alopecia Tool Score, Hair Regrowth

How to Cite:

Masood, R., Asad, F., Tariq, H., Amin, U., & Haq, A. U. (2026). Comparative Efficacy of Microneedling with and without Topical Vitamin D3 in Localized Alopecia areata : Microneedling with and without Topical Vitamin D3 in Localized Alopecia areata. Pakistan Journal of Health Sciences, 7(8), 58-64. <https://doi.org/10.54393/pjhs.v7i8.3670>

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Received Date: 14th December, 2025

1st Revision Received: 19th January, 2026

2nd Revision Received: 2nd March, 2026

3rd Revision Received: 12th March, 2026

Acceptance Date: 11th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Alopecia areata represents a T-cell-mediated autoimmune disorder causing non-scarring hair loss. While microneedling demonstrates therapeutic potential, adjunctive strategies to enhance efficacy remain underexplored. **Objectives:** To compare the efficacy and safety of microneedling combined with topical vitamin D3 versus microneedling monotherapy in localized *alopecia areata*. **Methods:** An open-label randomized controlled trial enrolled 80 participants (April–October 2025) with localized patchy *alopecia areata* affecting <50% scalp. Participants were randomly allocated to microneedling combined with topical vitamin D3 (MN+VD3, n=40) or microneedling alone (MN, n=40). Treatment consisted of six biweekly sessions over 12 weeks. Primary efficacy endpoints included Severity of Alopecia Tool (SALT) score reduction and percentage hair regrowth. **Results:** Mean SALT reduction was significantly greater in the MN+VD3 group (13.27 ± 4.284 points) compared with MN (9.66 ± 3.827 points, $p=0.001$). Hair regrowth percentage was superior in MN+VD3 ($65.737 \pm 18.6252\%$) versus MN ($48.137 \pm 24.0500\%$, $p<0.001$). Excellent or good response was achieved in 82.5% of MN+VD3 participants versus 50.0% of MN participants ($p=0.002$). Stratified analysis demonstrated consistent treatment superiority across age groups (18–40 and 41–60 years), both sexes, and disease duration categories. Adverse events were mild and transient, occurring in 30.0% overall with no serious complications or treatment discontinuations. **Conclusions:** Topical vitamin D3 combined with microneedling substantially enhances therapeutic outcomes compared with monotherapy, with excellent tolerability and sustained efficacy across demographic substrata. These findings support adjunctive vitamin D3 as an effective treatment strategy for localized *alopecia areata*.

INTRODUCTION

Alopecia areata is a relapsing autoimmune disorder of the hair follicle that presents with non-scarring, well-demarcated patches of hair loss on the scalp or other hair-bearing sites [1]. Global lifetime prevalence is estimated at 1% to 2.1%, while point prevalence in population-based studies is approximately 0.1% to 0.2% [2, 3]. The course is difficult to predict; some individuals have transient episodes with spontaneous regrowth, whereas others experience recurrent or persistent disease over many years [4]. Beyond cosmetic change, visible hair loss can impair social functioning and psychological well-being,

with increased anxiety and depressive symptoms reported in many patients. Given relapse tendency and the need for repeated outpatient treatment, safe and acceptable interventions that produce meaningful regrowth remain a clinical priority [5]. Pathogenesis involves loss of hair follicle immune privilege during the anagen phase in genetically susceptible individuals. This immune dysregulation permits antigen recognition and is associated with perifollicular infiltration of cytotoxic and helper T lymphocytes, alongside increased interferon-gamma, interleukin-15, and other inflammatory mediators



[6, 7]. Vitamin D receptor signalling in keratinocytes and hair follicle cells influences hair cycle dynamics and cutaneous immune responses, and reduced vitamin D status has been reported frequently in individuals with *alopecia areata*, suggesting a biologically plausible link between vitamin D pathways and disease activity [8]. Current management of localized *alopecia areata* relies mainly on corticosteroid-based approaches, which may induce regrowth but are limited by incomplete response, relapse after cessation, and concerns regarding adverse effects [9, 10]. Microneedling has gained attention as a simple office procedure that produces controlled micro-injury in the scalp, stimulates the release of growth factors, improves perifollicular vascularity, and increases penetration of topical preparations [11]. In parallel, topical vitamin D3 formulations have been proposed to support hair follicle cycling and to modulate local immune activity in *alopecia areata* [12]. Whether combining microneedling with topical vitamin D3 offers superior clinical benefit to microneedling alone in patients with patchy *alopecia areata* remains uncertain, and a controlled comparison is required to clarify the added value of topical vitamin D3 in this setting.

Although there are already others on the quality of life in parents, there is little literature on it that looks at parenting of children with intellectual disabilities within local contexts, especially taking into account such factors as work shifts, emotional stress, and support systems. This presents a research issue of how these factors affect their overall well-being and where they lack in support. This study aimed to evaluate the quality of life of parents, identify disparities depending on working shifts, and determine important factors influencing the physical, emotional, and social well-being to propose effective interventions.

METHODS

This study was a non-blinded randomized clinical trial comparing microneedling combined with topical vitamin D3 against microneedling alone in localized *alopecia areata*. The trial is registered at a clinical trial registry (NCT07243977). Participants and treating clinicians were not blinded; however, outcome assessment was performed by a dermatologist who was not involved in treatment delivery and remained blinded to treatment allocation. Recruitment and all procedures take place in the outpatient dermatology clinic of the Services Institute of Medical Sciences from April to October 2025, with a 1:1 allocation ratio between the two treatment groups. Approval has been obtained from the Institutional Review Board (IRB/2025/1571/SIMS; dated 29th March 2025), and written informed consent is secured from every participant before enrolment. Eligible participants are adults aged 18

to 60 years with clinically diagnosed localized *alopecia areata* involving less than 50 % of the scalp. The diagnosis is confirmed by dermoscopic features such as black dots, yellow dots, short broken hairs, tapering hairs, or vellus regrowth. Both sexes are included. Individuals must not have received topical or systemic treatment for *alopecia areata* during the 4 weeks preceding recruitment. Exclusion criteria comprise active bacterial, fungal, or viral scalp infection, visible scalp atrophy or scarring following previous intralesional steroid injections or other procedures, *alopecia totalis*, *alopecia universalis*, *ophiasis* pattern disease, or rapidly progressive *alopecia areata*. Patients with bleeding disorders or those on antiplatelet or anticoagulant therapy, as well as those with uncontrolled diabetes mellitus, severe hypertension, autoimmune diseases requiring systemic therapy, chronic liver disease, chronic kidney disease, or ongoing systemic immunosuppression, are also excluded. The sample size is calculated using the WHO calculator for comparison of two proportions, based on previously reported response rates of 4 percent for microneedling alone and 28 % for microneedling with topical vitamin D3, with a significance level of 5 % and power of 80 %, resulting in 80 participants, 40 in each group [13]. A computer-generated random sequence is used to assign participants to the two treatment arms in a 1:1 ratio, with allocation implemented in sequential order. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. Participants randomized to the microneedling plus vitamin D3 group (MN + VD3) receive treatment with an automated dermapen device (Dr. Pen, USA) fitted with adjustable needles set between 1.5 and 2.0 mm to reach the dermis overlying the follicular bulb. After cleansing the affected scalp areas with normal saline, microneedling is performed in vertical, horizontal, and diagonal directions until fine pinpoint bleeding appears, which is taken as the endpoint of each session. An aqueous cholecalciferol solution (Sunny D ampoule, 200,000 IU in 2 ml, equivalent to 2.5 mg/ml) is used as the topical vitamin D3 preparation. A small amount is applied to the lesion immediately before microneedling to facilitate transdermal delivery, and the remaining volume is spread evenly over the treated area once microneedling has been completed. The maximum dose per session is limited to 2.5 mg/ml [13]. Participants in the microneedling-alone (MN) group undergo the same procedure with the same device, needle depth, technique, and endpoint, but no active topical agent is applied before or after treatment. Standard cleaning and identical post-procedure care instructions are given to both groups, apart from the omission of vitamin D3 in the control arm. In each group, the treatment duration was 12 weeks (six sessions), and the primary endpoint assessment was performed at

week 12. Clinical response is assessed using the Severity of *Alopecia* Tool (SALT), which expresses the percentage of scalp surface affected by hair loss using categories S0 (no loss), S1 (1 to 24 %), S2 (25 to 49 %), S3 (50 to 74 %), S4 (75 to 99 %) and S5 (100 % loss). The area of involvement is estimated with the rule-of-thumb method, in which the patient's thumbprint approximates 1 % of the scalp, to provide consistent baseline and follow-up measurements. Percentage hair regrowth is calculated as: (SALT score at baseline minus SALT score at follow-up) multiplied by 100 and divided by the baseline SALT score. Responses (Efficacy) are further classified as poor (<25 % improvement), moderate (26 to 50 %), good (51 to 75 %), and excellent (≥ 75 % improvement) [14]. For the primary analysis, efficacy is defined as an excellent response at 12 weeks after initiation of treatment. Relapse is recorded when there is loss of newly regrown hair or the appearance of new *alopecia areata* patches during follow-up. Relapse assessment was confined to the treatment phase and the week 12 endpoint visit, as no extended post-treatment follow-up period was planned. Adverse events of interest include erythema, pain, bleeding, pigmentation changes, and pruritus. Participants attend six treatment visits at fortnightly intervals over three months; outcome evaluation is performed at the end of this period using a structured data collection form. Local reactions are managed according to a predefined protocol, and treatment is discontinued if any serious adverse event occurs that, in the investigator's judgment, makes further

sessions unsafe.

Data were entered and analyzed using SPSS version 23.0. Quantitative variables were summarized as mean and standard deviation. Qualitative variables were reported as counts and percentages. Between-group comparisons for categorical data were carried out with the chi-square test or Fisher's exact test. Independent samples t-tests were used to compare continuous measures between the two treatment arms. Changes in SALT scores over time within each group were examined using repeated-measures analysis of variance. Potential modifying factors such as age, sex, body mass index, and duration of symptoms were explored through stratification, followed by chi-square testing within strata. A p-value of less than 0.050 was regarded as statistically significant.

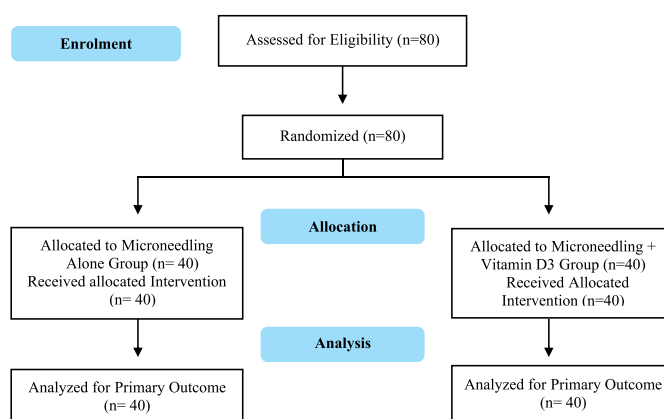


Figure 1: CONSORT Flow Chart

RESULTS

Baseline demographic variables and clinical characteristics were comparable between groups. The mean age was also similar between groups (35.08 ± 10.73 years in MN vs 36.78 ± 12.23 years in MN + VD3; $p=0.511$), showing that age distribution was balanced at baseline. Gender distribution was similar in both groups, with males constituting 62.5% in the MN group and 57.5% in the MN + VD3 group, while females constituted 37.5% and 42.5%, respectively ($p=0.648$). Mean disease duration was also comparable ($p=0.684$) (Table 1).

Table 1: Demographic Characteristics of the Study Population (n=80)

Demographic Variables	Total, n (%)	Microneedling Alone (MN), n=40	Microneedling + Vitamin D3 (MN + VD3), n=40	p-value
Age Group				
18–40 Years	51 (63.8%)	27 (67.5%)	24 (60.0%)	0.485
41–60 Years	29 (36.3%)	13 (32.5%)	16 (40.0%)	
Mean Age ± SD (Years)	35.93 ± 11.46	35.08 ± 10.73	36.78 ± 12.23	0.511
Sex				
Male	48 (60.0%)	25 (62.5%)	23 (57.5%)	0.648
Female	32 (40.0%)	15 (37.5%)	17 (42.5%)	
Disease Duration				
Up to 5 Months	50 (62.5%)	26 (65.0%)	24 (60.0%)	0.644
≥6 Months	30 (37.5%)	14 (35.0%)	16 (40.0%)	
Mean Duration ± SD (Years)	1.38 ± 0.49	5.13 ± 3.06	4.85 ± 2.97	0.684
Body Mass Index ± SD (kg/m²)	25.10 ± 3.48	25.04 ± 3.55	25.16 ± 3.45	0.886

Baseline SALT score was 19.85 ± 4.78 in the MN group and 20.20 ± 4.71 in MN + VD3, with statistically no significant difference

($p=0.743$), indicating similar disease severity at enrolment. The mean SALT score was significantly lower in the MN + VD3 group ($p=0.003$), demonstrating better results with combination treatment. Similarly, the mean absolute reduction in SALT score was also significantly greater in the MN + VD3 group compared with the MN group (13.27 ± 4.28 vs 9.66 ± 3.83 ; $p=0.001$), indicating that the addition of topical vitamin D3 resulted in a greater reduction in scalp hair loss (Table 2).

Table 2: SALT Score Changes and Hair Regrowth from Baseline to 12-Week Endpoint

Parameters	Microneedling Alone (MN) (n=40), Mean $\pm$ SD	Microneedling + Vitamin D3 (MN + Vd3), Mean $\pm$ SD	Mean Difference (95% CI)	p-value	Effect Size (Cohen's d)
Baseline SALT Score	19.85 $\pm$ 4.78	20.20 $\pm$ 4.71	0.35 (-1.76 to 2.46)	0.743	0.07
SALT Score at 12 Weeks	10.19 $\pm$ 5.18	6.93 $\pm$ 4.15	-3.26 (-5.35 to -1.17)	0.003	0.70
Absolute SALT Reduction	9.66 $\pm$ 3.83	13.27 $\pm$ 4.28	3.61 (1.55 to 5.67)	0.001	0.89
Percentage Hair Regrowth (%)	48.14 $\pm$ 24.05	65.74 $\pm$ 18.63	17.60 (8.02 to 27.17)	<0.001	0.82

At 12 weeks, the treatment response was significantly better in the MN + VD3 group than in the MN group ($\chi^2 = 10.265$, $p=0.016$). When responses were grouped, good or excellent hair regrowth was found in 50.0% of patients in the MN group compared with 82.5% in the MN + VD3 group ($\chi^2 = 9.534$, $p=0.002$), indicating that combination therapy reported better results compared to microneedling alone (Table 3).

Table 3: Treatment Response Classification at 12-Week Endpoint Based on Percentage Hair Regrowth (n=80)

Response Category	Microneedling Alone (MN) (n=40), n (%)	Microneedling + Vitamin D3 (MN + VD3) (n=40), n (%)	χ^2	p-value	Effect Size
Poor (<25% regrowth)	7 (17.5%)	2 (5.0)	10.265	0.016	0.358
Moderate (26–50% regrowth)	13 (32.5%)	5 (12.5%)	—	—	—
Good (51–75% regrowth)	11 (27.5%)	14 (35.0%)	—	—	—
Excellent ($\geq 75\%$ regrowth)	9 (22.5%)	19 (47.5%)	—	—	—
Combined Good/Excellent ($\geq 51\%$ regrowth)	20 (50.0%)	33 (82.5%)	9.534	0.002	0.345

Overall comparison of the four response categories was performed using the Chi-square test (df = 3), and effect size is reported as Cramér's V. For the dichotomized comparison (Good/Excellent vs Poor/Moderate), the Chi-square test (df = 1) was applied, and effect size is reported as Phi (Φ).

Adverse events were mild and transient. Overall frequency of any adverse event was similar between groups (27.5% in MN group vs 32.5% in MN + VD3 group; $p=0.626$). No serious adverse events, systemic reactions, or treatment discontinuations occurred (Table 4).

Table 4: Adverse Events Frequency and Distribution by Treatment Group

Adverse Event	Microneedling Alone (MN) (n=40), n (%)	Microneedling + Vitamin D3 (MN + VD3) (n=40), n (%)	χ^2	p-value
Erythema	9 (22.5%)	9 (22.5%)	0.000	<0.001
Pruritus	8 (20.0%)	8 (20.0%)	0.000	<0.001
Pinpoint Bleeding	5 (12.5%)	8 (20.0%)	0.827	0.363
Post-Inflammatory Hyperpigmentation	1 (2.5%)	3 (7.5%)	1.053	0.305
Any Adverse Event	11 (27.5%)	13 (32.5%)	0.238	0.626

Stratified comparisons for good/excellent response ($\geq 51\%$ regrowth) across age, sex, and disease duration subgroups are summarized (Table 5).

Table 5: Stratified Analysis of Excellent/Good Treatment Response ($\geq 51\%$ Hair Regrowth)

Stratification Variables	Sub-group	Microneedling Alone (MN), n (%)	Microneedling + Vitamin D3 (MN + Vd3), n (%)	χ^2	p-value
Age Group					
18–40 years	Yes	17(63.0%)	22 (91.7%)	5.818	0.016*
	No	10 (37.0%)	2 (8.3%)		
41–60 years	Yes	3 (23.1%)	11(68.8)	5.992	0.014*
	No	10 (76.9%)	5 (31.2%)		
Sex					
Male	Yes	12 (48.0%)	19 (82.6%)	6.273	0.012*
	No	13 (52.0%)	4 (17.4%)		
Female	Yes	8 (53.3%)	14 (82.4%)	3.124	0.077
	No	7 (46.7%)	3 (17.6%)		
Disease Duration					
Up to 5 Months	Yes	13 (50.0%)	19 (79.2%)	4.608	0.032*
	No	13 (50.0%)	5 (20.8%)		
≥6 Months	Yes	7 (50.0%)	14 (87.5%)	5.000	0.025*
	No	7 (50.0%)	2 (12.5%)		

An excellent/good response is defined as achieving $\geq 51\%$ hair regrowth from baseline to 12-week endpoint. Data presented as n

(%). Chi-square tests are employed for stratified comparisons. Asterisk (*) indicates $p < 0.050$. Fisher's exact test p -values are presented where appropriate due to small expected cell frequencies

DISCUSSION

This randomized trial showed that adding topical vitamin D₃ to microneedling improved outcomes in adults with localized *alopecia areata*. Baseline demographic features, disease duration, and SALT scores were similar in both groups, indicating successful randomization. Over 12 weeks, scalp involvement decreased with both regimens, but the reduction was greater with combination therapy: mean SALT at week 12 was significantly lower in the MN + VD3 arm than in the MN arm ($p = 0.003$), with a larger absolute fall from baseline. Expressed as percentage hair regrowth, microneedling alone achieved roughly 48% mean regrowth, whereas microneedling plus vitamin D₃ achieved about 66% ($p < 0.001$), corresponding to an absolute difference of approximately 18 percentage points. Categorical responses reflected the same pattern, with good or excellent regrowth ($\geq 51\%$ regrowth) observed in 82.5% of participants receiving MN + VD3 compared with 50.0% receiving microneedling alone ($p = 0.002$). Both regimens were well tolerated. Adverse effects were limited to mild, short-lived erythema or pruritus in about one-fifth of participants in each group, and no serious events, treatment discontinuations, or procedure-related complications occurred. Microneedling alone produced improvement in SALT scores in this trial, in keeping with prior reports that scalp micro-injury can be followed by regrowth in alopecia areata [14]. Mohammed described early regrowth within one month and near-complete recovery by three months in 20 patients treated with microneedling, without major toxicity [15]. Randomized comparisons with cryotherapy or intralesional agents have also reported SALT reductions over time [16, 17]. In the present study, microneedling alone was associated with improvement in SALT score and categorical response, although response rates were lower than those observed with adjunctive vitamin D₃. Ali et al. similarly reported higher-grade regrowth with MN + vitamin D₃ than MN alone [13]. Other vitamin D-based approaches also support a treatment role in *alopecia areata*. Intralesional cholecalciferol achieved at least 75% regrowth in about half of treated patients, with minimal response in saline controls [18], while topical calcipotriol produced high-grade regrowth in roughly two-thirds of treated sites and relapse rates comparable to or lower than clobetasol [19]. Small series and case reports describing near-complete regrowth and restoration of vitamin D receptor expression further strengthen the rationale for combining topical vitamin D₃ with microneedling [20, 21]. The present trial

supports the concept that vitamin D₃ acts as an effective adjunct when delivered through microneedling channels. Combination treatment produced a higher mean percentage regrowth and a greater proportion of good or excellent responders than microneedling alone, consistent with data from androgenetic *alopecia* in which microneedling enhances the effect of topical minoxidil and other agents [22]. Clinical evidence indicates that microneedling can augment drug delivery and improve responses to minoxidil, triamcinolone, platelet-rich plasma, and related therapies in hair-loss disorders [22–24]. Safety findings in this study, limited to brief erythema, pruritus, and pinpoint bleeding, are in line with previous microneedling and vitamin D-based literature, where local irritation and erythema are generally mild, and serious adverse effects, including atrophy or systemic complications, are uncommon [18, 19]. *Alopecia areata* is an immune mediated disorder in which collapse of follicular immune privilege permits T-lymphocyte infiltration around the hair bulb, leading to premature catagen and telogen transition. Vitamin D3 has been reported to influence antigen presentation and cytokine balance, with reduced Th1 signaling and increased regulatory mediators [25]. If enhanced delivery occurs through microneedling, local immune activity might be tempered, which could contribute to regrowth. Vitamin D receptor signaling also affects keratinocyte differentiation and hair cycling, and low vitamin D has been described in *alopecia areata* in patients [26]. Microneedling may assist hair regrowth by triggering a local repair response after controlled dermal injury. This process has been linked to the release of growth factors, stimulation of dermal papilla activity, activation of follicular stem cell niches, and improved perifollicular blood flow, which may support anagen entry and follicle persistence [11]. Experimental models also show upregulation of WNT pathway genes and even new follicle formation after repeated wounding [20, 27]. Creation of transient microchannels further enhances penetration of topical agents, providing a plausible explanation for the superior responses seen with microneedling plus vitamin D₃ in this trial [13]. However, comparison across studies is difficult because vitamin D has been delivered as intralesional cholecalciferol, topical calcipotriol, or microneedling-assisted solutions, while microneedling protocols differ in device, depth, and frequency, and outcomes range from simple regrowth scores to SALT-based measurements [22, 24]

Key strengths of this trial are its randomized design with well-balanced baseline characteristics, use of validated SALT scoring with both continuous and categorical outcomes, stratified analyses by age, sex, and disease duration, and prospective recording of adverse events that

support a reliable safety profile. This trial has important constraints, including a sample of 80 patients from a single centre, a lack of blinding, and follow-up limited to twelve weeks. Serum vitamin D levels were not measured, which limited the correlation of treatment response with vitamin D status. Stratified comparisons and multiple analyses were performed, which may increase the risk of type I error due to multiple comparisons. Despite these limitations, microneedling with topical vitamin D3 produced greater SALT improvement, higher mean regrowth, and better or excellent responses than microneedling alone without additional clinically relevant adverse events. Larger multicenter studies with longer follow-up and quality of life outcomes are required to confirm these findings.

CONCLUSIONS

This study suggests that adding topical vitamin D₃ to microneedling may improve treatment response in localized patchy *alopecia areata* compared with microneedling alone. A higher proportion of patients achieved clinically meaningful hair regrowth with combination therapy, and the benefit was observed across the main subgroups assessed by age, sex, and disease duration. These findings support topical vitamin D₃ as a potential adjunct to microneedling in localized disease; however, confirmation in larger blinded trials with longer follow-up is required.

Authors' Contribution

Conceptualization: RM

Methodology: FA, HT, UA, AUH

Formal analysis: RM, HT, UA

Writing and Drafting: RM, FA, HT, UA, AUH

Review and Editing: RM, FA, HT, UA, AUH

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Effectiveness of Pressurized Metered Dose Inhaler (pMDI) Versus Dry Powder Inhaler (DPI) in Delivering Inhaled Corticosteroid and Long-Acting Beta Agonist among Patients with Uncontrolled Asthma in a Tertiary Care Hospital

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ARTICLE INFO

Keywords:

Asthma, Dry Powder Inhaler, Inhaled Corticosteroid, Long-Acting Beta-Agonist, Pressurized Metered-Dose Inhaler

How to Cite:

Qamar, X., Hussain, M., Ayyaz, S., Saif, S., Anjum, S., & Butt, L. Q. (2026). Effectiveness of Pressurized Metered Dose Inhaler (pMDI) Versus Dry Powder Inhaler (DPI) in Delivering Inhaled Corticosteroid and Long Acting Beta Agonist Among Patients with Uncontrolled Asthma in a Tertiary Care Hospital: pMDI versus DPI in Delivering Inhaled Corticosteroid and Long-Acting Beta Agonist. *Pakistan Journal of Health Sciences*, 7(8), 65-71. <https://doi.org/10.54393/pjhs.v7i8.3989>

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Received Date: 19th February, 2026

1st Revision Received: 25th March, 2026

2nd Revision Received: 4th April, 2026

Acceptance Date: 15th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Uncontrolled asthma remains common in Pakistan despite regular use of inhaled corticosteroid and long-acting beta-agonist combination therapy. Drug delivery may differ according to the inhaler device. Pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the most frequently prescribed devices, but local comparative evidence remains limited.

Objective: To compare the short-term effectiveness of pMDI and DPI in delivering inhaled corticosteroid and long-acting beta-agonist therapy among adults with uncontrolled asthma in a tertiary care hospital. **Methods:** This parallel randomized controlled trial was conducted at the Department of Pulmonology, Services Institute of Medical Sciences, Lahore. A total of 146 adults with uncontrolled asthma were randomized equally to pMDI (n=73) or DPI (n=73). The primary outcome was the proportion of participants achieving at least a 0.5-point reduction in Asthma Control Questionnaire (ACQ) score at 8 weeks. Secondary outcomes included mean ACQ change, change in forced expiratory volume in one second (FEV₁ % predicted), exacerbations, inhaler technique score, and adverse events. **Results:** Baseline age, sex, body mass index, asthma duration, baseline FEV₁ % predicted, and ACQ score were comparable between groups. Greater mean ACQ improvement was observed in the pMDI group than in the DPI group (4.6 ± 3.1 vs 3.2 ± 2.9; p = 0.006). FEV₁ improvement was also greater with pMDI (p=0.021). Exacerbations occurred in 24.7% of pMDI users and 39.7% of DPI users (p=0.048). Adverse events were mild and similar between groups. **Conclusion:** pMDI use was associated with better short-term asthma control and fewer exacerbations; larger multicentre studies are needed.

INTRODUCTION

Asthma remains one of the critical public health concerns in the world as it influences millions of people and leads to regular hospitalizations. It has been reported by a national survey that about 4.3% of adults in Pakistan live with asthma [1]. It seems that the burden among children and adolescents is even greater. The Global Asthma Network study illustrates that present-day wheeze has reached almost 11% of Pakistani school-going children [2], which

suggests that an appreciable percentage of patients live their lives with a symptom. The prevalence of asthma is reported to be significant in Asia. A survey conducted on a significantly large number of Asians showed that over half of patients report uncontrolled asthma even after medication [3]. Poor outcomes in South Asia can be facilitated by a lack of access to expert care and poor inhaler technique. Most patients use the inhalers



improperly, and this may decrease the amount of drug that goes to the pulmonary system and amplify the side effects at the location [4]. It is estimated that globally, 262 million people suffer from asthma, and that more than 450,000 deaths occur due to asthma per year. Though the mortality rates in high-income countries are reduced, the control rates are below optimal levels. As it has been reported in North America, about 40% of treated adults have uncontrolled symptoms [5]. Regular exacerbations and increased health-care utilization in Europe have been linked with inadequate compliance with inhaled corticosteroid therapy [6]. The combination of inhaled corticosteroid and long-acting beta-agonist therapy is the foundation of the treatment of moderate to severe asthma. Inhaled corticosteroids help in lowering airway inflammation, but long-acting beta-agonists offer prolonged bronchodilation of the respiratory tract. The Global Initiative for Asthma suggests this combination when used in patients who have persisting symptoms [7]. However, there is a significant effect on drug delivery depending on the kind of inhaler device used. The most prevalent respiratory appliances are pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs). Despite the fact that these two modalities are therapeutically effective when appropriately handled, mistakes made during device handling are common. According to a multinational study, up to fifty percent of patients made at least one critical error in inhaler execution [8]. Another study in Europe implicated critical errors in insufficient control of asthma and a higher rate of exacerbations [9]. It is important to note that the resistance of the device, the actual inspiratory flow needed, and the coordination methods vary between pMDIs and DPIs. These variations can potentially change clinical response. Most of the comparative trials have been conducted in high-income environments with mixed outcomes. Although some of them have shown similar clinical results when sufficient inhalation technique is used [10], some studies have indicated that excessive dependence on devices and their usability could affect adherence and symptom control. The comparison focused on improvement in asthma control measured by Asthma Control Questionnaire (ACQ) score after 8 weeks of treatment. Secondary objectives were to compare changes in forced expiratory volume in one second (FEV₁ % predicted), frequency of exacerbations, inhaler technique performance, and adverse events between the two inhaler device groups.

Limited evidence exists on the use of inhaler technique in Pakistan; the current literature is more focused on the prevalence or educational intervention to achieve this objective. Therefore, there is a dearth of direct comparisons of pMDIs and DPIs in combination therapy in

patients having uncontrolled asthma in a tertiary care setting. This study aimed to compare the effectiveness of pressurized metered-dose inhaler (pMDI) and dry powder inhaler (DPI) in delivering inhaled corticosteroid and long-acting beta-agonist combination therapy among adults with uncontrolled asthma in a tertiary care hospital.

METHODS

It comprised a superiority, parallel, single-centre, randomized, controlled trial which was conducted in the Department of Pulmonology, Services Institute of Medical Sciences, Lahore. The allocation ratio was 1:1. This was a nine-month study (1 February 2025 to 30 November 2025), involving 8 weeks of follow-up of individual participants who had commenced the intervention. The last follow-up of the patient who was last enrolled was done on 30 January 2026. Institutional Review Board approval was obtained under reference IRB/2025/1520/SIMS; dated 27th January 2025, and the trial was post-hoc registered on ClinicalTrials.gov (registration number NCT07372573). Adult patients who had been diagnosed with asthma by a physician and were aged between 18 and 60 years were screened. It had already been diagnosed on the basis of reversible airflow limitation, which is an increase of at least 12% in forced expiratory volume in one second and 200 mL of forced expiratory volume after taking bronchodilators. Only patients with uncontrolled forms of asthma were included; they had to have received inhaled corticosteroid and long-acting beta-agonist treatment at least three months before they were enrolled. Patients who had chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, active pulmonary tuberculosis, pregnancy, or severe heart disease were excluded. Those who could not perform spirometry reliably were also excluded. Informed consent was taken in writing before enrollment. The recruitment process was conducted using inpatient clinics, and eligibility was affirmed by a consultant pulmonologist. The sample size was calculated to detect a minimum clinically important difference of 0.5 points in the Asthma Control Questionnaire (ACQ) score between two independent groups. A standard deviation of 0.9 was assumed based on previous adult asthma trials evaluating inhaled corticosteroid and long-acting beta-agonist therapy [11]. Using a two-sided alpha of 0.05 and a power of 80%, the required minimum sample size was calculated. After accounting for possible attrition, 146 participants (73 per group) were enrolled. Participants were selected at random to take either the pressurized metered-dose inhaler or a dry powder inhaler to give them an inhaled corticosteroid and a long-acting beta-agonist. The creation of the random sequences was done via a variable block-based, computer-generated block-randomization scheme. Sequentially numbered, opaque,

and sealed envelopes were used to provide allocation concealment. At the end of the assessment, randomization took place. The study shows the CONSORT diagram of participant inclusion and allocation (Figure 1).

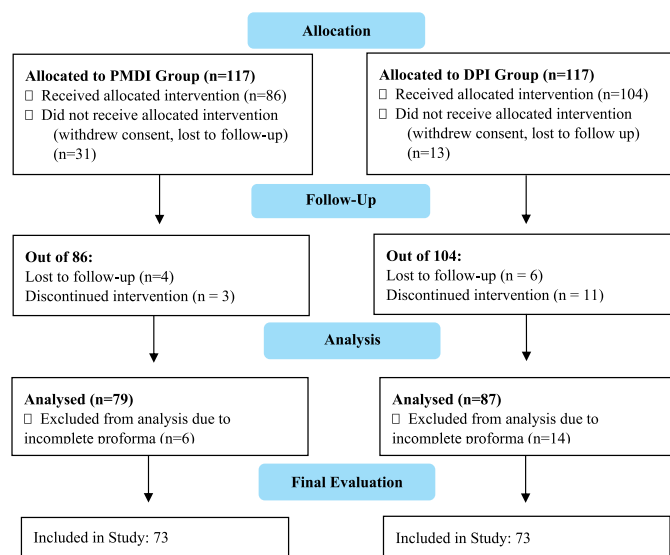


Figure 1: CONSORT 2010 Flow Diagram of the Included Participants

The patients receiving the dry powder inhaler (DPI) group were given 400/12 µg of formoterol-budesonide per day, twice daily, in a single puff. The members of the pressurized metered-dose inhaler (pMDI) cohort were given 200/6 µg of the same formulation, but in two puffs twice daily, so that it yielded an equivalent amount of 800/24 µg each day. This dosing was consistent with previous published literature [12]. Each of the participants was provided with personalized training on inhaler technique, based on a standardized checklist including ten essential steps. The technique was then reviewed at every planned visit. Uncontrolled asthma was operationalized as the use of 400/12 µg of formoterol-budesonide and an Asthma Control Questionnaire (ACQ) score of 3 and above at the time of presentation to the outpatient department. The criterion of treatment effect was a decrease in the ACQ score of at least 0.5 points compared to baseline that was achieved after eight weeks of treatment [13]. Every patient was given a standard dosage of inhaled corticosteroid and long-acting beta-agonist (ICS/LABA), at DPI (400/12 micrograms, 1 puff, twice a day) or pMDI (200/6 micrograms, 2 puffs, twice a day), so that all participants had the same total dose of 800/24 micrograms. The continuous baseline variables included age (years), body mass index (kg m^{-2}), years of asthma (years), baseline forced expiratory volume in one second (FEV1) as percent-predicted, and baseline ACQ score. Spirometry was performed using a MIR Spirobank II Basic spirometer (Medical International Research, Rome, Italy) according to

American Thoracic Society/European Respiratory Society standards. The device was calibrated daily before patient testing, and three reproducible manoeuvres were recorded for each participant. The spirometric tests were performed with a validated spirometer as per the guidelines of the American Thoracic Society; three maneuvers that were reproducible were taken. Body mass index was computed as weight (kg)/height squared (m^2). The categorical variables were gender, smoking status, the existence of allergic rhinitis, exposure to biomass smoke, and previous hospitalization for asthma in the last year. The smoking population was arranged into never smokers, former smokers, and current smokers. Exposure to biomass was categorized as frequent exposure to wood or coal smoke over a duration of more than five years. The major outcome was the difference between baseline and the 4- and 8-week Asthma Control Questionnaire (ACQ) score. Secondary outcomes were the change in forced expiratory volume in one second percent predicted, exacerbations during follow-up, and inhaler technique score. Exacerbation was considered to be symptoms that worsened to the extent that they required systemic corticosteroids during a period of at least three days or an emergency department visit. The score on the inhaler technique was assessed using a 10-point checklist; a value of 8 and above was deemed as correct technique [14]. A random selection of consenting participants already taking the baseline dose of DPI (400/12 micrograms of Formoterol-Budesonide) was put into either formulation of inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) (Budesonide and Formoterol), either by the use of a pressurized metered-dose inhaler (pMDI) or the use of a dry powder inhaler (DPI). The study indicates that both of the devices that the asthma patients were using (Figure 2)

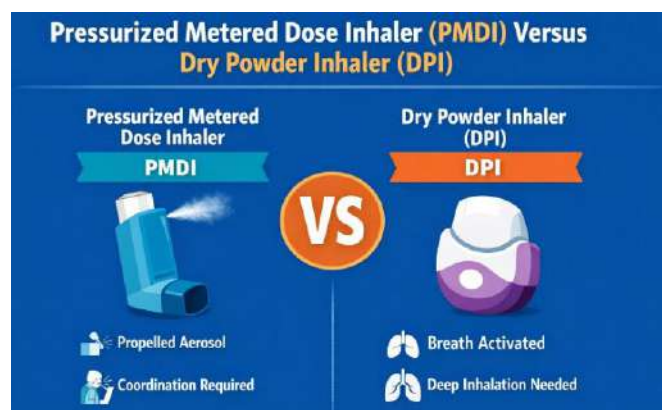


Figure 2: PMDI and DPI Devices Used by Asthma Patients

The Asthma Control Questionnaire (ACQ) at 8 weeks was prespecified as the primary outcome. Secondary outcomes were analysed as supportive exploratory endpoints; therefore, no formal adjustment for multiple comparisons was applied, and secondary outcome p-

values were interpreted cautiously. SPSS version 26.0 was used in statistical analysis. Means and standard deviations represented continuous variables, and frequencies and percentages represented categorical ones. The primary analysis was performed using analysis of covariance (ANCOVA), with 8-week Asthma Control Questionnaire (ACQ) score as the dependent variable, treatment group as the fixed factor, and baseline ACQ score as a covariate. A similar ANCOVA approach was used for FEV₁ % predicted at follow-up, adjusting for baseline FEV₁. Between-group adjusted mean differences with 95% confidence intervals were reported. Categorical outcomes were compared using the chi-square test or logistic regression, where appropriate. An independent consultant who had no part in the allocation of patients performed safety monitoring. Every protocol deviation was noted. There was no planned interim analysis. The trial was conducted in accordance with the Declaration of Helsinki [13]. Each participant provided written informed consent. The analysis of the data was in line with a prespecified statistical plan, ensuring transparency and methodological rigor.

RESULTS

A total of 146 participants were randomized equally to the pressurized metered-dose inhaler (pMDI) group (n=73) and the dry powder inhaler (DPI) group (n=73). All participants completed 8 weeks of follow-up and were included in the final analysis. No crossover between treatment groups occurred during follow-up. At 8 weeks, a clinically meaningful improvement in ACQ score (≥ 0.5 -point reduction from baseline) was achieved by 61 participants (83.6%) in the pMDI group compared with 49 participants (67.1%) in the DPI group. The study presents the demographic and exposure characteristics of participants at baseline. Continuous variables are expressed as mean $\pm$ standard deviation or median (interquartile range), while categorical variables are reported as frequencies and

percentages. No baseline demographic variable showed a statistically significant difference between the two treatment groups (Table 1).

Table 1: Baseline Demographic and Exposure Characteristics

Variables	pMDI Group (n=73)	DPI Group (n=73)	Test Statistic	p-value
Age (years)	40.3 $\pm$ 10.9	39.2 $\pm$ 11.5	t (144) = 0.61 ^a	0.540
Male Gender	42 (57.5%)	40 (54.8%)	χ^2 (1) = 0.13 ^c	0.710
Body Mass Index (kg/m ²)	27.6 $\pm$ 4.3	26.9 $\pm$ 4.7	t (144) = 1.08 ^a	0.280
Duration of Asthma (years)	6 (3-10)	6 (3-10)	Mann-Whitney U ^b	0.470
Current Smoker	16 (21.9%)	18 (24.7%)	χ^2 (1) = 0.29 ^c	0.590
Biomass Exposure	19 (26.0%)	22 (30.1%)	χ^2 (1) = 0.60 ^c	0.440
Allergic Rhinitis	31 (42.5%)	32 (43.8%)	χ^2 (1) = 0.02 ^c	0.890

Data were presented as mean $\pm$ SD, median (IQR), or n (%). Statistical significance set at p<0.005. ^aindependent sample t-test; ^bMann-Whitney U test; ^cchi-square test. Baseline clinical and pulmonary function parameters were also similar between groups. Mean baseline forced expiratory volume in one second (FEV₁ % predicted) and Asthma Control Questionnaire (ACQ) scores showed no statistically significant differences. These findings suggest that both treatment arms had similar initial asthma severity before intervention. The study summarizes baseline lung function and asthma symptom burden in both groups. All variables are presented as mean $\pm$ standard deviation. Statistical comparison confirmed no significant difference in baseline clinical severity (Table 2).

Table 2: Baseline Clinical and Lung Function Variables

Variables	pMDI Group (n=73)	DPI Group (n=73)	Test Statistic	p-value
FEV ₁ % predicted	62.4 $\pm$ 8.7	61.8 $\pm$ 9.1	t (144) = 0.41 ^a	0.680
ACQ score at presentation	4.3 $\pm$ 0.8	4.1 $\pm$ 0.9	t (144) = 0.33 ^a	0.740

Data are presented as mean $\pm$ SD. Statistical significance set at p<0.005. ^aindependent sample t-test. FEV₁ = forced expiratory volume in one second; ACQ = Asthma Control Questionnaire

Both treatment groups showed improvement during follow-up, although greater improvement was observed in the pMDI group at 8 weeks. A clinically meaningful reduction in ACQ score was achieved more frequently among pMDI users. Improvement in lung function and lower exacerbation frequency also favored pMDI. The study presents the primary and secondary clinical outcomes measured at 4 and 8 weeks. Continuous outcomes are shown as mean $\pm$ standard deviation, and categorical outcomes are shown as frequencies and percentages. Significant between-group differences were observed mainly at 8 weeks (Table 3).

Table 3: Clinical Outcomes at 4 and 8 Weeks

Variables	pMDI Group (n=73)	DPI Group (n=73)	Test Statistic	p-value
Change in ACQ Score at 4 Weeks	1.9 $\pm$ 0.8	1.7 $\pm$ 0.9	t (144) = 1.38 ^a	0.170
Change in ACQ Score at 8 Weeks	2.9 $\pm$ 1.1	2.3 $\pm$ 1.0	t (144) = 2.79 ^a	0.006
≥ 0.5 -Point ACQ Improvement at 8 Weeks	61 (83.6%)	49 (67.1%)	χ^2 (1) = 5.31 ^c	0.021
Change in FEV ₁ % Predicted at 4 Weeks	5.2 $\pm$ 4.6	4.5 $\pm$ 4.4	t (144) = 0.99 ^a	0.320
Change in FEV ₁ % Predicted at 8 Weeks	8.4 $\pm$ 6.2	6.1 $\pm$ 5.8	t (144) = 2.33 ^a	0.021

≥1 Exacerbation During Follow-Up at 4 Weeks	6 (8.2%)	12 (16.4%)	$\chi^2 (1) = 2.65^c$	0.100
≥1 Exacerbation During Follow-Up at 8 Weeks	18 (24.7%)	29 (39.7%)	$\chi^2 (1) = 3.91^c$	0.048
Correct Inhaler Technique at 4 Weeks	55 (75.3%)	47 (64.4%)	$\chi^2 (1) = 2.96^c$	0.090
Correct Inhaler Technique at 8 Weeks	61 (83.6%)	52 (71.2%)	$\chi^2 (1) = 3.11^c$	0.080

Statistical significance set at $p < 0.005$

Adverse events were infrequent and mild in both groups. No serious treatment-related complications were observed during follow-up. Improvement in inhaler technique showed a moderate positive correlation with improvement in symptom control. The results present safety outcomes and correlation analysis. Local adverse effects were similar between groups, while correlation analysis demonstrated a statistically significant relationship between inhaler technique improvement and ACQ reduction (Table 4).

Table 4: Safety Outcomes and Correlation Analysis

Variables	pMDI Group (n=73)	DPI Group (n=73)	Test Statistic	p-value
Oral Candidiasis	6 (8.2%)	9 (12.3%)	$\chi^2 (1) = 0.69^c$	0.410
Dysphonia	4 (5.5%)	6 (8.2%)	$\chi^2 (1) = 0.43^c$	0.510
Any Local Adverse Effect	10 (13.7%)	9 (12.3%)	$\chi^2 (1) = 0.06^c$	0.810
Correlation Between Inhaler Technique Improvement and ACQ Score Change	—	—	$r = 0.34$, $t (144) = 4.32^f$	<0.001

Data are presented as n (%) or correlation coefficient (r). Statistical significance set at $p < 0.005$. ^cchi-square test; ^fPearson correlation

DISCUSSION

The findings of the present study should be interpreted in the context of prior literature on asthma burden, inhaler technique, and treatment control. World Medical Association highlighted the persistent global burden of asthma, emphasizing that asthma remains a major public health problem across regions and healthcare systems [13]. This broader context supports the clinical relevance of our findings, as even modest improvements in controller therapy delivery may translate into meaningful gains in disease control. In our trial, patients using pMDI achieved greater improvement in ACQ score and FEV₁, with fewer exacerbations than those using DPI, suggesting that device choice may contribute to better short-term outcomes in uncontrolled asthma. Melani *et al.* reported that incorrect inhaler technique is common among asthma patients in Pakistan, which is consistent with our observation that inhaler technique performance improved over follow-up and was positively correlated with improvement in symptom control [14]. The current results extend their findings by showing that, despite training in both groups, the pMDI group achieved better clinical outcomes, indicating that device-related differences may remain important even under supervised conditions.

Similarly, Zhang *et al.* found that poor asthma control persists in a substantial proportion of treated adults, suggesting that pharmacologic treatment alone does not guarantee adequate disease control [15]. This aligns with our results, where both groups received equivalent budesonide-formoterol doses, yet the pMDI group demonstrated superior improvement, reinforcing the importance of delivery efficiency in addition to medication selection. Irfan *et al.* showed that inhaler-use errors remain frequent across devices and are associated with poorer outcomes [16]. However, the greater gains observed in the pMDI arm suggest that, when patients are properly instructed, pMDI may offer a practical advantage in drug delivery and clinical response in this setting. Collectively, these studies support our conclusion that inhaler device selection, together with structured education, can meaningfully influence asthma outcomes. Biological plausibility is worthy of consideration. Airway inflammation is reduced by inhaled corticosteroids, which inhibit eosinophilic activity and cytokine secretion. An effective anti-inflammatory effect demands proper pulmonary deposition. The condition may lead to chronic inflammation and relapsing current symptoms [17]. Various empirical studies have revealed that non-adherence and incorrect methods are linked to increased eosinophil counts and reduced disease control [18]. The correlation observed between enhanced technique and improvement in symptom scores may hence indicate this mechanistic pathway [19,20].

The strengths of the study are random allocation, standardization, and the variability of dosing and objective lung function (spirometry). Follow-up was done for all subjects, and symptom scores, as well as lung function, were measured. However, there were some limitations. The research was done at one tertiary care unit and not at a rural or primary care setting. The sample size was not large, despite the fact that it was calculated correctly. The maximum follow-up period was eight weeks, and the patterns of long-term adherence were not determined. Biomarkers like fractional exhaled nitric oxide were not measured.

CONCLUSIONS

In this single-centre randomized study, the pressurized metered-dose inhaler was associated with greater improvement in asthma control and lung function compared with the dry powder inhaler over 8 weeks of follow-up among adults with uncontrolled asthma. These

findings suggest that device selection and structured inhaler education may influence short-term asthma outcomes in similar tertiary care settings.

Authors' Contribution

Conceptualization: SS

Methodology: MH, SA², LQB

Formal analysis: SA¹

Writing and Drafting: XQ

Review and Editing: XQ, MH, SA¹, SS, SA², LQB

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article
Professionalism in Medical Students: Emotional Intelligence Matters
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ARTICLE INFO
Keywords:

Emotional, Intelligence, Medical, Professionalism, Students

How to Cite:

 Din, M. U., Hassan, A., Ijaz, I., Anwar, A., Arshad, C. M. U., Mishal, T., Tahir, M. M., Yousaf, K., & Iqbal, M. T. (2026). Professionalism in Medical Students: Emotional Intelligence Matters: Emotional Intelligence and Professionalism in Medical Students. *Pakistan Journal of Health Sciences*, 7(8), 72-78. <https://doi.org/10.54393/pjhs.v7i8.3870>
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 Received Date: 23rd January, 2026

 1st Revision Received: 28th February, 2026

 2nd Revision Received: 24th March, 2026

 Acceptance Date: 15th April, 2026

 Published Date: 31st August, 2026

ABSTRACT

Emotional intelligence (EI) and professionalism are the core competencies that medical education requires; however, their interconnection is still not explored much. **Objectives:** To identify the relationship between EI and professionalism in clinical-year medical students, as well as to investigate the differences based on gender and academic year. **Methods:** A comparative cross-sectional study was performed among 191 MBBS students of Aziz Fatima Medical and Dental College, Faisalabad. All the participants filled out the Trait Emotional Intelligence Questionnaire-Short Form (TEIQue-SF) and a modified version of the Professionalism Mini Evaluation Exercise (PMEX). Statistical techniques such as Pearson's correlation, independent t-tests, ANOVA, and multiple linear regression were employed for data analysis. **Results:** Global EI and professionalism relationship was weak but positive and significant ($r=0.216$, $p=0.003$). EI domains displayed opposite correlations: emotionality ($r=0.285$) and sociability ($r=0.371$) were positively correlated, and well-being ($r=-0.419$) and self-control ($r=-0.306$) were negatively correlated with professionalism, all at $p < 0.01$. Third-year students had significantly higher well-being scores as compared to fourth-year students ($p=0.021$). Regression analysis revealed global EI to be an independent predictor of professionalism ($B=0.657$, $p=0.005$), explaining 7.7% of the variance. **Conclusions:** Emotional intelligence significantly predicts professionalism, with global EI emerging as an independent predictor. Emotionality and sociability showed positive associations, while self-control and well-being showed negative associations with professionalism. Well-being declines significantly from the third to fourth year, while no gender differences were observed.

INTRODUCTION

Medical educators and accrediting bodies have increasingly put more emphasis on the cultivation of non-technical attributes over the last few decades, which then complement scientific knowledge. Among these, emotional intelligence (EI) and professionalism have been recognized as the main foundations upon which the "good" and "competent" physician development relies. Emotional intelligence, which enables a person to recognize, comprehend, control, and direct not only his/her emotions but also those of other people, has been correlated with improved communication, reduced burnout, and better clinical performance [1]. Simultaneously, professionalism,

a term that includes clinical competence, ethical practice, reliability, and respect, is still a central point of medical practice and a required result in undergraduate medical education [2]. Globally, research shows a positive link between EI and professionalism among medical students. Western studies, particularly in the United States and Europe, reported moderate to strong positive correlations between them [3]. For example, a study on dental students in the U.S. has found that professionalism domains like ethical practice and interpersonal communication are significantly related to EI [4]. Likewise, study from Japan reported similar results regarding higher EI with better

patient communications and ethical decision-making process [5]. Nevertheless, there are instances where certain research has pointed out very little or no connection at all, thus indicating the possible effect of cultural, curricular, and methodological factors [6]. Despite the fact that the Pakistan Medical and Dental Council (PMDC) recognizes professionalism as a major competency, the formalized training and assessment of EI in undergraduate classes are not very common [7]. The recent studies in Pakistan have opened a new area of research concerning the EI levels of medical students, giving a report of moderate scores along with the differences among institutions [8]. However, the evidence to support the link between EI and professionalism in Pakistan is scanty. A study conducted in Karachi showed a moderate positive correlation between students' EI and their professionalism, but it involved only one institution and did not consider differences in academic years or demographics [9]. The present study has three main parameters to address these research gaps. The first parameter involves including students from multiple academic years for the purpose of studying developmental trends. The second parameter requires using the TEIQue-SF multi-domain EI assessment tool to measure how different EI domains relate to professional behavior. The third parameter uses the modified PMEX professionalism scale, which has been adapted for use in Pakistan [10]. These parameters enable researchers to examine how different EI components display professional behavior patterns across various stages of medical training.

To this time, there has been no published research that investigates this relationship across MBBS years, nor is there any study that has used a multi-domain EI tool along with a validated professionalism scale. The socio-cultural and educational contexts in Pakistan - marked by high patient load and lack of resources - may have a special impact on the traits of EI and professionalism in medical students [10]. Knowing for sure if and how EI is related to professionalism in this environment is necessary to create the appropriate educational interventions. Consequently, the research will be done to explore the relationship between emotional intelligence and professionalism of the undergraduate medical students of Aziz Fatimah Medical and Dental College, Faisalabad. Therefore, this study aimed to find out the relationship between EI and professionalism scores, to investigate the differences between the two genders concerning these variables, and to look at the differences among academic years.

METHODS

A comparative cross-sectional study was conducted over a period of seven months from July 2025 to December 2025 in Aziz Fatima Medical and Dental College, Faisalabad.

Ethical approval by the Institutional Ethics Committee (Ref No.: IEC/368-25; dated 6th May 2025) was taken. The study included third, fourth, and final-year students as its main subject since these groups are the most involved in the clinics and their professional identity and emotional skills are more developmentally influenced by the interactions with patients and clinical duties than the pre-clinical students (first and second years), who have almost no patient contact [11]. According to the formula for correlation studies, the sample size was calculated based on an expected correlation coefficient of $r = 0.412$ obtained from a previous local study with a significance level of 0.05 and power of 90% [12]. The resulting number was 62 as the minimum required sample size. To improve the representation of subgroups and compensate for possible non-response, we intended to recruit a total of 191 participants by the same proportion as in the third, fourth, and final academic years. Each student was asked for voluntary participation and provided with written informed consent. The data collection process was anonymous, with online forms used and distributed through the institutional social media platforms. To measure emotional intelligence, the 30-item Trait Emotional Intelligence Questionnaire-Short Form (TEIQue-SF) was used, a self-report tool that is freely accessible and has good psychometric properties [13]. The responses were obtained through a 7-point Likert scale, where 1 means completely disagree, and 7 means completely agree. After reversing the scores of certain items, four domain scores - well-being, self-control, emotionality, and sociability - were calculated, and a global EI score was deduced as the average of all items. The Professionalism Mini Evaluation Exercise (PMEX) is a 20-item assessment. A modified version of this tool, developed by Rehman and Mehmood for Pakistani medical students, was used with permission [12, 14]. The researchers made language easier to understand and created assessment items that matched local cultural and educational practices while maintaining the primary professional conduct assessment elements. Responses were recorded on a 5-point frequency scale (1=never to 5=always). For each participant, total professionalism score (20-100) and mean professionalism score (1-5) were computed. The data were evaluated through IBM SPSS version 25.0 software. Continuous variables were presented with mean $\pm$ standard deviation, while categorical variables were presented with frequencies and percentages. The use of Pearson's correlation coefficient uncovered the degree to which the EI scores were related to professionalism scores. The male-female comparisons were done with independent t-tests, and the academic year comparisons with one-way ANOVA. To identify whether EI was a predictor of professionalism or not,

multiple linear regression analysis was done after controlling for demographic variables. The level of significance for the test was set at $p < 0.05$.

RESULTS

The sample included a balanced gender distribution with 91 (47.6%) males and 100 (52.4%) females. The participants included students from the third academic year (35.1%), fourth academic year (36.1%), and final academic year (28.8%). More, The scores of emotional intelligence domains were generally moderate to high, with self-control having the highest mean (4.31 ± 1.16) and well-being the least (3.69 ± 0.96). The global EI score was 3.96 ± 0.26 , the score for professionalism was 3.80 ± 0.85 on a 5-point scale, which signified that the participants considered their professionalism to be at a moderate level (Table 1).

Table 1: Socio-Demographic Characteristics of the Study Participants and Descriptive Statistics of Emotional Intelligence and Professionalism Scores ($n=191$)

Variables	Categories / Min-Max	n (%) / Mean $\pm$ SD
Gender	Male	91 (47.6%)
	Female	100 (52.4%)
Year of Study	3 rd Year MBBS	67 (35.1%)
	4 th Year MBBS	69 (36.1%)
	Final Year MBBS	55 (28.8%)

Family Income (PKR)	< 50,000	16 (8.4%)
	50,000 – 99,999	15 (7.9%)
	100,000 – 149,999	21 (11.0%)
	150,000 – 199,999	42 (22.0%)
	$\geq 200,000$	97 (50.8%)
Current Residence	Day Scholar	147 (77.0%)
	Hostelite	44 (23.0%)
Permanent Residence	Urban	145 (75.9%)
	Rural	46 (24.1%)
Age (Years)	Mean $\pm$ SD	22.52 $\pm$ 1.37
Factors of TEIQue-SF		
Well-being	1.60–6.00	3.69 $\pm$ 0.96
Self-control	1.00–7.00	4.31 $\pm$ 1.16
Emotionality	2.56–6.11	4.17 $\pm$ 0.60
Sociability	1.00–6.63	3.90 $\pm$ 1.14
Global EI Score	3.37–4.60	3.96 $\pm$ 0.26
Total Professionalism	19–95	72.12 $\pm$ 16.18
Mean Professionalism	1.00–5.00	3.80 $\pm$ 0.85

Professionalism had negative correlations with both well-being and self-control, which were significant ($r = -0.419$ and -0.306 , respectively). On the other hand, emotionality and sociability showed positive significant correlations ($r = 0.285$ and $.371$, respectively). The association between global EI and professionalism was very weak, yet positive ($r = 0.216$, $p = 0.003$) (Table 2).

Table 2: Pearson correlations between emotional intelligence domains, global EI, and professionalism ($n=191$)

Variables	Well-being	Self-control	Emotionality	Sociability	Global EI	Mean Professionalism
Well-being	1	0.591**	-0.571**	-0.742**	-0.427**	-0.419**
Self-control	0.591**	1	-0.262**	-0.819**	-0.414**	-0.306**
Emotionality	-0.571**	-0.262**	1	0.382**	0.581**	0.285**
Sociability	-0.742**	-0.819**	0.382**	1	0.725**	0.371**
Global EI	-0.427**	-0.414**	0.581**	0.725**	1	0.216**
Mean Professionalism	-0.419**	-0.306**	0.285**	0.371**	0.216**	1

**Correlation is significant at the 0.01 level (two-tailed)

There were no statistically significant differences between male and female medical students in any area of emotional intelligence or self-reported professionalism (all $p > 0.05$). Still, males were slightly higher than females on self-control and emotionality scores. In contrast, females were slightly higher than males on sociability and professionalism scores, though these differences were not statistically significant (Table 3).

Table 3: Comparison of Emotional Intelligence and Professionalism Scores by Gender

Variables	Male (n=91) Mean $\pm$ SD	Female (n=100) Mean $\pm$ SD	t	df	p-value
Well-being	3.66 $\pm$ 1.05	3.73 $\pm$ 0.88	-0.508	189	0.612
Self-control	4.48 $\pm$ 1.15	4.16 $\pm$ 1.16	1.906	189	0.058
Emotionality	4.23 $\pm$ 0.60	4.12 $\pm$ 0.59	1.246	189	0.214
Sociability	3.80 $\pm$ 1.18	4.00 $\pm$ 1.10	-1.196	189	0.233

Global EI	3.94 $\pm$ 0.29	3.98 $\pm$ 0.23	-0.917	189	0.360
Mean Professionalism	3.69 $\pm$ 0.89	3.89 $\pm$ 0.81	-1.650	189	0.101

The academic years had an influence on the well-being scores, and the difference was significant ($F = 3.93$, $p = 0.021$), with the third-year students being reported to have well-being significantly higher than fourth-year students. There were no such big differences in the other areas of EI, the global EI, or professionalism scores over the three academic years (Table 4).

Table 4: Comparison of Emotional Intelligence and Professionalism Scores Across Academic Years

Variables	3 rd Year (n=67) Mean $\pm$ SD	4 th Year (n=69) Mean $\pm$ SD	Final Year (n=55) Mean $\pm$ SD	F-value	p-value
Well-being	3.95 $\pm$ 1.03	3.51 $\pm$ 0.90	3.60 $\pm$ 0.90	3.93	0.012
Self-control	4.51 $\pm$ 1.32	4.21 $\pm$ 0.98	4.20 $\pm$ 1.16	1.48	0.058

Emotionality	4.07 ± 0.55	4.26 ± 0.58	4.19 ± 0.65	1.82	0.214
Sociability	3.70 ± 1.30	4.03 ± 1.03	4.00 ± 1.06	1.74	0.233
Global EI	3.94 ± 0.27	3.98 ± 0.26	3.97 ± 0.25	0.51	0.360
Mean Professionalism	3.70 ± 1.00	3.78 ± 0.78	3.93 ± 0.73	1.06	0.101

Note: $p < 0.050$ indicates a significant difference

The regression model was statistically significant ($F=3.07$, $p=0.011$) and accounted for 7.7% of the variance in professionalism ratings. Global emotional intelligence had the sole significant influence ($B=0.657$, $\beta=0.200$, $p=0.005$), meaning that with a one-point rise in global EI, professionalism ratings would be nearly 0.66 points up, adjusting for gender, age, year of study, and place of living. The influence of demographic factors on professionalism was not significant. To identify which specific EI domains impact professionalism, a second regression model was used to test all four EI domains as predictive factors. The model showed statistical significance and accounted for 18.7% of the variation in professionalism scores. The individual domains showed that well-being functioned as the only significant negative predictor (Table 5).

Table 5: Multiple Linear Regression Analysis Predicting Professionalism from Emotional Intelligence and Demographic Factors ($n=191$)

Predictor	B	SE	β	t	p	95% CI for B
Model 1 (Demographics + Global EI)						
Constant	1.510	1.477	—	1.022	0.308	[-1.40, 4.42]
Global EI	0.657	0.234	0.200	2.809	0.005	[0.20, 1.12]
Gender	0.137	0.124	0.080	1.103	0.271	[-0.11, 0.38]
Age	-0.034	0.061	-0.055	-0.562	0.575	[-0.15, 0.09]
Year of Study	0.128	0.106	0.120	1.209	0.228	[-0.08, 0.34]
Current Residence	-0.205	0.143	-0.102	-1.430	0.154	[-0.49, 0.08]
Model 2 (EI Domains)						
Constant	3.971	1.070	—	3.710	<0.001	[1.86, 6.08]
Well-being	-0.239	0.098	-0.270	-2.424	0.016	[-0.43, -0.05]
Self-control	-0.023	0.085	-0.031	-0.269	0.788	[-0.19, 0.14]
Emotionality	0.112	0.116	0.079	0.970	0.333	[-0.12, 0.34]
Sociability	0.086	0.103	0.115	0.829	0.408	[-0.12, 0.29]

DISCUSSION

The current study presents a detailed analysis of the correlation between emotional intelligence (EI) and professionalism in clinical-year medical students in Pakistan, showing both similarities to and differences from the existing literature. The observed moderate levels of global EI and professionalism are, in general, in line with the findings of previous regional and international studies, thereby supporting the idea that these traits are still in the process of development throughout medical education and not only during the initial clinical exposure [8, 12]. This development-based viewpoint is in harmony with the latest theories that perceive professionalism as a process that

takes a long time to yield results and is influenced by emotions, cognition, and context [2, 11]. The main takeaway from this research is the finding of a statistically significant but weak positive correlation between global EI and professionalism, where global EI turned out to be an independent predictor in the multivariable analysis. This finding supports earlier studies from Pakistan and other parts of the world that likewise report small effect sizes when examining EI as a factor determining professional behavior [3, 9]. Notably, the small percentage of variance accounted for by EI highlights that professionalism is not simply a matter of emotional skills but is also affected by factors such as institutional culture, role modeling, assessment systems, and the hidden curriculum [7]. This observation concurs with the latest systematic reviews that argue that while EI enables the conduct of professionals, its influence varies according to the environment and organizational factors [14, 15]. One of the big theoretical benefits the study offers is its area-specific examination of EI, which uncovered different links with professionalism. Traits like emotionality and sociability were positively correlated with professionalism, while well-being and self-control had an opposite relationship that was very strong. The connection between the EI domains of the interpersonal type and professionalism was backed by a lot of evidence, as these domains consist of empathy, emotional awareness, communication, and relationship management—the key components of professional medical practice [6, 10]. Researchers in the fields of medical and dental education have recently observed that students who master the emotional skills of interpersonal type are more sensitive to ethical issues, have better patient interactions, and are more cooperative in their teams than their peers with less developed emotional skills [3, 6]. On the other hand, the negative association of well-being and self-control with professionalism is hard to understand and requires a careful look. The somewhat controversial view of Trait EI theory considers well-being to be one's perception of oneself as happy, optimistic, and confident, and self-control means the regulating of one's emotions and withholding of one's impulses [13]. It is equally crucial to recognize, though, that these negative correlations may not actually reflect inverse connections but rather methodological artefacts such as cultural response tendencies, social desirability, or self-report bias. In very challenging clinical environments, such as those with a very high level of stress due to heavy workloads, limited resources, and strict hierarchies—these are the very conditions one typically finds in medical training in Pakistan—students with a lot of emotional self-awareness may be too critical of themselves and recognize their ethical dilemmas and shortcomings [7, 11]. Their increased reflexivity may ironically result in poor self-

assessments of professionalism, which is a phenomenon that has been described in the past as self-evaluative stringency [16]. Apart from that, self-control to an addictive extent may exhibit emotional suppression as a confounding factor rather than a positive regulation, especially in societies where emotional constraint is a social norm [17]. Emotional suppression results in two negative outcomes, which include emotional exhaustion and decreased authentic self-presentation during doctor-patient relationships [14, 18]. Research on health professions students' quality of life and patient safety in Pakistan and other countries found similar results [19, 20]. The above-mentioned keeps indicating that not all fields of EI are of the same quality regarding the good effects and points to the necessity to differentiate between adaptive emotional regulation and maladaptive emotional inhibition in medical education. The study found no significant gender-based differences between EI and professionalism scores. It may be because of three specific methodological issues. First, our sample size of 191 proved sufficient to identify moderate correlations but may have failed to identify small effect sizes. Second, the within-group variance in our study reached a substantial level, which decreased our ability to identify significant differences between the groups. Third, the measurement sensitivity of the instruments may play a role. Since the TEIQue-SF and modified PMEX are self-report tools, they might not be sensitive enough to pick up on subtle, gender-specific manifestations of professionalism and emotional intelligence [10, 18]. Literature from the past often pointed out female students as the ones with more empathy and emotionality, while nowadays it has been argued that the presence of the same standardized curricula, similar clinical responsibilities, and common stress factors for both genders might lead to the attenuation of gender-based differences during clinical years [21, 22]. Analysis of the academic years has shown that the fourth-year students' well-being has decreased significantly compared to the third-year students—a result that corroborates the “clinical transition effect” reports. The non-existence of continuous development in EI or professionalism over the years is another sign that clinical exposure is not enough to nurture these attributes. As our study design prevents us from identifying whether fourth-year students experience reduced well-being because of their academic requirements or clinical training, or other untested variables, these findings show that students will maintain their well-being when universities implement specific wellness programs that include structured clinical rotation orientation, mentorship initiatives, and student workload management during their clinical year transition process. This trend supports the recent suggestions for planned adoption of structured, longitudinal interventions, such as

reflective practices, mentorship, and EI-centered curricula, that will specifically aid in emotional and professional development [4, 15]. Regression analysis provided strong evidence that global EI is an independent predictor of professionalism even after demographic variables have been accounted for, thus firmly establishing its educational relevance. Yet its limited explanatory power should be seen as a signal to apply a more extensive pedagogical approach that combines emotional skills training with institutional strategies that deal with workload, assessment cultures, and professional role models [23]. This is a particularly pertinent situation in the context of medical education in Pakistan, since there the policy-makers officially stress the professionalism issue, but it is only applied in the curricula in a patchy manner [7, 11].

Several limitations need to be recognized. The cross-sectional design does not permit causal inference, and the use of self-reports may result in the presence of social desirability and response bias. The confines of a single-institution setting make it difficult to generalize the findings. Also, the modified professionalism instrument might not have captured all the professional behaviors that were observed fully. However, among the study's strengths are the use of validated tools, an adequate sample size, and a domain-specific analytical approach that provides novel insights into the EI-professionalism relationship.

CONCLUSIONS

Emotional intelligence significantly predicts professionalism, with global EI emerging as an independent predictor after adjusting for demographics. Of the four interpersonal EI domains (emotionality, sociability, self-control and well-being), emotionality and sociability showed positive associations with professionalism. However, self-control and well-being both showed negative associations. Using domain-level regression analysis, only well-being was a significant negative predictor of professionalism. Additionally, no significant gender differences existed, and a significant decline in well-being occurred in the third to fourth year, indicating a potential critical time for student support.

Authors' Contribution

Conceptualization: II

Methodology: MUD, AA, CMUA, TM, MMT, KY, MTI

Formal analysis: AH, II, AA, CMUA, TM, MMT

Writing and Drafting: AA, CMUA, TM, MMT, KY, MTI

Review and Editing: MUD, AH, II, AA, CMUA, TM, MMT, KY, MTI

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Grading Anterior Urethra Stricture to Predict Surgical Complexity and Outcome Using the Urethra Stricture Score

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ARTICLE INFO

Keywords:

Anterior Urethral Stricture, Urethrotomy, Urethroplasty, Surgical Complexity

How to Cite:

Akhter, N., Khan, A., Shaheen, U. B., Mughal, N., Qureshi, H. H., Hussain, M., & Kumar, P. (2026). Grading Anterior Urethra Stricture to Predict Surgical Complexity and Outcome Using the Urethra Stricture Score: Anterior Urethra Stricture: Surgical Complexity and Urethra Stricture Score. Pakistan Journal of Health Sciences, 7(8), 79-83. <https://doi.org/10.54393/pjhs.v7i8.1367>

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Received Date: 26th March, 2024

1st Revision Received: 21st June, 2025

2nd Revision Received: 19th January, 2026

3rd Revision Received: 3rd March, 2026

Acceptance Date: 9th March, 2026

Published Date: 31st August, 2026

ABSTRACT

Urethral stricture is a cause of impedance of urine outflow and is quite common in urology. 300 out of 100,000 men are affected by this disease. There is no objective system for determining the structure's complexity. **Objectives:** To appraise the relationship between Urethral Stricture Score (USS) and surgical complexity, standardize the surgical approaches, and predict the surgical outcomes with the use of USS. **Methods:** This was a descriptive study conducted in the Department of Urology, Sindh Institute of Urology and Transplantation, Karachi. The duration for sample collection was six months. Non-probability consecutive sampling was employed. Mean and standard deviation were computed for age, duration of disease, duration of surgery, BMI, and USS. Effect modifiers like age, duration of disease, and BMI were stratified to see the effect of this on the outcome. Post stratification spearman correlation and Anova test were applied. The p-value <0.005 was considered significant. **Results:** A total of 45 patients were included in this study that was diagnosed with anterior urethral strictures. We found a significant association of USS with surgical complexity. As the score increased, surgical complexity increased; the F-value of the ANOVA test was 61.25, and the p-value was <0.001. The study also found a significant correlation between USS and duration of surgery, with a correlation coefficient of 0.806 and p-value <0.001. **Conclusion:** This study affirms the positive correlation between the increasing USS and increasing surgical complexity.

INTRODUCTION

The key to maintaining optimal function of the kidneys is storage under low pressure and timely and complete emptying of the bladder. Impedance of either of the two parameters can inflict severe damage to renal parenchyma and hence renal function [1]. Urethral stricture is one such cause of impedance of urine outflow and is quite common in urology. 300 out of 100,000 men are affected by this disease [2]. The most common cause of urethral stricture is iatrogenic injury. This is followed by accidental urethral

strictures, for example, forgotten minor trauma. Some other causes include bacterial urethritis and lichen sclerosis. The stricture can be on a variety of locations, such as the bulbar or penile urethra, navicular fossa, and panurethra [3-5]. Anterior urethral stricture can cause significant morbidity amongst patients and presents with symptoms such as a weak stream, incomplete emptying, spraying of the urinary stream, dysuria, and sexual dysfunction [6, 7]. Several management options are

available to alleviate the symptoms and improve the quality of life of patients. These include urethral dilatation, urethroplasty, direct vision internal urethrotomy, and urinary diversion. The selection and employment of appropriate surgical technique involve consideration of several factors: Surgical acumen of the surgeon, location of the stricture, age of the patient, etiology of the stricture, and availability of resources [1]. There is no objective system to determine the complexity of the structure and thus no preference for surgical technique. Furthermore, the lack of an objective numerical system renders the statistical analysis of urethroplasty techniques and efficacy really difficult. To cater to this, Wiegand and Brandes developed the urethral stricture score (USS) to quantify the complexity of the strictures [8]. This scale calculates a score on the basis of location, etiology, number, and urinary retention. Urethral stricture Etiology: if inflammatory, then receives two points (maximum) while other etiologies receive one. One point is given for each structure (Number) and for each centimeter (Length). For Retention, one point if the urethra is patent and two (maximum) if it is obliterated. Regarding the anatomic location, one for the bulbar urethra, two for the penile urethra, and three (maximum) for pan-urethral or both penile and bulbar strictures [8]. Another iteration of this system is the U-score, which omits urinary retention as a category and simplifies the scores [9].

There is a lack of literature from Pakistan pertaining to the implementation of USS, which can provide an objective, standardized, and comprehensive assessment of the condition. This can predict the surgical outcomes and can help standardize the surgical approaches, which ultimately enhances the overall quality of care for patients. This study aimed to validate the scoring system for the local population of Pakistan, to appraise the relationship between USS and surgical complexity.

METHODS

A prospective descriptive study was conducted at the Department of Urology, Sindh Institute of Urology and Transplantation (SIUT) from 1st December 2022 till 31st May 2023. The institutional review board approval was duly obtained (SIUT-ERC-2020/A-255; dated 28th November 2020). Non-probability consecutive sampling was employed. The sample size of 45 was calculated using PASS 2020 Power Analysis and Sample Size Software (NCSS, LLC, Kaysville, Utah, USA), setting Spearman's correlation as 0.901, deduced from a previous study with a power set to 80%, along with 5% level of significance [10]. The Urethral stricture score (USS) and level of surgical complexity have been provided as a separate table. Higher scores represent a higher severity of the urethral stricture. The surgical complexity of three different procedures was ranked from

least complex to maximum complexity on the basis of operative times, blood loss, and transfusions. DVIU- Direct Vision Internal Urethrotomy- least complex, EPA- Excision and primary anastomosis, and BMG- Buccal Mucosal graft urethroplasty- most complex (Table 1).

Table 1: Description of the Urethral Stricture Score (USS) and Level of Complexity of Surgery

Variables	Points
Length of Stricture (cm)	
1 Point per cm of Length (to the Nearest 0.1 cm)	1
Retention	
Patent Urethra	1
Obliterated or Near Obliterated	2
Anatomic Location	
Bulbar Urethra	1
Penile Urethra	2
An-Urethra or Both Bulbar and Penile	3
Number of Strictures	
1 Point Per Stricture	1
Etiology	
(Non-Inflammatory) Trauma, Idiopathic, Iatrogenic	1
Inflammatory, Hypospadias	2
Level of Complexity of Surgery	
Direct Visual Internal Urethrotomy (DVIU)	1
Excision and Primary Anastomosis (EPA)	2
Buccal Mucosal Graft Urethroplasty (BMG)	3

All male patients aged 18-60 years with anterior urethral stricture and a duration of disease of more than one month with an American Society of Anesthesiologists (ASA) class of up to II were included in the study. Patients with posterior urethral strictures, prior open urethroplasty, confirmed diagnosis of benign prostate hyperplasia, on corticosteroids, and uncontrolled diabetes mellitus were excluded from the study. Those patients who did not consent to this study were also excluded. Written and informed consent was taken from the patients before enrollment. Detailed but pertinent history was obtained from the participants. Data were entered and analyzed on SPSS version 22.0. Mean and standard deviation were computed for age, duration of disease, duration of surgery, BMI, and urethral stricture score. Frequencies and percentages were computed for the type of stricture, retention, etiology, and surgical complexity. An ANOVA test was used to determine if there were significant differences in mean scores with surgical complexity. The obtained USS was related to the type of surgical procedure and duration that the patient underwent, and a correlation using Spearman's correlation coefficient was determined. Effect modifiers like age, duration of disease, and BMI were stratified to see the effect of these on outcomes. Post stratification spearman correlation was applied. The p-value <0.005 was considered significant.

RESULTS

A total of 45 patients were included in this study that was diagnosed with anterior urethral strictures. The descriptive statistics of the demographic and clinical characteristics of patients were determined (Table 2).

Table 2: Demographic and Clinical Characteristics of Patients

Variables	Age (years)	Duration of Disease (Days)	Duration of Surgery (minutes)	BMI (kg/m ²)	Urethral Stricture Score
Mean ± SD	44.60 ± 11.71	153.31 ± 64.69	133.27 ± 91.46	24.90 ± 1.97	8.68 ± 3.57
Minimum	18	30	10	21	4.40
Maximum	60	1825	290	29	18.00

Retention was found in 35 (77.77%) and not in 10 (22.22%) patients. Frequency of etiology, non-inflammatory (trauma, idiopathic, iatrogenic) was found in 34 (75.56%) and inflammatory in 11 (24.44%) patients. Stricture was located at the penile region in 07 (15.56%) patients, at the bulbar in 27 (60.00%), and pan-urethral in 11 (24.44%) patients. Mean length of stricture was 2.94 ± 2.29 cm while the mean number of strictures was 1.16 ± 0.37 . There was no blood products transfused within 24 hours post-operative period in 43 (95.56%) patients, and 01 blood product was transfused within 24 hours post-operative period in 02 (4.44%) patients. On frequency of complexity, DVIU (level 1) was performed in 15 (33.33%) patients, EPA (level 2) in 14 (31.11%), and BMG (level 3) in 16 (35.56%) patients. The study found a statistically significant relationship between USS and surgical complexity, with increasing USS corresponding to greater surgical complexity. This was confirmed by ANOVA, which demonstrated an F-value of 61.42 and a p-value <0.001 (Table 3).

Table 3: Comparison of Mean Urethral Stricture Score Across Surgical Complexity Levels Using One-Way ANOVA

Type of Surgery (Surgical Complexity)	Urethral Stricture Score (Mean ± SD)	F-value	p-value
DVIU (Level 1)	5.38 ± 0.94	61.42	<0.001
EPA (Level 2)	7.75 ± 1.15		
BMG (Level 3)	12.58 ± 2.74		

This study also found a significant correlation between USS and duration of surgery, with a correlation coefficient of 0.806 and a p-value <0.001. With increasing USS, the time of surgery was significantly increased (Table 4).

Table 4: Spearman's Correlation Matrix Between Urethral Stricture Score and Duration of Surgery

Variables	Urethral Stricture Score	Duration of Surgery
Urethral Stricture Score	1.00	0.806*
Duration of Surgery	0.806*	1.00
Sig. (2-tailed)	—	<0.001
N	45	45

*Correlation is significant at the 0.01 level (2-tailed).

When stratified based on duration of disease, there was a significant association of USS with surgical complexity, with an F-value of 58.19 and p-value <0.001 when duration of disease was <100 days. Similarly, in patients having a duration of disease ≥100 days, the F-value was 18.54, and the p-value was <0.001. In patients having a duration of disease <100 days, there was a significant correlation between USS and duration of surgery, with a correlation coefficient of 0.84 and a p-value <0.001. In patients having a duration of disease ≥100 days, the correlation coefficient between USS and duration of surgery was 0.87, and the p-value was <0.001. Stratification of age, duration, and BMI was done to evaluate the relationship between USS and surgical complexity (Table 5).

Table 5: Stratified One-Way ANOVA Showing Mean Urethral Stricture Scores by Surgical Complexity Across Age, Disease Duration, and BMI Groups

Variables	Type of Surgery	Urethral Score (Mean ± SD)	F-value	p-value
Age (years)	18-44	DVIU	5.37 ± 0.97	<0.001
		EPA	7.56 ± 1.29	
		BMG	13.58 ± 2.57	
	45-70	DVIU	5.38 ± 0.99	
		EPA	8.0 ± 1.00	
		BMG	10.91 ± 2.33	
Duration (days)	<100	DVIU	5.40 ± 0.95	<0.001
		EPA	9.50 ± 1.23	
		BMG	12.48 ± 2.47	
	>100	DVIU	6.26 ± 1.07	
		EPA	10.40 ± 0.98	
		BMG	14.96 ± 2.57	
BMI (kg/m ²)	≤ 24 kg/m ²	DVIU	5.30 ± 0.94	<0.001
		EPA	7.70 ± 1.22	
		BMG	12.55 ± 2.46	
	≥ 25 kg/m ²	DVIU	5.57 ± 1.07	
		EPA	7.87 ± 1.11	
		BMG	12.60 ± 3.03	

DISCUSSION

Anterior urethral stricture requires prompt management lest renal damage occur. There are several management options depending on the severity and complexity of urethral stricture [1]. Current study attempts to externally validate the USS (urethral stricture score) based on parameters such as etiology, urine retention, length, number, and location of strictures. Payne *et al.* discuss difficulties faced in low-income countries and identify several factors, such as the etiology of urethral strictures, length, and number of the strictures contributing to it [11]. Furthermore, owing to limited resources, it is imperative to opt for the best surgical approach, and for that, an objective scoring system is warranted. The scoring system used in this study, the USS, incorporates all these factors

mentioned above. Tritschler et al. document that 20% of the cases of urethral stricture arise from inflammation, and our study shows a similar rate of acquired inflammatory strictures, which was 11% [12]. Multiple studies have shown that the most common site for strictures is the bulbar urethra, followed by the penile and lastly by the navicular fossa [11-14]. A similar fashion was obtained from our results, and the most common site was found to be the bulbar urethra, followed by the penile urethra. The most common symptom at presentation is urinary retention, and this is what often brings this to the notice of patients [15]. This study consolidates this fact, and more than 75% of the patients had retention as a presenting symptom. The U-score eliminates the score for retention [9], but USS incorporates this in its scoring system and thus increases the scores of respective patients. Several approaches exist for the treatment of urethral strictures. These procedures are opted for on the basis of the complexities of the strictures. Verla et al. mention in their study that DVIU (Direct vision Internal Urethrotomy) is the simplest of procedures performed in patients with a single stricture of less than 1.5cm [16]. This corresponds to a low score on the USS scale, and this study opted for DVIU as a low complexity surgery. The results are promising; however, with increasing lengths, the results start to deteriorate [17, 18]. The complexity of the buccal mucosal graft is maximum and requires surgical expertise and a longer duration of surgery. Furthermore, it can cause significant discomfort to patients and lengthen their hospital stay. With all the demerits stated, this procedure nevertheless has been proven valuable and is widely used [19, 20]. This study institute resorted to this procedure where the urethral scores were high, and strictures were complicated. Using evidence from the world literature, we categorized the surgical approaches according to the level of their complexity, buccal mucosal grafts being the most complex, while DVIU remained the least complex. The results elucidate a significant relationship between increasing USS and increasing complexity of surgery. There is a positive correlation between the two. This score is of paramount importance as it not only predicts the surgical complexities but also forms the basis for future statistical analyses, as it objectively grades the complexity and can reliably compare the treatment modalities. It can also aid the urologists in determining the most appropriate surgical modality. A similar study conducted by Alwaal et al. also established a positive correlation between the U-score and surgical complexity [2]. U-score is an iteration of USS by Eswara et al. [9], which omits retention as a parameter but otherwise is similar to the USS. Our study also establishes a similar correlation. The parameters that positively correlated with the surgical complexity were

etiology, length of strictures, and number of strictures. There are a couple of studies in the literature that have attempted to validate the scoring system [9]. In contrast, our study used the USS instead of the U-score. To reprise, this study affirms the positive correlation between the increasing urethral stricture score and increasing surgical complexity.

The research is limited to one locality, the Sindh Institute of Urology and Transplantation, which makes it difficult to extrapolate to other Pakistani communities. The sample size of the study is relatively small (n=45) and might not fully reflect the range of diversity of urethral strictures. The non-probability consecutive sampling presents the issue of selection bias, and the 6-month period of study does not allow for evaluating the long-term results of surgery or recurrence rates. There are also subjective elements of the USS scoring system, such as the etiology classification, which could lead to inter-observer variability. The question that needs to be investigated by research is whether USS-guided surgical selection positively affects patient-reported outcomes and quality of life. USS-based procedure selection could be cost-effective to assist in resource allocation in the public sector hospitals.

CONCLUSIONS

This study demonstrates a significant correlation between increasing urethral stricture scores and surgical complexity. This key finding will aid urologists in opting for an optimal procedure in clinical settings and comparing different surgical approaches objectively.

Authors' Contribution

Conceptualization: NA, AK, HHQ, MH

Methodology: NA, UBS, NM

Formal analysis: NA, AK, UBS, NM

Writing and Drafting: NA, AK, UBS, NM, HHQ, MH

Review and Editing: NA, AK, UBS, NM, HHQ, MH, PK

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Impact of Iron Deficiency Anemia on the Severity of Bronchiolitis in Pediatric Patients

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ARTICLE INFO

Keywords:

Anemia, Bronchiolitis, Hemoglobin, Iron-Deficiency, Tachypnea

How to Cite:

Ali, R., Zafar, F., & Mukhtar, R. (2026). Impact of Iron Deficiency Anemia on the Severity of Bronchiolitis in Pediatric Patients: Iron Deficiency Anemia on the Severity of Bronchiolitis in Pediatric Patients. *Pakistan Journal of Health Sciences*, 7(8), 84-89. <https://doi.org/10.54393/pjhs.v7i8.3686>

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Received Date: 12th December, 2025

1st Revision Received: 23rd January, 2026

Acceptance Date: 15th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Bronchiolitis is an acute inflammatory respiratory illness involving the lower respiratory tract occurring in the first 2 years of life. **Objectives:** To determine the impact and outcomes of the severity of iron deficiency anemia (IDA) in patients with acute bronchiolitis (AB). **Methods:** This analytical, cross-sectional study was conducted in the Department of Pediatric Medicine, Ziauddin University Hospital, Karachi, Pakistan, from April 2025 to September 2025. A total of 126 children aged 2–23 months with AB were enrolled through non-probability consecutive sampling. Bronchiolitis severity was classified by the Wang score. Data were analyzed using SPSS version 26.0, with $p < 0.050$ considered significant. **Results:** In 126 children, 73 (57.9%) were males, and the median age was 10.0 months (IQR 6.0–14.0). Mild IDA was present in 38 (31.2%), moderate in 64 (50.8%), and severe in 24 (19.0%) cases. With increasing anaemia severity, weight decreased (8.7 vs 7.6 kg; $p = 0.038$), SpO_2 declined (92.4% vs 88.7%; $p = 0.016$), respiratory rate rose ($p = 0.009$), and Wang score increased (5.3 vs 9.4; $p = 0.004$). Severe IDA showed longer tachypnoea resolution (5.1 vs 3.2 days; $p < 0.001$), retraction recovery (6.2 vs 3.9 days; $p = 0.002$), greater oxygen requirement (18 [75.0%] vs 13 [34.2%]; $p = 0.002$), and prolonged hospital stay (7.2 vs 5.1 days; $p < 0.001$). Severe IDA was significantly associated with severe bronchiolitis ($p = 0.004$). **Conclusions:** The severity of IDA was strongly associated with worse clinical presentation and delayed recovery in children with acute bronchiolitis. Lower haemoglobin and microcytic indices correlated with higher Wang respiratory scores, greater oxygen support requirements, and longer hospital stays.

INTRODUCTION

Bronchiolitis is an acute inflammatory respiratory illness involving the lower respiratory tract occurring in the first 2 years of life [1]. Respiratory syncytial virus (RSV) is estimated to be involved in 60–80% of acute bronchiolitis (AB) cases among infants and may lead to severe disease and mortality in younger age groups [2, 3]. In Pakistan, AB affects around 5.7 per 10,000 population with approximately 2–3% of children requiring hospitalization within 1st year of life [4]. Gender, age, history of prematurity, and immunodeficiency or cardiopulmonary disease are some of the most commonly known risk factors for severe AB [5]. Although there is not enough evidence that significantly establishes the effect of iron deficiency anemia (IDA) on AB, IDA, by providing a hypoxic

environment in the respiratory circulation, can be one of the major contributors to lower respiratory tract infections (LRTIs) among children below 5 years of age [6, 7]. A study revealed that, among patients with AB aged below 24 months, IDA was observed in 36.6% of them [8]. In a case-control study conducted by Roma et al. anemia was found in 72% of cases and 34% of controls, with 86% of the anemic patients in the study group and 63% in controls having iron deficiency [9]. Not much contemporary literature is on view explaining the relationship between IDA and AB among children below 2 years of age. The findings of this research were thought to provide important insights that may aid clinicians in better identifying and treating IDA in bronchiolitis patients, which may ultimately lessen the

severity, length, and risk of complications of the illness. This study was planned with the aim of determining the impact and outcomes of the severity of IDA in patients with AB.

Although there is current evidence that iron deficiency anemia (IDA) is related to respiratory infections, there is a dearth of current data that specifically assesses its influence on the severity and clinical outcome of acute bronchiolitis in children under two years of age, especially in resource-limited areas where iron profile testing is not commonly performed. This leaves a loophole in knowledge about whether IDA has a solitary effect of deteriorating the disease and recovery. Thus, the gap that the current study will fill is the ambiguous role of the severity of IDA in determining the severity and outcomes of bronchiolitis. This study aims to establish the relationship between the severity of IDA and clinical severity, oxygen requirement, and outcome of recovery in children with acute bronchiolitis.

METHODS

This analytical, cross-sectional research was performed at the Department of Pediatrics, Ziauddin University Hospital, Karachi, Pakistan, from April 2025 to September 2025, after getting permission from the institutional ethical review committee (Ref. code: 9910225RAPED, dated: March 29, 2025). A sample size of 126 was calculated using the WHO sample size calculator by considering the anticipated frequency of IDA in children with AB as 80.0, with a 95% confidence level and a 7% margin of error [10]. The inclusion criteria were children of any gender, aged 2–23 months, diagnosed with acute bronchiolitis. The exclusion criteria were children with bronchopulmonary dysplasia, immunodeficiency, chronic lung disease (like cystic fibrosis), congenital or acquired heart disease, severe acute malnutrition, or neuromuscular disorders. All preterm children (≤ 34 weeks of gestation) or who left against medical advice (LAMA) within 24 hours of admission were also excluded. AB diagnosis was based on the presence of upper respiratory virus infection symptoms (like rhinorrhea, cough, and low-grade fever) and signs of lower respiratory tract involvement (like tachypnea, wheezing, crackles, or retractions) [11, 12]. A respiratory rate >50 breaths/min in children ≤ 1 year of age or a respiratory rate >40 breaths/min in children >1 year of age was considered tachypnea. The sampling technique used for sample selection was the “non-probability consecutive sampling technique”. The parents/legal guardians were briefed about the objective and safety of the study before obtaining informed and written consent from them. At the time of admission, demographics, clinical, and vital information were noted. Using an aseptic technique, 5 mL of venous blood was drawn and sent to the

institutional laboratory for a complete blood count (CBC) evaluation to mark IDA. Although IDA is diagnosed with iron profile studies, in the current resource-limited setting, where these tests might not be readily available for every patient, other CBC parameters, which included hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW), were used as the stand-in markers for IDA [13]. The parameters to label IDA included anemia (Hb level <11 g/dL), MCV <72 fL, RDW $>14\%$, a mean corpuscular hemoglobin (MCH) <27 pg/cell, and a Mentzer index (MCV/RDW) >13 [13, 14]. Wang bronchiolitis severity scores (WBSS) classified bronchiolitis as mild (1–3), moderate (4–8), or severe (9–12) bronchiolitis, using the clinical factors, which included respiratory rate, wheezing, retractions, and general appearance [15]. Severity scoring was done by the researchers themselves at the time of admission and then subsequently every 24 hours until discharge. All the patients were offered standard recommended care for bronchiolitis, including oxygen support, nebulization with hypertonic saline, hydration support, and frequent suction of nasal and oral secretions. The need for noninvasive ventilation (yes/no), duration of oxygen requirement (days), PICU stay (days), and hospital stay (days) were noted at the time of discharge. Discharge criteria were followed as per the hospital protocol for bronchiolitis. The association of IDA with the severity of bronchiolitis and its outcomes (duration of resolution of tachypnea, duration of resolution of retraction, and duration of hospital stay) was assessed. IDA was categorized as mild (Hb 10.0–10.9 g/dl), moderate (7.0–9.9 g/dl), and severe (Hb <7.0 g/dl) [16]. All of the relevant information was collected on a structured proforma, especially designed for this study.

The statistical analysis was performed using “IBM-SPSS Statistics” version 26.0. The qualitative variables were shown as frequency and percentage. The normality of the quantitative data was tested using the Shapiro-Wilk test. For the representation of numeric variables, means and standard deviations (SD) or medians and interquartile ranges (IQR) were computed, depending upon the normal distribution of the data. Effect modifiers were controlled by making a stratified table, and post-stratification, chi-square test, or analysis of variance / Kruskal-Wallis’ test were applied with respect to IDA severity, taking $p < 0.050$ as significant.

RESULTS

In a total of 126 children, the median age was 10.0 months (IQR 6.0–14.0). There were 73 (57.9%) males and 53 (42.1%) females. The overall median Hb was 9.2 g/dL (IQR 8.3–10.1), with corresponding red cell indices showing a microcytic, hypochromic pattern. The median MCV was 68.0 fL (IQR 63.5–72.0), mean MCH 25.0 pg (IQR 22.8–26.9), and red cell

distribution width (RDW) 15.3% (IQR 14.5–16.4). The Mentzer index was 12.6 (IQR 11.8–13.3), consistent with IDA. At the time of admission, the median oxygen saturation (SpO₂) was 91.0% (IQR 88.0–94.0). The median respiratory rate was 52 breaths/min (IQR 46–60), and the heart rate was 138 beats/min (IQR 124–148). Among these 126 children, 38 (31.2%) had mild IDA, 64 (50.8%) moderate IDA, and 24 (19.0%) severe IDA. Significant declining trend in age was seen with respect to the severity of IDA ($p=0.041$). The median weight progressively declined with increasing anemia severity ($p=0.038$). Oxygen saturation at admission showed a significant downward trend across anemia categories ($p=0.016$). The respiratory rate increased progressively with respect to the severity of IDA ($p=0.009$). The median Wang respiratory score increased from 5.3 (IQR 3.1–6.9) in mild IDA to 9.4 (IQR 7.4–10.9) in severe IDA ($p=0.004$), indicating greater bronchiolitis severity with worsening anemia. The median Hb decreased from 10.5 g/dL (IQR 10.2–10.8) in mild IDA to 6.5 g/dL (IQR 6.2–6.8) in severe IDA ($p<0.001$). The median MCV ($p<0.001$), and median MCH ($p=0.002$) declined significantly with increasing anemia severity. The RDW increased significantly with respect to the severity of IDA ($p=0.004$) (Table 1).

Table 1: Comparison of Baseline Characteristics of Children with Bronchiolitis According to Severity of Iron Deficiency Anemia (n=126)

Characteristics	Severity of Iron Deficiency Anaemia			p-value
	Mild (n=38)	Moderate (n=64)	Severe (n=24)	
Male	20 (52.6%)	39 (60.9%)	14 (58.3%)	0.870*
Female	18 (47.4%)	25 (39.1%)	10 (41.7%)	
Age (months)	12.0 (8.5–15.2)	9.5 (6.0–13.0)	8.4 (5.8–10.1)	0.041^
Weight (kg)	8.7 (7.9–9.6)	8.2 (7.3–9.0)	7.6 (7.0–8.5)	0.038^
SpO ₂ at Admission (%)	92.4 (90.3–94.8)	91.1 (88.2–93.5)	88.7 (86.1–90.8)	0.016^
Respiratory Rate (breaths/min)	48.7 (44.5–53.6)	53.2 (48.1–60.5)	56.8 (50.3–63.9)	0.009^
Heart Rate (beats/min)	132.5 (12.4–143.6)	138.6 (126.2–149.3)	142.9 (133.4–155.8)	0.073^
Wang Respiratory Score	5.3 (3.1–6.9)	7.1 (5.2–9.3)	9.4 (7.4–10.9)	0.004^
Haemoglobin (g/dl)	10.5 (10.2–10.8)	8.7 (8.2–9.3)	6.5 (6.2–6.8)	<0.001
Mean Corpuscular Volume (fL)	72.1 (69.5–74.0)	67.2 (63.1–70.3)	62.6 (60.1–65.2)	<0.001^
Mean Corpuscular Haemoglobin (pg)	26.6 (25.0–28.1)	24.8 (22.7–26.4)	22.5 (21.0–23.9)	0.002^
Red cell distribution width (%)	14.3 (13.7–15.1)	15.5 (14.8–16.3)	16.4 (15.5–17.3)	0.004^

^Kruskal–Wallis Test Applied; Values Are Median (IQR); *Chi-Square Test Applied

Bronchiolitis severity, assessed by Wang scoring, was significantly associated with severity of IDA ($p=0.004$). Among children with mild IDA, 17 (44.7%) had mild bronchiolitis, 14 (42.1%) had moderate, and 5 (13.2%) had severe bronchiolitis. In contrast, among those with severe IDA, 3 (12.5%) had mild, 9 (37.5%) had moderate, and 12 (50.0%) had severe bronchiolitis. Odds ratio for severe bronchiolitis in severe versus mild IDA was 6.6 (95% CI: 2.0–21.4), indicating a markedly higher likelihood of severe bronchiolitis in children with severe IDA compared with mild IDA (Table 2).

Table 2: Association Between Severity of Iron Deficiency Anemia and Severity of Bronchiolitis (n=126)

Bronchiolitis Severity	Severity of Iron Deficiency Anaemia			p-value
	Mild (n=38)	Moderate (n=64)	Severe (n=24)	
Mild (Wang 1–3)	17 (44.7%)	16 (25.0%)	3 (12.5%)	0.004
Moderate (Wang 4–8)	16 (42.1%)	33 (51.6%)	9 (37.5%)	
Severe (Wang 9–12)	5 (13.2%)	15 (23.4%)	12 (50.0%)	

Chi-square applied

The duration required for resolution of tachypnea increased from 3.2 days (IQR 2.4–4.1) in mild IDA to 5.1 days (IQR 4.0–6.2) in severe IDA ($p<0.001$). Retraction resolution prolonged from 3.9 days (IQR 3.0–5.1) to 6.2 days (IQR 5.1–7.9) ($p=0.002$). Oxygen support was required in 13 (34.2%) children with mild, 33 (51.6%) with moderate, and 18 (75.0%) with severe IDA ($p=0.002$). Although PICU admission increased from 3 (7.9%) in mild to 7 (29.2%) in severe IDA, the difference was not statistically significant ($p=0.109$). The duration of hospital stays increased from 5.1 days (IQR 4.3–6.2) in mild anemia to 7.2 days (IQR 6.0–9.0) in severe anemia ($p<0.001$). Details about clinical outcomes with respect to anemia severity are given (Table 3).

Table 3: Comparison of Clinical Outcomes According to the Severity of Iron Deficiency Anemia

Outcomes	Severity of Iron Deficiency Anaemia			p-value	Differences Between Severe vs. Mild IDA
	Mild (n=38)	Moderate (n=64)	Severe (n=24)		
Tachypnea–Resolution (Days)	3.2 (2.4–4.1)	4.0 (3.2–5.2)	5.1 (4.0–6.2)	<0.001^	1.9 days (95% CI: 1.1–2.5)
Retraction–Resolution (Days)	3.9 (3.0–5.1)	5.0 (4.1–6.3)	6.2 (5.1–7.9)	0.002^	2.3 days (95% CI: 1.2–3.1)
Oxygen Support	13 (34.2%)	33 (51.6%)	18 (75.0%)	0.002*	40.8% (95% CI: 17.8%–63.8%)
PICU Admission	3 (7.9%)	7 (10.9%)	7 (29.2%)	0.109*	21.1% (1.2%–41.4%)

Hospital Stays (Days)	5.1 (4.3-6.2)	6.0 (5.0-7.3)	7.2 (6.0-9.0)	<0.001 [^]	2.1 days (95% CI: 1.4-2.8)
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[^]Kruskal-Wallis test; *Chi-square test; quantitative data = median (IQR)

DISCUSSION

This study found a significant association between Hb concentration and bronchiolitis severity, as children with severe IDA had a median Hb of 6.5 g/dL compared with 10.5 g/dL in mild IDA. This aligns with the results of Celik et al. who reported that bronchiolitis cases with Hb ≤ 10 g/dL were 10 times more likely to develop severe disease, with a negative correlation between Hb and severity ($r = -0.423$, $p < 0.001$) [5]. These findings may highlight a potentially important role of IDA in aggravating hypoxemia and inflammatory responses during LRTIs [17]. The association of IDA with higher Wang scores in the present analysis is consistent with Gupta et al. who documented IDA in 70% of bronchiolitis cases compared with 35% of controls ($p = 0.001$) [10]. That study showed significant differences in MCV, MCH, and transferrin saturation between affected and control groups. The parallel findings reinforce that microcytosis and hypochromia represent the hematologic background favoring poorer respiratory outcomes. In the current study, significant deterioration in oxygen saturation and an increase in respiratory rate were observed with worsening anemia. Ragab et al. also demonstrated that infants with moderate and severe bronchiolitis had significantly lower Hb. and MCHC, with reduced serum iron and elevated TIBC in the severe group [18]. They identified Hb and serum iron as independent predictors of bronchiolitis severity, supporting the physiological plausibility that reduced oxygen-carrying capacity exacerbates hypoxemia and increases respiratory workload [18]. In the present work, the duration of hospital stays progressively increased with anemia severity. Sahu et al. similarly found that lower MCV, MCH, and serum iron levels in AB cases were correlated with prolonged hospitalization [19]. A study from Sri Lanka described the frequency of anemia to be significantly higher among children with acute LRTIs than controls (odds ratio: 1.6, $p = 0.045$). Oxygen support was needed in 75% of children with severe IDA in this study compared with 34% with mild IDA. There may be a role of IDA in impairing tissue oxygenation and respiratory muscle endurance, resulting in increased dependency on supplemental oxygen, but these assumptions require further research [20]. In this study, the severity of AB inversely correlated with Hb and directly with RDW, which may indicate greater erythrocyte size variability in severe anemia. Reported that RDW proportion was significantly higher among bronchiolitis patients compared to controls ($p < 0.050$) [21]. Multiple other studies have observed that anemia, particularly IDA, clearly increases the susceptibility to and severity of LRTIs

[9, 22]. The biological mechanism linking iron deficiency to severe bronchiolitis lies in impaired oxygen transport and altered immune defense [23]. Iron plays a pivotal role in cellular respiration, epithelial repair, and cytokine regulation. Deficiency results in decreased tissue oxygenation, diminished oxidative burst capacity of neutrophils, and impaired mucosal immunity [21, 24]. These physiological effects may collectively increase viral replication and inflammatory injury in bronchioles, leading to more severe clinical manifestations [25].

Single-centre study design with relatively modest sample size reduces the generalizability of these findings. The cross-sectional design restricted the ability to infer temporal causation between anemia and bronchiolitis severity. IDA diagnosis was based on hematological indices because iron profile testing, such as serum iron, ferritin, and transferrin saturation were not consistently feasible due to resource limitations. Longitudinal follow-up could clarify whether correction of anemia leads to improved clinical outcomes. It is suggested to conduct longitudinal and multicenter studies in the future to establish causal relationships and enhance generalizability. To improve the diagnostic accuracy, the complete iron profile parameters (e.g., serum ferritin, transferrin saturation) should be incorporated. Moreover, interventional research to evaluate the impact of early iron correction on bronchiolitis results is justified.

CONCLUSIONS

The severity of IDA was strongly associated with worse clinical presentation and delayed recovery in children with acute bronchiolitis. Lower Hb and microcytic indices correlated with higher Wang respiratory scores, greater oxygen support requirements, and longer hospital stays.

Authors' Contribution

Conceptualization: FZ

Methodology: RA

Formal analysis: RA

Writing and Drafting: RA, FZ, RM

Review and Editing: RA, FZ, RM

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Association Between Maternal Serum Ferritin Concentration and Risk of Gestational Diabetes Mellitus and Adverse Fetal Outcomes

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ARTICLE INFO

Keywords:

Gestational Diabetes Mellitus, Serum Ferritin, Pregnancy Outcomes, Macrosomia, Fetal Growth, Iron Supplementation, Maternal Health

How to Cite:

Naheed, N., Majeed, S., Iqbal, A., Noor, L., Noor, B., Javaria Majeed, & Attique, S. A. (2026). Association Between Maternal Serum Ferritin Concentration and Risk of Gestational Diabetes Mellitus and Adverse Fetal Outcomes: Maternal Serum Ferritin, GDM, and Adverse Fetal Outcomes. *Pakistan Journal of Health Sciences*, 7(8), 90-95. <https://doi.org/10.54393/pjhs.v7i8.3579>

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Received Date: 31st October, 2025

1st Revision Received: 12th December, 2025

2nd Revision Received: 28th February, 2026

3rd Revision Received: 27th March, 2026

Acceptance Date: 16th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Gestational diabetes mellitus (GDM) is a common pregnancy-related metabolic disorder linked to serious maternal and fetal complications. Rising evidence indicates that elevated maternal iron stores, especially serum ferritin, may contribute to GDM and adverse neonatal outcomes, yet data from South Asia, particularly Pakistan, are limited. **Objectives:** To evaluate the association between maternal serum ferritin concentrations at different gestational ages and the risk of GDM and adverse fetal outcomes. **Methods:** A retrospective cohort study of 146 singleton pregnancies at Combined Military Hospital Multan measured ferritin at 16–18 and 28–32 weeks. Participants were categorized into ferritin quartiles, GDM was diagnosed via a 75-g Oral Glucose Tolerance Test (OGTT), and logistic regression assessed associations after adjusting for key maternal covariates. **Results:** Higher mid-gestation serum ferritin levels demonstrated a significant relationship with increased risk of GDM (adjusted OR for Q4 vs. Q1: 1.43; $p=0.016$). Elevated ferritin was also linked to macrosomia (adjusted odds ratio (AOR)=2.01; 95% confidence interval (CI): 1.09–3.67), large for gestational age (LGA) infants (AOR=2.01; 95% CI: 1.09–3.72), and increased neonatal head circumference (AOR=2.70; 95% CI: 1.53–4.77). Although higher ferritin levels were associated with a reduced risk of small for gestational age (SGA) (AOR=0.44; 95% CI: 0.17–1.17), this association was not statistically significant. In late pregnancy, ferritin showed an inverse relationship with macrosomia, suggesting time-dependent effects. **Conclusions:** Elevated maternal serum ferritin levels during mid-pregnancy are associated with an increased risk of GDM and fetal overgrowth outcomes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is diagnosed during the second or third trimester of pregnancy with 16.7% prevalence worldwide [1]. GDM is most prevalent in the Southeast Asian region, with the highest rate of 27% and live births with the disease 2 [2]. It is more prominent in low-middle-income countries (LMIC) where access to maternity care is often inadequate [3]. According to a Pakistani study, the prevalence rate of cases of GDM was 13.9% among pregnant women in South Asian region [4]. A recent meta-analysis of 27,034 pregnant women reported

GDM prevalence of 16.7% in Pakistan, with provincial rates of 35.8% in Balochistan, 23.9% in Islamabad, 17.2% in Khyber Pakhtunkhwa, 13.2% in Sindh, and 11.4% in Punjab [5]. Iron is a trace element that serves the biological purpose of pregnant women and fetuses [6]. Incidentally, blood volume increases by approximately 50% and total red blood cell mass by about 25% during pregnancy, which leads to a tremendous iron deficiency [7, 8]. Therefore, expectant mothers are recommended to supplement their intake of iron during the gestation period to prevent iron



deficiency anemia [9]. However, increased iron stores can as well increase susceptibility to some conditions, particularly glucose metabolism diseases [10]. The excessive iron stores result in increased reactive oxygen species and develop insulin resistance along with impairment of insulin production [11]. Hence, the balance of the risks and benefits of iron stores augmentation during pregnancy requires further studies [12]. Serum ferritin level (SFL) is a major indication of stores of iron and plays a crucial role in controlling the systemic iron balance. It is used frequently in clinical assessment to establish body iron stores [13]. Various prospective studies have been conducted to determine the correlation existing between maternal ferritin levels and the development of GDM, the findings of which have often been contradictory [14].

In spite of the literature, there is no uniform and region-specific evidence on the role of maternal serum ferritin levels in relation to the timing of onset of GDM and poor fetal outcomes in Pakistan, which demonstrates a knowledge gap. This poses a clinical dilemma on whether iron supplementation should be balanced with possible metabolic dangers in pregnancy. Therefore, this retrospective study aimed to evaluate the association between maternal serum ferritin concentrations at different gestational ages and the risk of GDM, as well as to find the linkage between SFL and adverse fetal outcomes in a Pakistani population.

METHODS

A retrospective analysis was carried out involving 146 participants in the Combined Military Hospital, Multan, between March 2024 and March 2025. The sample size was calculated using the single population proportion formula; $n = Z^2 p(1-p)/d^2$, assuming a 20% prevalence (p) of GDM, 95% confidence level ($Z=1.96$), and 6.5% margin of error (d). Women at least 18 years old with confirmed singleton pregnancy and prenatal and delivery records were included. Exclusion criteria comprised multiple gestations, pre-existing diabetes, liver or renal disease (including

nephritis), cardiovascular disorders, and acute respiratory infections during pregnancy. Maternal and neonatal baseline and follow-up data, including adverse effects, were collected using structured questionnaires and verified with hospital records (Feb-Mar 2025). Birth measurements were recorded, and serum ferritin and hemoglobin levels were analyzed. Ferritin change was calculated as the difference between 28-32 and 16-18 weeks' concentrations. GDM was identified using a 75-g oral glucose tolerance test performed during the 24-28 weeks of the gestation period. The SFL in both gestation periods was analyzed in the same hospital lab through standardized laboratory practices [13]. Blood glucose levels were assessed at fasting, one hour, and two hours following glucose consumption. The thalassemia history and hemoglobin levels were extracted from antenatal clinical records and laboratory reports. Neonatal anthropometric measurements and adverse outcomes were obtained from delivery records. Premature rupture of membranes (PROM), low birth weight (LBW), and stillbirth were recorded based on standard obstetric documentation. There were four groups based on serum ferritin quartiles. Medians and interquartile ranges described continuous data, while percentages summarized categorical variables. The chi-square and Kruskal-Wallis tests assessed group differences for categorical and continuous values, respectively. A subgroup analysis compared GDM and non-GDM participants, referencing the highest ferritin quartile. SPSS version 28.0 was used with significance set at $p < 0.050$ (two-tailed). Before enrolment, every participant gave written informed consent. The ethical approval was obtained from the institutional Ethical Committee of Combined Military Hospital, Multan (ERC No. 09/2024/13/Trg; dated 12th January 2024). Surgical procedures were carried out in compliance with the Declaration of Helsinki.

RESULTS

The maternal age was similar in quartile ranges, with a median of 31.0-32.0 years. The median body mass index (BMI) was 20.5 kg/m², with 88.4% of women below 24.0 kg/m². Education was mainly college level and above (78.8%) and an equal distribution of quartiles ($p=0.477$). Smoking (0.7%) and alcohol use (0.7%) were not common. All pregnancies were natural (99.3%), with no substantial interquartile variation ($p=0.939$). Interestingly, there was a significant increase in fasting and 1-2-hour post-load glucose levels with the increase in serum ferritin concentrations ($p < 0.050$). GDM was most common in Q3 and Q4 (24% and 24% respectively) relative to 18-20% ($p=0.008$).

Table 1: Demographic and Baseline Characteristics of Participating Women

Characteristics	Total (n=146)	Q1 <18.32 µg/L (n=37)	Q2 18.32-31.34 µg/L (n=36)	Q3 31.34-55.90 µg/L (n=37)	Q4 >55.90 µg/L (n=36)	p-value
Maternal Age (Years)	30.0 (28.5, 34.0)	30.0 (28.5, 33.0)	33.0 (28.0, 34.0)	33.0 (28.0, 33.0)	32.0 (30.0, 33.0)	0.254
BMI (kg/m ²)	20.5 (18.8, 22.3)	20.4 (18.8, 22.1)	20.4 (18.8, 22.2)	20.6 (19.0, 22.3)	20.6 (18.8, 22.5)	0.634
BMI < 24.0 (n, %)	129 (88.4%)	33 (89.2%)	31 (86.1%)	33 (89.2%)	32 (88.9%)	0.527

BMI ≥ 24.0 (n, %)	17 (11.6%)	4 (10.8%)	5 (13.9%)	4 (10.8%)	4 (11.1%)	
Education – College & above	115 (78.8%)	28 (75.7%)	28 (77.8%)	30 (81.1%)	29 (80.6%)	0.477
Smoking status (n, %)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0.237
Alcohol consumption (n, %)	1 (0.7%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.018
Conception – Natural (n, %)	145 (99.3%)	36 (97.3%)	36 (100%)	37 (100%)	36 (100%)	0.939
Parity – Nulliparous (n, %)	108 (74.0%)	28 (75.7%)	26 (72.2%)	27 (73.0%)	27 (75.0%)	0.469
Abortion History (n, %)	47 (32.2%)	11 (29.7%)	12 (33.3%)	12 (32.4%)	12 (33.3%)	0.673
Thalassemia History (n, %)	8 (5.5%)	1 (4.0%)	1 (3.0%)	3 (9.0%)	2 (8.0%)	0.775
Delivery Time Gestational Age (Weeks)	38.5 (37.0, 41.0)	38.5 (37.0, 41.0)	38.5 (37.0, 41.0)	38.5 (37.0, 41.0)	38.5 (37.0, 41.0)	0.336
Hemoglobin (g/L)	116.0 (114.0, 120.0)	114.0 (112.0, 118.0)	116.0 (114.0, 120.0)	116.0 (114.0, 121.0)	116.5 (114.0, 121.0)	<0.001

There was an increasing birth weight and head circumference with an increasing level of maternal serum ferritin. The highest quartile recorded the most prevalence of macrosomia (>4000 g) and large for gestational age (LGA) infants (16% and 20% each; $p=0.020$ each). However, small for gestational age (SGA) incidence decreased in quartiles ($p=0.033$), with an inverse relationship with ferritin levels. There was a substantial difference in large head circumference, Q1 to Q4 of 4% to 24% ($p=0.002$), but no significant difference in small head circumference. There was a statistical comparison in the rates of LBW, stillbirth, and PROM, though PROM and stillbirth rates were lower in the highest quartile.

Table 2: Newborn and Adverse Outcomes

Newborn Characteristics	Total (n=146)	Q1 <18.32 $\mu\text{g/L}$ (n=37)	Q2 $18.32-31.34$ $\mu\text{g/L}$ (n=36)	Q3 $31.34-55.90$ $\mu\text{g/L}$ (n=37)	Q4 >55.90 $\mu\text{g/L}$ (n=36)	p-value
Male (n, %)	82 (56.2%)	14 (56%)	18 (55%)	19 (58%)	14 (56%)	0.855
Female (n, %)	64 (43.8%)	11 (44%)	15 (45%)	14 (42%)	11 (44%)	
Birth weight (g)	3300 (3085, 3530)	3280 (3050, 3515)	3300 (3080, 3520)	3320 (3100, 3550)	3340 (3100, 3570)	0.058
Head circumference (cm)	33.8 (33.0, 34.4)	33.6 (33.0, 34.2)	33.8 (33.0, 34.4)	33.9 (33.0, 34.4)	34.0 (33.0, 34.5)	0.043
Chest circumference (cm)	32.8 (32.0, 33.6)	32.8 (32.0, 33.5)	32.7 (32.0, 33.5)	32.8 (32.0, 33.6)	32.9 (32.0, 33.7)	0.201
Adverse effects in Mothers and Neonates						
PROM (n, %)	19 (13.0%)	3 (12%)	4 (12%)	4 (12%)	4 (16%)	0.020
GDM (n, %)	31 (21.2%)	5 (20%)	6 (18%)	8 (24%)	6 (24%)	0.008
Macrosomia (n, %)	15 (10.3%)	2 (8%)	3 (9%)	4 (12%)	4 (16%)	0.020
LBW (n, %)	6 (4.1%)	1 (4%)	1 (3%)	2 (6%)	1 (4%)	0.568
LGA (n, %)	20 (13.7%)	2 (8%)	4 (12%)	6 (18%)	5 (20%)	0.020
SGA (n, %)	10 (6.8%)	2 (8%)	2 (6%)	3 (9%)	1 (4%)	0.033
Stillbirth (n, %)	2 (1.4%)	0 (0%)	0 (0%)	1 (3%)	1 (4%)	0.178
Big head circumference (n, %)	21 (14.4%)	1 (4%)	3 (9%)	5 (15%)	6 (24%)	0.002
Small head circumference (n, %)	6 (4.1%)	1 (4%)	2 (6%)	2 (6%)	1 (4%)	0.842

During 16–18 weeks of gestation, as SFL increased across quartiles, the proportion of women diagnosed with GDM also rose from 6.3% in the lowest quartile to 8.8% in the highest quartile. The women in the highest serum ferritin quartile (>35.90 $\mu\text{g/L}$) had significantly higher odds of developing GDM compared to those in the lowest quartile (adjusted odds ratio (AOR): 1.43), with a clear positive trend across quartiles ($p=0.016$).

Table 3: Association Between Maternal Serum Ferritin and GDM

Variables	Q1 <18.32 $\mu\text{g/L}$ (n=37)	Q2 $18.32-31.34$ $\mu\text{g/L}$ (n=36)	Q3 $31.34-55.90$ $\mu\text{g/L}$ (n=37)	Q4 >55.90 $\mu\text{g/L}$ (n=36)	p-value	Per-SD Increase
n (%)	8 (6.3%)	8 (6.3%)	9 (6.9%)	12 (8.8%)	—	—
OR (95% CI)	1.00 (ref)	1.12 (0.84–1.48)	1.06 (0.80–1.40)	1.46 (1.11–1.92)	0.020	1.15 (1.05–1.27)
Multivariable Model	1.00 (ref)	1.05 (0.78–1.41)	1.01 (0.76–1.35)	1.43 (1.08–1.91)	0.016	1.15 (1.05–1.26)

Higher levels of serum ferritin in the mother at 16–18 weeks of gestation were strongly correlated with bad perinatal outcomes. Prevalence of PROM increased in the four quartiles up to 2.7% in the highest group ($p=0.014$). High levels of ferritin were also associated with increased risks of macrosomia and LGA, and both showed significant trends ($p=0.020$), with crude and adjusted odds ratios showing greater than twofold increases in the highest quartile. Conversely, SGA incidence decreased with a rise in ferritin, with an 0.7% in Q4 ($p=0.033$). Big head circumference escalated by quartiles ($p=0.002$), but little association was observed with small head circumference.

Table 4: Association Between Maternal Serum Ferritin Levels and Adverse Effects in Mothers and Neonates(16-18 Weeks)

Outcomes	Q1 <18.32 µg/L (n=37)	Q2 18.32-31.34 µg/L (n=36)	Q3 31.34-55.90 µg/L (n=37)	Q4 >55.90 µg/L (n=36)	p-value	Per-SD Increase
Premature Birth	2 (1.4%)	2 (1.4%)	2 (1.4%)	2 (1.4%)	0.903	1.08 (0.91-1.27)
OR (95% CI)	1.00 (ref)	1.01 (0.48-2.10)	0.98 (0.47-2.07)	1.21 (0.71-2.05)		
AOR (95% CI)	1.00 (ref)	1.01 (0.47-2.16)	0.97 (0.46-2.06)	1.20 (0.70-2.06)		
PROM	3 (2.1%)	3 (2.1%)	3 (2.1%)	4 (2.7%)	0.014	1.18 (1.03-1.34)
OR (95% CI)	1.00 (ref)	1.13 (0.63-2.01)	1.14 (0.63-2.06)	1.81 (1.16-2.83)		
AOR (95% CI)	1.00 (ref)	1.15 (0.63-2.12)	1.14 (0.63-2.08)	1.82 (1.16-2.84)		
Macrosomia	2 (1.4%)	2 (1.4%)	3 (2.1%)	4 (2.7%)	0.020	1.19 (1.02-1.39)
OR (95% CI)	1.00 (ref)	1.13 (0.56-2.30)	1.69 (0.93-3.07)	2.00 (1.10-3.64)		
AOR (95% CI)	1.00 (ref)	1.14 (0.56-2.32)	1.66 (0.91-3.03)	2.01 (1.09-3.67)		
LGA	3 (2.1%)	4 (2.7%)	5 (3.4%)	5 (3.4%)	0.020	1.15 (1.03-1.30)
OR (95% CI)	1.00 (ref)	1.48 (0.77-2.82)	2.11 (1.15-3.89)	2.00 (1.09-3.69)		
AOR (95% CI)	1.00 (ref)	1.48 (0.77-2.83)	2.12 (1.15-3.91)	2.01 (1.09-3.72)		
SGA	2 (1.4%)	2 (1.4%)	1 (0.7%)	1 (0.7%)	0.033	0.86 (0.75-0.99)
OR (95% CI)	1.00 (ref)	0.96 (0.45-2.06)	0.47 (0.18-1.22)	0.45 (0.17-1.18)		
AOR (95% CI)	1.00 (ref)	0.96 (0.44-2.07)	0.47 (0.18-1.22)	0.44 (0.17-1.17)		
Big Head Circumference	2 (1.4%)	3 (2.1%)	4 (2.7%)	6 (4.1%)	0.002	1.24 (1.08-1.42)
OR (95% CI)	1.00 (ref)	1.28 (0.70-2.35)	2.01 (1.13-3.58)	2.71 (1.54-4.79)		
AOR (95% CI)	1.00 (ref)	1.28 (0.69-2.36)	2.00 (1.12-3.58)	2.70 (1.53-4.77)		
Small Head Circumference	1 (0.7%)	2 (1.4%)	2 (1.4%)	1 (0.7%)	0.654	0.91 (0.70-1.18)
OR (95% CI)	1.00 (ref)	1.92 (0.82-4.47)	1.92 (0.83-4.46)	0.96 (0.35-2.62)		
AOR (95% CI)	1.00 (ref)	1.92 (0.82-4.48)	1.92 (0.83-4.47)	0.95 (0.34-2.61)		

DISCUSSION

This research investigated the connections between SFL among pregnant women and the risks of GDM and neonatal adverse effects. The greater serum levels of ferritin at 16-18 weeks were correlated with much higher odds of GDM (adjusted OR of Q4 vs. Q1=1.43; $p=0.016$), macrosomia (AOR=2.01; 95% CI: 1.093.67), LGA (AOR=2.01; 95% CI: 1.093.72) and large head circumference (AOR=These findings are similar to the Xie et al. who provided the results on a prospective study with 2,361 pregnant women in the multi-ethnic cohort in the United States. Their analysis estimated serum ferritin values at 10 weeks and 14-weeks of gestation and concluded that the highest quartile of women had a 2.43-fold higher risk of GDM (95% CI: 1.583.72) with no effect on BMI, age, race, dietary iron, and CRP [15]. Likewise, another research of 1,143 pregnant women in China, Fan et al. found that GDM was more prevalent in higher SFL (>70 ng/mL) during early pregnancy. Their adjusted OR associated with GDM in the highest quartile is 3.17 (95% CI: 1.74- 5.76), which is significantly higher than this study's findings. However, dose-response correlation was similar to this study ($p=0.016$) [16]. Differences in ferritin cut-offs, background iron deficiency, and population characteristics may account for this variation, highlighting the need for population-specific ferritin thresholds for GDM risk prediction [17]. Conversely, we do not find the same results as Gautam et al. who in their study assessed 570 pregnant women in Colombia and did not find

significant correlations between the levels of ferritin in the first trimester and GDM in the post-partum period after controlling for the level of BMI and markers of inflammation. Their research stated an OR of 1.12 (95% CI: 0.761.66) of GDM among females with an SFL over 45 ng/mL [18]. This study also found that increased SFL at 16-18 weeks was linked with increased probabilities of macrosomia (more than 4000 g) and LGA infants. This agrees with the results of Zhang et al. who provided a prospective cohort study on 328 pregnant Turkish women. They reported that the ferritin level over 60 ng/mL showed a significant correlation with both the macrosomia (OR = 2.89; 95% CI: 1.23-6.77) and the high level of cord blood insulin, which indicated the mediation of a ferritin level by intrauterine hyperglycemia [19]. Furthermore, the negative correlation between high serum ferritin and SGA babies in our cohort (AOR in Q4=0.44; 95% CI: 0.171.17) is a reflection of the Li et al. study. They discovered that low periconceptual ferritin (<12 µg/L) was also significantly related to high risk of SGA (OR=1.96; 95% CI: 1.263.05) that was probably mediated by maternal anemia and placental oxygen delivery [20].

However, this study has some limitations, i.e., small sample size ($n=146$), retrospective design, and lack of inflammatory markers (e.g., CRP), which confound ferritin interpretation. So, a single-center military setting may limit generalizability. Future large-scale, multicenter

prospective studies incorporating inflammatory and nutritional biomarkers are recommended to establish population-specific ferritin thresholds and clarify the causal relationship between maternal iron status, GDM, and adverse neonatal outcomes.

CONCLUSIONS

This research found that elevated maternal SFL during the mid-gestational period was linked to a greater likelihood of developing GDM. Elevated ferritin was also significantly associated with macrosomia, large for gestational age infants, and increased neonatal head circumference; however, no statistically significant association was observed with small for gestational age.

Authors' Contribution

Conceptualization: SM

Methodology: AI

Formal analysis: NN, LN, BG, JM

Writing and Drafting: NN

Review and Editing: NN, SM, AI, LN, BG, JM, SAA

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Prognostic Factors Associated with Renal Survival in Children with Rapidly Progressive Glomerulonephritis

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ARTICLE INFO

Keywords:

Rapidly Progressive Glomerulonephritis, Renal Prognosis, Crescent, Fibrous Crescent, Hypertension

How to Cite:

Safdar, R. S., Fayyaz, A., Irshad, S., Qaiser, T., Amjad, K., & Maab, G. (2026). Prognostic Factors Associated with Renal Survival in Children with Rapidly Progressive Glomerulonephritis: Renal Survival in Children with Rapidly Progressive Glomerulonephritis. *Pakistan Journal of Health Sciences*, 7(8), 97-101. <https://doi.org/10.54393/pjhs.v7i8.3934>

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Received Date: 5th February, 2026

1st Revision Received: 25th February, 2026

2nd Revision Received: 7th April, 2026

Acceptance Date: 17th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Rapidly progressive glomerulonephritis (RPGN) is a severe pediatric renal disorder characterized by rapid deterioration in kidney function. In low-resource settings such as Pakistan, delayed presentation and limited access to specialized nephrology services may adversely affect renal outcomes. **Objectives:** To identify clinical, serological, histopathological, and healthcare access-related predictors of renal survival in children diagnosed with RPGN. **Methods:** This prospective observational cohort study was conducted at the Department of Pediatric Nephrology, The Children's Hospital and Institute of Child Health, Multan, between 15 February 2025 and 15 October 2025. All patients were followed for three months after confirmation of diagnosis. Children aged 1–18 years diagnosed with RPGN were consecutively enrolled after informed consent. Participants were followed for three months from diagnosis or until development of end-stage kidney disease (ESKD), whichever occurred first. Multivariable logistic regression was used to identify independent predictors of ESKD. **Results:** Among 110 enrolled children, 78 (70.9%) achieved renal survival, while 32 (29.1%) progressed to ESKD. Patients developing ESKD had significantly lower baseline estimated glomerular filtration rate (eGFR), higher serum creatinine and urine protein-to-creatinine ratio, longer delay before nephrology consultation, and greater crescent burden on biopsy (all $p \leq 0.006$). **Conclusions:** Histopathological severity, impaired baseline renal function, hypertension, and treatment delay are key determinants of short-term renal survival in pediatric RPGN.

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a severe and potentially life-threatening form of glomerular disease characterized by rapid deterioration of renal function over days to weeks. In low- and middle-income countries, including Pakistan, delayed presentation of pediatric renal disease remains common, often due to limited access to specialized nephrology services and financial constraints [1, 2]. These systemic barriers contribute to advanced disease at first evaluation and adversely affect renal outcomes. Pathologically, pediatric RPGN is defined by a rapid decline in glomerular filtration rate accompanied by

crescent formation in the majority of glomeruli on renal biopsy [3]. Crescent formation occurs following disruption of the glomerular capillary wall, leading to fibrin leakage and inflammatory cell migration into Bowman's space, with subsequent proliferation of parietal epithelial cells that compress the glomerular tuft [4]. The principal immunopathological categories include antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-glomerular basement membrane (anti-GBM) disease, and immune-complex-mediated disorders such as lupus nephritis and infection-related glomerulonephritis [5].



Early diagnosis and prompt initiation of immunosuppressive therapy are critical determinants of renal recovery. KDIGO guidelines emphasize urgent biopsy, rapid induction therapy, and strict blood pressure control to prevent irreversible renal damage [6]. Delays in recognition or treatment may result in progression to end-stage kidney disease (ESKD). Several international studies have identified key prognostic factors in pediatric crescentic glomerulonephritis. An Indian cohort study reported lupus nephritis as the most common etiology, accounting for approximately 45% of cases, with nearly one-third progressing to chronic kidney disease or renal failure; higher crescent percentage and delayed presentation were associated with poorer renal survival [7]. Similarly, a multicenter cohort from North America demonstrated that greater crescent burden and reduced baseline estimated glomerular filtration rate (eGFR) were independently associated with adverse renal outcomes [8]. European registry data further confirmed that hypertension at biopsy, more than 50% crescents, and low baseline eGFR significantly increase the risk of renal failure [9]. In children with ANCA-associated vasculitis, long-term follow-up studies report renal failure in up to 25–40% of patients, particularly in those presenting with severe initial renal impairment [10,11].

Although several international studies have reported prognostic factors in pediatric rapidly progressive glomerulonephritis, most data come from high-income countries and may not reflect the healthcare realities in Pakistan. The rationale of this study was to address this local evidence gap. This study aimed to identify clinical, histopathological, and healthcare-related predictors of short-term renal survival in Pakistani children with RPGN.

METHODS

This was a prospective observational cohort study conducted at the Department of Pediatric Nephrology, The Children's Hospital, and The Institute of Child Health, Multan. The study was hospital-based and single-centered. Participants were recruited consecutively between February 2025 and October 2025, and all eligible children presenting during this period were invited to participate. The study received ethical approval before commencement under (Ref no:194; dated 1st February 2025). Written informed consent was obtained for all participants, and confidentiality was maintained in accordance with institutional guidelines. Because of limited local data on prognostic outcomes in pediatric RPGN, the sample size was estimated using a single-proportion approach based on the reported frequency of adverse renal outcomes in a comparable regional cohort [12]. It is acknowledged that this method is not ideal for multivariable prognostic modeling; therefore, the number

of predictors included in the final regression model was restricted to minimize overfitting. Using the World Health Organization sample size calculator, with a 95% confidence level and 5% margin of error, and an expected ESKD frequency of 7.7% [12], the required sample size was calculated as 110 children. Each participant was followed for three months from diagnosis or until development of end-stage kidney disease (ESKD), whichever occurred earlier. Children aged 1–18 years diagnosed with RPGN were included after written informed consent from a parent or legal guardian. Diagnosis was based on rapid deterioration in renal function, supported by clinical findings and laboratory evidence. Children with pre-existing ESKD, prior kidney transplantation, known congenital renal anomalies, or conditions precluding biopsy or standard treatment were excluded. A control group was not included, as the study focused specifically on prognostic factors within the affected cohort. Serological tests included ANCA, anti-GBM antibodies, complement levels (C3 and C4), and serum albumin. Kidney biopsy was performed when clinically indicated, and samples were evaluated by an experienced histopathologist who reported the percentage of crescents and the presence of fibrous crescents. Hypertension was defined as systolic or diastolic blood pressure ≥ 95 th percentile for age, sex, and height. Hypocomplementemia was defined as serum C3 and/or C4 levels below the institutional reference range. eGFR was expressed in mL/min/1.73 m² in accordance with KDIGO standards, and renal impairment was defined as eGFR <60 mL/min/1.73 m². Normality of continuous variables was assessed using the Shapiro–Wilk test and visual inspection. Normally distributed variables were summarized as mean $\pm$ standard deviation, while non-normally distributed data were expressed as median with interquartile range. Categorical variables were presented as frequencies and percentages. Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminatory performance of the final multivariable logistic regression model for predicting progression to end-stage kidney disease (ESKD). Model discrimination was quantified by calculating the area under the ROC curve (AUC) with 95% confidence intervals. An AUC of 0.5 indicated no discrimination, whereas higher values reflected better predictive ability. Model calibration was assessed separately to evaluate the agreement between predicted and observed outcomes.

Statistical analysis was performed using IBM SPSS version 26.0. Descriptive analysis was followed by appropriate inferential testing based on data distribution. Associations between biopsy findings, treatment delay, and renal function were examined. Variables with $p < 0.100$ in univariate analysis and clear clinical relevance were entered into the multivariable logistic regression model.

Statistical significance was set at $p < 0.005$. Before multivariable modeling, multicollinearity was assessed using variance inflation factors (VIF) and tolerance statistics. Serum creatinine was excluded from the regression model due to strong correlation with eGFR. All retained variables demonstrated VIF values below 2.5, indicating the absence of significant multicollinearity. The assumption of linearity in the logit was formally evaluated for continuous predictors included in the multivariable logistic regression model. In particular, baseline eGFR and time to induction therapy were assessed using Box-Tidwell transformation terms. As no statistically significant deviation from linearity was identified, both variables were retained as continuous linear terms in the final model. Given the exploratory nature of univariate comparisons, formal adjustment for multiple testing was not applied. These analyses were primarily used to identify clinically relevant variables for multivariable modeling rather than to establish independent effects.

RESULTS

A total of 110 children were enrolled in the study. Out of these, 78 (70.9%) achieved renal survival, while 32 (29.1%) progressed to end-stage kidney disease (ESKD) during follow-up. There were no drop-outs, and all participants were included in the final analysis. Participants were categorized into two outcome groups: renal survival and ESKD. Mean age did not differ significantly between the groups. Similarly, diastolic blood pressure z-scores were comparable. However, systolic blood pressure z-scores

were significantly higher in children who progressed to ESKD. Several key clinical variables showed non-normal distribution and differed meaningfully between outcome groups. These included estimated glomerular filtration rate (eGFR), serum creatinine, urine protein-to-creatinine ratio (UPCR), duration from symptom onset to nephrology consultation, distance traveled to the tertiary center, percentage of glomerular crescents, and time to initiation of induction therapy. The most pronounced differences were observed in baseline eGFR and serum creatinine, reflecting more severe renal impairment at presentation among children who later developed ESKD. Correlation analysis showed that crescent percentage positively correlated with UPCR and inversely correlated with eGFR. Longer delay in induction therapy was associated with lower eGFR. On multivariable analysis, higher crescent percentage, presence of fibrous crescents, lower baseline eGFR, hypertension, and delayed induction therapy independently predicted ESKD. Model calibration was satisfactory. Formal assessment of the linearity-in-the-logit assumption showed no significant departure from linearity for baseline eGFR and time to induction therapy. Box-Tidwell transformation terms for these predictors were not statistically significant. Accordingly, both variables were entered into the final multivariable logistic regression model as continuous linear predictors. Summarizes continuous variables using appropriate parametric and non-parametric tests with corresponding p-values and confidence intervals (Table 1).

Table 1: Descriptive and Comparative Statistics for Continuous Variables by Renal Outcome (Renal Survival n=78; End-Stage Kidney Disease n=32; Total n=110)

Variables	Shapiro-Wilk W (p)	Total	Renal survival (n=78)	End-Stage Kidney Disease (n=32)
Age, Years*	0.973 (0.072)	11.3 ± 3.7	10.9 ± 3.8	12.2 ± 3.4
Systolic BP z Score*	0.981 (0.118)	1.12 ± 0.86	0.98 ± 0.79	1.44 ± 0.90
Diastolic BP z Score*	0.977 (0.095)	0.91 ± 0.74	0.86 ± 0.70	1.03 ± 0.81
eGFR, mL/min/1.73 m ²	0.881 (<0.001)	48.6 (31.8–63.4)	55.1 (41.0–68.0)	28.9 (21.4–39.6)
Serum Creatinine, mg/dL	0.864 (<0.001)	2.3 (1.6–3.5)	1.9 (1.4–2.7)	3.9 (3.1–5.0)
UPCR, mg/mg	0.842 (<0.001)	2.7 (1.9–3.8)	2.4 (1.7–3.2)	3.6 (2.8–4.6)
Symptom-to-Nephrology, Days	0.891 (<0.001)	12 (7–22)	10 (6–18)	19 (12–29)
Crescents on Biopsy, %	0.903 (<0.001)	58 (42–72)	51 (38–64)	74 (62–86)
Time to Induction, Days	0.892 (<0.001)	3 (2–6)	3 (2–5)	5 (3–8)

Values Are Mean ± SD For Normally Distributed Data and Median (IQR) For Non-Normal Data. BP, Blood Pressure; Egfr, Estimated Glomerular Filtration Rate; UPCR, Urine Protein-To-Creatinine Ratio

Contains the categorical variables and counts and percentages of different groups of renal survival and end-stage kidney disease. It utilized the chi-square or Fisher's exact test as determined by the data distribution. Where necessary, reference categories were defined, and precise p-values were stated (Table 2).

Table 2: Categorical Variables by Renal Outcome with Comparative Testing (Renal Survival n=78; End-Stage Kidney Disease n=32; Total n=110)

Variables	Total, n (%)	Renal Survival, n (%)	End-stage Kidney Disease, n (%)	p value
Sex (Male)	57 (51.8%)	39 (50.0%)	18 (56.3%)	0.640

Oliguria (Yes)	71 (64.5%)	43 (55.1%)	28 (87.5%)	0.007
Macroscopic Hematuria (Yes)	59 (53.6%)	43 (55.1%)	16 (50.0%)	0.549
Hypertension $\geq$ 95th Percentile (Yes)	63 (57.3%)	40 (51.3%)	23 (71.9%)	0.013
Nephrotic-Range Proteinuria (Yes)	74 (67.3%)	48 (61.5%)	26 (81.3%)	0.026
Low Complement C3 (Yes)	46 (41.8%)	31 (39.7%)	15 (46.9%)	0.348
Low Complement C4 (Yes)	19 (17.3%)	14 (17.9%)	5 (15.6%)	0.663
Anca Positive (Yes)	28 (25.5%)	19 (24.4%)	9 (28.1%)	0.269
Anti-GBm Positive (Yes)	10 (9.1%)	3 (3.8%)	7 (21.9%)	0.021
Kidney Biopsy Performed (Yes)	104 (94.5%)	73 (93.6%)	31 (96.9%)	0.692
Biopsy Pattern: Pauci-Immune (Ref Immune-Complex)	35 (31.8%)	20 (25.6%)	15 (46.9%)	0.010
Fibrous Crescents Present (Yes)	39 (35.5%)	19 (24.4%)	20 (62.5%)	0.002
Acute Dialysis at Presentation (Yes)	31 (28.2%)	14 (17.9%)	17 (53.1%)	0.004
Adherence $\geq$ 80% (Ref Good)	71 (64.5%)	56 (71.8%)	15 (46.9%)	0.018
Induction Regimen: Steroids Only (Ref Cyclophosphamide)	22 (20.0%)	15 (19.2%)	7 (21.9%)	0.219

Chi-Square Was Applied Unless the Symbol Stated that the Fisher Exact Test Was Used Because There Were Small Expected Counts; ANCA Refers to Antineutrophil Cytoplasmic Antibody; Anti-GBM Refers to Anti-Glomerular Basement Membrane

It shows the outcome of an end-stage kidney disease of a multivariate binary logistic regression model on the covariates, prespecified. Adjusted odds ratios, which have 95% confidence intervals, as well as exact p-values, are provided (Table 3).

Table 3: Multivariable Logistic Regression for End-Stage Kidney Disease (n=110)

Predictors	Adjusted OR (95% CI)	p-value
Crescents On Biopsy, Per 1% Increase	1.06 (1.03–1.09)	<0.001
Fibrous Crescents Present (Yes Vs No)	3.42 (1.48–7.91)	0.004
Egfr, per 1 ml/min/1.73 m ² Increase	0.96 (0.94–0.98)	<0.001
Hypertension $\geq$ 95th Percentile (Yes Vs No)	2.11 (1.02–4.37)	0.044
Time To Induction, Per Day	1.12 (1.01–1.25)	0.034
ANCA Positive (Yes Vs No)	1.28 (0.55–2.95)	0.570
Anti-GBM Positive (Yes Vs No)	2.49 (0.76–8.16)	0.129

It is a correlation and subgroup analysis based on a priori methodological criteria. Spearman rank correlations were used to evaluate non-normal variables, but Pearson product-moment correlations were used to evaluate variables that met the standards of normality. Some correlations were also found to be modest between age and systolic blood pressure z-score as well (Table 4).

Table 4: Correlation and Subgroup Analyses (n=110)

Analysis	Coefficient (95% CI)	Test statistic (p)
Crescents (%) vs UPCR (Spearman ρ)	0.34 (0.16 to 0.50)	$\rho = 0.34$ ($p < 0.001$)
Time to induction (days) vs eGFR (Spearman ρ)	-0.29 (-0.45 to -0.11)	$\rho = -0.29$ ($p = 0.002$)
Age vs systolic BP z score (Pearson r)	0.21 (0.02 to 0.38)	$r = 0.21$ ($p = 0.026$)

Bp- Blood Pressure, Egfr- Estimated Glomerular Filtration Rate

Shows the receiver operating characteristic (ROC) curve for the final multivariable logistic regression model predicting progression to end-stage kidney disease in

children with rapidly progressive glomerulonephritis. The model demonstrated good discrimination, with an area under the curve of 0.84 (95% CI 0.76–0.91) (Figure 1).

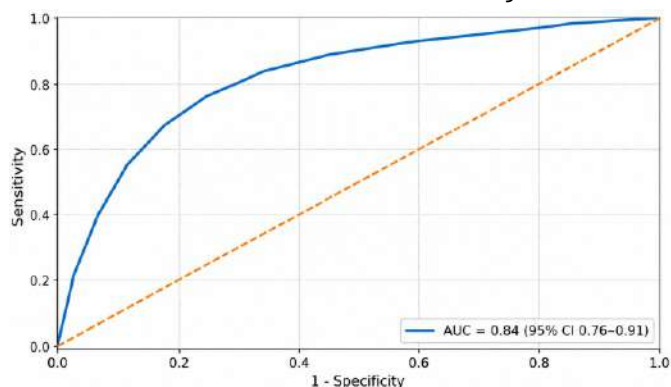


Figure 1: ROC Curve for Predicting Progression to ESKD

DISCUSSION

The main findings of this study highlight the combined influence of disease severity and healthcare access on short-term renal outcomes in children with RPGN. Better renal survival was associated with lower crescent burden, absence of fibrous crescents, higher baseline eGFR, lower systolic blood pressure z-scores, and shorter delay before initiation of induction therapy. In contrast, children requiring acute dialysis at presentation or those positive for anti-GBM antibodies were more likely to progress to ESKD. Differences in health coverage and distance to care further suggest that access-related factors contribute meaningfully to outcomes. Poor early adherence was also more common among those with adverse outcomes. The positive correlation between crescent burden and proteinuria, and the inverse association between treatment delay and eGFR, reinforce the role of both intrinsic disease severity and system-level delays. Our findings align with regional data. Indian cohorts have similarly demonstrated that higher crescent percentage,

fibrous crescents, and delayed presentation predict poorer renal survival [13, 14]. Chinese studies report worse outcomes in anti-GBM-predominant disease and in cases with chronic histological changes at diagnosis [15]. Immune-complex-mediated disease was more frequent among children with renal survival in our study, consistent with previous regional observations [16]. International literature further supports these associations. Greater crescent burden, hypertension at biopsy, reduced baseline eGFR, and fibrous crescents are recognized predictors of renal failure [17]. Severe initial injury in ANCA-associated vasculitides and anti-GBM disease is linked to poorer outcomes. Current recommendations emphasize early biopsy, timely induction therapy, and strict blood pressure control [18]. Our findings support these principles and underscore the additional relevance of healthcare access in low- and middle-income settings. Clinically, readily available indicators such as hypertension, oliguria, and baseline eGFR may aid early risk stratification while awaiting histopathology. Larger regional collaborations could further refine time-to-biopsy and induction benchmarks [19, 20].

This study has important limitations. As a single-center tertiary-care cohort, referral bias is likely, with possible overrepresentation of severe cases. The single-center design limits generalizability beyond similar hospital settings. Despite multivariable adjustment, residual confounding from unmeasured socioeconomic, genetic, or treatment-related factors cannot be excluded. Additionally, the modest number of outcome events may affect the precision of regression estimates. The sample size was based on a prevalence approach rather than a dedicated prognostic modeling framework. The relatively modest events-per-variable ratio may affect model stability, and findings should be interpreted with caution.

CONCLUSIONS

In this single-center cohort of children with RPGN, greater crescent burden, fibrous crescents, baseline hypertension, lower baseline eGFR, and delayed initiation of induction therapy independently predicted poorer short-term renal survival. These findings may assist risk stratification in comparable tertiary-care settings; however, multicenter studies are needed to confirm broader applicability.

Acknowledgement

The authors would like to acknowledge Mr. Muhammad Muawaz for his help in the statistical analysis of the manuscript.

Authors' Contribution

Conceptualization: RSS, AF

Methodology: KA, GM

Formal analysis: SI, TQ, RSS

Writing and Drafting: KA, TQ, GM, RSS

Review and Editing: KA, TQ, GM, RSS, SI, TQ, RSS

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Frequency of Thrombocytopenia and Its Etiologies in the Last Trimester of Pregnancy

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ARTICLE INFO

Keywords:

Thrombocytopenia, Pregnancy, Gestational Thrombocytopenia, Hypertensive Disorders of Pregnancy, Platelet Count

How to Cite:

Fatima, T., Zulfiqar, S., Younas, S., Anjum, F., & Shoukat, S. (2026). Frequency of Thrombocytopenia and Its Etiologies in the Last Trimester of Pregnancy: Frequency and Causes of Third Trimester Thrombocytopenia. *Pakistan Journal of Health Sciences*, 7(8), 102-108. <https://doi.org/10.54393/pjhs.v7i8.3867>

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Received Date: 21st January, 2026

1st Revision Received: 12th March, 2026

Acceptance Date: 8th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Thrombocytopenia is a frequent hematological abnormality in late pregnancy with diverse etiologies and potential maternal-fetal implications. **Objective:** To determine the frequency of thrombocytopenia and its etiologies in pregnant women in the last trimester. **Methods:** A descriptive cross-sectional study was conducted in the Department of Obstetrics and Gynecology, Sheikh Zayed Hospital, Rahim Yar Khan, from June to December 2025. A total of 210 pregnant women in the third trimester were enrolled through non-probability consecutive sampling. Demographic and obstetric data were recorded, and platelet counts were assessed using a complete blood count. Thrombocytopenia severity and etiologies were determined using standardized clinical and laboratory criteria. **Results:** Among 210 women evaluated in the last trimester, the mean maternal age was 29.63 ± 5.03 years, and the mean gestational age was 36.46 ± 3.21 weeks. Mean gravidity and parity were 2.79 ± 1.26 and 1.90 ± 1.26 , respectively, with overall platelet count $210.26 \pm 57.04 \times 10^3/\mu\text{L}$. Thrombocytopenia was detected in 26 (12.4%). Platelet counts differed significantly between thrombocytopenia and non-thrombocytopenia groups (115.73 ± 32.45 vs $223.61 \pm 46.08 \times 10^3/\mu\text{L}$; $p < 0.001$). Severity was mild in 18 (69.2%), moderate in 6 (23.1%), and severe in 2 (7.7%). Gestational thrombocytopenia predominated (57.7%), followed by pre-eclampsia (11.5%), eclampsia (7.7%), disseminated intravascular coagulation (7.7%), infection-related causes (7.7%), HELLP syndrome (3.8%), and immune thrombocytopenic purpura (3.8%) overall. **Conclusions:** Thrombocytopenia affected 12.4% of late-pregnancy women, mostly mild. Gestational thrombocytopenia predominated, with smaller contributions from hypertensive disorders, disseminated intravascular coagulation, and infections.

INTRODUCTION

Pregnancy is a physiological phenomenon of human reproduction, which brings about various changes in the normal physiological functions of the body [1]. Amongst hematological changes, thrombocytopenia or reduced platelet count is one of the most commonly encountered changes in pregnant women [2]. It has been reported in a bulletin of the "American College of Obstetrics and Gynecology" that 12% pregnant women develop thrombocytopenia of some severity, which can either be due to a physiologic process or can indicate a serious underlying pathology that can pose a serious risk to mother and fetus [3]. In Pakistan, hospital-based data show wide

variation in late-pregnancy thrombocytopenia prevalence (2–40%), depending on case mix and inclusion criteria, with most cases occurring in the third trimester and gestational thrombocytopenia being the leading cause [4, 5]. Thrombocytopenia, defined as a platelet count below $150,000/\mu\text{L}$, is a frequent hematological abnormality in pregnancy and is often detected during late gestation when physiological haemodilution and increased platelet consumption contribute to a decline in circulating platelets [6, 7]. In clinical obstetrics, severity is commonly stratified as mild ($100,000$ to $149,000/\mu\text{L}$), moderate ($50,000$ to $99,000/\mu\text{L}$), and severe ($<50,000/\mu\text{L}$) because of an

underlying pathological process, and the anticipated bleeding risk rises as platelet levels fall [8]. Gestational thrombocytopenia causes about 40%–75% of pregnancy thrombocytopenia, is usually mild, presents in the late second or third trimester, and resolves postpartum [9]. Hypertensive disorders, particularly preeclampsia and HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet syndrome), account for roughly 10%–30%, are often moderate to severe, and are linked with preterm birth, placental abruption, and stillbirth [10]. Immune thrombocytopenia, including immune thrombocytopenic purpura, contributes about 3%–17% overall and is a major cause of platelets $<50 \times 10^9/L$, often presenting earlier [11]. A study conducted in Pakistan reported that the frequency of thrombocytopenia in pregnant women was 10.5% [12]. Another study, in addition to these, reported a frequency of etiological factors of thrombocytopenia in pregnant women, including gestational thrombocytopenia (57.50%), pre-eclampsia (16.10%), eclampsia (16.10%), HELLP syndrome (12%), disseminated intravascular coagulation (3.40%), and immune thrombocytopenic purpura (3.30%) [13].

A gap persists in locally generalizable evidence, quantifying the frequency and severity of thrombocytopenia specifically in the last trimester and simultaneously characterizing its major etiologies using uniform, predefined clinical and laboratory criteria, as existing reports show wide variability by setting and diagnostic workup. This limits risk stratification and timely etiological evaluation during the last trimester, when thrombocytopenia may reflect benign gestational change or serious hypertensive, consumptive, immune, or infection-related pathology with maternal-fetal implications. Therefore, the present study aimed to determine the frequency and severity of thrombocytopenia among last trimester of pregnant women and to find the major etiologies of thrombocytopenia.

METHODS

A descriptive cross-sectional study was conducted in the Department of Obstetrics and Gynecology, Sheikh Zayed Hospital, Rahim Yar Khan, over six months from June to December 2025. Ethical approval was obtained from the institutional review committee (779/IRB/SZMC/SZH; dated 21st September 2023). Non-probability consecutive sampling was used to recruit eligible pregnant women presenting for routine antenatal care, scheduled delivery, or general obstetric evaluation in the third trimester. The sample size of 210 was calculated using the World Health Organization sample size calculator by assuming a 95% confidence level, 3.5% margin of error, and an anticipated frequency of thrombocytopenia in term pregnant women

of 7.20% [14]. Pregnant women aged 16 to 45 years with singleton pregnancy confirmed on obstetric ultrasound and gestational age at or above 26 weeks based on last menstrual period or dating scan were included, irrespective of blood pressure status. Women with multiple pregnancy on obstetric ultrasound, documented medical comorbidities including smoking, diabetes mellitus, chronic liver disease, or chronic renal failure, pre-existing thrombocytopenia such as idiopathic thrombocytopenic purpura, and known hematological disorders associated with thrombocytopenia, including aplastic anemia or leukemia, were excluded. At enrolment, after taking written informed consent, demographic and obstetric variables, including maternal age, gestational age, gravidity, and parity, were recorded on the study proforma. A 3 mL venous blood sample was collected under aseptic precautions and transferred to a complete blood count vial for platelet count assessment in the hospital laboratory, which served as the primary assessing tool. Thrombocytopenia was defined as a platelet count below $150,000/mm^3$ measured on a complete blood count, and severity was categorized as mild ($100,000$ to $149,000/mm^3$), moderate ($50,000$ to $99,000/mm^3$), and severe ($<50,000/mm^3$). Samples with thrombocytopenia on complete blood count were rechecked by repeat platelet estimation to exclude pseudothrombocytopenia. In women identified with thrombocytopenia, etiological assessment was performed. Gestational thrombocytopenia was characterized by mild to moderate thrombocytopenia, clinical stability, absence of hypertension and proteinuria, normal liver function tests, and no features suggestive of immune-mediated or consumptive coagulopathy. Pre-eclampsia was defined as systolic blood pressure at or above 140 mmHg or diastolic blood pressure at or above 90 mmHg on two readings at least four hours apart after 20 weeks' gestation with proteinuria of at least 300 mg/24-hour urine collection. Eclampsia was defined as pre-eclampsia with seizures. HELLP syndrome was defined by schistocytes on peripheral smear with elevated hepatic enzymes (aspartate aminotransferase or alanine aminotransferase >70 U/L or lactate dehydrogenase >600 U/L) and platelet count below $150,000/mm^3$. Immune thrombocytopenic purpura was defined as an isolated thrombocytopenia below $100,000/mm^3$ without systemic illness or secondary causes, supported by a peripheral smear showing small-sized platelets without hemolysis or schistocytes. Disseminated intravascular coagulation was diagnosed in clinically suspected bleeding diathesis when at least three criteria were present, including platelet count below $100,000/mm^3$, prolonged prothrombin time >3 seconds above control, and/or activated partial thromboplastin time >5 seconds above control, elevated fibrin degradation

products or D-dimer $>0.5 \mu\text{g/mL}$, and fibrinogen below 150 mg/dL . Malaria was diagnosed clinically with parasitological confirmation on peripheral smear or malarial antigen testing, while dengue fever was diagnosed on a compatible febrile illness with laboratory confirmation by NS1 antigen or immunoglobulin M testing as per illness day. Etiologies were classified as mutually exclusive. If more than one diagnostic category was fulfilled, the primary etiology was assigned using a prespecified hierarchy to minimize misclassification.

Data were entered and analyzed using Statistical Package for the Social Sciences version 22.0. Normality of quantitative variables was assessed by using the Shapiro-Wilk test. Continuous variables were summarized as mean and standard deviation, while categorical variables were presented as frequencies and percentages. To address potential confounding, stratification was performed for maternal age, gestational age, gravidity, and parity, followed by post-stratification comparisons using the Chi-square test for associations between categorical variables. Comparison for continuous data was made using the Independent Samples t-test. A p-value of 0.05 or less was considered statistically significant.

RESULTS

The mean maternal age of the participants was 29.63 ± 5.03 years, with 128 (61.0%) women aged 16–30 years and 82 (39.0%) aged 31–45 years. The mean gestational age at assessment was 36.46 ± 3.21 weeks. The mean gravidity was 2.79 ± 1.26 , and the mean parity was 1.90 ± 1.26 . The overall mean platelet count was $210.26 \pm 57.04 \times 10^3/\mu\text{L}$ (Table 1).

Table 1: Baseline Demographic and Obstetric Characteristics of the Study Population (n=210)

Variables	Categories	n (%) / Mean $\pm$ SD
Maternal Age (Years)	Mean $\pm$ SD	29.63 ± 5.03
	16–30 Years	128 (61.0%)
	31–45 Years	82 (39.0%)

Gestational Age at Assessment (Weeks)	Mean $\pm$ SD	36.46 ± 3.21
	≤ 30 Weeks	20 (9.5%)
	31–36 Weeks	54 (25.7%)
	> 36 Weeks	136 (64.8%)
Gravidity	Mean $\pm$ SD	2.79 ± 1.26
	1–2	95 (45.2%)
	≥ 3	115 (54.8%)
Parity	Mean $\pm$ SD	1.90 ± 1.26
	0–2	139 (66.2%)
	≥ 3	71 (33.8%)
Platelet count ($10^3/\mu\text{L}$)	Mean $\pm$ SD	210.26 ± 57.04

Values are presented as mean $\pm$ standard deviation for continuous variables and number (percentage) for categorical variables. SD = standard deviation; n = number of participants

The frequency of thrombocytopenia among the participants was 26 (12.4%), while 184 (87.6%) women had normal platelet counts (Figure 1).

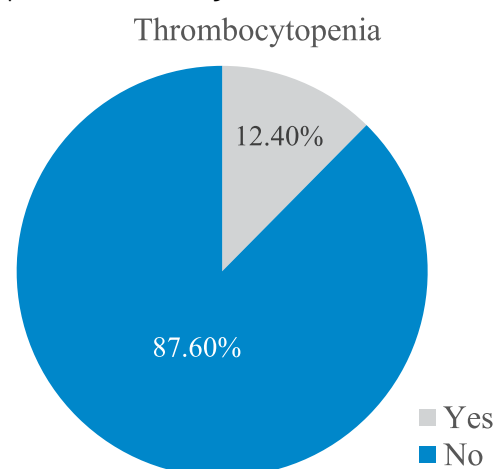


Figure 1: The Frequency of Thrombocytopenia Among Study Participants

Among the 210 pregnant women evaluated in the last trimester, the mean platelet count was significantly lower in the thrombocytopenia group ($115.73 \pm 32.45 \times 10^3/\mu\text{L}$) compared with the non-thrombocytopenia group ($223.61 \pm 46.08 \times 10^3/\mu\text{L}$) ($p < 0.001$) (Table 2).

Table 2: Comparison of Baseline Characteristics by Thrombocytopenia Status (n=210)

Variables	Categories	Thrombocytopenia		Statistical Test Value	p-value
		Present, (n=26)	Absent, (n=184)		
Maternal Age (Years)	Mean $\pm$ SD	28.42 ± 5.04	29.80 ± 5.01	$t = -1.309$	0.192
Gestational Age (Weeks)	Mean $\pm$ SD	36.54 ± 2.96	36.45 ± 3.25	$t = 0.138$	0.891
Gravidity	Mean $\pm$ SD	2.58 ± 1.17	2.82 ± 1.28	$t = -0.900$	0.369
Parity	Mean $\pm$ SD	1.77 ± 1.37	1.91 ± 1.25	$t = -0.544$	0.587
Platelet ($10^3/\mu\text{L}$)	Mean $\pm$ SD	115.73 ± 32.45	223.61 ± 46.08	$t = -14.954$	<0.001
Maternal Age	16–30 years	19 (73.1%)	109 (59.2%)	$\chi^2 = 1.833$	0.176
	31–45 years	7 (26.9%)	75 (40.8%)		
Gestational Age	≤ 30 weeks	2 (7.7%)	18 (9.8%)	$\chi^2 = 1.248$	0.536
	31–36 weeks	9 (34.6%)	45 (24.5%)		
	> 36 weeks	15 (57.7%)	121 (65.8%)		

Gravidity	1-2	16 (61.5%)	79 (42.9%)	$\chi^2 = 3.183$	0.074
	≥ 3	10 (38.5%)	105 (57.1%)		
Parity	0-2	21 (80.8%)	118 (64.1%)	$\chi^2 = 2.818$	0.093
	≥ 3	5 (19.2%)	66 (35.9%)		

Values are presented as mean $\pm$ SD for continuous variables and n (%) for categorical variables. SD = standard deviation; t = independent samples t-test; χ^2 = Pearson Chi-square test statistic, and $p < 0.001$ indicates statistical significance

Among the 26 women diagnosed with thrombocytopenia, 18 (69.2%) had mild thrombocytopenia, 6 (23.1%) exhibited moderate thrombocytopenia, and 2 (7.7%) had severe thrombocytopenia (Figure 2).

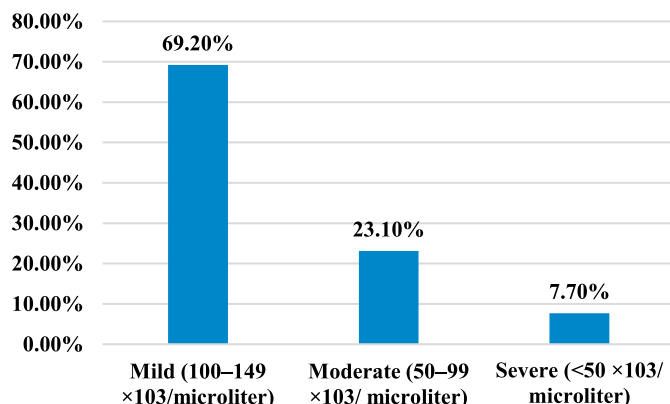


Figure 2: Severity of Thrombocytopenia

Gestational thrombocytopenia was identified in 15 (57.7%) patients, pre-eclampsia in 3 (11.5%), eclampsia in 2 (7.7%), HELLP syndrome in 1 (3.8%), immune thrombocytopenic purpura in 1 (3.8%), disseminated intravascular coagulation in 2 (7.7%), and infection-related thrombocytopenia in 2 (7.7%) (Table 3).

Table 3: Etiological Distribution of Thrombocytopenia Among Affected Pregnant Women (n=26)

Etiology	Count (%)
Gestational Thrombocytopenia	15 (57.7%)
Pre-Eclampsia	3 (11.5%)
Eclampsia	2 (7.7%)
HELLP Syndrome	1 (3.8%)
Immune Thrombocytopenic Purpura (ITP)	1 (3.8%)
Disseminated Intravascular Coagulation (DIC)	2 (7.7%)
Infection-Related Thrombocytopenia	2 (7.7%)

DISCUSSION

In the present cross-sectional study of 210 women assessed in the last trimester, thrombocytopenia was identified in 12.4%, with a mean maternal age of 29.63 ± 5.03 years and a mean gestational age of 36.46 ± 3.21 weeks. Mild thrombocytopenia predominated (69.2%), while moderate and severe disease accounted for 23.1% and 7.7%, respectively. Gestational thrombocytopenia was the leading etiological category (57.7%), followed by hypertensive disorders of pregnancy and smaller contributions from consumptive, immune, and infection-

related causes. The observed frequency of 12.4% lies within the range reported by several studies using the same diagnostic threshold of platelet count $<150 \times 10^9/\text{L}$. Similar prevalence was reported by Begam et al. as 13.4% and by Tirago et al. as 14.8%, while Hanif et al. reported 10.0%, and Mumtaz et al. reported 12.1% [15-18]. The pooled prevalence from Ethiopian studies was 10.7% (95% confidence interval 8.6% to 13.0%), providing a benchmark that closely approximates the present estimate [19]. Lower frequencies were reported in larger screening datasets, including 5.6% among women beyond 28 weeks and 7.20% across deliveries from a large retrospective series [14, 20]. In contrast, a markedly higher frequency of 24.8% was documented in a Pakistani study [21]. Differences across studies are plausibly attributable to recruitment windows, referral patterns, exclusion criteria, distribution of hypertensive disease, and infection-related exposures, as several studies implemented expanded diagnostic workups, including dengue and malaria testing in febrile women and coagulation testing when disseminated intravascular coagulation was suspected. Maternal age was not significantly associated with thrombocytopenia in the present study, with comparable mean ages in the thrombocytopenia versus non-thrombocytopenia groups ($p=0.192$) and no difference across age categories ($p=0.176$). Similar null associations have been reported previously, including Athira et al. ($p=0.481$), Hanif et al. ($p=0.601$), and Mumtaz et al. ($p=0.637$), indicating minimal age-related confounding in series dominated by gestational thrombocytopenia, although age may become more influential in severity-enriched samples [17, 18, 22]. Gestational age also showed no association with thrombocytopenia in the present dataset ($p=0.891$), consistent with Sridhar et al. ($p=0.12$). However, some reports suggest gestational timing affects detection, with higher frequency at >34 weeks in Hanif et al. ($p=0.030$) and an enrolment gestational age association in Athira et al. ($p=0.002$). As 64.8% of participants were assessed beyond 36 weeks, late gestation sampling may have preferentially captured physiological gestational thrombocytopenia and underrepresented earlier, more severe systemic etiologies [17, 22]. Non-significant associations with maternal age, gestational age, gravidity, and parity suggest no clear clustering of thrombocytopenia within these baseline strata in this sample. Nonetheless, smaller effects cannot be excluded due to the limited numbers in the

thrombocytopenia group. Platelet count metrics were consistent with comparative literature. The overall mean platelet count was $210.26 \pm 57.04 \times 10^3/\mu\text{L}$, which closely aligns with the mean platelet count reported by Hanif *et al.* at 213 ± 78.33 [17]. As expected, the thrombocytopenia group in the present study had substantially lower platelet counts than the non-thrombocytopenia group ($115.73 \pm 32.45 \times 10^3/\mu\text{L}$ vs $223.61 \pm 46.08 \times 10^3/\mu\text{L}$, $p < 0.001$). Comparable values were reported by Bai *et al.* where thrombocytopenic women had a mean platelet count of $117 \times 10^9/\text{L}$, supporting similarity in the phenotype of thrombocytopenia detected in late pregnancy [13]. The present severity pattern, with mild predominance (69.2%), is consistent with previous literature. Athira C *et al.* reported mild 76.2%, moderate 19.0%, severe 4.8%, and Saba *et al.* reported mild 64.5%, moderate 29.0%, severe 6.5% [22]. Al Husban *et al.* reported mild disease in 78.53% and moderate to severe disease in 21.47% [14]. In contrast, Begam *et al.* documented a higher proportion of moderate thrombocytopenia (53.7%) relative to mild (35.8%) [15]. Etiological distribution in the present study is consistent with the literature, showing gestational thrombocytopenia as the most frequent cause. Gestational thrombocytopenia accounted for 57.7% in the present analysis, similar to Bai *et al.* (57.5%) and Chandil *et al.* (61.53%) [13, 23]. The contribution of hypertensive disorders was also comparable across studies. In the present study, pre-eclampsia, eclampsia, and HELLP syndrome together accounted for 23.0%, approximating Athira *et al.* where gestational hypertension or preeclampsia accounted for 11.9% and HELLP for 4.8%, and aligning with Chandil *et al.* where hypertensive disorders accounted for 32.69%, including preeclampsia 23.07% and eclampsia 7.69% [22, 23]. Infection and consumptive states were also consistently represented across series, including dengue 7.9% in Sridhar *et al.* viral fever 4.8% in Athira *et al.* The present identification of disseminated intravascular coagulation in 7.7% and infection-related thrombocytopenia in 7.7% is directionally concordant with reports where disseminated intravascular coagulation contributed 3.4% in Bai *et al.* and constituted a notable fraction in more severe restricted samples [13]. In a study limited to platelet counts below $100 \times 10^9/\text{L}$, thrombocytopenia incidence was 3.0%, with obstetric causes comprising 80% and including gestational thrombocytopenia 38%, preeclampsia 20%, and disseminated intravascular coagulation 12%, while immune thrombocytopenia and dengue each contributed 8%, illustrating how etiologic distributions shift when only moderate to severe thrombocytopenia is captured [24]. Although near-term platelet surveillance is useful for late-pregnancy detection, earlier risk-based screening may

improve identification of clinically significant non-gestational thrombocytopenia.

This study quantified the prevalence, severity, and etiological profile of thrombocytopenia in late pregnancy using a standardized diagnostic method with structured clinical and laboratory assessment. Stratified analyses across maternal age, gestational age, gravidity, and parity strengthened interpretability. Limitations included the cross-sectional design, which precluded causal inference and outcome tracking; most participants were assessed beyond 36 weeks of gestation, and the single-center setting, which may limit external validity. Exclusion of major comorbidities may have reduced generalizability to higher-risk pregnancies. Future work should include multi-center prospective designs with serial platelet measurements and linked maternal and neonatal outcomes to refine risk stratification and management pathways.

CONCLUSIONS

Thrombocytopenia was observed in 12.4% of women evaluated during late pregnancy and was predominantly of mild severity. Gestational thrombocytopenia emerged as the most frequent etiology, while hypertensive disorders of pregnancy, disseminated intravascular coagulation, immune thrombocytopenic purpura, and infection-related causes accounted for smaller but clinically relevant subsets. These findings support routine platelet surveillance near term and prompt etiological assessment to guide safe obstetric management.

Authors' Contribution

Conceptualization: SZ

Methodology: TF, SZ, SY

Formal analysis: FA, SS

Writing and Drafting: TF, SZ, SY,

Review and Editing: TF, SZ, SY, FA, SS

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Association between CT-Detected Coronary Artery Calcification and Serum Homocysteine Level in Asymptomatic Adults

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ARTICLE INFO

Keywords:

Computed Tomography, Coronary Artery Calcification, Serum Homocysteine, Asymptomatic

How to Cite:

Safdar, M., Aslam, S., Anwar, W., Ali, S. L., Anwar, K., & Ishrat, S. (2026). Association between CT-Detected Coronary Artery Calcification and Serum Homocysteine Level in Asymptomatic Adults: CT-Detected Coronary Artery Calcification and Serum Homocysteine Level in Asymptomatic Adults. Pakistan Journal of Health Sciences, 7(8), 109-115. <https://doi.org/10.54393/pjhs.v7i8.4072>

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ABSTRACT

The association between CT-detected CAC and serum homocysteine levels in asymptomatic adults may provide valuable insights into the pathophysiological mechanisms underlying subclinical atherosclerosis. **Objectives:** To determine the association between CT-detected coronary artery calcification and serum homocysteine levels in the asymptomatic Pakistani population. **Methods:** A cross-sectional analytical study was conducted on 384 asymptomatic Pakistani adults aged 30–65 years. Coronary artery calcification was assessed using non-contrast CT (Agatston score), and serum homocysteine levels were measured. Associations were analyzed using descriptive statistics and Pearson correlation using SPSS. **Results:** Among 384 asymptomatic adults, coronary artery calcification (CAC) was detected in 41.7% of participants. Individuals with CAC had significantly higher serum homocysteine levels compared to those without calcification ($p < 0.001$). Serum homocysteine increased progressively with CAC severity and showed a significant positive correlation with CAC score. Statistical testing demonstrated that serum homocysteine was significantly associated with coronary artery calcification after adjusting for traditional cardiovascular risk factors. **Conclusions:** Elevated serum homocysteine was independently associated with the presence and severity of CT-detected coronary artery calcification in asymptomatic adults. These findings suggest that homocysteine may serve as a useful biomarker for identifying individuals at increased risk of subclinical coronary atherosclerosis.

INTRODUCTION

Coronary artery disease (CAD) is one of the most common causes of morbidity and mortality globally and often progresses asymptotically before clinical symptoms start to appear [1]. For effective prevention and risk stratification of subclinical atherosclerosis, especially in asymptomatic individuals, it is crucial to identify it as early as possible [2]. Coronary artery calcification (CAC) can serve as an indicator of coronary atherosclerotic burden and can be detected via non-invasive techniques such as computed tomography (CT) [3]. In individuals without a

symptomatic cardiovascular risk factor or overt disease, the extent of CAC independently predicts adverse cardiovascular events and correlates strongly with the total burden of the disease [4]. Using CT, CAC can be calculated using the coronary artery calcium score (CACS). Future risk of any adverse cardiovascular event and atherosclerosis (not clinically evident) can be detected early via CACS, especially in the asymptomatic population for primary prevention [5]. CAC detects inflammation, any chronic vascular injury, and osteogenic changes of



vascular smooth cells within plaques of atherosclerosis [6]. Scoring of CAC based on CT-scan (non-contrast) is mostly quantified with the help of the Agatston method. It is a highly reliable and reproducible scoring system for the assessment of coronary risk. The likelihood of an adverse cardiovascular event increases with higher scores on CAC [7]. Assessment using CAC helps in terms of prognostic value apart from the traditional cardiovascular risk factors. This makes it specifically valuable in an asymptomatic population, wherein conventional risk scorings might either under- or over-estimate the true burden of disease [8]. Sulfur-containing amino acid homocysteine, formed during the metabolism of methionine, has been identified as a distinct risk factor for atherosclerosis and cardiovascular disease [9]. Elevated blood homocysteine levels are believed to induce oxidative stress, prothrombotic states, vascular smooth muscle proliferation, and endothelial dysfunction, all of which contribute to the onset and advancement of atherosclerosis [10]. Homocysteine is more prevalent in calcified atheroma than in non-calcified lesions and increases the production of reactive oxygen species and inflammatory signals. Although hyperhomocysteinemia has been associated with increased cardiovascular risk, its role in the initiation and progression of coronary calcification remains incompletely understood [11]. Homocysteine reduces nitric oxide, disrupts antioxidant systems, and increases reactive oxygen species (ROS), driving endothelial activation and lipid oxidation, early steps in plaque formation. In hyperhomocysteinemia, plaques are larger, more inflammatory, and less collagen-rich. Homocysteine activates NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3) and induces macrophage pyroptosis via ER stress, mitochondrial dysfunction, and calcium dysregulation, and stimulates vascular smooth muscle cell (VSMC) proliferation and pro-atherogenic gene programs, partly via miRNA-mediated and methylation [12]. Reactive metabolites like homocysteine-thiolactone and N-homocysteinylated proteins promote clot formation and impair fibrinolysis, adding a thrombotic layer to established plaque disease. In patients with angina and non-obstructive CAD, higher homocysteine ($>9 \mu\text{mol/L}$, upper quartile) independently predicts coronary microvascular endothelial dysfunction, a marker of early atherosclerosis [13]. Previous literature suggests a potential link between elevated homocysteine levels and arterial calcification. However, findings have been inconsistent, particularly in asymptomatic adults, where the interplay between biochemical markers and structural vascular changes is more understated. Moreover, the majority of existing studies have focused on symptomatic patients or those with established cardiovascular disease,

limiting their applicability to early disease detection and primary prevention [14]. Understanding the association between CT-detected CAC and serum homocysteine levels in asymptomatic adults may provide valuable insights into the pathophysiological mechanisms underlying subclinical atherosclerosis. Such an association could support the combined use of imaging biomarkers and biochemical risk indicators for more comprehensive cardiovascular risk assessment [15]. This approach may enhance early identification of high-risk individuals and allow timely lifestyle and therapeutic interventions to lessen the burden of subsequent cardiovascular events [16]. In Pakistan, cardiovascular diseases (CVD) continue to be the primary cause of morbidity and mortality, with a rising prevalence observed at younger ages compared to Western populations [17]. Early identification of at-risk individuals, particularly among asymptomatic adults, is therefore a critical public health priority in Pakistan [18]. CT-based CAC scoring allows early risk stratification before the onset of clinical symptoms [19]. However, its use in routine screening within resource-limited settings such as Pakistan necessitates the identification of complementary and cost-effective biochemical markers [20]. Elevated serum homocysteine levels are commonly observed in South Asian populations, potentially due to nutritional deficiencies (particularly folate and vitamin B12), genetic predisposition, and lifestyle factors prevalent in Pakistan [21].

Although coronary artery calcification (CAC) is a well-established marker of subclinical atherosclerosis and cardiovascular risk, limited data exist regarding its association with serum homocysteine levels in asymptomatic populations, particularly in developing countries. Previous studies have primarily focused on symptomatic patients or individuals with established cardiovascular disease, leaving a gap in understanding the relationship between homocysteine and early coronary atherosclerosis among apparently healthy adults. Furthermore, regional epidemiological data examining biochemical risk markers alongside imaging-based indicators of coronary artery disease remain scarce. Homocysteine has been recognized as an emerging cardiovascular risk factor that may contribute to endothelial dysfunction, oxidative stress, and vascular inflammation, all of which play key roles in the development of atherosclerosis. Coronary artery calcification detected by non-contrast CT serves as a reliable imaging biomarker of coronary plaque burden and future cardiovascular risk. Investigating the relationship between serum homocysteine levels and CAC in asymptomatic individuals may provide valuable insights into early cardiovascular risk assessment and help identify individuals who may benefit from preventive interventions. This study aimed to

evaluate the association between CT-detected coronary artery calcification and serum homocysteine levels in asymptomatic adults. It was hypothesized that higher serum homocysteine levels are associated with increased coronary artery calcification, reflecting a greater burden of subclinical atherosclerosis. This study aimed to investigate the correlation between serum homocysteine levels and the degree of coronary artery calcification in the Pakistani population, as well as the association between CT-detected coronary artery calcification and serum homocysteine levels in the asymptomatic population.

METHODS

To assess the relationship between blood homocysteine levels and CT-detected coronary artery calcification (CAC) in asymptomatic individuals in the Pakistani adult population, a cross-sectional analytical investigation was carried out. The study was carried out at Shahida Islam Medical College & Teaching Hospital, Lodhran, Pakistan, for a period of six months, June 2025 to November 2025, after taking approval from the institutional review board IRB letter number: SIMC/ET.C/003/0009/01/25 approved on 6th June 2025. Asymptomatic adults of either gender, aged 30–65 years, presenting for routine health screening were enrolled after obtaining informed consent. Individuals with a prior history of coronary artery disease, myocardial infarction, stroke, chronic kidney or liver disease, inflammatory conditions, pregnancy, or those receiving folate or vitamin B12 supplementation were excluded to minimize confounding factors. For the calculation of sample size, OpenEPI software was used, which is a freely available, authentic online tool. Keeping 50 % prevalence of CAC, 95 % confidence level, and 5 % confidence limits, the sample size came out to be 384. Therefore, using a non-probability convenience sampling technique, 384 participants visiting the outpatient clinic were included in the study. After recruitment, a systematic proforma was used to capture clinical and demographic information, such as age, gender, body mass index, smoking status, and the relevant medical history of participants. For coronary artery calcium scoring, non-contrast computed tomography was performed on each participant. Using the Agatston scoring system, coronary artery calcification was measured and classified as no calcification (score 0), mild (1–99), moderate (100–399), or severe (≥ 400). Serum homocysteine levels were assessed in a laboratory using a standardized enzymatic or immunoassay method after venous blood samples were obtained aseptically. Homocysteine levels were classified as normal or elevated according to established reference ranges. Coronary artery calcification was assessed using non-contrast cardiac computed tomography (CT). This technique detects calcified plaques in the coronary arteries based on

their high radiographic density compared with surrounding tissues. During image acquisition, calcified lesions are identified as areas with attenuation values greater than 130 Hounsfield units (HU) and covering at least three contiguous pixels. The extent of coronary calcification was quantified using the Agatston scoring method, in which the area of each calcified lesion is multiplied by a weighting factor based on peak CT attenuation (130–199 HU=1, 200–299 HU=2, 300–399 HU=3, and ≥ 400 HU=4). The scores from all coronary artery segments are then summed to obtain the total coronary artery calcium (CAC) score, which reflects the overall burden of coronary atherosclerotic calcification. The patients were selected from the Department of Medicine (including patients referred to Radiology for a CT scan and Hematology Lab for Serum Homocysteine level. Data collection was carried out by the principal investigator (mentioned in author contributions). A CT scan was carried out by the Department of Radiology and was also reported and interpreted by an expert radiologist with at least 5 years of experience.

The SPSS, version 23.0 was used for data entry and analysis. Laboratory, clinical, and demographic characteristics were summarized using descriptive statistics. Categorical variables were displayed as frequencies and percentages, whilst continuous variables were given as mean $\pm$ standard deviation. The association between serum homocysteine levels and coronary artery calcification scores was assessed using the Pearson correlation coefficient. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

The baseline characteristics of research participants based on their Coronary Artery Calcification (CAC) status. The mean age of participants with no calcification was 44.8 ± 8.6 years, while that of participants with calcification was 56.2 ± 9.4 years, with a significant association of $p < 0.001$. Systolic blood pressure, total cholesterol, LDL-C, HDL-C, triglycerides, and serum homocysteine showed a significant association of $p < 0.001$ with CAC status. BMI, diastolic blood pressure, fasting glucose levels, and smoking status also showed a significant association of $p = 0.05$, $p = 0.04$, $p = 0.02$, and $p = 0.001$, respectively, with CAC status. Gender was found to be insignificantly associated with CAC status (Table 1).

Table 1: Baseline Characteristics of Study Participants According to Coronary Artery Calcification (CAC) Status

Variables	CAC = 0 (No Calcification) (n = 224)	CAC > 0 (Calcification Present) (n = 160)	p-value
Age (Years)	44.8 ± 8.6	56.2 ± 9.4	< 0.001
Male Gender, n (%)	102 (45.5 %)	104 (65 %)	0.038

BMI (kg/m ²)	25.6 ± 3.9	28.4 ± 4.2	0.050
Systolic BP (mmHg)	122.4 ± 12.6	134.8 ± 15.2	<0.001
Diastolic BP (mmHg)	78.2 ± 8.4	84.1 ± 9.6	0.040
Fasting Glucose (mg/dL)	107.77 ± 21.51	121.65 ± 33.67	0.020
Total Cholesterol (mg/dL)	182.6 ± 32.4	205.8 ± 38.6	<0.001
LDL-C (mg/dL)	108.2 ± 26.4	132.6 ± 31.2	<0.001
HDL-C (mg/dL)	46.8 ± 9.2	41.4 ± 8.6	<0.001
Triglycerides (mg/dL)	142.3 ± 58.6	176.2 ± 72.4	<0.001
Serum Homocysteine (μmol/L)	9.8 ± 2.6	15.6 ± 4.2	<0.001
Smoking Status (Current), n (%)	38 (17 %)	52 (32.5 %)	0.001

In 224 participants with no CAC, mean serum homocysteine levels were found to be 9.8 ± 2.6 μmol/L. In 64 patients with mild CAC (1-99), mean serum homocysteine levels were 13.2 ± 3.4 μmol/L. In 58 patients with moderate CAC (100-399), mean serum homocysteine levels were 16.1 ± 3.8 μmol/L. In 38 patients with severe CAC (>400), mean serum homocysteine levels were 19.4 ± 4.6 μmol/L. A significant association was observed between CAC score categories and serum homocysteine levels (Table 2).

Table 2: Serum Homocysteine Levels Across Coronary Artery Calcification Severity (n=384)

CAC Category (Agatston Score)	N	Serum Homocysteine (μmol/L)	p-value
CAC=0	224	9.8 ± 2.6	<0.001
CAC 1-99 (Mild)	64	13.2 ± 3.4	
CAC 100-399 (Moderate)	58	16.1 ± 3.8	
CAC >400 (Severe)	38	19.4 ± 4.6	

The graphical representation demonstrates significantly higher serum homocysteine levels in asymptomatic adults with CT-detected coronary artery calcification compared to those without calcification (Figure 1).

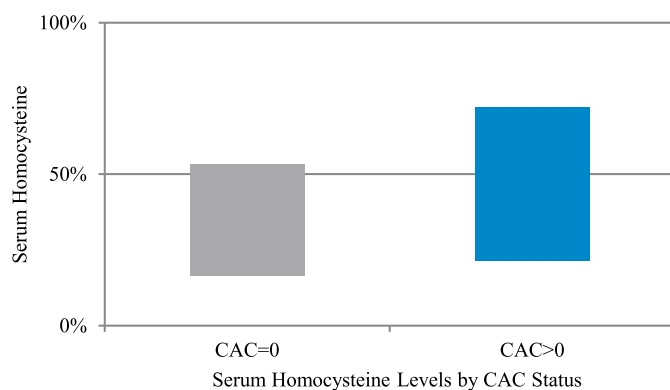


Figure 1: Comparison of Serum Homocysteine Levels by CAC Status

Scatter plot showing a positive correlation ($r=0.82$, $p<0.001$) between coronary artery calcium score and serum homocysteine levels in asymptomatic adults, indicating increasing homocysteine concentration with greater calcific burden (Figure 2).

Serum Homocysteine (umol/L)

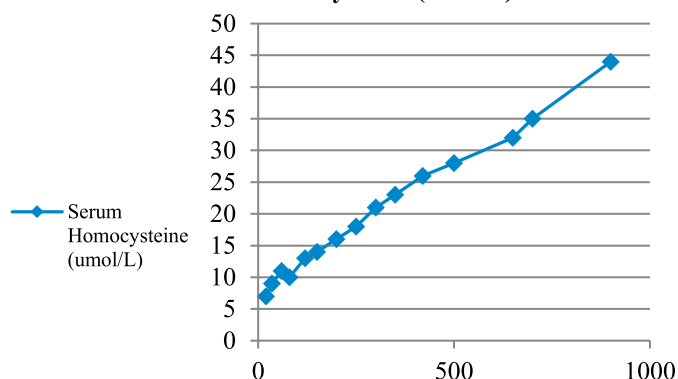


Figure 2: Correlation between Coronary Artery Calcium Score and Serum Homocysteine Level ($r=0.82$ - indicating a strong correlation, $p<0.001$)

DISCUSSION

The findings of this research showed a significant association between CT-detected CAC as well as serum homocysteine levels among asymptomatic adults with CAC. 160 (41.7 %) out of 384 asymptomatic adults were found to have CAC. Our study also reported that sub-clinical atherosclerosis was a common entity even in asymptomatic adults. Furthermore, CAC was more commonly observed among older adults, predominantly males, concluding that age and male gender remained a strong non-modifiable determinant of CAC. Other factors, such as higher BMI, blood pressure, triglycerides, LDL, and lower HDL levels, were reported to have CAC, thereby clustering the fact that classical cardiac and metabolic risk factors were in line with CT findings of CAC and serum homocysteine. Elevated levels of CAC were strongly linked with CAC, demonstrating a dose-response relationship which supports its biological plausibility. The higher the level of serum homocysteine, the greater the burden of calcification. Consequently, homocysteine may be considered a marker of subclinical atherosclerosis. Similar to the findings of our study, Liaquat et al. in a local study, investigated the use of coronary artery calcium scoring through CT scan risk stratification. A substantial positive correlation between CAC and coronary artery stenosis (on CT scan) was discovered among the 1014 participants included in the study. In addition, age above 45 years, diabetes, and hypertension were all substantially linked to an increased risk of CAC [22]. Likewise, Van et al. in their research highlighted that CAC scoring can be of great value in guiding clinical management, especially in asymptomatic cases of CAC using a simple non-contrast CT. This further highlights the significance of our study, which is in line with the above-reported literature [23]. In accordance with our study findings, Karger et al. conducted a MESA (Multi-ethnic Study of Atherosclerosis) to examine the relationship between elevated serum

homocysteine and calcification and its significance as a cardiovascular risk factor. The study found that elevated serum homocysteine levels may be a risk factor for the advancement of coronary artery calcification [15]. Similarly, another research by Jung et al, in their study on the identification and prevention of modifiable risk factors for cardiovascular diseases. The study observed that higher levels of homocysteine were linked to calcified plaques and vascular calcifications [24]. In yet another study by Jung et al. serum homocysteine levels were significantly associated with increased coronary artery calcification [25].

Although the findings of this research were in line with the published literature, this was one-of-a-kind research in the local population evaluating both CT- scan associated CAC as well as serum homocysteine levels. Limitations of the study were a single-center study with a limited sample size, with limited generalizability. The findings of this study have important clinical and public health implications. The observed association between elevated serum homocysteine levels and coronary artery calcification suggests that homocysteine may serve as a useful biochemical marker for identifying individuals at increased risk of subclinical atherosclerosis. Incorporating serum homocysteine assessment alongside imaging-based measures such as CT-detected coronary artery calcification could enhance early cardiovascular risk stratification in asymptomatic adults. Early identification of high-risk individuals may facilitate timely preventive strategies, including lifestyle modification and targeted medical interventions, potentially reducing the future burden of cardiovascular disease. This study has several limitations that should be considered when interpreting the findings. Further research should also evaluate additional biochemical and inflammatory markers along with nutritional factors such as vitamin B12 and folate, to better understand the underlying mechanisms and potential preventive strategies.

CONCLUSIONS

In asymptomatic individuals, elevated blood homocysteine is independently linked to the existence and degree of coronary artery calcification shown on CT. According to these results, homocysteine may be a helpful biomarker for identifying those who are more likely to develop subclinical coronary atherosclerosis.

Authors' Contribution

Conceptualization: MS

Methodology: SA

Formal analysis: WA, SLA, KA

Writing and Drafting: SA, SLA, SI

Review and Editing: MS, SA, WA, SLA, KA, SI

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Maternal Outcomes in Pregnant Females at Term Having Low Amniotic Fluid Index

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ARTICLE INFO

Keywords:

Low Amniotic Fluid Index, Maternal Outcomes, Induction of Labor, Cesarean Section, Parity, Prolonged Labor, Postpartum Hemorrhage, Previous Cesarean Section

How to Cite:

Iqbal, S., Akram, U., Shafqat, H., Ali, M. Z., Shoaib, M., & Arshad, M. (2026). Maternal Outcomes in Pregnant Females at Term Having Low Amniotic Fluid Index: Maternal Outcomes: Pregnant Females Having Low Amniotic Fluid Index. Pakistan Journal of Health Sciences, 7(8), 116-121. <https://doi.org/10.54393/pjhs.v7i8.3809>

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Received Date: 9th January, 20261st Revision Received: 12th March, 20262nd Revision Received: 25th March, 2026Acceptance Date: 8th April, 2026Published Date: 31st August, 2026

ABSTRACT

Low amniotic fluid index (AFI) at term is associated with increased obstetric intervention, but its relationship with maternal outcomes remains uncertain. **Objectives:** To assess maternal outcomes in term pregnancies with low AFI and evaluate their association with maternal age, BMI, parity, and previous cesarean section. **Methods:** This analytical cross-sectional study included 137 singleton term pregnancies with low AFI (<5 cm) admitted to a tertiary care hospital in Quetta from 22-09-2025 to 30-12-2025. Sample size was estimated using $n = Z^2P(1-P)/d^2$ at a 95% confidence level with $P = 65\%$ and $d = 8\%$. Outcomes included induction of labor, mode of delivery, prolonged labor, instrumental delivery, postpartum hemorrhage, infection, and hospital stay. Chi-square or Fisher's exact test was applied as appropriate. **Results:** Mean age was 28.39 ± 6.65 years, and mean BMI was 27.00 ± 4.82 kg/m². Median hospital stay was 3 days (IQR: 2-4). Labor was induced in 101 (73.7%) patients, cesarean section occurred in 94 (68.6%), prolonged labor in 32 (23.4%), instrumental delivery in 13 (9.5%), postpartum hemorrhage in 11 (8.0%), and infection in 7 (5.1%). No statistically significant association was found between maternal outcomes and age group, BMI, parity, or previous cesarean section (all $p > 0.050$). **Conclusions:** In this analytical cross-sectional study, pregnancies with low AFI at term showed high rates of induction and cesarean delivery; however, maternal age, BMI, parity, and previous cesarean section were not significantly associated with adverse maternal outcomes within the study sample.

INTRODUCTION

The amniotic fluid is essential for fetal growth and maintenance of a stable intrauterine environment. It provides mechanical protection, facilitates fetal movement, helps maintain temperature, and supports normal pulmonary and musculoskeletal development. The amniotic fluid index (AFI) is widely used to assess fetal well-being, and an AFI <5 cm is generally considered oligohydramnios or low AFI [1]. Low AFI at term is increasingly recognized in routine obstetric practice because of the widespread availability of ultrasonography

[2]. It may arise in association with placental insufficiency, fetal growth restriction, post-term pregnancy, or membrane-related abnormalities. In otherwise low-risk term pregnancies, low AFI has been associated with higher rates of obstetric intervention and adverse perinatal outcomes, although the extent to which it independently affects maternal outcomes remains uncertain [3-5]. Several studies suggest that low AFI does not merely represent a numerical ultrasonographic finding, but may also act as a marker of impaired placental function and fetal



compromise. In this context, labor induction, cesarean delivery, and closer fetal surveillance may be undertaken because of concern for non-reassuring fetal status, cord compression, or reduced uteroplacental perfusion [6-8]. From a maternal perspective, pregnancies complicated by low AFI may be accompanied by prolonged labor, operative delivery, postpartum hemorrhage, infection, and longer hospitalization. However, these outcomes may be influenced not only by AFI itself, but also by maternal age, BMI, parity, previous cesarean history, and local institutional practices[9-11].

Despite the recognized clinical importance of low AFI, most published work has focused predominantly on fetal and neonatal outcomes, whereas maternal outcome data remain relatively limited. Therefore, the present study was designed to assess maternal outcomes among term pregnant women with low AFI and to evaluate their association with maternal demographic and obstetric characteristics to address this knowledge gap and support evidence-based clinical decision-making.

METHODS

This analytical cross-sectional study was conducted in the Department of Obstetrics and Gynecology, Tertiary Care Hospital, Quetta, from 22-09-2025 to 30-12-2025. The primary objective was to evaluate maternal outcomes in pregnant women at term with low amniotic fluid index (AFI). Study approval was obtained from the Ethical Committee (No. CMH QTA-IERB/117/2025; dated 22nd September 2025, and written informed consent was obtained from every patient. The study included pregnant women aged 18 to 40 years with singleton pregnancies who delivered at term (37-40 weeks) and had low AFI (<5 cm) on transabdominal ultrasonography using the standard four-quadrant technique. Women with medical comorbidities, including hypertension, gestational diabetes mellitus, thyroid disorders, and multiple gestations, were excluded to reduce confounding and improve internal validity; however, this may limit the generalizability of the findings. The sample size was estimated by using Open Epi version 3.01 and the single population proportion formula $n = Z^2P(1-P)/d^2$, where $Z = 1.96$ for a 95% confidence level, $P = 0.65$ based on the reported cesarean section proportion in women with low AFI, and $d = 0.08$ as the margin of error. The calculated minimum sample size was 136.56, which was rounded to 137 participants [12]. Enrollment was performed through non-probability consecutive sampling. After written consent, data were recorded on a predesigned proforma. Maternal outcome measures included induction of labor, mode of delivery (vaginal or cesarean), prolonged labor, instrumental delivery, postpartum hemorrhage (PPH), puerperal fever/infection, and hospital stay. Other variables recorded were maternal

age, parity, BMI, gestational age at delivery, and history of previous cesarean section.

Data were entered and analyzed using IBM SPSS Statistics version 26.0. Normality of quantitative variables was assessed before selecting summary statistics. Age and BMI are presented as mean $\pm$ standard deviation, while hospital stay is presented as median with interquartile range (IQR). Categorical variables are presented as frequencies and percentages in n (%) format. Stratification was performed according to age group, BMI category, parity, and previous cesarean section. Chi-square test was applied for categorical associations, while Fisher's exact test was used for 2x2 tables with small expected cell frequencies. A p-value ≤ 0.050 was considered statistically significant.

RESULTS

A total of 137 patients with low AFI at term were included in the study. The mean age of the participants was 28.39 ± 6.65 years (range: 18-40 years), and the mean BMI was 27.00 ± 4.82 kg/m² (range: 19-35 kg/m²). Hospital stays ranged from 2 to 6 days, with a median of 3 days (IQR: 2-4). Among the study population, induction of labor was performed in 101/137 (73.7%) patients, cesarean section was observed in 94/137 (68.6%), prolonged labor in 32/137 (23.4%), instrumental delivery in 13/137 (9.5%), postpartum hemorrhage in 11/137 (8.0%), and infection in 7/137 (5.1%) (Table 1).

Table 1: Frequency Distribution of Maternal Outcomes (n=137)

Variables	Category	n (%)
Induction of Labor	Yes	101 (73.7%)
	No	36 (26.3%)
Mode of Delivery	Vaginal	43 (31.4%)
	Cesarean	94 (68.6%)
Prolonged Labor	Yes	32 (23.4%)
	No	105 (76.6%)
Instrumental Delivery	Yes	13 (9.5%)
	No	124 (90.5%)
Postpartum Hemorrhage (PPH)	Yes	11 (8.0%)
	No	126 (92.0%)
Infection	Yes	7 (5.1%)
	No	130 (94.9%)

Maternal outcomes were compared across age groups. Induction of labor ranged from 21/31 (67.7%) in women aged ≥ 35 years to 24/27 (88.9%) in those aged 30-34 years, while cesarean delivery ranged from 20/31 (64.5%) to 31/44 (70.5%). Prolonged labor was highest in women aged 30-34 years, 9/27 (33.3%), followed by those aged ≥ 35 years, 9/31 (29.0%). Instrumental delivery, postpartum hemorrhage, and infection remained uncommon across all age groups. No statistically significant association was found between age group and any maternal outcome (all $p > 0.050$) (Table 2).

Table 2: Association of Maternal Outcomes with Age Group(n=137)

Outcome Variables	Subgroup	<25 Years (n=44)	25-29 Years (n=35)	30-34 Years (n=27)	≥35 Years (n=31)	p-value
Induction of Labor	Yes	31(70.5%)	25(71.4%)	24(88.9%)	21(67.7%)	0.249
	No	13(29.5%)	10(28.6%)	3(11.1%)	10(32.3%)	
Mode of Delivery	Vaginal	13(29.5%)	11(31.4%)	8(29.6%)	11(35.5%)	0.950
	Cesarean	31(70.5%)	24(68.6%)	19(70.4%)	20(64.5%)	
Prolonged Labor	Yes	7(15.9%)	7(20.0%)	9(33.3%)	9(29.0%)	0.303
	No	37(84.1%)	28(80.0%)	18(66.7%)	22(71.0%)	
Instrumental Delivery	Yes	5(11.4%)	2(5.7%)	2(7.4%)	4(12.9%)	0.725
	No	39(88.6%)	33(94.3%)	25(92.6%)	27(87.1%)	
Postpartum Hemorrhage	Yes	4(9.1%)	2(5.7%)	1(3.7%)	4(12.9%)	0.572
	No	40(90.9%)	33(94.3%)	26(96.3%)	27(87.1%)	
Infection	Yes	1(2.3%)	3(8.6%)	1(3.7%)	2(6.5%)	0.610
	No	43(97.7%)	32(91.4%)	26(96.3%)	29(93.5%)	

The association of maternal outcomes with BMI category (non-obese versus obese) also showed no statistically significant differences. Induction of labor occurred in 69/94 (73.4%) non-obese and 32/43 (74.4%) obese women, while cesarean section was observed in 67/94 (71.3%) and 27/43 (62.8%), respectively. Prolonged labor was numerically more frequent among obese women, 14/43 (32.6%) versus 18/94 (19.1%), whereas instrumental delivery, postpartum hemorrhage, and infection remained infrequent in both groups. Fisher's exact test was used for instrumental delivery, postpartum hemorrhage, and infection because of small expected cell counts (Table 3).

Table 3: Association of Maternal Outcomes with BMI Groups

Outcome Variables	Subgroup	Non-obese (n=94)	Obese (n=43)	p-value
Induction of Labor	Yes	69(73.4%)	32(74.4%)	0.900
	No	25(26.6%)	11(25.6%)	
Mode of Delivery	Vaginal	67(71.3%)	27(62.8%)	0.321
	Cesarean	27(28.7%)	16(37.2%)	
Prolonged Labor	Yes	18(19.1%)	14(32.6%)	0.085
	No	76(80.9%)	29(67.4%)	
Instrumental Delivery	Yes	10(10.6%)	3(7.0%)	0.754
	No	84(89.4%)	40(93.0%)	
Postpartum Hemorrhage (PPH)	Yes	8(8.5%)	3(7.0%)	1.000
	No	86(91.5%)	40(93.0%)	
Infection	Yes	6(6.4%)	1(2.3%)	0.433
	No	88(93.6%)	42(97.7%)	

Note: Fisher's exact test was used for instrumental delivery, postpartum hemorrhage, and infection because of small expected cell frequencies

Similarly, no statistically significant differences in maternal outcomes were found between primigravida and multigravida women. Induction of labor was performed in 46/64 (71.9%) primigravidas and 55/73 (75.3%) multigravidas, while cesarean delivery occurred in 40/64 (62.5%) and 54/73 (74.0%), respectively. Prolonged labor was more frequent in primigravidas, 19/64 (29.7%), than in multigravidas, 13/73 (17.8%), but the difference was not

statistically significant. Instrumental delivery, postpartum hemorrhage, and infection were uncommon in both parity groups, and Fisher's exact test was applied for these outcomes (Table 4).

Table 4: Association of Maternal Outcomes with Parity(n=137)

Outcome Variables	Subgroup	Primigravida, n (%)	Multigravida, n (%)	p-value
Induction of Labor	Yes	46(71.9%)	55(75.3%)	0.645
	No	18(28.1%)	18(24.7%)	
Mode of Delivery	Vaginal	24(37.5%)	19(26.0%)	0.149
	Cesarean	40(62.5%)	54(74.0%)	
Prolonged Labor	Yes	19(29.7%)	13(17.8%)	0.101
	No	45(70.3%)	60(82.2%)	
Instrumental Delivery	Yes	6(9.4%)	7(9.6%)	1.000
	No	58(90.6%)	66(90.4%)	
Postpartum Hemorrhage (PPH)	Yes	6(9.4%)	5(6.8%)	0.755
	No	58(90.6%)	68(93.2%)	
Infection	Yes	2(3.1%)	5(6.8%)	0.448
	No	62(96.9%)	68(93.2%)	

*Indicates statistical significance at $p \leq 0.050$. No statistically significant associations were observed in this table. Fisher's exact test was used for instrumental delivery, postpartum hemorrhage, and infection

Maternal outcomes also did not differ significantly between women with and without a history of previous cesarean section. Induction of labor occurred in 25/32 (78.1%) women with previous cesarean section and 76/105 (72.4%) women without, while cesarean delivery was observed in 23/32 (71.9%) and 71/105 (67.6%), respectively. Prolonged labor was reported in 8/32 (25.0%) versus 24/105 (22.9%), instrumental delivery in 1/32 (3.1%) versus 12/105 (11.4%), postpartum hemorrhage in 2/32 (6.3%) versus 9/105 (8.6%), and infection in 2/32 (6.3%) versus 5/105 (4.8%). Again, none of the associations were statistically significant, and Fisher's exact test was used for sparse cell frequencies where appropriate (Table 5).

Table 5: Association of Previous Cesarean Section with Maternal Outcomes(n=137)

Maternal Outcomes	Previous CS	Yes, n (%)	No, n (%)	p-value
Induction of Labor	Yes	25 (78.1%)	76 (72.4%)	0.518
	No	7 (21.9%)	29 (27.6%)	
Mode of Delivery	Vaginal	9 (28.1%)	34 (32.4%)	0.650
	Cesarean	23 (71.9%)	71 (67.6%)	
Prolonged Labor	Yes	8 (25.0%)	24 (22.9%)	0.802
	No	24 (75.0%)	81 (77.1%)	
Instrumental Delivery	Yes	1 (3.1%)	12 (11.4%)	0.299
	No	31 (96.9%)	93 (88.6%)	
Postpartum Hemorrhage (PPH)	Yes	2 (6.3%)	9 (8.6%)	<0.001
	No	30 (93.8%)	96 (91.4%)	
Infection	Yes	2 (6.3%)	5 (4.8%)	0.665
	No	30 (93.8%)	100 (95.2%)	

*Indicates statistical significance at $p \leq 0.050$. No statistically significant associations were observed in this table. Fisher's exact test was used for instrumental delivery, postpartum hemorrhage, and infection

DISCUSSION

In this cohort of 137 term pregnancies with low AFI, induction of labor occurred in 101/137 (73.7%) and cesarean section in 94/137 (68.6%), whereas prolonged labor, instrumental delivery, postpartum hemorrhage, and puerperal infection were less frequent at 32/137 (23.4%), 13/137 (9.5%), 11/137 (8.0%), and 7/137 (5.1%), respectively. None of these outcomes showed a statistically significant association with maternal age, BMI, parity, or previous cesarean section. Although prolonged labor appeared numerically higher among obese women (32.6% vs. 19.1%) and primigravidas (29.7% vs. 17.8%), these differences did not reach statistical significance. Overall, the pattern suggests that once low AFI is identified at term, the decision to intervene may be influenced more by concern for fetal compromise and institutional management protocols than by baseline maternal demographic characteristics alone. Similar findings were reported by Rehman *et al.* who documented a cesarean section rate of 65% among women with low AFI at term [12]. Chaudhary *et al.* likewise found higher intervention rates in oligohydramnios, reporting induction of labor in 50% versus 38% and cesarean delivery in 46% versus 20% compared with women having normal AFI [13]. Vyas *et al.* also reported increased cesarean delivery and meconium-stained liquor in pregnancies with borderline AFI. Compared with these studies, the intervention rates in our cohort were somewhat higher, which may reflect tertiary-care referral patterns, differences in case selection, and local thresholds for induction or operative delivery [14]. Patil *et al.* reported cesarean delivery in more than half of pregnancies complicated by oligohydramnios [15], while Sawant *et al.* documented a 69.1% cesarean section rate,

largely in association with fetal distress and abnormal surveillance findings [16]. Shiferaw *et al.* similarly found cesarean delivery in 40.8% of late-term and post-term pregnancies with oligohydramnios [17]. These reports support the interpretation that reduced AFI frequently acts as a clinical trigger for intervention, especially when accompanied by non-reassuring fetal assessment, rather than serving as a direct determinant of maternal morbidity by itself. Mathuriya *et al.* observed that elective and emergency cesarean section rates were approximately twice as high in term pregnancies with low AFI compared with controls [18], whereas Majumdar *et al.* emphasized declining AFI in late gestation as a marker warranting closer surveillance [19]. Khan and Iftikhar reported that borderline AFI was not associated with a higher cesarean rate, but it was linked with increased NICU admission and meconium-stained liquor [20]. Taken together, the available evidence and the present findings indicate that low AFI at term may serve both as a surrogate marker of placental insufficiency and as a practical trigger for intensified surveillance and delivery planning. However, because this was a single-center study without a normal-AFI comparison group and without multivariable adjustment, the present results should not be interpreted as proving an independent causal effect of low AFI on maternal outcomes.

The present study has several limitations. It was a single-center hospital-based study without a comparison group of women with normal AFI. AFI was determined using a single ultrasonographic measurement, which may be affected by operator variability and short-term fluid fluctuation. In addition, women with medical comorbidities were excluded to improve internal validity, which may reduce generalizability. Finally, multivariable regression was not performed, so residual confounding cannot be excluded. These limitations should be considered when interpreting the findings.

CONCLUSIONS

In this analytical cross-sectional study of term pregnancies with low AFI, induction of labor and cesarean section were common maternal outcomes. However, maternal age, BMI, parity, and previous cesarean section were not significantly associated with prolonged labor, instrumental delivery, postpartum hemorrhage, or infection. These findings suggest that the high intervention rates observed in low-AFI pregnancies may be related more to the clinical significance of low AFI and local management protocols than to baseline maternal demographic or obstetric characteristics. Larger comparative studies with serial AFI assessment and multivariable adjustment are needed to clarify causal pathways and improve evidence-based management.

Authors' Contribution

Conceptualization: SI

Methodology: SI, MS

Formal analysis: SI, MS

Writing and Drafting: SI, UA, HS, MZA, MS, MA

Review and Editing: SI, UA, HS, MZA, MS, MA

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Frequency of Cystic Duct Anatomical Variations on ERCP- A Retrospective Cross-Sectional Study

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ARTICLE INFO

Keywords:

Common Bile Duct, Cystic Duct, Endoscopic Retrograde Cholangiopancreatogram, Anatomical Variations

How to Cite:

Rasheed, S., Farooq, M. A., Malik, K., Rehman, H., Mushtaq, H. I., Dilshad, A., & Tayyab, G. U. N. (2026). Frequency of Cystic Duct Anatomical Variations on ERCP-A Retrospective Cross-Sectional Study: Frequency of Cystic Duct Anatomical Variations on ERCP. Pakistan Journal of Health Sciences, 7(8), 122-126. <https://doi.org/10.54393/pjhs.v7i8.2831>

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Received Date: 3rd June, 2025

1st Revision Received: 24th December, 2025

2nd Revision Received: 10th February, 2026

3rd Revision Received: 24th March, 2026

Acceptance Date: 15th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Cystic duct (CD) anatomical variations are common, but they frequently go unrecognized. Their prevalence differs among different studies. A proper understanding of these variations is important before performing any percutaneous, surgical, or endoscopic interventions to avoid complications. **Objectives:** To evaluate the frequency of anatomical variations of cystic duct insertion observed on endoscopic retrograde cholangiograms. **Methods:** A total of 500 cholangiograms (2020-2022) fulfilling the inclusion criteria were analyzed retrospectively for various CD insertion patterns from the Endoscopy suite of Lahore General Hospital, Lahore, after approval from the IRB. Patient information, including age, gender, and indication of ERCP were also recorded. Data were processed on SPSS v.25. Results of continuous measurements were expressed as mean $\pm$ SD (min, max), and results of categorical measurements were presented as number (%). **Results:** Among 500, there were 45% male and 55% female. Normal cystic duct mid-lateral insertion was seen in 62.2% of patients, while 37.8% showed anatomical variations. Among these variations, the most frequent one was low medial (15.4%), followed by middle medial (8.6%) and high lateral (7%). **Conclusions:** The study identified a high frequency of CD variations, thus highlighting the importance of imaging for the identification of these variations before performing any surgical or endoscopic procedures.

INTRODUCTION

The cystic duct is a long tubular structure connecting the gall bladder with the extrahepatic bile duct. Its normal width is 1-5 mm and length 2-4 cm. It normally inserts to the right side of the common hepatic duct and then forms the common bile duct [1]. However, there are various anatomical variations of cystic duct insertion, such as low medial or high lateral. Similarly, other variations like long parallel course of CD or a short CD are also common. If

these variations go unrecognized while performing endoscopic or surgical procedures, complications may arise [2]. The most common complication encountered during surgery due to these variations is bile duct injury leading to biliary leakage, especially in a long parallel course or a short CD due to difficulty in dissection and ligation, respectively [3]. Similarly, while performing ERCP, the low medial insertion variant poses difficulty in



cannulation or instrumentation. In some studies, this variant is also linked with high recurrence of gallstones and CBD stones [4]. Imaging modalities like MRCP (accuracy 90%) and ERCP are critical for detecting CD variations [5]. ERCP is not only the best diagnostic but also a minimally invasive therapeutic tool to treat biliary and pancreatic pathologies by offering high-resolution visualization during endoscopic interventions [6]. Many studies have been published so far describing the prevalence of these variations, but results vary among studies (22.8% to 48.5%). Similarly, the most prevalent anatomical variation also differs among studies, some showing it to be a high insertion [7] while others favor mid-posterior [8]. The likely reasons for such differences might be the different study populations and their ethnicities, imaging techniques, and use of nomenclature for describing these variations. Some studies included anomalous variations like short, long, or bifurcated CD, and others also included aberrant insertion like into the right or left hepatic duct, among anatomical insertion variations as well. Data from Pakistan is sparse; one study reported 8.33% variation rate during cholecystectomy, potentially underestimating true prevalence due to limited imaging, and also only anomalous variations, e.g., short, long, double, or absent cystic duct, were included in the study [9].

Although there are several international reports regarding the cystic duct anatomical variations, the results are inconsistent, and the Pakistani data are also quite limited and probably under-estimated because of the lack of imaging testing of the results. The presence of unidentified variation may augment the threat of bile duct injury, leakage, and the complexity of the procedure in the course of surgery or ERCP. This study aimed to determine the prevalence of CD anatomical variations using ERCP cholangiograms to characterize local patterns and enhance the safety of surgical and endoscopic procedures.

METHODS

This retrospective cross-sectional study was carried out at the Department of Gastroenterology, Lahore General Hospital, after approval from the institutional ethical committee (Reference No. AMC/PGMI/LGH/Article/Research No/2025/ERC/37; dated 1st April 2025). After taking written departmental permission for data access, a total of 1474 ERCP cholangiogram images from March 2020 to October 2022 were collected and reviewed from the Picture Archiving Communication System (PACS) of the endoscopy suite. Two endoscopists with 8 years and 5 years of experience in advanced endoscopy reviewed the ERCP images. Both were blinded to clinical data and reviewed images on separate occasions for interobserver agreement analysis. Cholangiograms of patients aged >18 years that clearly demonstrated the cystic duct anatomy

were included. However, images of patients who had a history of biliary surgery, distorted anatomy, or incomplete images were excluded. A total of 500 cholangiograms that met the inclusion criteria were selected for the study using a non-probability purposive sampling technique. These images were reviewed for anatomical variations of the cystic duct based on insertion type (medial and lateral) and level (high, mid, and low). Patient information, including age, gender, and pathological diagnosis for which ERCP was done, was also recorded from the database. All participants provided verbal informed consent telephonically for the use of their data in the study. The sample size was calculated using the primary outcome variable, i.e., the prevalence of cystic duct anatomical variations on ERCP. Based on previously reported prevalence of CD variations of 39.5%, a 95% confidence interval (CI), and a 5% margin of error, the initial sample size was calculated to be 368 cholangiograms [10]. To enhance the statistical power and robustness of current findings, the sample size was subsequently increased to 500 images. The classification of Cystic Duct (CD) insertion patterns was systematically determined based on the cranio-caudal (vertical) and transverse (horizontal) union with the extrahepatic duct (EHD), a system chosen because ERCP provides 2D cholangiograms with excellent visualization of these major biliary channels and their junctions. The EHD itself was defined as the segment beginning at the confluence of the right and left hepatic ducts and terminating at the point where the Common Bile Duct (CBD) opens into the Ampulla of Vater. To classify the vertical level of insertion, the EHD was divided subjectively into three equal thirds, classifying the union as high, middle, or low (Figure 1).

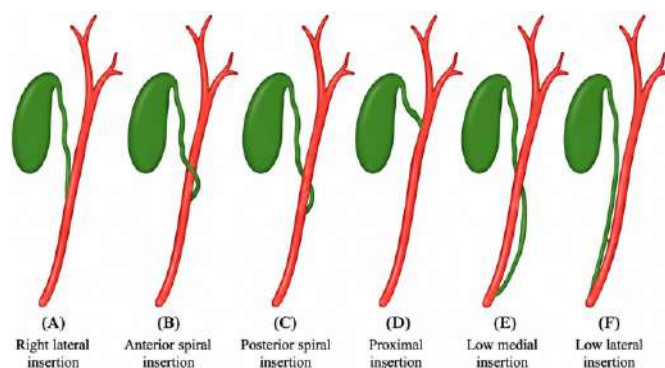


Figure 1: Various Cystic Duct Insertions into the Common Bile Duct [11]

The transverse union was classified based on the perceived side of insertion relative to the EHD in the 2D image, categorizing it as Lateral (insertion from the right side) or Medial (insertion from the left side). CD insertion was considered Normal only when it joined the EHD through the middle one-third of its lateral border, while all other

insertion patterns were consequently recorded as anatomical variants (Figure 2).



Figure 2: Various Insertion Patterns of Cystic Duct Seen on ERCP images

Statistical analysis was carried out with SPSS version 25.0. In current study, descriptive and inferential analyses were carried out. Continuous measurements are calculated as mean $\pm$ SD (min, max), while results of categorical measurements are presented as frequencies and percentages. The chi-square test was used to assess the association between craniocaudal and transverse cystic duct insertion patterns. A p-value of <0.05 was considered statistically significant. Interobserver agreement was analyzed by using Cohen's Kappa statistic.

RESULTS

The cohort consisted primarily of females 275 (55%), with males accounting for 225 (45%) of the sample. The mean age was 45.6 ± 12.52 years (range: 25–74 years). The predominant indication for ERCP in this study was choledocholithiasis (79.6%) (Table 1).

Table 1: Demographics of Patients

Demographic Features	Frequency (%)
Gender	
Male	225 (45%)
Female	275 (55%)
Age (Years)	
Mean $\pm$ SD	45.6 ± 12.52
25–49	304 (60.8%)
50–74	196 (39.2%)
Diagnosis	
Choledocholithiasis	398 (79.6%)
Distal Stricture	43 (8.6%)
Hilar Stricture	25 (5.0%)
Biliary Leak	08 (1.6%)
Mirizzi Syndrome	17 (3.4%)
IGg4 Cholangiopathy	08 (1.6%)
Post LT	01 (0.2%)

311 (62.2%) cholangiograms showed normal insertion (Middle Lateral) pattern, while anatomical variations were seen in 189 (37.8%) images. Low Medial insertion (15.4%) was the most common variation type, while the least common was high medial (1.2%). To ensure reliability, interobserver agreement was assessed using Cohen's Kappa (κ) statistic and was found to be substantial ($\kappa=0.693$) (Table 2).

Table 2: Distribution of All Cystic Duct Insertion Patterns in Whole Cohort

Craniocaudal Insertion, n (%)	Transverse Insertion, n (%)		
	Lateral	Medial	Total
High	38 (7.6%)	6 (1.2%)	44 (8.2%)
Middle	311 (62.2%)	43 (8.6%)	354 (70.8%)
Low	25 (5%)	77 (15.4%)	102 (20.4%)
Total	374 (74.8%)	126 (25.2%)	500 (100%)

Chi-Square Test: p-value = <0.001

The study summarizes previously published literature regarding cystic duct anatomical variations using different imaging and assessment modalities rather than findings from the present study (Table 3).

Table 3: Comparative Distribution of Cystic Duct Insertion Patterns and Anatomical Variants of Different Studies

Sr. No.	Study/ Country	Imaging/ Assessment Modality	Reported CD variation (%)	Most Common Variants	Classification system
1-	Present study (Pakistan)	ERCP	37.8	Low Medial (15.4%) Middle Medial (8.6%)	ERCP 2D image-based Insertion classification
2-	Turkish Study (10)	ERCP	39.5	Middle Medial (9.8%), Low Medial (6.8%)	Insertion variations
3-	Turkish Study (14)	MRCP	60	Lateral Insertion: 40%. Medial Insertion: 24.3%. High Insertion (14.7%)	Anomalous & Insertion variations
4-	Nepal Study (15)	MRCP	52.38%	Posterior Insertion (14.3%)	Variable classification
5-	Cadaveric Study (17)	Liver specimen in Anatomy Department	10.3	High union 7.2%	Insertion variations according to level and mode of insertion
6-	Odisha Study (18)	MRCP	—	Posterior Insertion 42.8%	Insertion Classification

DISCUSSION

Gall bladder and biliary tree pathologies are usually managed by a surgical and endoscopic approach. Both are invasive means of management and linked with complications. One important reason for complications like injury or ligation of the bile duct is the failure to recognize the ductal anatomy variations [12]. As a whole, total biliary tree variations are seen in 42% of the population and are the frequent cause of iatrogenic bile duct injury [13]. The incidence of CD anatomical variation in present study was 37.8%, with other studies showing a range from 39% to 60% depending upon imaging modality and classification criteria (Table 3). Current results align

with the Turkish study reporting 39.5% variations, with middle medial being the most frequent one (9.8%) [10]. Some studies reported quite high percentages of CD variations up to 60% [14, 15]. The higher percentages might be because of the use of different imaging modalities (MRCP) and the use of anomalous union in addition to insertion variations in nomenclature. These studies also included various courses of the cystic duct, like short, parallel, or spiral courses, which essentially are not the insertion variations. A local study from Pakistan reported the incidence of CD variants of only 4.4% [16]. It's likely due to a smaller sample size and reliance on Laparoscopic observation. Also, the nomenclature for various insertion variations was not mentioned. A significant observation of present study was a higher prevalence of low medial insertion (15.4%) in contrast with studies reporting lower rates. Among these, one study conducted on 100 cadaveric specimens showed 3.1% incidence [17]. Another larger study on the Odisha population of 1038 patients showed low medial insertion was present in 3.8% patients [18]. It's possibly due to population-specific embryological differences or ERCP's enhanced visualization compared to MRCP or surgical findings. Clinically, low medial insertions pose challenges for ERCP cannulation or instrumentation and increase the risk of CBD stone recurrence [19]. Pre-procedural MRCP, being noninvasive, can guide endoscopists and surgeons, reducing risks like pancreatitis, bile duct injury, or leakage. In current study, the second most common variant was middle medial with an incidence of 8.6%. Sherifi *et al.* reported the incidence of 6.3%, which was nearly comparable to present study [20]

Limitations of current study include single center retrospective design, subjective classifications of insertion levels, and a lack of MRCP or surgical correlations. Overall, present study results revealed a higher frequency of CD variations. However, larger multicenter studies are required to compare the results of ERCP images with MRCP and intraoperative surgical anatomy. Such validation will help refine the classification system and ultimately enhance procedural safety across diverse populations.

CONCLUSIONS

The anatomical variations observed in current population are quite high (37.8%), with low medial insertion being the most common. Given the clinical challenges these variants pose, we strongly recommend mandatory pre-procedural imaging, preferably MRCP, to reduce the risk of iatrogenic injury and complications during both surgical and endoscopic biliary procedures. Furthermore, these findings underscore the importance of enhanced education and training for endoscopists and surgeons regarding biliary anatomy and its variants to ensure optimal procedural safety.

Authors' Contribution

Conceptualization: SR, MAF, KM, HR, HIM, GUNT

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Formal analysis: SR, MAF, KM, HR, HIM, GUNT

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Self-Reported Personal Hygiene Practices and Associated Factors among Prison Inmates in a Jail in Pakistan

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ARTICLE INFO

Keywords:

Personal Hygiene, Practices, Prison Inmates, Nara Jail

How to Cite:

Nisar, M., Soomro, F., Jokhio, F., Hunebia, ., Zeba, N., Qureshi, Z., & Naqvi, S. A. (2026). Self-Reported Personal Hygiene Practices and Associated Factors among Prison Inmates in a Jail in Pakistan: Self-Reported Personal Hygiene Practices and Associated Factors among Prison Inmates. *Pakistan Journal of Health Sciences*, 7(8), 127-132. <https://doi.org/10.54393/pjhs.v7i8.3840>

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ABSTRACT

Prison inmates are a vulnerable population with increased risk of exposure to poor water, sanitation, and hygiene (WASH) conditions, which raises communicable diseases. **Objective:** To determine self-reported personal hygiene practices and associated factors among inmates in Nara Jail, Hyderabad. **Methods:** This institution-based cross-sectional observational study was conducted at Nara Jail, Hyderabad (November 2025–January 2026). Ninety-one inmates were selected through simple random sampling. Data were collected using a structured interviewer-administered questionnaire and a standardized observational checklist adapted from WHO WASH guidelines. Associations were analyzed using Chi-square or Fisher's exact tests, with statistical significance set at $p < 0.050$. **Results:** Although 96.7% of inmates acknowledged the importance of soap use, only 40.7% had prior awareness of formal WASH practices, and nearly all reported the absence of hygiene education during incarceration. While 94.5% reported handwashing after toilet use, 23.1% relied solely on water. Direct observation identified poor hygiene conditions, including unclean fingernails (42.9%) and visible dermatological conditions (31.9%). Poor fingernail hygiene was significantly associated with recent gastrointestinal morbidity ($p < 0.050$). **Conclusions:** There were significant gaps in formal WASH knowledge, institutional hygiene support, and observed hygiene conditions among prison inmates. Structural deficiencies in prison WASH infrastructure and lack of institutional health education contribute to preventable health risks, highlighting the need for evidence-based prison health reforms in Pakistan.

INTRODUCTION

Maintaining personal hygiene is a fundamental determinant of health and human dignity. It includes appropriate hand hygiene, safe water use, bathing, oral care, nail and hair cleanliness, and the use of clean clothing [1]. Adequate hygiene practices are essential to prevent communicable diseases, particularly those transmitted through fecal-oral routes, such as diarrhea, vomiting, skin

infections, and parasitic infestations [2]. In overcrowded and resource-limited environments, maintaining recommended hygiene behaviors becomes challenging, increasing the risk of infectious disease transmission and adverse health outcomes [3]. Prisons and jails are internationally recognized as high-risk institutional settings where overcrowding, limited infrastructure, and



inadequate access to water, sanitation, and hygiene (WASH) services compromise inmate health [4]. Globally, more than 10 million individuals are incarcerated, and this number continues to rise [5]. Although international standards such as the United Nations Standard Minimum Rules for the Treatment of Prisoners (Nelson Mandela Rules) emphasize adequate sanitation and healthcare services, implementation remains inconsistent, particularly in low- and middle-income countries (LMICs) [6]. Overcrowded cells, insufficient water supply, shared sanitation facilities, and limited access to hygiene materials create environments conducive to the rapid spread of communicable diseases [7]. Evidence from LMICs and Asian countries indicates that prison populations experience disproportionately higher rates of infectious diseases compared to the general population [8]. Studies conducted in Ethiopia and India have reported suboptimal hygiene practices and limited institutional WASH support among inmates [9, 10]. Research further highlights discrepancies between self-reported hygiene practices and directly observed hygiene conditions, often influenced by structural constraints and restricted access to hygiene supplies [11]. In Pakistan, prison health remains an under-researched public health issue. Reports indicate overcrowding, unsafe drinking water, and inadequate sanitation services in several prisons [12-14]. However, empirical data assessing personal hygiene practices and their association with health outcomes among Pakistani inmates remain scarce. By generating local evidence, this study provides a rationale for strengthening prison-based WASH infrastructure, institutional hygiene education programs, and policy-level interventions to protect inmate health and uphold human dignity.

Despite increasing global recognition of prison health as a public health priority, there is limited context-specific evidence from Pakistan examining both self-reported and directly observed hygiene practices and their association with recent morbidity. Most existing research in Pakistani prisons focuses primarily on tuberculosis and mental health, with limited attention to routine hygiene behaviors and WASH-related determinants. Therefore, this study was conducted to address this research gap. This study aimed to assess self-reported personal hygiene practices and their associated factors among prison inmates in a jail in Pakistan. Specifically, the objectives were to evaluate WASH-related knowledge, examine observed hygiene conditions, and determine their association with recent gastrointestinal morbidity.

METHODS

This cross-sectional observational study was conducted at Nara Jail, Hyderabad, Pakistan, from November 2025 to January 2026. Approval from the Ethical Review

Committee (ERC) was obtained from Liaquat University of Medical and Health Sciences (LUMHS), Approval No. LUMHS/REC/-872; dated 8th July 2025) before the data collection. Permission was also obtained from jail authorities. Participation was voluntary, and written or verbal informed consent was obtained from all eligible inmates. The sample size was calculated using the RaoSoft sample size calculator, and after adding a 10% allowance for non-response, the final sample size was 91 inmates. Simple random sampling was used to select participants from the official inmate list provided by jail administration. Inmates aged 18 years and above, incarcerated for at least four weeks, and willing to participate were included. Those who were critically ill, unable to communicate, or refused consent were excluded. Data were collected using two tools: a structured interviewer-administered questionnaire and a direct observational hygiene checklist. The questionnaire was developed based on the World Health Organization (WHO) guidelines on water, sanitation, and hygiene (WASH) in institutional settings and adapted from previously published prison hygiene assessment studies [15]. Thus, the questionnaire represents a standardized and validated tool for assessing WASH knowledge and practices. The tool was translated into Sindhi and Urdu and reviewed by public health experts for content validity. Two trained data collectors conducted face-to-face interviews in designated private areas within the prison to maintain confidentiality and minimize reporting bias. The questionnaire consisted entirely of structured closed-ended questions; no open-ended questions or qualitative interviews were conducted. Hygiene practices were assessed using a structured observational checklist, and data collectors were trained to follow standardized procedures to minimize observer bias. The questionnaire comprised three sections. The first section included sociodemographic and incarceration-related variables such as age, marital status, residence (urban/rural), education level, occupation before imprisonment, income before imprisonment, duration of incarceration, and number of inmates per cell. The second section assessed WASH-related knowledge and self-reported hygiene practices, including daily water consumption, access to toilet facilities, waiting time, availability of hygiene materials, frequency of handwashing before meals and after toilet use, materials used for handwashing, bathing frequency, clothes washing practices, and oral hygiene practices. Responses were recorded in categorical formats (Yes/No, Always/Sometimes/Never). Based on predefined criteria aligned with WHO hygiene standards, self-reported hygiene practices were categorized as adequate or inadequate. No Likert scale was used. The third section consisted of a structured observational checklist

assessing visible hygiene indicators such as cleanliness of clothes, hair, fingernails, teeth, and feet, and the presence of lice or visible skin conditions. Observations were recorded at the time of the interview without interfering with routine activities. Recent gastrointestinal morbidity was assessed through self-reported episodes of diarrhea and vomiting during the preceding two weeks.

Data were entered and analyzed using SPSS version 29.0. Descriptive statistics, including frequencies, percentages, and mean $\pm$ standard deviation, were used to summarize the variables. Associations between hygiene practices and selected variables were examined using Chi-square tests. Chi-square tests were applied where the assumptions of the test were met (i.e., expected cell counts ≥ 5 in at least 80% of cells), while Fisher's exact test was used in comparisons with small cell sizes to ensure accurate statistical inference. A p-value < 0.050 was considered statistically significant. Due to the relatively small number of outcome events, the assumptions required for reliable multivariable regression analysis (minimum events per variable) were not met; therefore, adjusted analysis was not performed.

RESULTS

A total of 91 inmates participated in the study. The mean age of participants was 35.5 ± 12.9 years. The mean duration of imprisonment was 5.6 ± 12.3 months, and inmates shared cells with a mean of 60.6 ± 26.5 individuals. All participants were male. Most inmates were married (66.7%) and resided in urban areas before imprisonment (71.4%). More than half had primary education or below, whereas 19.8% had attained college-level education or above. Before imprisonment, the majority were engaged in informal or miscellaneous occupations (61.5%). Sociodemographic and incarceration-related characteristics are presented, Table 1.

Table 1: Sociodemographic and Imprisonment-Related Characteristics of Inmates (n=91)

Variables	n (%)
Marital Status	
Single	39 (33.3%)
Married	60 (66.7%)
Education Status	
Illiterate	23 (25.3%)
Primary	31 (34.1%)
Secondary	19 (20.9%)
College and above	18 (19.8%)
Occupation Before Imprisonment	
Civil Servant	12 (13.2%)
Farmer	11 (12.1%)
Private Worker	12 (13.2%)
Other	56 (61.5%)

Daily Income Before Imprisonment (PKR)	
100-700	18 (19.8%)
701-1000	27 (29.7%)
1001-1500	20 (22.0%)
1501-2500	26 (28.6%)
Residence	
Urban	65 (71.4%)
Rural	26 (28.6%)

Although 97.8% of inmates recognized the importance of handwashing after toilet use and 96.7% believed that soap reduces disease transmission, only 40.7% had heard of formal WASH practices. Nearly all participants (96.7%) reported not receiving hygiene education during incarceration. While 94.5% reported always washing hands after toilet use, 23.1% relied solely on water without soap. Daily bathing was reported by 84.6% of inmates; however, only 34.1% brushed their teeth daily. Safe water intake was inadequate, with 95.6% consuming less than 2 liters per day, Table 2.

Table 2: WASH-Related Knowledge and Self-Reported Hygiene Practices (n=91)

Variables	n (%)
Heard About WASH	
Yes	37 (40.7%)
No	54 (59.3%)
Received Hygiene Education in Prison	
Yes	3 (3.3%)
No	88 (96.7%)
Water Consumption	
< 2 Liters/Day	87 (95.6%)
≥ 2 Liters/Day	4 (4.4%)
Handwashing After Toilet	
Always	86 (94.5%)
Sometimes	5 (5.5%)
Handwashing Material	
Water Only	21 (23.1%)
Water and Soap	70 (76.9%)
Daily Bathing	77 (84.6%)
Daily Tooth Brushing	31 (34.1%)

Only 63.7% of inmates had hygienic clothing, while 42.9% had dirty fingernails. Clean teeth were observed in just 54.9% of participants. Signs of lice infestation were present in 12.1%, and 31.9% showed visible skin conditions, including scabies. Regarding morbidity, 9.9% of inmates reported experiencing diarrhea in the preceding two weeks, and an equal proportion reported vomiting during the same period, Figure 1.

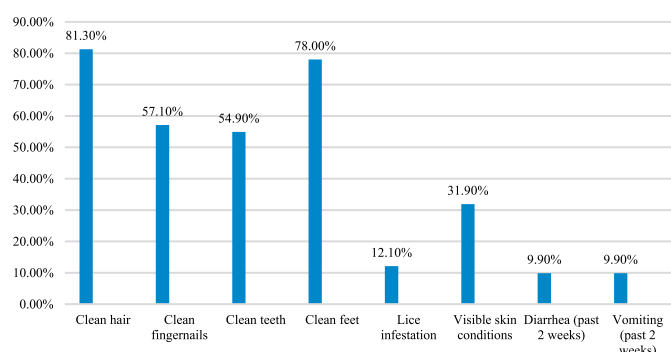


Figure 1: Observed Hygiene Status and Recent Illness Among Inmates (n=91)

The association between selected sociodemographic variables and awareness of WASH practices was examined using Chi-square and Fisher's exact tests where appropriate. No statistically significant association was observed between age group, occupation, or daily income and WASH awareness ($p > 0.050$). However, educational status was significantly associated with WASH awareness ($p = 0.030$), with inmates having secondary education or above being more likely to have heard of WASH practices, Table 3.

Table 3: Association Between Sociodemographic Characteristics and Awareness of WASH Practices (n=91)

Variables	Category	Heard About WASH, n (%)	Not Heard, n (%)	p-value
Age Group	≤ 35	19 (41.3%)	27 (58.7%)	0.890
	> 35	18 (40.0%)	27 (60.0%)	
Education Status	Illiterate/Primary	24 (34.8%)	45 (65.2%)	0.030*
	Secondary and above	13 (59.1%)	9 (40.9%)	
Occupation	Civil Servant	6 (50.0%)	6 (50.0%)	0.910
	Farmer	4 (36.4%)	7 (63.6%)	
	Private Worker	5 (41.7%)	7 (58.3%)	
	Other	22 (39.3%)	34 (60.7%)	
Income (PKR)	100-700	7 (38.9%)	11 (61.1%)	0.980
	701-1000	11 (40.7%)	16 (59.3%)	
	1001-1500	9 (45.0%)	11 (55.0%)	
	1501-2500	10 (38.5%)	16 (61.5%)	

There was no statistically significant association between daily water consumption and recent diarrhea or vomiting ($p = 0.498$). Although all reported cases occurred among inmates consuming less than 2 liters per day, this difference did not reach statistical significance, Table 4.

Table 4: Association Between Daily Water Consumption and Recent Morbidity (n=91)

Water Consumption	Diarrhea Yes, n (%)	Diarrhea No, n (%)	Vomiting Yes, n (%)	Vomiting No, n (%)	p-value
< 2 L/day	9 (10.3%)	78 (89.7%)	9 (10.3%)	78 (89.7%)	0.498
≥ 2 L/day	0 (0.0%)	4 (100%)	0 (0.0%)	4 (100%)	

Fisher's exact test demonstrated a statistically significant association between observed fingernail cleanliness and recent gastrointestinal morbidity. Inmates with unclean

fingernails had higher odds of diarrhea compared with those with clean fingernails (OR = 2.97, 95% CI: 0.69-12.7). A similar pattern was observed for vomiting (OR = 2.97, 95% CI: 0.69-12.7). However, the confidence intervals were wide, reflecting the small number of cases, and included unity, indicating that the estimates should be interpreted with caution, Table 5.

Table 5: Association Between Observed Fingernail Cleanliness and Recent Morbidity (n=91)

Fingernail Cleanliness	Diarrhea Yes, n (%)	Diarrhea No, n (%)	p-value	Vomiting Yes, n (%)	Vomiting No, n (%)	p-value
Not Clean (n=39)	6 (15.4%)	33 (84.6%)	0.004	6 (15.4%)	33 (84.6%)	0.003
Clean (n=52)	3 (5.8%)	49 (94.2%)		3 (5.8%)	49 (94.2%)	

DISCUSSION

This study assessed hygiene practices, WASH-related knowledge, and associated factors among prison inmates in Pakistan using both structured self-reported measures and direct observation. The demographic profile of inmates in this study is consistent with recent prison-based research conducted in low- and middle-income countries (LMICs), where incarcerated populations predominantly consist of young to middle-aged males with low to moderate educational attainment [10, 11]. More than half of the inmates had primary education or below and were engaged in informal occupations before imprisonment. Overcrowding was evident, with inmates sharing cells with a large number of individuals. Similar patterns of overcrowding and institutional constraints have been reported in contemporary prison health studies, emphasizing structural limitations within LMIC correctional facilities [14]. A key finding of this study was the discrepancy between self-reported hygiene practices and directly observed hygiene conditions. Although most inmates reported frequent handwashing and bathing, direct observation revealed substantial levels of poor fingernail hygiene, dental hygiene deficiencies, and visible skin conditions. Comparable inconsistencies between reported and observed hygiene behaviors have been documented in prison settings in South Asia and Africa [12, 13]. Such differences may reflect social desirability bias inherent in self-reported data, as well as structural barriers including limited access to water, hygiene materials, and sanitation facilities [14]. Despite high awareness of handwashing after toilet use and the role of soap in disease prevention, formal awareness of WASH as a structured public health concept was limited. Nearly all inmates reported not receiving hygiene education during incarceration, indicating the absence of organized prison-based health promotion programs. Similar findings have been reported in recent prison health literature, where informal hygiene knowledge was not supported by institutional education initiatives [15, 16]. Water access

was critically inadequate, with nearly all inmates consuming less than two liters per day, below recommended minimum standards for drinking and personal hygiene. Although no statistically significant association was observed between water consumption and recent gastrointestinal morbidity, uniformly low water availability may have reduced variability and limited the ability to detect meaningful statistical associations. International WASH research consistently emphasizes that inadequate water access fundamentally compromises hygiene practices and infection prevention in institutional settings [7, 17]. Educational status demonstrated a significant association with awareness of WASH practices, supporting evidence that education influences health knowledge and preventive behaviors [14]. However, education was not associated with observed hygiene practices, reinforcing the understanding that institutional conditions often supersede individual-level determinants within correctional settings. The study also found a statistically significant association between observed fingernail cleanliness and recent gastrointestinal morbidity. Although the number of morbidity cases was small, inmates with unclean fingernails showed higher proportions of reported diarrhea and vomiting. However, multivariable analysis to adjust for potential confounders such as education level, overcrowding, and duration of imprisonment was not performed due to the limited number of outcome events, which may influence the observed associations. Poor nail hygiene may facilitate fecal-oral transmission of enteric pathogens, particularly in overcrowded environments with shared sanitation facilities. Recent intervention-based evidence has demonstrated that improved hand hygiene significantly reduces diarrheal episodes in high-density living conditions [18]. Furthermore, contemporary systematic reviews continue to identify inadequate hand and nail hygiene as a major contributor to diarrheal disease burden in institutional settings [19, 20]. Overall, the findings reinforce emerging evidence that prisoners' health outcomes are primarily shaped by institutional determinants rather than individual awareness alone. Without adequate WASH infrastructure, hygiene materials, and structured health education programs, improvements in inmate health remain limited.

This one-center study in the NARA Jail, Hyderabad, restricts the generalization to other prisons in Pakistan that may vary in their overcrowding levels, resources, and geographical location. The cross-sectional design does not allow developing causal associations between hygiene practices and morbidity outcomes. Future studies will need to involve water quality testing of bacteriological contamination, microbiological stool testing and will have

to measure other consequences like skin infections and parasitic infestations. Female prisons should also be considered in studies to investigate gender-specific hygiene requirements.

CONCLUSIONS

This study demonstrates that although prison inmates in Pakistan possess basic awareness regarding hygiene practices, significant institutional deficiencies in WASH infrastructure and hygiene education persist. The discrepancy between self-reported and observed hygiene conditions, along with the association between poor fingernail hygiene and recent gastrointestinal morbidity, highlights the urgent need for structured prison-based WASH interventions. Strengthening institutional water supply, sanitation facilities, hygiene material availability, and health education programs is essential to reduce communicable disease risks and improve inmate health outcomes.

Acknowledgment

The authors would like to express their sincere gratitude to the administration of NARA Jail, Hyderabad, for granting permission and facilitating the conduct of this study. We are especially thankful to all participating inmates for their cooperation and willingness to contribute to this research. We also acknowledge the efforts of the trained data collectors for their support during data collection. Ethical approval and institutional support provided by Liaquat University of Medical and Health Sciences (LUMHS) are gratefully acknowledged.

Authors' Contribution

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Methodology: MN, FS, NN, FJ

Formal analysis: FS

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Comparison of Incision and Drainage with Needle Aspiration in the Treatment of Breast Abscess

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ARTICLE INFO

Keywords:

Breast Abscess, Incision and Drainage, Needle Aspiration, Lactational Mastitis, Ultrasound-Guided Aspiration

How to Cite:

Mubashir, A., Tahir, A., Ahmad, S., & Ahmed, S. (2026). Comparison of Incision and Drainage with Needle Aspiration in the Treatment of Breast Abscess: Incision and Drainage with Needle Aspiration in the Treatment of Breast Abscess. *Pakistan Journal of Health Sciences*, 7(8), 133-138. <https://doi.org/10.54393/pjhs.v7i8.3587>

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ABSTRACT

Breast abscess is a common complication of mastitis in low- and middle-income countries and may impair cosmetic appearance and breastfeeding. Conventional incision and drainage (I/D) are effective but associated with scarring and delayed recovery. Ultrasound-guided needle aspiration is a minimally invasive alternative. **Objective:** To compare the efficacy of ultrasound-guided needle aspiration and I/D in the management of breast abscesses. **Methods:** This retrospective comparative study was conducted in the Department of Surgery, Hayatabad Medical Complex, Peshawar, from August to October 2025. A total of 110 female patients (18–60 years) with breast abscesses of ≥ 3 days duration was included using record-based sampling. Patients with BMI >29.9 kg/m², chronic diabetes, or recent breast intervention were excluded. Group A (n=55) underwent I/D, while Group B (n=55) received ultrasound-guided needle aspiration. All patients received antibiotics. The primary outcome was treatment success (complete resolution without recurrence). Data were analyzed using SPSS version 23.0, and a chi-square test was applied. A p-value <0.05 was considered significant. **Results:** Mean age was 29.17 ± 9.44 years in Group A and 30.11 ± 8.56 years in Group B. Overall, 63.6% were lactating women. Treatment success was achieved in 37/55 (67.3%) patients in Group A and 53/55 (96.4%) in Group B. The difference was statistically significant ($p<0.01$). **Conclusions:** Ultrasound-guided needle aspiration demonstrated significantly higher success rates than I/D and offers a less invasive approach with a better recovery profile. It should be considered the preferred first-line treatment in appropriately selected patients.

INTRODUCTION

The complication of the breast abscess is a rare event of mastitis, especially when the treatment is inadequate or delayed [1]. To women, this disease brings a lot of concern [2]. Regardless of being puerperal or not, the traditional treatment was the incision and drainage, but this method is expensive, leaves scars, and requires follow-ups, which are usually post-surgical, such as cessation of breastfeeding [3]. Non-puerperal breast abscess is a rare phenomenon whose recurrence and microbiological range are severe, whereas puerperal breast abscess is a common problem in nursing women [4, 5]. Infected and noninfectious mastitis

occur in 9%–33% of nursing mothers, and the abscesses occasionally worsen the mastitis up to 11%. *Staphylococcus aureus* (SA) is the most common pathogen in up to 100 percent of cases that have culture-confirmed postpartum breast abscesses. Previously, most of the studies examined factors that put women at risk of developing breast abscesses and found that obesity, low parity, and early maternal age are predictors of postpartum development of breast abscesses [6, 7]. The gold standards of treating breast abscesses are surgical incision, drainage, and systemic administration of



antibiotics. Knowledge of the kind of pathogens that cause the breast abscesses and their trends of resistance can help the surgeon in choosing the most effective empirical therapy to enhance the outcome of acute bacterial mastitis and the least invasive drainage methods combined with the use of antimicrobial drugs. Breast abscesses can be treated by repeated aspiration with or without ultrasound guidance [8]. This treatment has been successfully used and associated with early recovery, early restoration of breastfeeding, and excellent cosmetic results. The mean day 3 pain score of the incision and drainage group was 4.22 ± 2.82 , and that of the needle aspiration group was 5.72 ± 1.82 , according to one trial previously carried out. The mean pain score of the incision and drainage group was 1.73 ± 2.87 and 3.89 ± 2.12 for the needle aspiration group on day 14 [9, 10]. 94% of the needle aspiration group participants had no pain on day 14 [9, 10]. In one other study, incision, drainage, and needle aspiration success rates were 82.9, 97.1%, respectively [11]. I/D normally serves as the treatment of breast abscesses, although it leads to further discomfort and cosmetic damage, which is why it is not recommended by surgeons or patients. As the literature suggests, needle aspiration is an excellent choice of cosmetic treatment and, at the same time, this method is effective in reducing post-procedure pain and facilitating a rapid recovery. The results of the study assist us in identifying the local success rate of I/D and needle aspiration in patients with breast abscess, and the results also assist us in making recommendations as regards to needle aspiration in the future. This paper is a comparison of the effectiveness of needle aspiration and incision and drainage of the breast abscess. The presence of a breast abscess was confirmed by the presence of bacterial growth on the laboratory test of the hospital, where the woman had a history of breast ulcer and purulent material discharge. The effectiveness of the treatment is assessed by the degree of pain that will be reported on the 7th day after the therapy. Patients will be classified as having successfully been treated on a score that is lower than 3. Visual Analogue Scale will be adopted to assess the pain; 0 will represent the absence of pain and 10 the worst possible discomfort. Particularly, this assessment will be performed on the seventh day after the surgery.

Although increasing evidence supports needle aspiration as compared to incision and drainage in the management of breast abscesses, various gaps in the literature exist. Pakistan does not have any large-scale, prospective, multicenter comparative data on these two treatment modalities, and most of the existing data is based on small, single-center retrospective studies or global cohorts that may not be representative of local patients, healthcare facilities, and resistance patterns of pathogens. This study aimed to compare the efficacy of ultrasound-guided

needle aspiration and incision and drainage in the treatment of breast abscesses in a tertiary care unit in Pakistan.

METHODS

This retrospective comparison study was conducted in the Department of Surgery, Hayatabad Medical Complex, Peshawar, within a three-month duration (August 2025 to October 2025), with the institutional ethical review commission (IRB Approval number 2687; dated 13th August 2025) concurring with it. An assessment of patient data was conducted retrospectively by reviewing medical records of the hospital and departmental surgical logs. The necessary number of cases per group was set to 55 to achieve a 95% confidence level and 80% test power since the former had been reported to be 97.1% successful with needle aspiration and 82.9% successful with incision and drainage. Patients were put in the right therapy groups based on the management they had before recorded in their medical records. The trial involved female subjects aged 18 to 60 years who had a breast abscess lasting at least three days that was treated using ultrasound-guided needle aspiration or incisions and drainage. The patients with a body mass index (BMI) above 29.9, a history of chronic diabetes mellitus, or other severe comorbidities that may interfere with wound healing or response to infections had been excluded. These exclusion criteria were employed to minimize the chances of confounding factors and ensure that the comparability of the two groups was achieved. Patient data, including demographic, clinical presentation, method of treatment, antibiotic regimen, and postoperative follow-up information, were obtained in the hospital using the electronic and manual medical records. Procedural details were checked by using operative notes and ultrasound reports. Group A comprised patients who had been treated by incision and drainage under general anesthesia, and Group B comprised patients treated by ultrasound-guided needle aspiration, which was done within up to three consecutive sessions by a surgeon with at least five years of experience. All patients took 1 gram of oral cotrimoxazole daily for 14 days as a part of their usual treatment regimen. Pain assessment levels and treatment outcomes were recorded in the outpatient follow-up charts during the follow-up visits, which were normally around the seventh day after the surgery. The primary outcome was treatment success (complete abscess closure without recurrence or further surgical intervention). Secondary outcomes were recovery time and levels of surgical pain. Pain scale measurement was an evaluation of the visual analogue scale (VAS), which was introduced into patient charts. The research was conducted in accordance with the permission granted by the Institutional Review Board. Going by ethical provisions

of retrospective research, individual informed permission was not necessary since the research involved the use of already-existing hospital information and not direct interaction with the patients. All patient information was anonymized and kept confidential before the analysis.

Data were analyzed using SPSS version 23.0. Continuous variables such as age and BMI were expressed as mean $\pm$ standard deviation and compared between groups using the independent samples t-test. Categorical variables, including treatment success and lactational status, were presented as frequencies and percentages and compared using the Chi-square test. Chi-square (χ^2) values and corresponding p-values were reported for frequency comparisons. A 95% confidence interval was applied, and a p-value of less than 0.05 was considered statistically significant. Chi-square analysis was then done in a post-stratification manner. To make it clear, the results were provided in tables and graphs.

RESULTS

Demographic features of the two study groups were the same in terms of age and body mass index (BMI). In the first group, Group A, which included the patients with incision and drainage (I/D), the mean age was 29.17 years, and the standard deviation was 9.44 years. Group B consisted of patients whose average age was 30.11 years, and the standard deviation was 8.56 years; they had ultrasound-guided needle aspiration. The BMI scores were similar across the groups, with Group A having a mean BMI of 23.6 kg/m² and Group B having just a slightly higher mean BMI of 24.2 kg/m². The data reveal that there was no significant difference between the two groups in terms of demographics, and this minimized the chances of confounding factors in terms of age or BMI difference (Table 1).

Table 1: Baseline Demographic Characteristics of Patients Undergoing Incision & Drainage (I/D) and Ultrasound-Guided Needle Aspiration (n=110)

Variables	Group A (I/D) (n=55), Mean $\pm$ SD	Group B (Needle Aspiration) (n=55), Mean $\pm$ SD	p-value
Age (years)	29.17 $\pm$ 9.44	30.11 $\pm$ 8.56	0.58
BMI (kg/m ²)	23.6 $\pm$ 2.9	24.2 $\pm$ 3.1	0.41

Independent samples t-test applied. A p-value <0.05 was considered statistically significant

To answer the question of whether the status of breastfeeding may play a role in the outcome of the treatment, the proportion of lactating and non-lactating women in the two treatment groups was studied. Group A (incision and drainage) contained 55 patients, with 39 (70.9%) being nursing and 16 (29.1%) not. Group B (needle aspiration) consisted of 24 (43.6%) and 31 (56.4%) patients who were not and were lactating, respectively. Out of the total number of patients, 110, 70 (63.6%) were nursing and

40 (36.4%) were not. Despite having a larger number of lactating women in Group A, compared to Group B, both groups had a mix of patients who were and were not nursing, which made it possible to assess the effectiveness of the treatment between such groupings (Table 2).

Table 2: Distribution of Lactational Status Among Patients in Both Treatment Groups

Lactation Status	Group A, n (%)	Group B, n (%)	p-value
Yes	39 (70.9%)	31 (56.4%)	0.08
No	16 (29.1%)	24 (43.6%)	
Total	55 (100%)	55 (100%)	—

The acuity of the success of the treatment in the two groups showed a statistically significant difference. In Group A (incision and drainage), 37 of 55 (67.3%) of patients were successfully treated, and in Group B (needle aspiration), 53 of 55 patients (96.4%) were successfully treated. Group A had 18 patients (32.7% fail to respond to treatment) and Group B had 2 patients (3.6%), who had an overall success rate of 90 of 110 in both groups. The Chi-square test was used to determine the difference between the success rates of the two groups, and a p-value of less than 0.01 was obtained, which implied that the difference was highly significant. This observation indicates that ultrasound-directed needle aspiration is much more effective than incision and drainage in the management of breast abscesses (Table 3).

Table 3: Comparison of Treatment Success Between Incision & Drainage and Ultrasound-Guided Needle Aspiration

Outcomes	Group A (I/D), n (%)	Group B (Needle Aspiration), n (%)	χ^2	p-value
Success	37 (67.3%)	53 (96.4%)	17.82	<0.01*
Failure	18 (32.7%)	2 (3.6%)		
Total	55 (100%)	55 (100%)	—	—

*Chi-square test applied

DISCUSSION

The breast is one of the female secondary sex characteristics. To ensure that the breast is preserved in value and functionality throughout the course of treatment, one should make an effort to minimize any form of compromise against the shape and contour of the breast. In developed countries, breast abscesses are decreasing due to the improved maternal nutrition level, hygiene, standard of living, and early treatment with antibiotics. Nevertheless, breast abscess is still a major issue in women in developing countries [12]. In case of the occurrence of a breast abscess, draining and excising of the pus is the targeted intervention; it is offered as the first-line treatment. Incision drainage is an invasive procedure in breast abscesses, which can leave an unsightly scar, take more time to heal, leave the mother with an unpleasant wound on the breast (it is a very

innervated organ, especially around the nipple areola complex), require general anesthesia and repeated dressings following the procedure, as well as leaving the mother with problems breastfeeding [12, 13]. Other possible effects include Keloid growth and hypertrophic scarring. A mammary fistula can be caused by opening up a milk duct in the process of surgery to deal with a subareolar breast abscess due to periductal mastitis. Breast deformity and adhesions of the glandular tissue can also result from surgical drainage [12]. The latest form of treatment for most abscesses is multiple needle aspirations with antibiotic cover. In most of the instances of breast abscess, it is a less invasive care method that may replace surgery. As it has been demonstrated, needle aspiration is the most desirable way of treating breast abscesses [14, 15]. The findings of this research indicate that ultrasound-assisted needle aspiration is evidently better than incision and drainage (I/D) in the treatment of breast abscesses, particularly in terms of patient outcome and success of its treatment. The baseline demographics of the two treatment groups (age and body mass index, BMI) did not differ significantly between the two treatment groups. This ensured that the nature of the intervention methods, rather than demographic variables, would be the ones to blame for the treatment outcomes. Traditionally, breast abscesses have been treated with the help of surgical incision and drainage, yet this approach has several drawbacks, including the prolonged period of recovery, scarring, inability to breastfeed, and additional discomfort in patients [16]. The present study is aligned with the newer data indicating that ultrasound-guided needle aspiration is a less invasive procedure that enhances patient adherence and accelerates the healing process [16-18]. In this research, 96.4 percent of patients in Group B (needle aspiration) were symptom-relieved, which is significantly higher than the 67.3 percent of patients in Group A (I/D). The practical value of this difference ($p < 0.01$) indicates the effectiveness of needle aspiration. In a study, similar results showed that ultrasound-guided aspiration recorded a 95 percent success rate as opposed to 86 percent for incision and drainage [19]. This implies that needle aspiration is not only an effective means of first-line treatment of uncomplicated breast abscesses, but also an effective mode of treatment. The lactation status was also determined to determine its potential impact on the outcome of treatment. The fact that both groups were composed of a large proportion of a mix of lactating and non-lactating patients, even though Group A consisted of more lactating women than Group B, made an objective assessment across subgroups possible. The general preponderance of breastfeeding women represented in the sample indicates the prevalence of lactational breast

abscesses due to earlier studies indicating lactation to be an important risk factor [20]. The proper localization of the abscess cavity, avoidance of considerable tissue trauma, reduction of pain, and maintenance of breastfeeding are just some of the advantages of needle aspiration, especially when performed under ultrasound guidance [21]. These benefits are critical in the case of nursing moms who often desire to continue breastfeeding during and after chemotherapy. Also, eliminating the need to admit patients to a hospital and general anesthesia, many aspirations can be performed as outpatient procedures, which lessens the economic and resource burden on health systems. Conversely, although considered to be the standard treatment in the past, incision and drainage are associated with long recovery periods and may cause disruptions with breastfeeding [22]. The increased failure rate that was demonstrated in I/D group in this study may be due to incomplete drainage, reinfection, or complications of surgical intervention. The current findings add to the growing body of information that there should be a shift in the clinical practice towards the less invasive methods of treatment of breast abscesses, particularly when it comes to patients who have been thoroughly selected. The most important thing to keep in mind is that larger or multiloculated abscesses or those that fail to respond to the early needle aspiration may still require surgical drainage. Thus, when developing individualized treatment recommendations, patient choices, abscess characteristics, and clinical manifestations must all be considered.

This study has several limitations. First, the retrospective design limits the ability to establish causal relationships and is subject to selection and information bias due to reliance on existing medical records. Second, the study was conducted at a single tertiary care center over a short duration, which may limit the generalizability of the findings to other settings. Third, cosmetic outcomes were not objectively measured using a standardized scoring system, and detailed quantitative comparison of postoperative pain scores was not separately tabulated, which restricts comprehensive assessment of patient-centered outcomes. Additionally, long-term recurrence rates were not evaluated beyond the routine follow-up period. Future prospective multicenter studies with standardized outcome measures and longer follow-up are recommended to validate these findings.

CONCLUSIONS

This study demonstrates that ultrasound-guided needle aspiration is more effective than incision and drainage in the management of breast abscesses. It offers several advantages, including a minimally invasive approach, improved clinical recovery, preservation of breastfeeding,

and better cosmetic outcomes. Given its favorable patient-centered profile and reduced tissue trauma, ultrasound-guided needle aspiration should be considered the preferred first-line treatment in appropriately selected patients with uncomplicated breast abscesses, while surgical drainage may still be required in complex or refractory cases.

Authors' Contribution

Conceptualization: AT

Methodology: AM, AT

Formal analysis: AAT, SA¹

Writing and Drafting: AM, AT, SA¹, SA²

Review and Editing: AM, AT, SA¹, SA²

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Effectiveness of Intravitreal Bevacizumab (Avastin™) in Vitreous Hemorrhage Associated with Proliferative Diabetic Retinopathy

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ARTICLE INFO

Keywords:

Bevacizumab, Proliferative Diabetic Retinopathy, Vitreous Haemorrhage, Visual Acuity

How to Cite:

Zarkesha, ., Iqbal, S., Khalid, M. K., & Ullah, M. I. (2026). Effectiveness of Intravitreal Bevacizumab (Avastin™) in Vitreous Hemorrhage Associated with Proliferative Diabetic Retinopathy: Bevacizumab for Vitreous Hemorrhage in Proliferative Diabetic Retinopathy. *Pakistan Journal of Health Sciences*, 7(8), 139-143. <https://doi.org/10.54393/pjhs.v7i8.3814>

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ABSTRACT

Proliferative diabetic retinopathy (PDR) is a major cause of vision loss in diabetic patients. Vitreous haemorrhage (VH) is a common complication of PDR that significantly affects visual acuity. Intravitreal bevacizumab (Avastin™) has been used as a treatment option for VH associated with PDR. **Objectives:** To determine the effectiveness of intravitreal bevacizumab (Avastin™) in clearing vitreous haemorrhage and improving visual acuity in patients with PDR. **Methods:** This quasi-experimental study was conducted at the Ophthalmology Department, Hayatabad Medical Complex, Peshawar, from 01-01-2025 to 30-06-2025. A total of 79 patients with PDR-associated VH were included. Patients received three intravitreal bevacizumab injections at monthly intervals. Outcomes included VH clearance, improvement in best corrected visual acuity (BCVA), and requirement of pars plana vitrectomy. Data were analysed using SPSS version 22.0. Paired sample t-test and Chi-square test were applied, with $p \leq 0.05$ considered statistically significant. **Results:** The mean age of participants was 41.49 ± 10.54 years. VH clearance was observed in 67 (84.8%) patients, while improvement in BCVA occurred in 57 (72.2%) patients. Pars plana vitrectomy was required in 14 (17.7%) patients. Mean BCVA significantly improved from 0.81 ± 0.10 logMAR pre-therapy to 0.45 ± 0.24 logMAR post-therapy ($p < 0.001$). Significant associations were observed between baseline BCVA and improvement in visual acuity ($p = 0.011$) and requirement of vitrectomy ($p = 0.046$). **Conclusions:** Intravitreal bevacizumab (Avastin™) is an effective treatment for VH in PDR, resulting in significant improvement in visual acuity, enhanced haemorrhage clearance, and reduced need for surgical intervention.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the largest growing epidemic globally, with a reported recent prevalence of 10.5%, which approximates to half a billion people [1]. In Pakistan, this epidemic is also on the rise, making this country rank in the top ten nations that are sufferers of this potentially life-threatening condition, with a prevalence of 10%, approximating to a population of 24 million people [2]. This disease can impact the life of a sufferer since it can not only reduce the quality of life of patients but also cause a significant economic burden [3, 4]. One reason that can be attributed to this high economic burden, as well as the

decline in quality of life, is the development of diabetic retinopathy (DR), which is among the leading causes of permanent blindness globally [5]. The primary mechanism by which this complication of T2DM develops is the production of abnormally high amounts of vascular endothelial growth factor (VEGF) in response to oxidative stress caused by persistently deranged glycaemic control. VEGF results in progressive proliferation of vessels in the retina, leading initially to non-proliferative and subsequently proliferative DR (PDR), which can result in intra-vitreous haemorrhage (VH) [6]. In these cases,



Avastin™ (bevacizumab) is considered effective due to its anti-VEGF activity. Not only is this pharmacological agent believed to effectively clear the PDR-related VH, but it also prevents the development of VH in patients with PDR [7, 8]. In this instance, a study recently conducted reported that in patients who developed VH secondary to PDR, intravitreal bevacizumab (IVB) effectively cleared VH in 92% of the cases. Moreover, it was also found that IVB reduced the requirement of pars plana vitrectomy (PPV) by 72% and improved the best corrected visual acuity (BCVA) in 66% of the patients [9].

IVB can serve as a useful intervention in PDR and associated VH; however, supporting evidence in the local population is not only lacking but is also outdated. Furthermore, availability and cost are other factors that affect its usage in our community. This study was thus conducted to determine the effectiveness of IVB in the treatment of VH associated with underlying PDR. This study aimed to evaluate the effect of intravitreal bevacizumab in the treatment of vitreous hemorrhage in proliferative diabetic retinopathy.

METHODS

This quasi-experimental study was held at Hayatabad Medical Complex, Ophthalmology Department, Peshawar, Pakistan, from 1 January 2025 to 30 June 2025. Ethical approval was obtained from the Institutional Research & Ethical Board / Hospital Research and Ethical Committee (IREB), Hayatabad Medical Complex, Peshawar (Approval No. 939; dated 16th December 2022). The sample size was calculated for the estimation of a single proportion using the formula $n = Z^2 \times p(1-p) / d^2$, where $Z=1.96$ for 95% confidence level, $p=0.92$ (anticipated frequency of vitreous haemorrhage clearance based on Wirkkala et al.), and $d = 0.06$ (margin of error) [9]. This yielded a minimum sample size of approximately 79 participants. The calculation was performed using the WHO sample size calculator/software. Before inclusion, it was ensured that all the parents of the patients gave their explicit informed consent in written form, for which a dedicated pre-printed form was used. Patients aged 25-60 years, male or female gender, who suffered from PDR and associated VH were included. Patients who previously used intravitreal Avastin™, had undergone pan-retinal photocoagulation (PRP) previously, pregnant women, had tractional or any other retinal detachment on B scan, which is a contraindication for intravitreal anti-VEGF injection, and those who had VH due to causes other than PDR (like retinal detachment, retinal vein blockage) were excluded. Diagnosis of PDR and associated VH was made through indirect funduscopy showing dot and blot haemorrhages, hard exudates, and a network of abnormal new vessels on the retina, along with visualization of blood in the vitreous. Baseline

characteristics, including age, gender, and BCVA, were documented. After that, all the included patients were treated with a course of three injections of bevacizumab in the vitreous that was given at one monthly interval under aseptic conditions. At the end of three months, patients were assessed for the effectiveness of bevacizumab. The primary measure of effectiveness was the frequency of clearance of VH. Secondary outcome measures of effectiveness were improvement in BCVA and the requirement of PPV in case VH was not cleared after therapy. Assessment of effectiveness outcomes was made after one week of completion of therapy.

All the collected data were input and analyzed with SPSS version 22.0. Qualitative and quantitative variables were collected using descriptive statistics. Qualitative variables (gender, clearance of VH, BCVA improvement, and requirement of PPV) were measured as frequency and percentage. Quantitative variables (age and BCVA) were measured as mean $\pm$ standard deviation (SD). VH clearance frequency stratification was based on age, gender, and pre-therapy BCVA. Post-stratification analysis was done using the chi-square test. A p -value ≤ 0.05 was considered significant.

RESULTS

In this study, 79 patients were included. Mean age was 41.49 ± 10.54 years. There were 49 (62.00%) male and 30 (38.00%) female patients. Mean pre-therapy BCVA was 0.80 ± 0.10 logMAR (Table 1).

Table 1: Pre-therapy demographic characteristics of patients (n=79)

Characteristics	Mean $\pm$ SD / n (%)
Mean Age (years)	41.49 $\pm$ 10.54
< 42 years	45 (57.00%)
≥ 42 years	34 (43.00%)
Gender	
Male	49 (62.00)
Female	30 (38.00)
Mean BCVA (logMAR)	0.80 $\pm$ 0.10
< 0.9 logMAR	36 (45.60)
≥ 0.9 logMAR	43 (54.40)

SD=Standard deviation

The frequency of VH clearance in patients who were treated with intravitreal bevacizumab was 67 (84.80%). The frequency of improvement of BCVA post-therapy in these patients was 57 (72.20%). PPV was required in 14 (17.70%) patients. Stratification of effectiveness outcomes based on confounding variables, including age, gender, and pre-therapy BCVA (Table 2).

Table 2: Stratification of Effectiveness Outcomes Based on Confounding Variables(n=79)

Outcomes	<42 years % (n=45)	≥42 years % (n=34)	p-value ^c
Age			
VH clearance	36	31	0.171
Improvement in BCVA	32	25	0.812
PPV Required	11	3	0.072
Outcomes	Male % (n=49)	Female % (n=30)	p-value ^c
Gender			
VH clearance	42	25	0.775
Improvement in BCVA	34	23	0.484
PPV Required	9	5	0.848
Outcomes	<0.9 logMAR (n=36)	≥0.9 logMAR (n=43)	p-value ^c
Pre-therapy BCVA			
VH clearance	33	34	0.120
Improvement in BCVA	31	26	0.011*

PPV required	3	11	0.046*
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VH=Vitreous haemorrhage, BCVA=Best corrected visual acuity, PPV=Pars plana vitrectomy, c=Chi-square test
*indicates statistical significance at $p \leq 0.050$

A paired sample t-test was conducted to compare the best corrected visual acuity before and after intravitreal Bevacizumab injection. The mean pre-therapy BCVA was 0.81 ± 0.10 logMAR, which significantly improved to 0.45 ± 0.24 logMAR post-therapy. The mean improvement was 0.36 logMAR (95% CI: 0.30–0.41; $t=13.16$, $df=78$, $p<0.001$). These findings demonstrate that intravitreal Bevacizumab is highly effective in improving visual acuity in patients with vitreous hemorrhage due to proliferative diabetic retinopathy. This improvement corresponds approximately to a change from 6/38 to 6/17 vision, indicating a major functional gain (Table 3).

Table 3: Comparison of Pre-therapy and Post-therapy BCVA(logMAR) Using Paired t-Test(n=79)

Variables	Mean $\pm$ SD	Mean Difference	95% CI of Difference	t-value	df	p-value
Pre-therapy BCVA	0.8089 $\pm$ 0.1002	—	—	—	—	—
Post-therapy BCVA	0.4519 $\pm$ 0.2380	0.35696 $\pm$ 0.24109	0.30296 to 0.41096	13.160	78	<0.001*

BCVA = Best corrected visual acuity,

* Indicates statistical significance at $p \leq 0.050$

DISCUSSION

The present study focused on one of the therapeutic interventions of PDR, which is one of the prevailing ocular morbidities contributing to the high global burden of permanent visual loss [10]. In current study, focus was put on PDR cases further complicated by VH, which is a well-known complication of this diabetic complication of the retina [11, 12]. Therapeutic intervention in the present study was selected based on one of the most common pathophysiological mechanisms involved in the development of this condition, which is aberrant VEGF production mediated by neo-angiogenesis [13]. In the present study, the mean age of the patients suffering from PDR was 41.49 years. In comparison, a study found that the mean age of the patients suffering from this diabetic complication of the eye was 52 years, which is comparable to the present study [14]. In another study, in which clinical characteristics of patients with DR were analysed, it was found that the age range that was affected most by this diabetic complication was between 41 and 60 years [15]. This trend was also similar to the trend of age group distribution of this retinal disease in the present study, with more patients with this condition belonging to the older age group. One major reason that explains this trend is that as people grow older, their duration of having DM increases, which predisposes them to develop complications of this multi-system disease. Upon analysis of the distribution of

this condition in genders, there was a clear male predominance observed in the present study, with males making up 62% of the study population. Similar to this trend observed in the present study, a study was conducted recently in Pakistani diabetic populations in which it was observed that among male patients, PDR was found in 25.2%, while in female patients, it was only found in 8.5%, exhibiting a clear male predominance [16]. In another study, similar male predominance was observed in the frequency distribution of DR among diabetic patients, with males making up the majority of patients having DR, reaching as high as 71.77% [17]. The exact mechanism of male predominance in this condition is not known, but according to previous literature, this difference is driven by multifactorial pathophysiology, including the gender differences in sex hormones, inflammatory cytokine profiles, and socio-behavioural aspects of life [18]. In the present study, the frequency of VH clearance in patients who were treated with intravitreal bevacizumab was 67 (84.80%). The frequency of improvement of BCVA post-therapy in these patients was 57 (72.20%). PPV was required in 14 (17.70%) patients. Compared to this, a study conducted in HD-treated patients with PDR-related VH with intravitreal bevacizumab. The results showed that VH was completely cleared in 92% of patients, and the BCVA was significantly improved compared to the pre-therapy

BCVA in 66% of patients. In addition, they also reported that PPV was required in only 28% of the patients after this therapy [9]. Another study was conducted with a similar aim in Pakistan, in which 131 patients with concomitant VH and PDR were included. These patients were treated with the Avastin™ therapy administered into the vitreous cavity at one-month intervals. After treatment, assessment was made in these patients, and it was found that only 33% patients exhibited no improvement in BCVA, while all other patients showed improved BCVA after therapy. Similarly, it was found that PPV was performed in 23.8% of the patients after administration of this useful therapy [19]. Similarly, in a comparative study, one group of PDR patients received bevacizumab therapy, and it was observed that the post-therapy BCVA was significantly improved as compared to the pre-therapy levels ($p < 0.001$), thereby exhibiting the effectiveness of this therapy in managing patients with PDR, which is a major vision-threatening diabetic complication [20]. The present study provides useful insights regarding the effectiveness of Avastin™ therapy in managing patients with VH related to PDR. Its uniqueness lies in the fact that this study, instead of focusing on the PDR patients, focused on a specific subset of PDR patients who had VH, who often are managed surgically through PPV. Results from this study suggest that with the use of this intravitreal therapy, the rate of PPV can be reduced and VH can be managed effectively with favourable visual outcomes. Lack of control arm was the only limitation of the present study, for which the conductance of further clinical trials with a control arm in this specific subset of PDR patients is highly recommended.

Limitations of the study included that it was performed at a single tertiary care centre with a small sample size and a short duration of follow-up (three months). This study was also quasi-experimental and did not have a control or comparison group (laser photocoagulation or early vitrectomy). The outcome in terms of vitreous haemorrhage clearance and improvement in BCVA was observed without a detailed study of recurrence or long-term complications. We recommend conducting large multicenter randomized controlled trials with longer follow-up to evaluate sustained visual outcome, haemorrhage recurrence, and the need for later surgical intervention. Comparison with other modalities of treatment in proliferative diabetic retinopathy patients will add more strength to the present study.

CONCLUSIONS

In conclusion, intravitreal Avastin™ (bevacizumab) is a highly effective therapy in managing patients with proliferative diabetic retinopathy-related vitreous haemorrhage since it not only provides favourable outcomes in the form of clearance of vitreous

haemorrhage and improvement in visual acuity but also reduces the need for surgical intervention in the form of pars plana vitrectomy.

Authors' Contribution

Conceptualization: Z

Methodology: Z

Formal analysis: Z, SI, MKK

Writing and Drafting: Z

Review and Editing: Z, SI, MKK, MIU

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Efficacy of Oral Potassium Citrate in Reducing Double-J Ureteric Stent Encrustations: A Retrospective Cohort Study from a Single Tertiary Care Center

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ARTICLE INFO

Keywords:

Double-J Stent, Encrustations, Potassium Citrate, Urine Alkalinization, Stent Complications

How to Cite:

Irfan, M., Cheema, U. K., Habib, T., Manzoor, I. B., & Ali, R. N. (2026). Efficacy of Oral Potassium Citrate in Reducing Double-J Ureteric Stent Encrustations: A Retrospective Cohort Study from a Single Tertiary Care Center: Oral Potassium Citrate in Reducing Double-J Ureteric Stent Encrustations. *Pakistan Journal of Health Sciences*, 7(8), 144-149. <https://doi.org/10.54393/pjhs.v7i8.4107>

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ABSTRACT

Double-J (DJ) ureteric stent encrustation is a significant complication in endourological practice. The role of oral potassium citrate in mitigating stent encrustations remains inadequately studied. **Objectives:** To evaluate the efficacy of oral potassium citrate supplementation in reducing DJ stent encrustations and identify associated risk factors. **Methods:** A retrospective cohort study was conducted at Gujranwala Teaching Hospital (October 2022 to October 2025) involving 504 patients with DJ stents. Group 1 (n=249) received oral potassium citrate (20 mEq twice daily) until stent removal; Group 2 (n=255) received no supplementation. Encrustation was assessed using the KUB grading system. **Results:** Overall encrustation prevalence was 18.05% (91/504) with a mean KUB score of 6.2 ± 2.90 . Encrustation rates were significantly lower in Group 1 (5.2%) versus Group 2 (30.58%) ($p < 0.001$). Urinary tract infections were more common in Group 2 (55.8%) than in Group 1 (30%) ($p = 0.006$). Multivariate regression identified non-utilization of potassium citrate (adjusted OR: 0.52, 95% CI: 0.37-0.74), prolonged indwelling duration >180 days (adjusted OR: 3.45, 95% CI: 2.41-4.94), and male gender (adjusted OR: 1.62, 95% CI: 1.18-2.23) as independent predictors (all $p < 0.005$). **Conclusions:** Oral potassium citrate supplementation significantly reduced DJ stent encrustations. Male gender, prolonged indwelling time, and non-utilization of potassium citrate were strong independent predictors. Prospective randomized trials are recommended to validate these findings.

INTRODUCTION

The field of endourology is greatly reliant on the use of double-J (DJ) ureteric stents since their introduction by Finney in 1978 [1]. These ureteral stents are predominantly deployed after stone disintegration procedures to maintain effective urinary drainage postoperatively. Ureteral stents come in various configurations, including single-J, double-J, magnetic-tip, and straight-tip designs [2]. They are further classified by material composition into synthetic (silicone and polyurethane) and biodegradable (polylactic acid and glycolic acid) categories [3]. These stents are typically placed for approximately six weeks and require replacement thereafter due to the development of stent-related complications, including infections, lower urinary

tract symptoms, hematuria, and stent encrustations [4]. Prolonged indwelling may additionally result in stent fragmentation, obstruction, migration, and secondary stone formation [5]. Various interventional procedures, including extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, and percutaneous approaches, may be required for the removal of neglected or encrusted DJ stents [6]. The pathophysiology of DJ stent encrustation is multifactorial and incompletely understood. Biofilm formation and bacterial colonization by urease-producing organisms such as *Proteus*, *Klebsiella*, and *Pseudomonas* species contribute to encrustation development [7]. However, calcium oxalate remains the most common



encrustation component, suggesting that non-infectious mechanisms also play a significant role [8]. Changes in urinary composition, including supersaturation, deficiency of crystallization inhibitors, and metabolic derangements, promote encrustation even under sterile conditions [9]. Prolonged indwelling time is the most extensively studied risk factor, with significant encrustations potentially compromising stent tensile strength and leading to fracture during removal [10]. Furthermore, chronic encrustations may cause ureteral damage or avulsion during extraction and can result in complete obstruction of urinary drainage, potentially leading to loss of renal function [11]. In addition to surgical management of encrusted stents, various oral agents have been investigated for prevention. Elatreisy *et al.* studied ascorbic acid supplementation for reducing DJ stent encrustations [12]. Multiple studies have demonstrated the efficacy of potassium citrate in alkalinizing urine and preventing calcium oxalate and uric acid crystal formation [13, 14].

However, there is limited evidence specifically examining the impact of oral potassium citrate supplementation on DJ stent encrustation. This study aimed to evaluate the efficacy of oral potassium citrate supplementation in reducing the incidence of DJ stent encrustations and to identify predictive risk factors associated with stent encrustation in a large retrospective cohort.

METHODS

This was a single-centre, retrospective (non-concurrent) cohort study conducted at the Department of Urology, Gujranwala Teaching Hospital, from 22nd October 2022 to 23rd October 2025. The study was approved by the Institutional Review Board of Gujranwala Medical College (Protocol Number: Admin R.C. No. 5169; dated 2nd August 2022). Patients were counselled regarding the use of potassium citrate supplementation, potential adverse effects, and the study objectives. For the retrospective component, a waiver of written consent was obtained from the Institutional Review Board, given the non-interventional nature of data collection. The sample size was determined based on the number of eligible patients presenting during the study period, as this was a non-concurrent cohort study. A total of 504 patients met the inclusion criteria. The study included patients aged 18 years or older, irrespective of gender, who underwent endourological procedures with DJ stent placement for an intended duration of six weeks. Patients were excluded if they were pregnant, on digoxin therapy, had pre-existing hyperkalaemia, had a history of metabolic disorders, or had silicone ureteric catheters placed. Group assignment was based on clinical decision and patient compliance. Group 1 (n=249) comprised patients who were prescribed and

demonstrated regular usage of oral potassium citrate (K-stone tablets, 20 milliequivalents twice daily, total dose 40 mEq/day) from discharge until DJ stent removal. Regular usage was defined as self-reported daily intake of the prescribed medication at each scheduled follow-up visit, confirmed by review of pharmacy dispensing records where available. Group 2 (n=255) comprised patients who did not receive or did not use the potassium citrate supplement. It should be noted that this was not a randomized allocation, and potential selection bias is acknowledged as a limitation of the study design. Before DJ stent removal, all patients underwent plain radiography of the kidneys, ureters, and bladder (X-ray KUB). Patients presenting beyond the six-week timeframe were additionally evaluated with non-contrast computed tomography (NCCT). The severity of DJ stent encrustation was assessed using the KUB scoring system described by Arenas *et al.*, which grades each portion of the stent (K = upper coil, U = shaft, B = lower coil) individually on a scale of 1 to 5 based on encrustation severity. The total cumulative score ranges from 3 to 15. KUB scoring was performed by the operating urologist, who was not blinded to group allocation, which is acknowledged as a potential source of observer bias. Laboratory investigations, including complete urine examination, serum creatinine, complete blood count, serum electrolytes (potassium and calcium), and urine culture, were performed before the procedure and weekly for six weeks until the DJ stent removal. No cases of hyperkalaemia or other clinically significant adverse drug reactions were documented in either group during the monitoring period. No significant drug-drug interactions were identified. All patients received prophylactic ceftriaxone 1g intravenously before DJ stent removal under spinal or general Anesthesia. Stents were removed cystoscopically using forceps. ESWL, ureteroscopy, and laser fragmentation were not required in any patient. The primary outcome was the rate of DJ stent encrustation. Secondary outcomes included encrustation severity (KUB score), stent-related adverse events (urinary tract infections, haematuria), and identification of predictive risk factors. Forgotten or neglected stents were defined as those with an indwelling time exceeding six weeks.

Data were analyzed using SPSS version 29.0. Numerical data were summarized as means $\pm$ standard deviations (SD). Categorical data were expressed as frequencies and percentages. An independent t-test was used for normally distributed continuous variables, while the Mann-Whitney U test was applied for non-normally distributed variables. The chi-square test was used for categorical comparisons. Univariate logistic regression was performed to identify potential predictors of stent encrustation. Variables with $p < 0.200$ on univariate analysis were entered into a

multivariate logistic regression model. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). The Hosmer-Lemeshow goodness-of-fit test was used to assess model calibration. Statistical significance was defined as $p < 0.005$.

RESULTS

A total of 504 patients were enrolled in this study with a mean age of 40.56 ± 17.40 years. Of these, 91 patients (18.05%) developed stent encrustations. The mean K, U, and B encrustation scores were 2.04 ± 1.32 , 1.90 ± 1.28 , and 2.05 ± 1.35 , respectively, with a mean total KUB score of 6.2 ± 2.90 . The results present the demographic characteristics, stone specifications, and clinical outcomes for both study groups. The groups were comparable in terms of age, gender distribution, stone laterality, stone size, and stone site. The mean KUB sub-scores and total encrustation scores were significantly higher in Group 2 (non-supplementation) compared to Group 1 (supplementation). The encrustation rate was 5.2% in Group 1 compared to 30.58% in Group 2 ($p < 0.001$). Urinary tract infections were more prevalent in Group 2 (55.8%) compared to Group 1 (30%) ($p = 0.060$). Haematuria rates did not differ significantly between groups ($p = 0.070$) (Table 1).

Table 1: Patient Demographic Data and Clinical Outcomes by Study Group

Variables	Group I (n=249), Mean $\pm$ SD / %	Group II (n=255), Mean $\pm$ SD / %	p-value
Age (Range)	40.2 $\pm$ 16.8 (19-71)	41.1 $\pm$ 17.9 (20-72)	0.740
Gender Male/Female	44%/56%	40%/60%	0.960
K score	1.80 $\pm$ 1.12	2.21 $\pm$ 1.45	0.020
U score	1.73 $\pm$ 1.08	2.30 $\pm$ 1.52	0.030
B score	1.42 $\pm$ 0.98	2.53 $\pm$ 1.61	0.010
Total Score	4.57 $\pm$ 2.34	8.03 $\pm$ 3.18	<0.001
Stone laterality (Right/Left)	53%/47%	49%/51%	0.910
Stone Size (mm)	8.1 $\pm$ 2.3	8.3 $\pm$ 2.5	0.670
Stone site (renal/ureteric)	59%/41%	61%/39%	0.450
Haematuria	34.9%	30.1%	0.070
Urinary Tract Infection	30%	55.8%	0.060
Encrustation	5.2%	30.58%	<0.001

SD = Standard Deviation, p-values < 0.005 are considered statistically significant

The study compares the demographic and clinical characteristics of patients with and without stent encrustations. DJ stent encrustations were significantly more frequent in males (70%) compared to females (30%) ($p = 0.004$). Patients with encrustation had a significantly longer median stent indwelling duration (270 days) compared to those without encrustation (110 days) ($p < 0.001$). Body mass index did not differ significantly between the groups ($p = 0.200$) (Table 2).

Table 2: Demographic And Clinical Characteristics of Patients with and Without Stent Encrustations

Variables	Encrustation (n=91)	No Encrustation (n=413)	p-value
Gender Male/Female	70%/30%	36%/64%	0.004
Median stent duration (days)	270	110	<0.001
BMI (Mean $\pm$ SD)	26.12 $\pm$ 2.14	25.76 $\pm$ 2.92	0.200
UTI (%)	55.8%	30%	0.060
Haematuria (%)	34.9%	30.1%	0.070

SD = Standard Deviation, p-values < 0.005 are considered statistically significant

The study presents the results of the univariate logistic regression analysis. Several variables were identified as potential predictors of stent encrustation, including male gender (OR: 1.75, 95% CI: 1.42-2.85, $p < 0.001$), potassium citrate intake (OR: 0.60, 95% CI: 0.45-0.87, $p < 0.001$), and stent duration exceeding 180 days (OR: 3.80, 95% CI: 2.70-6.40, $p < 0.001$) (Table 3).

Table 3: Univariate Logistic Regression Analysis of Variables Associated with Stent Encrustations

Variables	Odds Ratio (95% CI)	p-value
Age	1.01 (0.95-1.07)	0.870
Male Gender	1.75 (1.42-2.85)	<0.001
Potassium Citrate Intake	0.60 (0.45-0.87)	<0.001
Duration of Stent >180 Days	3.80 (2.70-6.40)	<0.001
BMI	1.03 (0.91-1.17)	0.620
UTI	1.45 (0.88-2.39)	0.140

CI = Confidence Interval; OR = Odds Ratio, p-values < 0.005 are considered statistically significant

The study presents the multivariate logistic regression results. After adjusting for confounders, three variables remained independently significant predictors of stent encrustation: non-utilization of potassium citrate (adjusted OR: 0.52, 95% CI: 0.37-0.74, $p < 0.001$), male gender (adjusted OR: 1.62, 95% CI: 1.18-2.23, $p = 0.003$), and prolonged stent indwelling duration exceeding 180 days (adjusted OR: 3.45, 95% CI: 2.41-4.94, $p < 0.001$). The Hosmer-Lemeshow goodness-of-fit test yielded a non-significant result ($p = 0.420$), indicating adequate model calibration (Table 4).

Table 4: Multivariate Logistic Regression Analysis of Independent Predictors of Stent Encrustations

Variables	Adjusted Odds Ratio (95% CI)	p-value
Male Gender	1.62 (1.18-2.23)	0.003
Potassium Citrate Intake	0.52 (0.37-0.74)	<0.001
Duration of Stent >180 Days	3.45 (2.41-4.94)	<0.001

CI = Confidence Interval; OR = Adjusted Odds Ratio, Hosmer-Lemeshow goodness-of-fit test: $p = 0.420$. p-values < 0.005 are considered statistically significant

DISCUSSION

Double-J stent encrustation is a well-documented urological complication that increases patient morbidity and may necessitate advanced interventional procedures for stent removal, including extracorporeal shock wave lithotripsy, ureterorenoscopy, and percutaneous approaches [15]. The pathogenesis of encrustation is multifactorial; Singh *et al.* demonstrated that multiple factors contribute to encrustation formation on polyurethane stents, including prolonged indwelling time, chronic infections, recurrent stone-forming history, sepsis, and atypical renal tract anatomy [16]. Tunney *et al.* compared five different stent materials in in-vitro models of hydroxyapatite and struvite encrustation and reported that silicone stents demonstrated greater resistance to encrustation compared to other materials [17]. Tomer *et al.* identified two primary mechanisms underlying encrustation: bacterial colonization by urease-producing organisms (*Proteus*, *Klebsiella*, and *Pseudomonas* species) and elevated urinary mineral concentrations, including oxalate, phosphate, and calcium [7]. Kawahara *et al.* further demonstrated that stent caliber influences encrustation risk, with larger-caliber stents showing reduced encrustation rates [18]. Several oral supplementation strategies have been investigated for the prevention of DJ stent encrustations. Torrecilla *et al.* demonstrated promising outcomes using a compound comprising a urine pH modifier and a crystallization inhibitor to reduce ureteric stent encrustations in a randomized controlled trial [19]. Compositional analysis of encrustations by Scarneciu *et al.* and Giannossi *et al.* revealed that the majority of encrustations consist of calcium oxalate and uric acid crystals without evidence of significant infection, providing a rationale for the use of potassium citrate in encrustation prevention [20, 21]. The proposed mechanism involves the binding of calcium ions with citrate to form soluble complexes, thereby reducing the supersaturation of calcium salts and preventing crystal deposition on the stent surface. Importantly, potassium citrate alkalinizes rather than acidifies urine, which further inhibits uric acid crystal formation. It should be noted that while Tavoosian *et al.* conducted a randomized trial with a smaller sample (n=70), our retrospective cohort study provides complementary evidence from a larger patient population (n=504), though with inherent limitations associated with observational study design [22].

This study has several important limitations that should be carefully considered when interpreting the results. First, the retrospective design introduces the possibility of recall bias and incomplete data capture. Second, the non-randomized group assignment may introduce selection bias, as patients who adhered to potassium citrate

supplementation may differ systematically from those who did not in ways not captured by the measured variables. Third, certain clinically relevant parameters, including serial urinary pH readings, comprehensive urine metabolic profiles, hydration status, and detailed compositional analysis of encrustations, were not consistently available and could not be included in the regression model despite being acknowledged as central to encrustation risk. Fourth, the KUB scoring was performed by the operating urologist without blinding to group allocation, introducing potential observer bias. Fifth, the sample size was based on eligible patients during the study period rather than a formal a priori power calculation, which may affect the generalizability and statistical power of the findings. Future prospective, double-blinded, randomized controlled trials with formal power calculations, objective adherence monitoring (such as urinary citrate levels), serial urinary pH measurements, comprehensive metabolic profiling, blinded outcome assessment, and longer follow-up periods are recommended to validate and extend these findings. Multi-center studies would further enhance the generalizability of the results.

CONCLUSIONS

This study demonstrates that oral potassium citrate supplementation is associated with a significant reduction in the incidence of DJ ureteric stent encrustations. Non-utilization of potassium citrate, male gender, and prolonged stent indwelling time were identified as strong independent predictors of stent encrustation on multivariate analysis. These findings support the consideration of potassium citrate supplementation as an adjunctive strategy for encrustation prevention, although further prospective randomized studies are warranted to confirm these results.

Acknowledgement

The authors acknowledge Professor Muhammad Khalid Butt for his guidance in the preparation of this academic work.

Authors' Contribution

Conceptualization: MI

Methodology: MI, UKC, IBM

Formal analysis: UKC, TH

Writing and Drafting: MI, IBM

Review and Editing: MI, UKC, TH, IBM, RNA

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Evaluation of Radiopacity of Endosequence Bio-ceramic Sealer and AH Plus by Digital Radiography

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ARTICLE INFO

Keywords:

AH Plus, BC Sealer, Endodontic Sealers, Radiography

How to Cite:

Qureshi, S., Kalhoro, F. A., Oad, H., Panhwar, M. A., Manzoor, F., & Shujrah, F. A. (2026). Evaluation of Radiopacity of Endosequence Bio-ceramic Sealer and AH Plus by Digital Radiography: Radiopacity of Endosequence Bio-ceramic Sealer and AH Plus by Digital Radiography. *Pakistan Journal of Health Sciences*, 7(8), 150-154. <https://doi.org/10.54393/pjhs.v7i8.3785>

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Received Date: 1st January, 2026

1st Revision Received: 5th March, 2026

2nd Revision Received: 8th April, 2026

Acceptance Date: 28th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Radiopacity is a key requirement for endodontic sealers to allow radiographic distinction between obturation material and surrounding tooth structures. American National Standards Institute (ANSI) and American Dental Association (ADA) mandate a minimum of 3 millimetres of aluminium (mm Al). **Objectives:** To compare, in vitro, the radiopacity of Endo-Sequence BC Sealer versus AH Plus using digital radiography on extracted human single-rooted teeth. **Methods:** An experimental in vitro study was conducted at the Department of Operative Dentistry, Liaquat University of Medical and Health Sciences, Jamshoro. A total of 60 single-rooted teeth were selected using a non-probability convenience sampling method and allocated into two groups (n=30 each) without randomization. Care was taken to ensure that the two groups were comparable in terms of tooth type and root morphology and obturated with gutta-percha plus either Endosequence BC or AH Plus. After 7 days at 37°C/100 % humidity, radiopacity was expressed as millimetres of aluminium (mm Al). Data were compared using an independent-samples t-test ($\alpha = 0.05$). **Results:** The sample analyzed consisted of 60 samples (30 samples per group). AH Plus demonstrated significantly higher radiopacity (6.94 ± 0.46 mm Al) compared to Endosequence BC (3.83 ± 0.35 mm Al). The confidence intervals were not overlapping (AH Plus: $6.77-7.10$ mm Al; Endosequence BC: $3.71-3.96$ mm Al). The difference was statistically very significant ($p < 0.01$). **Conclusions:** AH Plus demonstrated significantly higher and more consistent radiopacity than Endosequence BC, offering superior radiographic contrast and a wider safety margin for clinical detection of obturation quality.

INTRODUCTION

The root canal system is usually filled using a combination of sealer and gutta-percha. The most common reason to use gutta-percha is its good physical and biological characteristics [1]. The disadvantage of the lack of adherence of the gutta-percha to both the cement and canal walls is also a major drawback of this material. Consequently, a sealer must be employed to ensure an intimate fit of the gutta-percha to the dentinal walls [2]. Radio-opacity is considered one of the significant properties of endodontic sealers [3]. Among other

physical/chemical properties, it has been stated that the ideal root canal filling material must have a stated degree of opacity to radio-applications so that a difference may be distinguished between the material and the surrounding anatomical structure, so that the quality of root fillings can be evaluated [4-6]. The American National Standards Institute / American Dental Association (ANSI/ADA) criteria to determine the minimum requirement of the radio-opacity of the root canal filling material is that the content thereof should meet a value of radio-opacity of 3mm of

aluminum at a thickness of 1mm [7, 8]. Radio-opacity value of Endosequence BC sealer (3.834 ± 0.346 mm Al) and Radio-opacity of AH plus (6.936 ± 0.462 mm Al) [9, 10].

This study compares the radiopacity of the end sequence Bio Ceramic sealer and AH plus by using digital radiography. No local study has been conducted yet on this topic, and the radiopacity of endodontic sealers is a material-specific property that allows adequate visualization on radiographs, independent of operator skill or patient population. This study aimed to verify that the tested sealers meet the minimum radiopacity standards recommended by international guidelines.

METHODS

An experimental in vitro study was conducted at the Department of Operative Dentistry, Liaquat University of Medical and Health Science, Jamshoro, Hyderabad, in a time span of one year (i.e., 1-2-2020 to 31-1-2021) after the approval of the research proposal by CPSP/REU/DSG-2016-166-1860; dated 31st January 2020. A non-probability convenience sampling technique was used. The sample size was calculated by using the Open EPI sample size calculator. Sample size was calculated using Open Epi software by taking mean radiopacity values from previously published studies comparing calcium silicate-based and resin-based endodontic sealers. Based on reported mean [11] radiopacity values of approximately 3.8 ± 0.3 mm Al for bio ceramic sealers and 6.9 ± 0.4 mm Al for AH Plus, with a confidence interval of 95% and power of 90%, the required sample size was calculated to be 60 specimens (30 in each group). The study included single-rooted teeth with a mature apex as confirmed on radiographs and without any root fractures. Teeth were excluded if they had extensive caries or restorations affecting the root structure, previous endodontic treatment, periodontal disease compromising tooth stability, resorption or other internal pathology were excluded from the study. 60 extracted single-rooted teeth that satisfy the inclusion criteria were collected and were cleaned by immersing into hydrogen peroxide solution for some hours to remove any blood remnant. Access cavity was prepared, and working length was determined with a 10k file until the tip was seen to exit at the major foramen. Working length was calculated by subtracting 1mm from this measurement. Root canal was prepared with Protaper rotary files. During shaping, irrigation with 2.5% NaOCl was performed between each file. The root canal was dried with a paper point according to the filling material used. All teeth were divided into two groups. In group 1, teeth were filled with Endosequence BC sealer. In group 2, teeth were filled with AH plus sealer. In all groups, a gutta-percha cone was used. Sealers were applied with a lentulo spiral. Obturation was followed by the use of a heated Plugger to remove an

excessive amount of gutta-percha to the level just short of the canal orifice, and it was compacted, and the orifice of each canal was sealed with coronal orifice. Specimens were radiographed under standardized exposure parameters with an aluminum step wedge placed alongside them for calibration. Digital images were obtained, and standardized regions of interest were selected for each specimen. Mean grey values were measured using image analysis software. A calibration curve was generated by plotting the grey values of the aluminium step wedge against its known thicknesses, and these values were used to convert specimen grey values into millimetres of aluminium (mm Al). To ensure reproducibility, measurements were performed by a calibrated examiner and repeated after a time interval, with intra-observer reliability assessed using the Intraclass Correlation Coefficient (ICC), demonstrating high agreement. Following a period of seven days, at a 37°C temperature in a humid atmosphere containing 100 percent humidity. To determine the outcomes, a digital radiograph was carried out. Radiographs were taken with the radiograph unit of 60kv and 10mA, exposure time of 0.3 seconds, and at a focus-film distance of 30cm, and then the radiographs were digitized with the use of Nikon D40 and Nikon 50-mm macro lens, and then imported into Digora 1.51 for Windows software. The values of Radiopacity are calculated based on the radiographic dentistry, which is translated to millimeters of aluminum. In this study, radiopacity was measured in root canals after obturation with the sealer and gutta-percha to simulate clinical conditions. Although gutta-percha contributes to overall radiopacity, this method reflects the material's radiographic appearance in situ, which is clinically relevant.

Data analysis was done using the Statistical Package for the Social Sciences (SPSS) version 26.0 software. Mean standard deviation was calculated for quantitative variables. Quantitative variable Radiopacity (mm Al) and Qualitative variable, like type of material or group, were measured. Normality of quantitative data was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated using Levene's test before selecting appropriate parametric or non-parametric statistical tests. The t-test was applied by comparison between two groups, considering a p-value <0.005 significant.

RESULTS

The results show radiopacity values of millimetres of aluminium (mm Al) and show a distinct difference between the two sealers. The mean radiopacity of Endosequence BC was 3.83 mm Al $\pm$ 0.35 mm Al with the 95 percent confidence interval of 3.71 mm Al to 3.96 mm Al. Conversely, AH Plus had a significantly greater mean radiopacity of 6.94 $\pm$ 0.46 mm Al with the 95% confidence interval (6.77 - 7.10

mm Al) not overlapping with that of Endosequence BC, which demonstrates that these two materials are distinctively different. This difference is also supported by the median values (6.90 mm Al of AH Plus and 3.80 mm Al of Endosequence BC) and the ranges of these values, where AH Plus is always higher than Endosequence BC. Furthermore, AH Plus has a higher degree of conformity as indicated by the comparatively low variability, which implies more consistency. The p-value (<0.001) indicates that this difference is statistically very significant. In general, AH Plus has better and more stable radiography than Endosequence BC, showing a higher chance of radiographic visibility in clinical practice (Table 1).

Table 1: Radiopacity Values Expressed as Millimetres of Aluminium (mm Al)

Sealer	n	Mean $\pm$ SD (mm Al)	Median	Min-Max	95 % CI for Mean	p-value
EndoSequence BC	30	3.83 $\pm$ 0.35	3.80	3.10 – 4.50	3.71 – 3.96	<0.001
AH Plus	30	6.94 $\pm$ 0.46	6.90	6.00 – 7.80	6.77 – 7.10	–

The left panel shows a tooth obturated with AH Plus Sealer, demonstrating dense radiopacity along the canal and extending to the apex. The right panel shows a tooth obturated with BC (bioceramic) Sealer, showing radiopaque filling with slight extrusion beyond the apex (Figure 1).



Figure 1: Radiographic Illustration of Root Canal Treatment Using Two Different Sealers

DISCUSSION

The present study demonstrated that AH Plus exhibits significantly greater radiopacity (6.94 $\pm$ 0.46 mm Al) than Endosequence BC sealer (3.83 $\pm$ 0.35 mm Al, $p < 0.001$), a difference that exceeds the ANSI/ADA minimum threshold of 3 mm Al for root-canal filling materials (ANSI/ADA, 2000). This finding corroborates the earlier digital radiography work of Sen et al. who reported comparable values of 3.83 mm Al for EndoSequence BC [11], and supports the consensus that epoxy-resin sealers containing zirconium oxide achieve higher radiopacity than calcium-silicate-based materials [12, 13]. Clinicians will therefore perceive the distinction without sophisticated software, facilitating immediate chair-side evaluation of obturation quality. Second, AH plus surpasses the ANSI/ADA minimum by 131 %, whereas Endosequence BC exceeds it by only 28 %. This narrow margin for the bioceramic sealer raises concern that minor variations in powder-to-liquid ratio or moisture contamination during clinical use could reduce its radiopacity below the critical 3 mm Al, a risk less likely with AH Plus [14, 15]. A study by Jafari and Jafari, indicates that the leaching of radiopaque fillers can decrease contrast over time [16]. From a materials-science perspective, the superior radiopacity of AH Plus can be attributed to its inclusion of zirconium dioxide particles, which possess a high atomic number and density. Endosequence BC relies on bismuth oxide and calcium tungstate [17], yet the lower atomic number of bismuth compared with zirconium, combined with the lower filler loading required to maintain hydraulic properties, results in

reduced X-ray attenuation [18]. Manufacturers of bioceramic sealers could therefore consider increasing the bismuth oxide fraction or exploring alternative high-Z additives without compromising flow or setting expansion [19]. Within the context of minimally invasive endodontics, the choice of sealer must balance biological performance with diagnostic visibility. Endosequence BC offers excellent biocompatibility and osteogenic potential, but its modest radiopacity may necessitate additional radiographic angulations to detect voids or missed canals. Conversely, AH Plus provides outstanding radiographic contrast, yet its cytotoxicity during the first 24 hours remains a concern. Clinicians should weigh these factors when selecting a sealer, particularly in complex retreatment cases where radiographic clarity is paramount [20].

A potential limitation of the study is its exclusive use of single-rooted, extracted human teeth. Multi-rooted teeth with curved canals may produce differential attenuation artefacts that alter measured radiopacity. Furthermore, storage of specimens at 37°C in 100 % humidity for only seven days may not replicate the long-term ionic exchange that occurs in vivo. Future investigations should therefore incorporate thermo-cycling and extended aging to verify stability. Clinicians should therefore reserve AH Plus for cases demanding maximal radiographic certainty, such as retreatments, complex anatomy, or when follow-up radiographs are anticipated to be challenging, whereas Endosequence BC can be chosen for straightforward cases in which its documented biocompatibility and bioactivity are paramount. Future work should evaluate long-term radiopacity stability under simulated oral conditions and extend the comparison to curved or multi-rooted teeth to confirm the generalisability of these findings.

CONCLUSIONS

This in-vitro study confirms that AH Plus delivers significantly higher radiopacity (6.94 ± 0.46 mm Al) than Endosequence BC sealer (3.83 ± 0.35 mm Al, $p < 0.001$), exceeding the ANSI/ADA minimum by 131 %. Consequently, AH Plus offers superior contrast against dentine and bone, facilitating immediate identification of voids, over-extensions, or missed canals. Endosequence BC, while surpassing the regulatory threshold, provides only a narrow safety margin; minor variations in mixing or environmental moisture could theoretically depress its radiopacity below acceptable limits.

Authors' Contribution

Conceptualization: SQ, FAK

Methodology: SQ, HO, MAP

Formal analysis: SQ

Writing and Drafting: SQ, MAP, FM, FAS

Review and Editing: SQ, FAK, HO, MAP, FM, FAS

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Assessment of Mortality Rate Using qSOFA Score among Patients with Sepsis outside the Intensive Care Unit (ICU) in a Tertiary Care Hospital

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ARTICLE INFO

Keywords:

ICU, Mortality, Prognosis, Quick Sequential Organ Failure Assessment (qSOFA), Sepsis

How to Cite:

Iqbal, M. F., & Makki, K. U. (2026). Assessment of Mortality Rate Using qSOFA Score among Patients with Sepsis outside the Intensive Care Unit (ICU) in a Tertiary Care Hospital: qSOFA and Mortality in Sepsis Outside ICU. *Pakistan Journal of Health Sciences*, 7(8), 155-160. <https://doi.org/10.54393/pjhs.v7i8.3892>

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ABSTRACT

Sepsis is a severe condition associated with a high risk of death. The Quick Sequential Organ Failure Assessment (qSOFA) score is an easy bedside instrument for mortality prediction.

Objective: This study aims to assess the mortality rate in patients with sepsis having a qSOFA score of 2 or more. **Methods:** This cross-sectional research was done for 6 months, from July 2025 to December 2025, among 196 patients at Liaquat National Hospital Karachi. The sample comprised patients with sepsis, not admitted to the ICU, and aged between 18 and 75 years, with qSOFA assessed at admission, and followed until discharge or death. A qSOFA score of 2 was determined to be a predictive value of mortality. The statistical analysis was done in SPSS version 25.0; stratification and the Chi-square or Fisher's exact test were. A p-value < 0.05 was considered statistically significant. **Results:** 196 non-ICU sepsis patients were included (mean age 55.9 ± 17.9 years; 55.1% male). The median qSOFA score was 2, with 104 (53.1%) patients having qSOFA ≥ 2. In-hospital mortality occurred in 97 (49.5%) patients. qSOFA ≥ 2 was significantly associated with older age, male gender, rural residence, hypertension, diabetes, anemia, hypotension, tachypnea, and GCS < 15 (all p < 0.05). ROC analysis showed good performance in predicting mortality (AUC = 0.862, 95% CI 0.805-0.907), with sensitivity 60.8% (95% CI 50.1-70.8%) and specificity 100% (95% CI 96.1-100%). **Conclusion:** qSOFA is a handy bedside tool that proves to be effective in mortality prognosis of sepsis when patients are not in the ICU.

INTRODUCTION

The critical aspect in enhancing patient survival and reducing mortality is the early detection of sepsis victims at risk of clinical degradation. Many clinical scoring systems have been created to predict disease severity and mortality among septic patients, and they include the Sequential Organ Failure Assessment (SOFA), Systemic Inflammatory Response Syndrome (SIRS), and quick Sequential Organ Failure Assessment (qSOFA). Comparative research has shown that the SOFA and qSOFA scores are important instruments in the determination of mortality in seriously ill patients with sepsis [1]. The Quick Sequential Organ Failure Assessment (qSOFA) score is a

relatively straightforward bedside assessment instrument applied on the premise of three clinical variables, which are altered mental status, systolic blood pressure of 100 mmHg, and respiratory rate of 22 breaths per minute. It has been extensively used as a quick screening device to detect septic patients who are at risk of having dismal outcomes. Research has shown that qSOFA is a convenient prognostic factor in predicting mortality in the short term among infected patients satisfying sepsis criteria [2]. Systematic reviews have assessed the predictive ability of qSOFA as applied to mortality in patients presenting with suspected sepsis to the emergency department and have



demonstrated that qSOFA is a good predictor of mortality [3]. Other meta-analyses that compared qSOFA with clinical scoring systems, including SIRS and NEWS, have stated the same capability to predict mortality in the context of infected patients [4]. Recent cohort studies have stated that qSOFA is a relevant predictor of mortality in patients who present with suspected sepsis and that it is useful in early risk stratification and clinical decision-making [5]. Researchers have also found the prognostic value of qSOFA for mortality prediction in patients with septic shock in diverse healthcare settings and income levels [6]. Local investigations have shown that mortality rates in septic patients with a qSOFA score that exceeded two are widely high, proving that it is a useful clinical tool in forecasting adverse outcomes [7]. The predictive validity of qSOFA to mortality in patients with sepsis in Asian populations has also been proven [8]. Sepsis is a fatal dysfunction of the organism as a result of an uncontrolled host reaction to infection and is one of the significant issues in health worldwide. Sepsis has been estimated to impact about 49 million individuals per year, according to recent world data, and nearly 11 million deaths per year, almost a fifth of the world's deaths, are attributed to sepsis. This burden is especially in the countries with low and middle incomes, largely in Asian countries, where untimely recognition, healthcare resource bases, and access to intensive care services lead to higher morbidities and deaths. National epidemiological data on sepsis are sparse, but sepsis is a frequent cause of hospitalization and in-hospital mortality in Pakistan, particularly in tertiary care units [9]. The Quick Sequential Organ Failure Assessment (qSOFA) score has been suggested as a fast bedside tool to determine patients with an increased likelihood of poor outcomes. Past research, such as the one conducted by Khan and Aslam, has made comparisons between qSOFA and SIRS and SOFA scores and has proven it to be a valuable tool in predicting mortality among septic patients [10]. Yet, the majority of the available literature concentrated on the emergency department or in the intensive care unit, and there is not much information on non-ICU hospitalized patients, especially in Pakistan. The prognostic values of qSOFA might not be equal in these groups because of the severity of the disease, the level of monitoring, and management approaches may vary in the ICU and the non-ICU setting [11].

In terms of outcome assessment, this study particularly measured in-hospital mortality as the main outcome measure. Death during the same hospital admission was termed as mortality. Mortality rate was determined as the ratio of deaths to the total number of patients who were enrolled in sepsis within the duration of the study. Although qSOFA is widely used, scanty information exists on its capability in mortality prediction among patients with

sepsis admitted to the non-intensive care unit. The majority of the past research has been concentrated on emergency departments or even intensive care units, and there is no evidence on non-intensive hospitalized patients, especially in Pakistan. Unlike previous studies primarily conducted in ICU or emergency settings, this study evaluates the prognostic performance of qSOFA in non-ICU hospitalized patients in a Pakistani tertiary care setting, addressing an important gap in regional and clinical evidence. This study hypothesizes that higher qSOFA scores are associated with increased mortality rate in patients with sepsis admitted outside the intensive care unit. Accordingly, the study aimed to evaluate the predictive accuracy of the qSOFA score for mortality among sepsis patients in non-ICU settings at a tertiary care hospital.

METHODS

A six-month cross-sectional descriptive study was carried out in the Department of General Medicine at the Liaquat National Hospital, Karachi, between July 2025 and December 2025, with the permission of the Institutional Ethical Review Committee (IRB #: 1216-2025-LNH-ERC; dated 2nd July 2025). A total of 196 patients were recruited through non-probability consecutive sampling. Every participant signed a written informed consent form, and the confidentiality of patient data was ensured during the research. The sample size was recalculated to be in line with the main aim of assessing the predictive power of qSOFA to in-hospital mortality with the use of ROC analysis. It was calculated using the expected area under the curve (AUC), past research, a 95% confidence interval, and a margin of error of 0.05, which is sufficient to reject the null hypothesis [12]. The study included adult patients (18 to 75 years of both genders) diagnosed with sepsis based on the Sepsis-3 criteria (suspected infection + qSOFA score 2 or higher), but not admitted to the intensive care unit. Patients who had a hospital stay of less than 24 hours, were pregnant, or had a history of malignancy. Sepsis was determined based on Sepsis-3 criteria, and qSOFA was measured at the time of admission based on 3 parameters: systolic blood pressure 100 mmHg, respiratory rate 22 bpm, and Glasgow Coma Scale 15. Each of the criteria was rated with one point, and the total qSOFA score was between 0 and 3, where the final point was considered positive, which means that there is a high risk of mortality in the hospital. This was used as a cutoff point in all analyses, including assessment of ROC curves [12]. Demographic and clinical data were taken as baseline (age, sex, residence, comorbid conditions like diabetes mellitus, hypertension, and anemia). Diabetes and hypertension were determined by taking appropriate drugs for at least 3 months, and anemia was determined by taking hemoglobin levels <13.0 g/dL in

men and hemoglobin <12.0 g/dL in women. A predesigned pro forma was used to gather data to maintain standardization. The primary outcome was in-hospital mortality, defined as death during the same hospital admission. Mortality rate was calculated as the proportion of deaths among the total enrolled patients. Follow-up was done until discharge or in-hospital death of the patients; this was done at a minimum of 24 hours. The first outcome was the in-hospital mortality, which was recorded as the percentage of patients who died in the hospital. In patients with longer follow-up time-to-event analysis by Kaplan-Meier curves was taken.

The analysis of data was carried out with the use of SPSS version 25.0. Continuous variables were expressed in the form of mean and standard deviation, and frequencies and percentages were used to present categorical variables. The association between qSOFA scores and in-hospital mortality was determined using effect sizes, odds ratios, and confidence intervals. Analysis of ROC curves to determine the predictive performance of qSOFA, reporting the area under the curve, sensitivity, specificity, and 95% confidence intervals, was performed. Chi-square or Fisher's exact test was to be used to assess associations between categorical variables, and a p-value of less than 0.05 was to be regarded as statistically significant. Stratification of the analysis was done with potential confounders, such as age, sex, residence, comorbidities, and length of stay.

RESULTS

The demographic and clinical characteristics of the patients are summarized. This table shows the distribution of age, gender, residence, comorbidities, and key clinical parameters along with the association of qSOFA ≥ 2 with these variables (Table 1).

Table 1: Association of qSOFA ≥ 2 with Demographic, Comorbid, and Clinical Variables

Variables	Overall (n=196)	qSOFA <2 (n=92)	qSOFA ≥ 2 (n=104)	OR (95% CI)	p-value
Gender	—	—	—	—	0.002*
Male	108 (55.1%)	26 (28.0%)	82 (76.0%)	2.5 (1.3–4.7)	—
Female	88 (44.9%)	66 (75.0%)	22 (25.0%)	Ref	—
Age ≥ 55 years	118 (60.2%)	30 (25.4%)	88 (74.6%)	3.1 (1.7–5.5)	<0.001*
Rural residence	19 (9.7%)	0 (0%)	19 (100%)	—	<0.001*
Hypertension	119 (60.7%)	36 (30.3%)	83 (69.7%)	2.0 (1.1–3.6)	0.019*
Diabetes Mellitus	108 (55.4%)	34 (31.5%)	74 (68.5%)	1.8 (1.0–3.2)	0.037*
Obesity	81 (41.3%)	28 (34.6%)	53 (65.4%)	1.4 (0.8–2.5)	0.220
Anemia	50 (25.5%)	10 (20.0%)	40 (80.0%)	4.1 (1.9–8.7)	<0.001*
Systolic BP ≤ 100 mmHg	150 (76.5%)	45 (30.0%)	105 (70.0%)	4.7 (2.0–11.0)	<0.001*
Respiratory Rate ≥ 22 BPM	156 (79.6%)	38 (24.4%)	118 (75.6%)	8.5 (4.3–16.9)	<0.001*
GCS <15	79 (40.3%)	20 (25.3%)	59 (74.7%)	8.1 (4.0–14.3)	<0.001*

*Significant at 0.05

The relationship between qSOFA ≥ 2 and in-hospital mortality is presented. This table demonstrates that qSOFA ≥ 2 has a high association with mortality, with corresponding odds ratios and confidence intervals (Table 2).

Table 2: Association of Mortality with qSOFA ≥ 2

qSOFA Category	Deaths, n (%)	Survivors, n (%)	OR (95% CI)	p-value
<2	0 (0%)	92 (100%)	Ref	—
≥ 2	97 (93.3%)	7 (6.7%)	26.3 (14.8–46.7)	<0.001*

The predictive performance of qSOFA ≥ 2 for in-hospital mortality, including ROC analysis with sensitivity, specificity, and 95% confidence intervals (Table 3).

Table 3: ROC Analysis of qSOFA ≥ 2 for Predicting Mortality

AUC	Std. Error	95% CI	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	Youden Index
0.862	0.0198	0.805–0.907	≥ 2	60.8% (50.1–70.8%)	100% (96.1–100%)	0.608

Time-to-event analysis for patients with follow-up >24 hours. Patients with qSOFA ≥ 2 had significantly lower survival compared to those with qSOFA <2 (log-rank test, $p < 0.001$). Stratified analyses by age, sex, residence, and comorbidities confirmed that higher qSOFA consistently predicted higher in-hospital mortality (Figure 1).

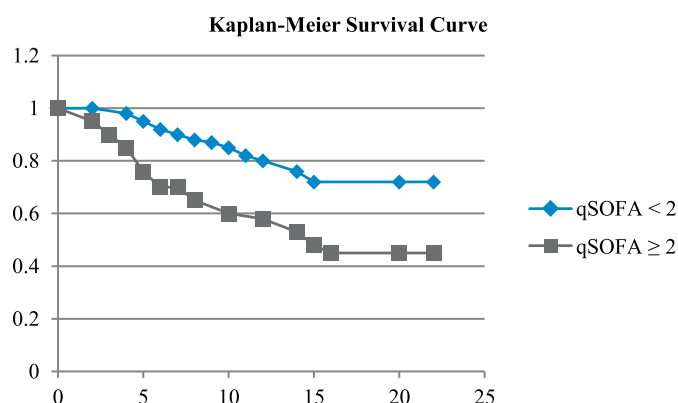


Figure 1: Observed Hygiene Status and Recent Illness Among Inmates(n=91)

DISCUSSION

The quick Sequential Organ Failure Assessment (qSOFA) score with a standardized cutoff of 2 or higher had a significant correlation with in-hospital mortality in this group of non-intensive care unit (non-ICU) adult sepsis patients. The discriminative ability (AUC=0.862) of the qSOFA to predict mortality was generally in line with current literature that indicates the use of qSOFA as an effective prognostic measure in the non-intensive care setting [11, 12]. Some studies have also compared the utility of qSOFA and other clinical scoring systems. Sreekanth *et al.* analyzed an emergency surgical population with possible sepsis and found that both qSOFA and SIRS (Systemic Inflammatory Response Syndrome) were equally accurate and that standard clinical scoring needed to be contextualized according to setting and outcome measures [12]. Similarly, Shahsavarinia *et al.* found that qSOFA outperformed in predicting patients in the emergency department but had poor sensitivity, as we have found moderate sensitivity with high specificity [13]. Studies that have incorporated qSOFA and biomarkers such as procalcitonin have demonstrated that high-risk patients can be better detected early on with the help of qSOFA, which may suggest that the indicator can be improved when combined with laboratory parameters [14]. Fernandes and Wyawahare found that qSOFA proves useful in suspected non-ICU patients with infections, and this finding supports the use of this tool in rapid bedside assessment [15]. Multiple scoring systems, such as SOFA (Sequential Organ Failure Assessment), SIRS, and qSOFA, have been assessed comparatively, and their individual performances have been found to have variations based on population and illness severity. Djikic *et al.* established that qSOFA is a valuable source of prognostic information, but its comparatively low performance could be found when compared with more complex scoring systems [16]. In their meta-analysis, Lan *et al.* showed that such criteria as SOFA and MEWS (Modified Early Warning Score) are occasionally

more discriminative of mortality than qSOFA alone, and that this effect is present in heterogeneous samples of patients [17]. The research into the methods of combination has also contributed to the further development of the knowledge about the scoring tools in sepsis. Ling *et al.* demonstrated that the addition of inflammatory mediator data can enhance the diagnostic performance of qSOFA, which supports the idea that qSOFA is not a standalone prediction tool but a part of a more comprehensive assessment [18]. A study by Oduncu *et al.* in which qSOFA, SIRS, and NEWS (National Early Warning Score) are compared, highlighted that qSOFA should not be considered a complete element of patient risk stratification, but it is easier and more specific, making it a viable initial tool in the risk stratification process [19]. Later, richer datasets have been used in more current studies to evaluate and optimize sepsis prediction models. According to Resok *et al.* the performance of qSOFA can be different across different places of infection and patient groups, which is why individual strategies of assessment are required [20]. Wang *et al.* compared qSOFA with SIRS and NEWS in predicting sepsis and high-risk mortality and were able to conclude that, when combined with other dynamic scoring systems, qSOFA can be used to enhance the aggregate predictive accuracy [21]. Combined with the existing literature, the current results are consistent with the overall findings: qSOFA ≥ 2 is linked to a substantially increased mortality rate among patients with suspected sepsis. Its high specificity contributes towards its use to identify patients prone to adverse events, whereas its moderate sensitivity warns against its use as an isolation tool when aiming to perform early screening. Clinicians must use qSOFA with other proven instruments, e.g., NEWS or MEWS, and, where feasible, supplement clinical scoring with biomarkers to improve early risk stratification based on these results and comparative evidence. In multifaceted presentation and comorbidity settings, a multimodal approach can be more effective in capturing high-risk patients.

The work has some limitations that are worth mentioning. Its single-center nature might restrict the applicability to other environments. This is because there was no multivariate regression; the adjusted effect estimates of independent predictors of mortality were not given, and future analysis should incorporate logistic regression to control confounding variables like age, sex, and burden of comorbidities. Also, its performance metrics in specificity are high, whereas the moderate sensitivity of qSOFA means that the tool requires additional screening tactics, in particular, in the context of the earlier detection of sepsis.

CONCLUSIONS

The qSOFA score is a useful bedside tool that can be employed in the mortality prediction of non-ICU sepsis patients. A value of 2 and above was always predictive of high-risk patients who were at risk of death, and survival with lesser values. Both increased qSOFA scores and mortality were closely associated with older age, comorbidities, hypotension, systolic blood pressure below 100 mmHg, respiratory rate exceeding 22 breaths/min, and a Glasgow Coma Scale score that was less than 15. High predictive power was demonstrated in the analysis, whereas the specificity was good at the threshold of ≥ 2 .

Authors' Contribution

Conceptualization: MFI

Methodology: MFI

Formal analysis: MFI, KUM

Writing and Drafting: MFI

Review and Editing: MFI, KUM

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Comparison of Early versus Late Trophic Feeding in Preterm Very Low Birth Weight Neonates at a Tertiary Care Hospital

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ARTICLE INFO

Keywords:

Preterm Very Low Birth Weight Neonates, Early Versus Late Trophic Feeding, Neonatal Outcomes, Complications

How to Cite:

Akram, N., Suleman, ., Nadeem, G., Hussain, A., Rehman, A. U., & Rafique, N. (2026). Comparison of Early versus Late Trophic Feeding in Preterm Very Low Birth Weight Neonates at a Tertiary Care Hospital: Early versus Late Trophic Feeding in Preterm Very Low Birth Weight Neonates. *Pakistan Journal of Health Sciences*, 7(8), 161-166. <https://doi.org/10.54393/pjhs.v7i8.3896>

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Received Date: 28th January, 2026

1st Revision Received: 11th April, 2026

2nd Revision Received: 24th April, 2026

Acceptance Date: 12th May, 2026

Published Date: 31st August, 2026

ABSTRACT

Very low birth weight (VLBW) neonates are vulnerable to complications, and nutritional management is an essential determinant of their outcomes. **Objective:** To compare the neonatal outcomes in early trophic feeding (TF) versus late TF in preterm VLBW neonates. **Methods:** This randomized controlled trial was performed at the Department of Paediatrics, Nishtar Hospital, Multan, Pakistan, from June 2025 to December 2025. Sixty preterm VLBW neonates were selected through simple random sampling. Infants were randomized (30 in each group) into early TF (≤ 48 hours) or late TF (≥ 72 hours) groups. Feeding was given via orogastric tube using expressed breast milk or preterm formula, along with parenteral nutrition. Outcomes included incidence of necrotizing enterocolitis (NEC), mortality, and hospital stay. Data were analyzed using SPSS 26.0, with $p \leq 0.005$ considered statistically significant. **Results:** In a total of 60 neonates, 35 (58.3%) were males, with a mean gestational age of 33.1 ± 2.1 weeks, and a birth weight of 1360.1 ± 67.2 grams, respectively. Overall, NEC occurred in 2 (3.3%), and mortality occurred in 4 (6.7%) neonates. The overall mean hospital stay was 15.4 ± 1.9 days, significantly shorter with early feeding (13.0 ± 1.7 vs 19.3 ± 2.1 days, $p < 0.001$). **Conclusions:** The early TF within 48 hours significantly reduced the hospital stay without increasing NEC or mortality among preterm VLBW infants.

INTRODUCTION

Human milk provides the most suitable nutrition for premature infants, offering well-established benefits in host defense, digestion, neurodevelopment, gastrointestinal maturation, and psychological well-being [1]. Its bioactive components, including immunoglobulins, growth factors, and enzymes, play a vital role in protecting vulnerable preterm neonates against infections and inflammatory conditions. In addition to supporting optimal growth, human milk enhances intestinal barrier function and promotes the development of a healthy microbiome. These effects are particularly crucial in very low birth

weight (VLBW) infants, whose physiological immaturity predisposes them to multiple complications [2]. Globally, preterm birth remains a significant public health concern, with an estimated 15 million infants born prematurely each year, accounting for more than one in ten live births [2]. Among these, nearly one million deaths occur annually due to complications associated with prematurity [3]. The burden is especially pronounced in low- and middle-income countries, where healthcare resources are often limited. In Pakistan, the estimated prevalence of preterm births ranges between 15% and 22%, placing it among the

highest worldwide [4, 5]. This high prevalence results in a substantial number of VLBW neonates requiring specialized neonatal care. These infants are particularly susceptible to complications such as respiratory distress, sepsis, feeding intolerance, and necrotizing enterocolitis (NEC), all of which contribute significantly to neonatal morbidity and mortality [5]. Nutritional management plays a central role in determining outcomes in preterm VLBW neonates, and optimizing feeding strategies remains a key clinical priority [6]. Trophic feeding (TF), also known as minimal enteral nutrition, has gained considerable attention in recent years due to its potential benefits [7]. TF involves the early administration of small volumes of enteral feeds to stimulate gastrointestinal function without imposing a significant metabolic burden [8]. Evidence suggests that TF improves feeding tolerance, reduces dependence on parenteral nutrition, enhances intestinal motility, and accelerates the achievement of full enteral feeding [9]. TF has been associated with shorter intestinal transit time and improvements in biochemical markers of nutritional status compared to parenteral nutrition alone [10, 11].

Despite these advantages, the optimal timing for initiation of trophic feeding remains a subject of ongoing debate, particularly in resource-limited settings where clinical practices may vary. Early initiation of TF has been proposed to reduce the incidence of NEC and shorten hospital stay, whereas delayed initiation is often practiced due to concerns regarding feeding intolerance and potential complications. Given the high burden of preterm VLBW infants in Pakistan, there is a critical need to evaluate feeding strategies that can improve neonatal outcomes in this setting. Therefore, this study was conducted to compare neonatal outcomes in early versus late trophic feeding among preterm VLBW infants, aiming to provide evidence to guide clinical practice in similar high-risk populations.

METHODS

This randomized controlled trial (NCT07229885) was conducted in the Department of Pediatrics, Nishtar Hospital, Multan, from June 2025 to December 2025, after approval from the Institutional Ethical Review Board (Ref. No. 8987/NMU; dated 12th May 2025). A sample size of 60 was calculated using the Open EPI online sample size calculator, taking the duration of hospitalization among late versus early TF as 12.1 ± 8.6 days vs 21.1 ± 1.2 days, respectively, with 95% significance level and 80 power of the study [10]. A total of 60 preterm VLBW neonates, aged 1–28 days of either gender, were included using a simple random sampling technique. Exclusion criteria included transfer from other hospitals after initiation of antibiotics, congenital anomalies, hypoxic-ischemic encephalopathy,

central nervous system impairment, neonatal sepsis, and multiple gestations. Written informed consent was obtained from parents or guardians before enrollment. VLBW was defined as live-born < 37 completed weeks of gestation with a birth weight ≤ 1500 g, measured using a calibrated digital scale [6]. At enrolment, gender, age, gestational age at delivery, and mode of delivery were documented. Participants were randomized into two groups using a computer-generated randomization sequence with a 1:1 allocation ratio. Allocation concealment was ensured using sequentially numbered, sealed, opaque envelopes prepared by an independent researcher not involved in patient recruitment. Each envelope contained the group assignment and was opened only after enrollment of the participant, thereby preventing selection bias. The early TF group received trophic feeding initiated within 48 hours following birth, whereas the late TF group received trophic feeding initiated after 72 hours. Feeding was administered through radio-opaque orogastric tubes (2×47 mm) placed by trained nurses and changed daily. Expressed breast milk was used when available; otherwise, preterm formula milk (Pre-NAN, Nestlé), prepared as two scoops in 60 ml of boiled water, was provided. Feeds were administered using a syringe at 1–2 ml/kg every 4–6 hours and advanced by 1–2 ml/kg/day as tolerated. Parenteral nutrition was provided to all infants. Feeding tolerance was assessed clinically before each feed. Tolerance was defined by the absence of significant gastric residuals (less than 50% of the previous feed volume), absence of abdominal distension (increase in abdominal girth > 2 cm from baseline), no visible bowel loops, and no episodes of bilious or blood-stained vomiting. Additional indicators of intolerance included apnea, bradycardia, or signs suggestive of necrotizing enterocolitis, such as abdominal tenderness or discoloration. In cases of feeding intolerance, feeds were withheld or reduced at the discretion of the attending neonatologist. Neonates were observed for the development of NEC during their NICU stay. NEC was labelled as clinical features of vomiting, abdominal distension, thrombocytopenia $< 100,000/\mu\text{L}$, blood in stools, along with radiological findings such as intramural bowel gas, portal venous gas, or pneumoperitoneum on abdominal X-ray. Each neonate was followed until discharge or death, and the hospital stay in days was documented.

Data were analyzed in IBM-SPSS Statistics, version 26.0. Quantitative data were expressed as mean $\pm$ standard deviation (SD), or median and interquartile range (IQR), as per the Shapiro-Wilk test. Categorical data were shown as frequencies and percentages. The hospital stay was compared using the independent samples t-test or Mann-Whitney U test (as appropriate). Potential effect modifiers

like gender, gestational age, birth weight, type of milk, and mode of delivery were controlled through stratification, followed by post-stratification analyses using an independent sample t-test or Mann-Whitney U test, taking $p < 0.005$ as significant. The CONSORT Diagram was shown. In a total of 60 neonates, 35 (58.3%) were males. The mean gestational age and birth weight were 33.1 ± 2.1 weeks and 1360.1 ± 67.2 grams, respectively. The residential status of 38 (63.3%) neonates was rural, and 22 (36.7%) urban (Figure 1).

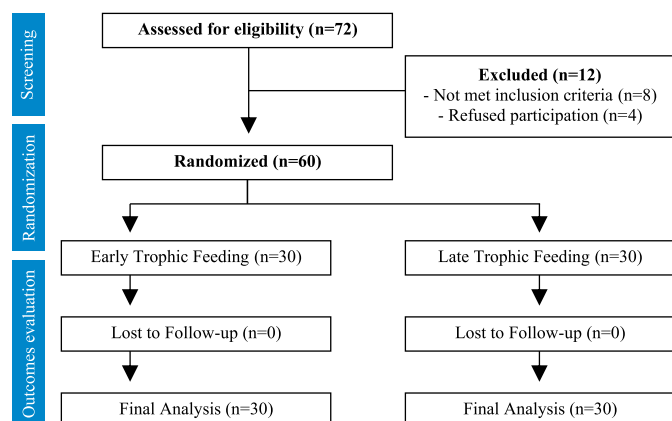


Figure 1: CONSORT Diagram

RESULTS

Among early TF neonates, 17 (56.7%) were male, and 13 (43.3%) were female, whereas in the late TF group, 18 (60.0%) were male and 12 (40.0%) were female ($p=0.793$). Gestational age ≤ 32 weeks was documented in 8 (26.7%) neonates in the early, and 12 (40.0%) in the late TF group, with >32 weeks in 22 (73.3%) and 18 (60.0%) neonates, respectively ($p=0.273$). Vaginal delivery was observed in 21 (70.0%) neonates in each group, and cesarean section in 9 (30.0%) neonates in each group. Birth weight ≤ 1300 g was recorded in 9 (30.0%) neonates in both groups, while >1300 g was noted in 21 (70.0%) neonates in each group. Human milk feeding was received by 19 (63.3%) neonates in the early group and 23 (76.7%) in the late TF group, whereas preterm formula was given to 11 (36.7%) and 7 (23.3%) neonates, respectively ($p=0.260$) (Table 1).

Table 1: Comparison of Baseline Characteristics among Study Groups (n=60)

Characteristics		Early TF (n=30, n (%))	Late TF (n=30, n (%))	p-value
Gender	Male	17 (56.7%)	18 (60.0%)	0.793
	Female	13 (43.3%)	12 (40.0%)	
Residence	Urban	10 (33.3%)	12 (40.0%)	0.592
	Rural	20 (66.7%)	18 (60.0%)	
Gestational Age (Weeks)	≤ 32	8 (26.7%)	12 (40.0%)	0.273
	> 32	22 (73.3%)	18 (60.0%)	

Milk Type	Human Milk	19 (63.3%)	23 (76.7%)	0.260
	Preterm Infant Formula Milk	11 (36.7%)	7 (23.3%)	

TF: trophic feeding; Chi-square test applied

NEC was documented among 2 (3.3%) neonates. Mortality was documented among 4 (6.7%) neonates. The overall mean duration of hospital stay was 15.4 ± 1.9 days. NEC was observed among 1 (3.3%) neonate in both study groups. Mortality was documented among 2 (6.7%) neonates in each study group. The mean duration of hospitalization was significantly shorter among the early TF group in comparison to the late TF group (13.0 ± 1.7 days vs. 19.3 ± 2.1 days, $p < 0.001$). Among males, the mean hospital stay was 12.8 ± 1.8 days with early feeding and 19.2 ± 2.3 days with late feeding ($p < 0.001$), while in females, it was 13.2 ± 1.5 days and 19.5 ± 1.6 days, respectively ($p < 0.001$). Urban neonates had a mean hospital stay of 12.6 ± 1.9 days in the early group compared with 19.3 ± 2.4 days in the late group ($p < 0.001$), and rural neonates had 13.0 ± 1.6 versus 19.2 ± 1.5 days, respectively ($p < 0.001$). For gestational age ≤ 32 weeks, the mean stay was 12.1 ± 1.3 days in the early TF group and 19.6 ± 2.0 days in the late TF group ($p < 0.001$), while for > 32 weeks it was 13.3 ± 1.8 and 19.1 ± 2.1 days, respectively ($p < 0.001$). Vaginally delivered neonates had a mean stay of 12.6 ± 1.7 days in the early group and 19.4 ± 2.1 days in the late group ($p < 0.001$), whereas cesarean section neonates had 14.0 ± 1.3 days and 19.0 ± 1.9 days, respectively ($p < 0.001$). Birth weight ≤ 1300 g was associated with 13.2 ± 1.2 days in the early group and 19.3 ± 1.7 days in the late group ($p < 0.001$), while neonates > 1300 g stayed 12.9 ± 1.9 and 19.3 ± 2.2 days, respectively ($p < 0.001$). Neonates receiving human milk had a mean stay of 13.2 ± 1.5 days in the early group and 19.0 ± 1.9 days in the late group ($p < 0.001$), while those on preterm formula stayed 12.7 ± 2.1 and 20.1 ± 2.4 days, respectively ($p < 0.001$). Subgroup analysis with respect to duration of hospitalization among study groups is shown (Table 2).

Table 2: Comparison of Hospital Stay with Respect to Study Variables among Study Groups (n=60)

Characteristics		Early TF (n=30)	Late TF (n=30)	p-value
Gender	Male	12.8 ± 1.8	19.2 ± 2.3	< 0.001
	Female	13.2 ± 1.5	19.5 ± 1.6	< 0.001
Residence	Urban	12.6 ± 1.9	19.3 ± 2.4	< 0.001
	Rural	13.0 ± 1.6	19.2 ± 1.5	< 0.001
Gestational Age (Weeks)	≤ 32	12.1 ± 1.3	19.6 ± 2.0	< 0.001
	> 32	13.3 ± 1.8	19.1 ± 2.1	< 0.001
Mode of Delivery	Vaginal Delivery	12.6 ± 1.7	19.4 ± 2.1	< 0.001
	Cesarean Section	14.0 ± 1.3	19.0 ± 1.9	< 0.001
Birth Weight (grams)	≤ 1300	13.2 ± 1.2	19.3 ± 1.7	< 0.001
	$> 1300-1500$	12.9 ± 1.9	19.3 ± 2.2	< 0.001
Milk Type	Human Milk	13.2 ± 1.5	19.0 ± 1.9	< 0.001
	Preterm Infant Formula Milk	12.7 ± 2.1	20.1 ± 2.4	< 0.001

TF: trophic feeding; Independent sample t-test applied

DISCUSSION

The present study demonstrated that early TF significantly reduced the duration of hospital stay among preterm VLBW infants compared with late TF. This finding carries important clinical and health system implications as prolonged hospitalization is a recognized burden in neonatal care in low- and middle-income countries [12]. Sallakh-Niknezhad and colleagues found a stay of 12.14 ± 8.61 days in the early TF group versus 21.11 ± 1.16 days in the late TF [10]. Biswas and colleagues also documented a longer stay in the late feeding group, although the differences in their cohort did not reach the same level of statistical contrast [12]. Variability in sample selection and local NICU practices may account for the smaller observed difference. The present study also showed that the beneficial effect of early TF on hospital stay persisted across subgroups of gender, gestational age, residence, birth weight, mode of delivery, and type of milk. These findings align with Maqbool et al. who reported hospital stay of 12.1 ± 8.6 days in the early group compared with 21.1 ± 9.1 days in the late group among neonates below 34 weeks of gestation [11]. The similarity of results across different trials suggests that early feeding is beneficial irrespective of small variations in gestational maturity, providing reassurance that the practice is safe in very preterm infants as well. Comparable outcomes have been described previously, evaluating full enteral feeding in preterm infants between 28 and 34 weeks and observed improved stability of weight gain and fewer complications when compared with partial feeding [13]. Mortality was relatively low in both study groups (6.7% with each approach). These findings align with Kennedy et al. who found no effect of early feeding on mortality in randomized clinical trials [14]. Biswas et al. also reported similar mortality in both groups, with 16.7% deaths in the early group and 16.9% deaths in the late group [12]. These concordant findings imply that while early feeding reduces hospitalization, it does not confer a measurable survival advantage. This may be explained by the multifactorial etiology of mortality in VLBW infants, which often involves severe comorbidities beyond feeding tolerance, such as sepsis, respiratory distress, or congenital malformations [15, 16]. NEC was diagnosed in only 1 infant in each study group in the present trial. This low frequency echoes the findings of Biswas et al. who reported NEC in 6.7% of early-fed and 7.7% of late-fed neonates [12], and Javied et al. who found NEC in 5.6% of infants receiving early TF [17]. Sallakh-Niknezhad and colleagues also documented a single NEC case in each group [10]. In this study, neonates receiving human milk in the early group had a mean hospital stay of 13.2 ± 1.5 days compared with 19.0 ± 1.9 days in the late group, while those on preterm formula stayed 12.7 ± 2.1

and 20.1 ± 2.4 days, respectively. Although both human milk and formula recipients benefited from early initiation, the absolute values indicate a slightly greater advantage in formula-fed neonates. This pattern may reflect the relatively slower adaptation of gut function in formula-fed neonates who start feeds late, rather than an inherent superiority of formula [18]. Human milk is consistently shown to reduce the risk of infection, enhance nutrient absorption, and improve long-term neurodevelopment [19]. These benefits were highlighted in earlier reports, including the review by Nangia et al. which showed reduced incidence of NEC and sepsis when early enteral feeding included human milk [20]. The present findings therefore reinforce the primacy of human milk as the feed of choice, while also demonstrating that early initiation is beneficial regardless of milk type [21].

The lack of observed mortality benefit despite a significant reduction in hospital stay likely reflects the multifactorial nature of mortality in preterm VLBW infants. In this study, mortality was low and comparable between groups, limiting the ability to detect a statistically significant difference. Early trophic feeding is primarily known to improve gastrointestinal function, feeding tolerance, and clinical stabilization, which may translate into shorter hospitalization rather than a direct survival advantage. Relatively modest sample size and a single-center study design may limit the generalizability of these findings. The use of biomarkers of gut maturity and immune function could provide mechanistic insights to explain observed differences. The study also noted only short-term outcomes, so more studies are required to see the long-term outcomes of various feeding strategies among preterm VLBW infants.

CONCLUSIONS

The early TF, within 48 hours, significantly reduced the hospital stay without increasing NEC or mortality among preterm VLBW infants. The findings support early initiation of minimal enteral nutrition.

Authors' Contribution

Conceptualization: S

Methodology: NA, S, GN, AH, AUR, NR

Formal analysis: NA, AH

Writing and Drafting: NA, S, GN, AUR, NR

Review and Editing: NA, S, GN, SH, AUR, NR

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Psychological Burden in Patients with Acne Vulgaris

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ARTICLE INFO

Keywords:

Acne Vulgaris, Psychological Burden, Anxiety, Social Stigma, Coping Mechanisms, Multidisciplinary Care

How to Cite:

Shafi, S., Minhas, A. H., Mehboob, F., Sarwar, A., Nazar, W., & Ibrar, M. (2026). Psychological Burden in Patients with Acne Vulgaris: Psychological burden and Acne Vulgaris. *Pakistan Journal of Health Sciences*, 7(8), 167-172. <https://doi.org/10.54393/pjhs.v7i8.3742>

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Received Date: 27th November, 2025

1st Revision Received: 15th January, 2026

2nd Revision Received: 19th March, 2026

Acceptance Date: 14th April, 2026

Published Date: 31st August, 2026

ABSTRACT

Acne vulgaris is a common and recurrent skin disorder that affects more than 70% of human beings across the world. Acne is associated with several psychological problems in addition to the physical ones. **Objective:** To evaluate the psychological burden of acne vulgaris, defined by anxiety levels (GAD-7) and acne-related quality of life (CADL), and to identify coping strategies among patients. **Methods:** This cross-sectional study was conducted at the Department of Dermatology, Combined Military Hospital, Kharian, between March and October 2024, and 135 patients aged 16 years and above, diagnosed with acne vulgaris, were enrolled through a non-probability convenience method. A pre-designed proforma was used to measure the demographic characteristics, clinical history, psychological burden (GAD-7 scale and Cardiff Acne Disability Index), and coping mechanisms. SPSS version 25.0 was used to conduct descriptive and inferential analysis. **Results:** 61.48% female and 38.52% male, 45.93% had moderate anxiety, and 20.00% severe anxiety. The perceived stigma was quite high, and 51.11% respondents reported differential treatment, as well as 43.70% respondents avoided social situations. The impact of acne on the day-to-day life was also negative, with 60.74% of the respondents expressing concerns and 48.89% showing reduced performance in work or school. The coping strategies were makeup or cosmetic (42.22%), avoidance (25.19%), and talking to friends and family (20.74%). **Conclusions:** Acne vulgaris has a very strong impact on psychological well-being, as it increases significantly the rate of anxiety, stigma, and poor quality of life.

INTRODUCTION

Acne vulgaris is a chronic and prevalent skin disorder that occurs in more than 70% of the global population and has a duration of at least three years, and is one of the most common dermatoses. Even though acne is most often considered a skin condition, its physical and psychological outcomes are severe, as acne impacts the self-esteem, psychological state, and overall well-being of patients. The majority of the affected population is comprised of adolescents and young adults, and it is reasonable to assume that they undergo distress daily due to the presence of lesions on the skin, which, despite being stigmatized, condemned, and leading to social exclusion, also result in the symptoms of a severe depressive disorder [1, 2]. There is a complex relationship between acne and

anxiety. It has been found that, in addition to skin-related problems, there were symptoms of stress, anxiety, depression, and even suicidal thoughts in the patients with acne [3, 4]. People with acne are more likely to experience depression than people without acne, according to another meta-analysis, which suggests that early psychological involvement is not to be overlooked [5]. Additionally, there is a significant association between the severity of acne and psychological outcomes, and patients express being less satisfied with their personal lives as the severity of their lesions increases [6]. Acne has more serious psychological impacts than other disorders because of societal stigma. Many people isolate themselves, perform poorly at work or school, and lose acquaintances because

they believe that their skin condition is being used as a basis for judgment [7, 8]. Stigma related to these conditions usually results in feelings of shame and low self-esteem, added to the psychological symptoms. Thus, these findings confirm the need for a multifaceted approach to acne treatment with reference to both dermatological and psychological interventions. Social media's influence on how people perceive beauty and self-worth contributes to these problems. According to various studies, when an individual is continuously exposed to envisioned photos on social media, their anxiety levels related to acne and body image may rise [9]. Twitter and Facebook even give the means to share experiences and interact with other people, but they also include advertisements for perfect skin and disseminate the psychological load of acne patients. Patients' strategies of handling situations can range from makeup and isolation to visiting a dermatologist and seeing a psychologist. The strategies, however, have an individual difference in applicability to particular conditions of a patient and the availability of integrated treatment services. It is still disputed when mental health screening should start as a routine approach, but new guidelines propose an interdisciplinary approach to treating acne, which involves mental health assessment along with dermatological assessment [10].

Although there is increased awareness of the psychological burden of acne, there are still gaps in the study of the multifaceted nature of such a burden. The proposed study will fill this gap by examining the psychological distress linked with acne vulgaris among acne patients. The research will inform the overall management of acne by assessing anxiety, the perception of stigmas, and coping among patients to enhance patient outcomes.

METHODS

This cross-sectional study was conducted after taking ethical approval (bearing no. A/24/07; dated March 2024) from the Ethical Committee/ Institutional Review Board of CMH Kharian. All diagnosed patients with acne vulgaris visiting the Department of Dermatology, Combined Military Hospital, Kharian, from March 2024 to October 2024 were enrolled for the study. All the patients who were selected for the study were briefly informed about the study purpose, and written informed consent was taken before being included in the study. A total of 135 patients diagnosed with acne vulgaris were recruited using a non-probability convenience sampling technique. The sample size was calculated by using the WHO sample size calculator with the help of 95% confidence level, anticipated population proportion (prevalence of patients having a significant psychological impact of Acne) of 66% [7], absolute precision required of 8%, and the sample size

turned out to be 135 patients. The study included patients aged 16 years or older with a clinical diagnosis of acne vulgaris and provided informed consent. Exclusion criteria comprised individuals with chronic psychiatric illnesses, ongoing psychiatric treatment, other significant dermatological conditions, severe systemic diseases, or those unwilling to participate. Data were collected through structured interviews using a pre-designed proforma. The proforma consisted of four sections. The initial section was a collection of demographic and general data, such as age, sex, education level, profession, marital status, and household earnings per month. The second part concerned the clinical history of acne, where data regarding the duration, the severity (mild, moderate, or severe according to clinical examination based on Investigator's Global Assessment (IGA), the types of lesions (comedones, papules, pustules, nodules, cysts), and information about the history of treatment were gathered. The third section was the evaluation of the psychological burden of acne. In this study, psychological burden was defined as the presence of anxiety symptoms (measured using the GAD-7 scale) and impairment in acne-related quality of life (measured using the Cardiff Acne Disability Index, CADi) (scores ranged between 0 and 15). The GAD-7 scale was used to assess the level of anxiety; the measures of anxiety were classified under mild (score 5-9), moderate (score 10-14), and severe (score 15-21). Both of these questionnaires were filled out by the researcher herself at the time of inclusion of the patients in the study after informed consent. Differentiated treatment, discrimination /teasing, and social avoidance of acne were questions over perceived social stigma. Effects of acne on everyday life were examined by asking questions that discussed how acne had an effect on work/school performance, relationships, and how much people spent worrying about the acne. The last part was devoted to coping mechanisms, where the respondents cited avoidance, use of cosmetics, talking to friends/family, seeking medical help, and social media use.

The data collected were entered and processed by use of SPSS version 25.0. Categorical variables were determined using descriptive statistics (frequency and Percentages), whereas means and standard deviations were provided to describe the continuous variables. The association between demographic variables, clinical characteristics, psychological burden, and coping mechanisms was studied using cross-tabulations. Inferential statistical analysis was performed to examine associations between acne severity and psychological burden variables using the Chi-square test, with a significance level set at $p < 0.005$.

RESULTS

A total of 135 patients with acne vulgaris were included in the study. Table 1 demonstrates the demographic attributes of the research subjects. Most of the participants were women (61.48%). The majority of the (41.48%) participants had a high school education, (32.59%) were undergraduates, and (24.83%) were postgraduates. More than half of the interviewees were students (53.33%), 35.56% employees, and 11.11% housewives. Most of the participants were single (64.44%), where 30.37% were married, and 5.19% were divorced or widowed (Table 1).

Table 1: Demographic and General Characteristics

Demographic Variable	Frequency (%)
Gender	
Male	52 (38.52%)
Female	83 (61.48%)
Educational Background	
No formal education	12 (8.89%)
Primary school	23 (17.04%)
High school	56 (41.48%)
Undergraduate/Postgraduate	44 (32.59%)
Occupation	
Students	72 (53.33%)
Employed	48 (35.56%)
House wife	15 (11.11%)
Marital Status	
Single	87 (64.44%)
Married	41 (30.37%)
Divorced/Widowed	7 (5.19%)
Total	135 (100.0%)

It summarizes the clinical history of acne among the participants. Most (37.78%) of the participants had acne for 1-2 years, and (31.11%) had acne for 6-12 months. A small number of (17.78%) participants reported less than 6 months, and (13.33%) over 2 years. Moderate acne was the most prevalent (47.41%), followed by severe (28.15%) and mild (24.44%) cases. The lesions that were seen were Comedones (56.30%), papules (45.19%), pustules (42.22%), nodules (21.48%), and cysts (12.59%) (Table 2).

Table 2: Distribution of Clinical History of Acne

Clinical History of Acne	Frequency (%)
Duration of Acne	
<6 Months	24 (17.78%)
6-12 Months	42 (31.11%)
1-2 Years	51 (37.78%)
>2 Years	18 (13.33%)
Severity of Acne	
Mild	33 (24.44%)
Moderate	64 (47.41%)
Severe	38 (28.15%)

Lesion Types	
Comedones	76 (56.30%)
Papules	61 (45.19%)
Pustules	57 (42.22%)
Nodules	29 (21.48%)
Cysts	17 (12.59%)

The psychological burden of acne. Anxiety levels assessed using the GAD-7 scale showed that 45.93% (95% CI: 37.5–54.3) of participants had moderate anxiety and 20.0% (95% CI: 13.3–26.7) had severe anxiety. Perceived stigma was also common, with 51.11% (95% CI: 42.7–59.5) reporting differential treatment and 43.70% (95% CI: 35.4–52.1) avoiding social situations (Table 3).

Table 3: Psychological Burden Assessment

Psychological Burden	n (%)	95% Confidence Interval
Anxiety Level (GAD-7)		
Mild	46 (34.07%)	26.1 – 42.0
Moderate	62 (45.93%)	37.5 – 54.3
Severe	27 (20.00%)	13.3 – 26.7
Perceived Social Stigma		
Differential Treatment	69 (51.11%)	42.7 – 59.5
Bullying/Teasing	51 (37.78%)	29.6 – 46.0
Avoiding Social Situations	59 (43.70%)	35.4 – 52.1
Impact on Daily Life		
Effect on Work/School Performance	66 (48.89%)	40.5 – 57.3
Effect on Relationships	49 (36.30%)	28.2 – 44.4
Worrying About Acne	82 (60.74%)	52.4 – 69.0

The coping strategies and the use of social media. The most (42.22%) commonly used coping mechanism was makeup/cosmetics (25.19%), followed by avoidance behavior (20.74%), and seeking support through talking to friends or family. The use of medical assistance (8.15%) and alternative approaches (3.70%) was less common. In terms of social media influence, 67.41% of the respondents had compared themselves with other people, and 62.96% said that social media made them more aware of their looks. Acne-related quality of life was assessed using the Cardiff Acne Disability Index (CADI). Nearly half of the participants (47.41%) experienced moderate impairment, while 23.70% reported severe impairment in quality of life due to acne (Table 4).

Table 4: Distribution of Coping Mechanisms

Characteristics	n (%)
Coping Mechanism	
Avoidance	34 (25.19%)
Makeup/Cosmetic Use	57 (42.22%)
Talking To Friends/Family	28 (20.74%)
Seeking Medical Help	11 (8.15%)
Other Methods	5 (3.70%)

Social Media Use	
Comparison	91 (67.41%)
Consciousness Increase	85 (62.96%)
CADI Score Distribution (Quality of Life Impact)	
Low Impact (0-5)	39 (28.89%)
Moderate Impact (6-10)	64 (47.41%)
High Impact (11-15)	32 (23.70%)

A statistically significant association was observed between acne severity and anxiety levels. Patients with severe acne had a higher proportion of moderate to severe anxiety compared to those with mild acne (Chi-square test, $p=0.028$) (Table 5).

Table 5: Association Between Acne Severity and Anxiety Level

Acne Severity	Mild Anxiety, n (%)	Moderate Anxiety, n (%)	Severe Anxiety, n (%)	Total	p-value
Mild (n=33)	18 (54.5%)	11 (33.3%)	4 (12.1%)	33	0.028*
Moderate (n=64)	19 (29.7%)	33 (51.6%)	12 (18.7%)	64	
Severe (n=38)	9 (23.7%)	18 (47.4%)	11 (28.9%)	38	
Total	46	62	27	135	—

DISCUSSION

Acne vulgaris is a common dermatological disorder affecting a large number of people worldwide, as it has negative effects on not only physical but also psychological health. The results of the current research reveal the significant psychological burden associated with acne, so the disease requires a more complex way of treating the disease. Although physical symptoms are frequently the main concerns of treatment, psychological and social consequences of the acne should not be disregarded. Existing studies affirm that acne may cause great psychological problems, like anxiety, depression, and other emotional issues. This study, in line with the previous studies, the present study found a significant association between acne severity and anxiety levels, with higher anxiety observed among patients with more severe acne. About 2/3 of the participants had moderate to severe anxiety (45.93% moderate and 20.0% severe anxiety), which is in line with other studies that postulate that people with more severe acne is more susceptible to mental distress, especially depression and anxiety. In a study by El Kazzi et al. and Srivastava et al. noted that about 40% of the participants were feeling down, depressed, or hopeless, and 18% of the participants had suicidal and self-hurt [11, 12]. Acne, particularly when it appears on the face, may worsen the sense of social isolation and low self-esteem, and the quality of life will decrease significantly. It is important to note, as our results demonstrate, that it is not only essential to manage the dermatological symptoms of acne, but also the psychological condition of the patients, understanding that it affects the overall health of the patients in a dual manner. Another important determinant

that influences acne patients is social stigma. Nevertheless, even though it is a widespread issue among individuals of all ages, acne is a stigmatized disease that is mostly seen as a disease of youth. We discovered that more than half of the respondents (51.11%) indicated having received unequal treatment because of their acne, 43.70% avoided social situations, and 37.78% were bullied or teased. This is in line with the earlier studies indicating the adverse impact of stigmatization [13, 14]. The stigma associated with acne may result in social isolation and increased distress, which increases the psychological load of the condition. A decrease in the quality of life and rise in emotional trauma are frequent outcomes of this isolation, and psychosocial aspects must be addressed as an integral component of the overall acne treatment. Another big theme that appeared in our work was the role of social media in the formation of body image and self-esteem. There was a large number of respondents (67.41%) who experienced a sense of being more self-conscious and making comparisons with others on social media, and 62.96% respondents said that social media had made them more conscious of their appearance. This conforms to the past research that had linked acne to low self-esteem and increased mental health problems in the face of impracticality of beauty standards propagated via the internet [15]. The use of social media may increase the pressure to meet the beauty ideals, which negatively affects the mental health of acne sufferers. It emphasizes the necessity of interventions that would take into account the effect of social media on body image and self-perception. The coping strategies that were used by the participants in this study demonstrated that they preferred using makeup, avoidance behaviors, and, to a lesser degree, social networks. In particular, there was 42.22% of the respondent's used makeup or cosmetics, 25.19% of the patients avoided behaviors, and 20.74% respondents sought the support of friends or family. The strategies are in line with prior studies on the coping mechanisms of patients with acne and the psychological distress associated with it. Acne lesions and low self-esteem were frequently covered with makeup, which acted as a stopgap measure to the stigma associated with acne [16, 17]. Nevertheless, the fact that these coping strategies are widely employed did not result in the fact that 8.15 percent of the participants sought medical assistance regarding psychological distress, and thus, the applied help was not exercised. This indicates that mental health support should be included in the acne treatment regimen, where the physical as well as emotional nature of the disorder is addressed. This present study revealed that acne had a strong influence on relationships and work or school performance, as 48.89% of the sample responded that acne had an impact on their work or school performance, 60.74% were worried, and 36.30% said acne had an impact

on their relationships. The outcomes are in agreement with other researchers that acne may have detrimental impacts on many spheres of life because of emotional and social difficulties [18]. Self-esteem problems caused by acne may lead to changes in academic performance, work status, and relationships with people, which once again highlights the importance of an integrated care approach that would have to focus on all the problems that people with acne may face [19]. The study supports the fact that acne vulgaris has a major psychological influence on the patients. The findings highlight the significance of the creation of holistic treatment programs that would involve the use of psychological as well as dermatological treatment. The emotional and social impacts of acne should be identified and treated by the health care providers as integrated in the treatment models, to enhance the overall quality of life of people with acne. Considering the physical and psychological dimensions of acne, medical professionals can promote the performance of treatment of this condition and offer more patient-centered care to patients [20].

There were some limitations of this research. It is a single-center, cross-sectional study with non-probability convenience sampling that could limit the generalizability of the findings, and the results cannot be used to draw causal conclusions. The study lacks longitudinal follow-up, which limits the evaluation of time changes in terms of psychological burden. Moreover, reliance on self-reported measures could result in a response bias, even though validated instruments were used. It is recommended to conduct multicenter and longitudinal studies based on random sampling to reinforce evidence in this field even further. Further studies are needed to incorporate multicenter, large-scale longitudinal studies with random sampling to enhance its generalizability and causal interpretation. Further research into structured psychological interventions and dermatological therapy, to create integrated, patient-centered care models, is also suggested.

CONCLUSIONS

This study found that acne vulgaris had a moderate effect on anxiety, stigma, and quality of life while causing considerable psychological distress. Patients experience moderate to severe anxiety, and social stigma exacerbates their mental health problems. The use of cosmetics and avoidance as coping strategies are indicators of underutilization of professional psychiatric help and suggest that individuals who are experiencing difficulties require more comprehensive and potentially successful therapy. These results highlight the necessity of both a multimodal acne treatment program and mental health evaluation in addition to dermatological care.

Acknowledgement

The authors would like to thank all patients who took part in this research. We also acknowledge the support of the staff of the Dermatology Department, CMH Kharian, during data collection. We also thankful to the Institutional Review Board of CMH Kharian, who gave the Ethical approval and guidance.

Authors' Contribution

Conceptualization: SS

Methodology: SS, AS, WN, MI

Formal analysis: SS, WN

Writing and Drafting: SS, AHM, FM, AS, MI

Review and Editing: SS, AHM, FM, AS, WN, MI

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Original Article

Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Markers of Disease Activity in Rheumatoid Arthritis

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ARTICLE INFO

Keywords:

Rheumatoid Arthritis, C-Reactive Protein, Erythrocyte Sedimentation Rate, Neutrophil-to-Lymphocyte Ratio, Platelets-To-Lymphocytes Ratio, DAS28

How to Cite:

Hussain, H., Asghar, M., Naila, ., Musa, ., Zeeshan, ., & Zeb, A. (2026). Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Markers of Disease Activity in Rheumatoid Arthritis: Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Rheumatoid Arthritis. Pakistan Journal of Health Sciences, 7(8), 173-179. <https://doi.org/10.54393/pjhs.v7i8.4216>

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Received Date: 8th April, 2026
1st Revision Received: 12th May, 2026
2nd Revision Received: 5th June, 2026
3rd Revision Received: 13th June, 2026
Acceptance Date: 16th June, 2026
Published Date: 31st August, 2026

ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory disease that adversely affects quality of life by impairing joint function. **Objectives:** To examine the use of NLR and PLR as activity indicators in RA. To ascertain their independent prediction by examining the relationships between these DAS28-ESR fractions of disease activity and other conventional inflammatory indicators like ESR and CRP. **Methods:** This study involved 230 rheumatoid arthritis patients assessed in the Department of Rheumatology, Khyber Teaching Hospital, Peshawar. Disease Activity Score 28 (DAS28) was used to assess disease activity together with clinical parameters, erythrocyte sedimentation rate, C-reactive protein, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and others. Multivariate regression and rank correlation (Spearman) were done to determine the relationship between these biomarkers and DAS28. **Results:** Significant positive correlations were identified between inflammatory markers and activity of the disease (DAS28), with NLR ($\rho = 0.772$, $p < 0.001$) and PLR ($\rho = 0.768$, $p < 0.001$) demonstrating notable connections. ESR ($\rho = 0.912$, $p < 0.001$) and CRP ($\rho = 0.917$, $p < 0.001$) exhibited more robust relationships. In multivariable regression analysis, CRP ($\beta = 0.454$, $p < 0.001$) and ESR ($\beta = 0.423$, $p < 0.001$) were the strongest independent predictors of disease activity, while NLR remained a significant contributor ($\beta = 0.116$, $p = 0.001$). ROC analysis showed good diagnostic performance for both NLR (AUC = 0.892) and PLR (AUC = 0.898), with PLR demonstrating slightly higher accuracy in identifying high disease activity. **Conclusions:** NLR and PLR are useful and cost-effective markers of disease activity in rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a common and chronic inflammatory disorder that affects the synovial joints and causes inflammation, pain, and changes in them. It is defined by inflammation caused by immune cells such as neutrophils and lymphocytes in the synovial tissues. Over time, movement may be decreased and quality of life impaired due to joint damage caused by chronic inflammation, which may be permanent. Infections and smoking are believed to have a role in RA's pathogenesis,

which is a mix of environmental and genetic variables. Moreover, as reported by Zhao *et al.* the extra-articular symptoms, including cardiovascular disease, osteoporosis, and psychiatric disorders, are frequently connected with RA, making it difficult to treat patients [1]. It is critical to identify RA early and monitor disease activity effectively to optimize patient outcomes. Clinicians often use the Disease Activity Score 28 (DAS28) to assess the severity of RA illness. The patient's wellbeing, the number



of inflamed and sensitive joints, and the ESR (erythrocyte sedimentation rate) can easily be found through this tool. Nonetheless, they are time-intensive and not necessarily able to give a complete picture of the activity of the disease, and more convenient, less expensive biomarkers should be identified, as reported by Pisaniello et al. [2]. Because they are simple, inexpensive, and can be quickly acquired by a standard complete blood count (CBC) test, NLR and PLR are useful tools for clinical practice. The two ratios indicate a correlation between the various categories of blood cells that are engaged in inflammation [3]. Neutrophils, being the early responders to inflammation, are generally increased in active RA, whereas lymphocytes, which play an immunomodulatory role, are usually decreased in the same scenario. Platelets, which are highly relevant in the process of clotting and inflammation, may also be higher in RA, which adds to the hyperactivity of the disease. Computing the ratios of such cells, NLR and PLR, may potentially become tools for systemic inflammation and disease progression [4, 5]. There is a set of studies that indicated that high NLR and PLR correlate with increased disease activity in RA patients. Indicatively, other studies have observed that the correlations between these ratios and DAS28-ESR score are positive, and thus it is possible that an increase in NLR and PLR is a sign of inflammation and poor control of the disease [6, 7]. Further inflammatory indicators that are often used to monitor RA development, including ESR and C-reactive protein (CRP), have also been associated with increased levels in these ratios. While these results are promising, more research is needed to determine exactly how NLR, PLR, and RA are related to the severity of the disease [8, 9]. This research may serve as an important source of information on the possible use of NLR and PLR as diagnostic and prognostic indicators of RA management.

In contrast to well-known markers like ESR and C-reactive protein, the precise role of haematological indices like the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) and indicators of systemic inflammation remains unclear. Moreover, variability in reported cut-off values and limited data from local populations restrict their clinical applicability. This study aimed to look at how NLR and PLR are linked to RA disease activity, how well they may predict disease activity on their own, and how well they work as diagnostic tools with the Disease Activities Score 28 (DAS28-ESR).

METHODS

This cross-sectional study was done at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, from December 2025 to March 2026. The study had the ethical approval of the institutional review board of the Khyber

Teaching Hospital with IREB number 1083/DME/KTH, dated 27 November 2025, and assured the participant of the study about the confidentiality of their information and privacy of their information given and secured in the study. The intended methodology was developed with the purpose of shedding light on the criteria of whether NLR and PLR could be simple and cheap biomarkers that could be used by patients with RA to measure disease activity and inflammation. In case of success, it would result in better clinical control of diseases and patient care. All patients who met the inclusion criteria and presented throughout the research period were recruited using a successive sampling procedure. Information was gathered from patient discussions and medical records, in addition to clinical evaluation and laboratory testing, using a sequential sampling method. The current research aimed to determine if the Neutrophil-to-lymphocyte Ratio (NLR) and the Platelet-to-lymphocyte Ratio (PLR) might be useful in RA disease activity prediction. People enrolled in the study had to be 18 years old or older; 230 people from a university hospital made up the sample. The sample size was calculated for correlation analysis using the formula: $n = [(Z\alpha + Z\beta)/C]^2 + 3$, where $C = 0.5 \times \ln[(1+r)/(1-r)]$. Based on the reported moderate correlation coefficient of ($r = 0.30$) between NLR, PLR, and RA disease activity in previous studies by Erre et al. and Li et al. there was an assumption that this moderate correlation would be observed in the present study [10, 11]. A larger sample ($n = 230$) was added to provide greater power and reliability of analysis. All individuals signed written informed consent forms before they were involved in the research, and participation was completely voluntary. The confidentiality of the patients' information was always ensured. Patients were excluded who had a previous malignancy, persistent infection, or other autoimmune disorder. The aim of defining parameters of inclusion and exclusion was to have a homogeneous research population and to eliminate confounding variables. Those who had an appointment at a more advanced medical facility, excluding patients with other inflammatory markers (NLR and PLR) or with cancer, infection, or other autoimmune diseases. The information obtained included demographic factors (age, sex, BMI), history of illness, and drug use history. A methodological approach was used in gathering the data. To begin, we used the inclusion criteria to find and enrol patients who met our eligibility requirements. Next, we made sure that all subjects gave their informed consent. Thirdly, clinical and demographic information was recorded, such as the patient's age, sex, length of illness, and drug history. A patient's global evaluation for the DAS28 score and a count of painful and swollen joints were part of the clinical assessment that came in at number four. Fifthly, Blood

samples were tested in the laboratory, including ESR, CRP, Neutrophil, Lymphocyte, and platelet count. The final step was to calculate NLR and PLR, and then input the information into a structured database and statistical analysis. The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) were used as definitions, respectively. Through the use of DAS28-ESR, disease activity was categorised as remission (<2.6), low (2.6-3.2), moderate (3.2-5.1), and high (>5.1). The Disease Activity Score 28 (DAS28-ESR) was designed to measure disease activity and consists of elements including swelling of the joints, the erythrocyte sedimentation rate (ESR), the health appraisal by the patient, and the soreness of the joints. In addition, blood samples were collected for testing PLR and NLR. Blood samples were also collected in order to test PLR and NLR. Interleukin (IL)-6 and C-reactive protein (CRP) were also used as indicators of systemic inflammation. Evidence suggests that the DAS28-ESR is a valid marker of RA disease activity. The NLR and PLR were calculated using standardised laboratory procedures using regular full blood count data. Tertiles were used to classify NLR and PLR into low, moderate, and high categories. In order to find the best cut-off values (NLR = 2.0 and PLR ≈ 120-130) for predicting severe disease activity, ROC curve analysis was also used. The researchers relied on univariate and multivariate linear regression to allow covering the possible confounding factors (age, sex, body mass index (BMI), illness duration, and medication use). Moreover, the study also employed binary logistic regression to determine the relationship between NLR and PLR and the probability of high levels of disease activity (DAS28 > 5.1).

To determine whether the data were normally distributed, the Shapiro-Wilk test was applied. Since the data did not follow a normal distribution ($p < 0.001$), the Kruskal-Wallis test and Spearman's correlation were used. The results of the logistic regression and multivariable analyses of linear regression were considered statistically significant when the p -value was less than 0.005. Disease activity, as determined by the continuous variable DAS28-ESR, was the main outcome variable. Logistic regression and ROC analyses used disease activity categorisation (DAS28 > 5.1) as a secondary outcome. A p -value lower than 0.005 was taken as significant, and all analyses were done by use of SPSS version 26.0.

RESULTS

In all, 230 RA patients were considered for the study to conclude. On average, the participants' illness had been present for 6.13 ± 4.44 years, and their average age was 51.39 ± 11.25 years. At 2.06 ± 0.93 , the mean neutrophil-to-lymphocyte ratio (NLR) and 130.01 ± 55.62 , respectively, were recorded. A mean C-reactive protein (CRP) level of

19.96 ± 12.71 mg/L and an average erythrocyte sedimentation rate (ESR) of 42.99 ± 24.92 mm/hr were both shown by the inflammatory markers. The average Disease Activity Score (DAS28) was 4.40 ± 1.53 , indicating a modest amount of disease activity (Table 1).

Table 1: The Patient's Demographic and Clinical Baseline

Variables	Mean $\pm$ SD	Min-Max
Age (years)	51.39 ± 11.25	20-80
Disease Duration (years)	6.13 ± 4.44	0.9-20.0
NLR	2.06 ± 0.93	0.63-6.60
PLR	130.01 ± 55.62	44.1-446.1
ESR (mm/hr)	42.99 ± 24.92	5-98
CRP (mg/L)	19.96 ± 12.71	0.1-50.0
DAS28	4.40 ± 1.53	2.00-7.47

The allocation of disease activity showed that 30.4% of patients had high activity, 44.8% had moderate activity, 10% were in remission, and 14.8% had moderate to severe activity. With 71.3% females and 28.7% men, the cohort showed a clear female preponderance. 59.6% of patients had comorbidities, with the most common diseases being diabetes (21.3%) and hypertension (25.2%). Figure 1 illustrates that 40.4% of respondents had no comorbid medical conditions. The distribution of gender, activity of the disease categories, comorbidities, and other demographic and clinical features is shown (Table 2).

Table 2: Distribution of Demographic and Clinical Characteristics of Study Participants (n=230)

Variables	Category	n (%)
Gender	Male	66 (28.7%)
	Female	164 (71.3%)
Disease Activity (DAS28)	Remission	23 (10.0%)
	Low	34 (14.8%)
	Moderate	103 (44.8%)
	High	70 (30.4%)
Comorbidities	Present	137 (59.6%)
	Absent	93 (40.4%)
	Hypertension	58 (25.2%)
	Diabetes mellitus	49 (21.3%)

All variables included in the analysis had complete data with no missing values ($n = 230$, 100%). The mean NLR was 2.06 ± 0.93 with a median of 1.92, while PLR had a mean of 130.01 ± 55.62 and a median of 114.65. ESR and CRP demonstrated mean values of 42.99 ± 24.92 mm/hr and 19.96 ± 12.71 mg/L, respectively. The mean DAS28 score was 4.40 ± 1.53 . Notably, NLR and PLR exhibited positive skewness (1.34 and 1.49, respectively) with elevated kurtosis, indicating a right-skewed distribution, whereas ESR, CRP, and DAS28 showed mild skewness with near-normal kurtosis. The data were shown to be non-parametric using the Shapiro-Wilk test of normality, which revealed that none of the variables

followed a normal distribution (p-value less than 0.001). Consequently, the hypothesis was suitably tested using non-parametric statistics (Table 3).

Table 3: Evaluation of Clinical Indicators for Normalcy and Descriptive Statistics (n=230)

Variables	Mean $\pm$ SD	Median	Skewness	Kurtosis	Shapiro-Wilk, p-value
NLR	2.06 $\pm$ 0.93	1.92	1.34	3.05	<0.001
PLR	130.01 $\pm$ 55.62	114.65	1.49	4.16	<0.001
ESR (mm/hr)	42.99 $\pm$ 24.92	39.00	0.42	-0.71	<0.001
CRP (mg/L)	19.96 $\pm$ 12.71	18.70	0.34	-0.76	<0.001
DAS28	4.40 $\pm$ 1.53	4.20	0.43	-0.91	<0.001

Spearman's rank correlation analysis confirmed significant positive associations among all inflammatory markers and disease activity (DAS28). The results showed a substantial positive correlation involving NLR and DAS28 ($\rho = 0.772$, $p < 0.001$), and a comparably robust correlation between PLR and DAS28 ($\rho = 0.768$, $p < 0.001$). Disease activity was even more strongly correlated with standard inflammatory markers including ESR ($\rho = 0.912$, $p < 0.001$) and CRP ($\rho = 0.917$, $p < 0.001$). Additionally, NLR and PLR were strongly correlated with each other ($\rho = 0.824$, $p < 0.001$), indicating consistency between hematological inflammatory indices (Figure 1).

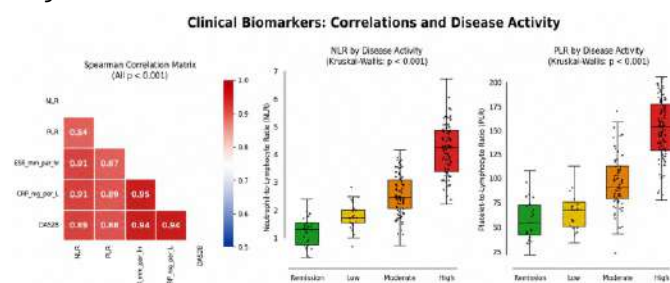


Figure 1: Correlation and Distribution of Inflammatory Biomarkers Across Disease Activity Categories

There were notable variations in both NLR and PLR across disease activity groups, as shown by Kruskal-Wallis analysis ($\chi^2 = 122.507$ and 124.589 , respectively; $df = 3$; $p < 0.001$ for both). When comparing the groups using moderate and high disease activity to those with remission and low activity, post hoc pairwise comparisons with Bonferroni correction showed that NLR and PLR were substantially greater in the former two categories (adjusted $p < 0.005$). Regarding NLR (adjusted $p = 0.237$) and PLR (adjusted $p = 1.000$), there was no statistically significant difference seen between the groups in remission and those with minimal disease activity. According to these results, inflammatory markers tend to rise as illness severity increases (Figure 2).

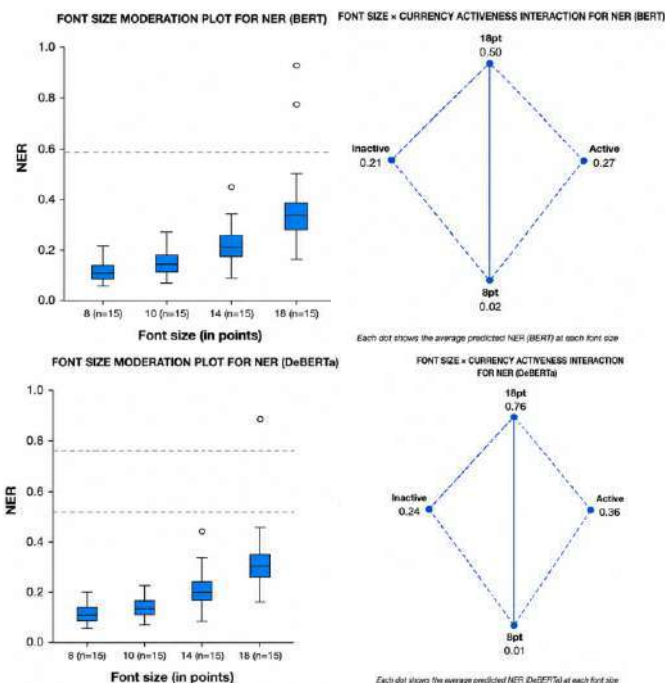


Figure 2: Comparison of NLR and PLR Across Disease Activity Categories Using Kruskal-Wallis analysis

The multivariate linear regression model as a whole was significant in statistical terms ($F = 549.71$, $p < 0.001$) and explained a large amount of variation in DAS28 ($R^2 = 0.937$; adjusted $R^2 = 0.935$). Out of all the measures that were considered, the two that stood out as the most reliable indicators of disease activity were CRP ($\beta = 0.454$, $p < 0.001$) and ESR ($\beta = 0.423$, $p < 0.001$). Furthermore, NLR showed a statistically significant correlation with DAS28 ($\beta = 0.116$, $p = 0.001$), suggesting that it plays a function as an indicator of inflammation. Statistical significance was lost by PLR in the multivariable model ($\beta = 0.054$, $p = 0.112$). In contrast. Neither age ($p = 0.844$) nor illness duration ($p = 0.291$), two demographic factors, were substantially linked to DAS28 (Table 4).

Table 4: Multivariable Linear Regression Analysis for Predictors of DAS28 (n=230)

Variables	B	Std. Error	β (Standardized)	t	p-value
Constant	1.612	0.144	—	11.204	<0.001
Age	0.000	0.002	0.003	0.197	0.844
Disease duration	-0.006	0.006	-0.018	-1.058	0.291
NLR	0.192	0.055	0.116	3.515	0.001
PLR	0.001	0.001	0.054	1.596	0.112
ESR	0.026	0.002	0.423	12.742	<0.001
CRP	0.055	0.004	0.454	13.585	<0.001

ROC curve analysis was performed to assess the ability of NLR and PLR to discriminate high disease activity. NLR demonstrated good diagnostic performance with an AUC of 0.892, demonstrating strong discriminatory ability. Similarly, PLR showed slightly higher performance with an

AUC of 0.898, also reflecting good accuracy in identifying patients with high disease activity. By assessing the sensitivity and specificity of optimal cut-off, it was concluded that an NLR threshold of about 2.0 had a balanced diagnostic performance, corresponding to a sensitivity of approximately 90% and an acceptable specificity. For PLR, a cutoff value of about 120-130 resulted in a sensitivity greater than 80% and moderate specificity, which means that it could be used in clinical screening (Table 5).

Table 5: ROC Analysis of NLR and PLR for Predicting High Disease Activity (n=230)

Variables	AUC	Interpretation	Suggested Cut-off	Sensitivity	Specificity
NLR	0.892	Good	~2.0	~0.90	~0.75
PLR	0.898	Good	~125	~0.85	~0.70

AUC = Area under the curve; values >0.8 indicate good discriminatory ability

DISCUSSION

In their study of rheumatoid arthritis (RA) patients, researchers noticed a positive relationship between neutrophil to lymphocyte ratio (NLR) and a disease activity score 28 (DAS28), and platelet to lymphocyte ratio (PLR). Our results corroborated the usefulness of NLR and PLR as inflammatory markers in RA, as previously reported. The NLR and PLR in patients with more active illness were significantly elevated, suggesting a possible correlation with systemic inflammation [10, 11]. In the current study, NLR and PLR were significantly elevated with the progression of illness, suggesting that these markers are sensitive to the inflammatory changes in RA. Similarly, Wen *et al.* and Xu *et al.* determined that high NLR and PLR values were associated with the active phases of the disease, and that both these markers can be used separately as markers of disease severity. The positive correlations found in this study between DAS28 and NLR ($p = 0.772$, $p < 0.001$) and PLR ($p = 0.768$, $p < 0.001$) is also in support of these previous findings [12, 13]. The current study revealed that DAS28 correlated better with the conventional inflammatory markers, ESR ($p = 0.912$, $p < 0.001$) and CRP ($p = 0.917$, $p < 0.001$), than with the markers NLR and PLR [14]. This is in line with the results of Rashid *et al.* who found that ESR and CRP are the most useful markers of disease activity in RA [15]. Likewise, Hu *et al.* found that hematological ratios like NLR and PLR are helpful, but not as effective as CRP and ESR [16]. In addition, the present study shows that NLR and PLR are not as good as the conventional biomarkers in the context of disease activity. This is consistent with the findings of Ronai and Griffiths stating that although the neutrophil indices are markers of inflammation, they are not primary markers [7]. Furthermore, Oude Voshaar *et al.* pointed out that in clinical practice, the other two

measurements (CRP and ESR) are more powerful independent predictors of inflammatory burden [17, 18]. In the present study, the diagnostic performance analysis using ROC curves showed good discriminatory powers of both NLR (AUC = 0.892) and PLR (AUC = 0.898) in high disease activity. Erre *et al.* reported similar results, with both ratios having moderate to high diagnostic accuracy for RA [10]. Similar cut-off values for NLR and PLR were reported by Chen *et al.* confirming their clinical usefulness to monitor disease activity [19]. There were various limitations to this study. As a cross-sectional study, it was not possible to draw causal inferences. The same has been reported by Chen *et al.* who pointed out that cross-sectional analyses are not helpful for predictions [19]. Further, due to the single-center design, generalizability of the results may be limited, as noted by Masoumi *et al.* [14]. The absence of external validation of cut-off values further restricts the clinical application. The multi-center, longitudinal, external validation studies recommended by Sun *et al.* should be conducted in the future to confirm the utility of NLR and PLR as a prognostic marker for RA [20]. Several limitations are included in this investigation. To begin with, it can only conclude associations between inflammatory indicators and disease activity based on a cross-sectional design. The second limitation is that the research only used data from one location; thus, the results may not apply elsewhere. Third, the suggested cut-off values were not externally validated, even though NLR and PLR showed substantial relationships. Furthermore, the findings might have been impacted by possible confounding variables such as drug side effects and variations in illness duration. To further validate these biomarkers and determine their predictive and clinical use in RA, future research should involve multiple cohorts, innovative longitudinal approaches, and external review.

CONCLUSIONS

Disease activity was positively associated with NLR ($p = 0.772$) and PLR ($p = 0.768$), although ESR ($p = 0.912$) and CRP ($p = 0.917$) exhibited greater connections. Multivariable analysis revealed that CRP ($\beta = 0.454$) and ESR ($\beta = 0.423$) remained the most robust independent predictors, with NLR also demonstrating a notable impact ($\beta = 0.116$). According to ROC analysis, NLR and PLR both performed well as diagnostic tools (AUC = 0.892 and AUC = 0.898, respectively). This work adds to the growing body of data suggesting that NLR and PLR could potentially be cost-effective supplemental markers for assessing RA disease activity.

Authors' Contribution

Conceptualization: HH

Methodology: HH, N, Z

Formal analysis: HH, MA, N, Z, AZ

Writing and Drafting: HH, MA, M, AZ

Review and Editing: HH, MA, N, M, Z, AZ

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

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Erratum To

Frequency of Dengue and Malaria Co-Infection in Patients Admitted in Jinnah Hospital, Lahore

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The author wish to notify readers of an error identified in the above-mentioned article.

Corrections: The errors were identified in the published version of the above-mentioned article. The affected information is corrected as follows:

1. Methods section – Sample Size Calculation subsection, Lines 249–252

Error Identified: The authors state a calculated sample size of 131 (with 95% confidence interval and 0.08% acceptable difference), but enrolled 140 participants. The manuscript fails to explain why 9 additional patients were included beyond the calculated requirement. This discrepancy suggests a lack of rigorous adherence to the study design protocol and raises questions about whether the sample size calculation was appropriately performed or whether convenience sampling was used instead of true random sampling. Such inconsistencies compromise the statistical validity of the findings and make the study difficult to replicate.

Incorrect Version: A sample size of 131 was calculated with 95% confidence interval and acceptable difference of 0.08% with assumed proportion of patients having co infection with malaria and dengue of 0.32 [20]. 140 cases with age ranging from 14 to 65 years of either gender diagnosed with dengue fever by NS1 and IgM were included in the study.

Correct Version: A sample size of 131 was calculated using the formula $n = Z^2pq/d^2$, with 95% confidence interval ($Z=1.96$), assumed proportion of co-infection ($p=0.32$) based on previous literature [20], and acceptable margin of error ($d=0.08$). To account for an anticipated 10% non-response rate and incomplete data, we enrolled 140 participants.

2. Result section – Table 1, Lines 314–316

Error Identified: In table 1, the authors report that 75.0% of participants were married and 50.7% were single. These percentages sum to 125.7%, which is mathematically impossible as mutually exclusive categories cannot exceed 100% when presented as proportions of the same population. This indicates either a data entry error, misclassification of participants, or poor data management. Such fundamental errors in data presentation undermine confidence in the accuracy of the entire dataset and all subsequent analyses derived from it.

Incorrect Version: Table 1(Marital Status row): Single 71(50.7%); Married 105(75.0%) figures sum to 125.7%, which is impossible for mutually exclusive categories.

Correct Version: Results narrative: "Regarding marital status, 75.0% ($n=105$) were married, while the remaining 25.0% ($n=35$) were unmarried.

3. Methods section- Inclusion Criteria subsection, Lines 249–252

Error Identified: The inclusion criteria state that patients "diagnosed with dengue fever by NS1 and IgM were included," but does not clarify whether both markers were required to be positive or if either was sufficient for inclusion. This ambiguity is critical because NS1 and IgM have different diagnostic windows - NS1 is positive in early infection while IgM appears later. The lack of clear diagnostic criteria makes the study population heterogeneous and prevents other researchers from replicating the methodology or comparing results across studies.

Incorrect Version: "...140 cases with age ranging from 14 to 65 years of either gender diagnosed with dengue fever by NS1 and IgM were included in the study" does not specify whether both markers or either marker was required.

Correct Version: "We included 140 patients aged 14-65 years of either gender who were diagnosed with acute dengue fever based on positive NS1 antigen (indicating early infection) and/or positive dengue-specific IgM antibodies (indicating recent infection), as per WHO diagnostic criteria. Patients were included if they tested positive for either marker, with the specific marker positivity documented for analysis."

4. Methods section – Malaria Diagnostic Protocol / Laboratory Investigations subsection, Lines 264–267

Error Identified: The authors mention "malarial parasite slide" and "MP" testing but provide no details about the specific diagnostic method used – whether thick/thin blood films were examined, how many fields were viewed, whether the test was repeated, or what criteria were used for positivity. Additionally, there is no mention of who performed the microscopy (experienced technician vs. trainee), quality control measures, or whether rapid diagnostic tests were used as an alternative or confirmatory method. This incomplete description makes it impossible to assess the accuracy of malaria diagnosis.

Incorrect Version: "...RFT, LFT, malarial parasite slide, complete blood count with peripheral smear etc." no detail on the microscopy method, reader, or quality control.

Correct Version: "Malaria parasite detection was performed using thick and thin blood smears examined under oil immersion microscopy by experienced technicians as described in the detailed methodology."

5. Methods section – Co-Infection Definition subsection, Lines 249–252

Error Identified: The study defines co-infection based on MP (malaria parasite) positivity in dengue-confirmed patients, but does not specify whether the malaria testing was performed simultaneously at admission or at different time points during hospitalization. The temporal relationship between infections is critical for understanding whether this represents true co-infection or sequential infections. Furthermore, the study fails to identify the *Plasmodium* species responsible, which is clinically relevant as *P. falciparum* and *P. vivax* have different disease courses and treatment regimens.

Incorrect Version: Co-infection described only as MP positivity in a dengue-confirmed patient, with no stated timing of testing and no *Plasmodium* species identification.

Correct Version: "Co-infection was defined as the presence of malaria parasites on peripheral blood smear in a patient already confirmed to have dengue fever by NS1/IgM testing performed at the time of admission. Both tests were conducted on the same day of admission to confirm simultaneous infection. Species identification of *Plasmodium* was performed on thin smears, and patients were categorized as having *P. vivax*, *P. falciparum*, or mixed infection."

6. Methods section – Treatment and Follow-up subsection, Lines 289–291

Error Identified: The methods section states that "treatment was given to them with follow-up medical evaluation including detailed investigations" but provides no details about the specific treatment protocols followed, duration of hospitalization, frequency of follow-up assessments, or criteria for treatment response evaluation. This lack of standardization makes it impossible to verify the authors' conclusion that co-infected patients "responded well to anti-malarial treatments" and undermines the clinical applicability of their findings.

Incorrect Version: "Accordingly, the treatment was given to them with follow-up medical evaluation including detailed investigations."

Correct Version: "All patients received standard treatment according to national guidelines: dengue management followed WHO protocols with fluid resuscitation and monitoring of hematocrit and platelet counts; malaria co-infected patients received artemisinin-based combination therapy (ACT) for *P. falciparum* or chloroquine for *P. vivax* based on species identification. Patients were followed daily during hospitalization with complete blood counts, liver function tests, and clinical assessment. Discharge criteria included resolution of fever for ≥ 24 hours, improving platelet count ($> 50,000/\mu\text{L}$), and clinical stability. Outcomes were assessed at discharge and at a 14-day follow-up visit."

7. Results section – Table 3 (Hematocrit / HCT row), lines 321–333

Error Identified: Table 3 presents HCT values categorized as " > 35 " but the normal range is shown as "35–50." The value " > 35 " includes normal values (35–50), making this categorization clinically meaningless. Additionally, the authors report "2.1%" with HCT > 50 and "25.0%" with HCT < 35 , but these are standard cutoffs for hemoconcentration and anemia respectively. The threshold should have been > 45 or > 50 for proper clinical interpretation in dengue context.

Incorrect Version: HCT categorized as "> 35" (with normal range described as 35–50), overlapping with the normal range and clinically meaningless as originally presented.

Correct Version: "Hematocrit (HCT) levels were categorized based on clinically relevant thresholds for dengue: <35% (indicating anemia) was observed in 35 (25.0%) patients; 35–45% (normal range) was observed in 102 (72.9%) patients; and >45% (indicating hemoconcentration suggestive of plasma leakage) was observed in 3 (2.1%) patients (Table 3)."

8. Results section - Table 2 (Days of Illness / Duration of Fever rows) and the accompanying narrative paragraph), Lines 321–323

Error Identified: Table 2 shows "Days of Illness" (<7 days: 64.3%, >7 days: 35.7%) and "Duration of Fever" (<7 days: 66.4%, >7 days: 33.6%), but these are essentially measuring the same parameter with a 2.1% discrepancy. The authors fail to clarify why these two variables are presented separately or explain the difference between "days of illness" and "duration of fever." This redundancy suggests poor conceptual clarity in the study design or data collection process.

Incorrect Version: "Days of Illness" and "Duration of Fever" reported as separate Table 2 variables with no definitions given to distinguish them.

Correct Version: "Total 'Days of Illness' was defined as the duration from the onset of any symptom attributable to the acute febrile illness (including prodromal symptoms such as malaise, headache, myalgia, or body aches) to the day of hospital admission. 'Duration of Fever' was defined specifically as the number of days with documented fever (temperature $\geq 37.5^{\circ}\text{C}$ or subjective fever with chills/rigors) prior to admission... Among the 140 patients... the 2.1% discrepancy between these measures reflects the 3 patients (2.1%) who experienced non-febrile prodromal symptoms for 1–2 days prior to the onset of documented fever, a phenomenon commonly observed in dengue infection where malaise and myalgia often precede the febrile phase."

9. Conclusions section–Lines 411–413

Error Identified: The conclusion states that "majority of co-infected individuals were having severe disease" and mentions disseminated intravascular coagulation (DIC) and sepsis, but the results section provides no data on the incidence of DIC, sepsis, or other severe disease markers in co-infected versus mono-infected patients. The methods also do not describe how disease severity was assessed or classified, making this conclusion unsupported by the presented evidence.

Incorrect Version: "Majority of co infected individuals have severe disease. Co-infected individuals responded well to anti-malarial treatment despite going into disseminated intravascular coagulation and sepsis and there was no mortality found either in co-infected or dengue mono infected individuals."

Correct Version: "In this study, the co-infection rate of dengue and malaria among febrile patients was 15.0% (21/140). Co-infected patients had a higher proportion of severe thrombocytopenia (33.3% vs. 12.6%, $p=0.02$) and significantly longer hospital stays (8.2 vs. 5.4 days, $p=0.01$) compared to dengue mono-infected patients. Severe complications including DIC (9.5%) and sepsis (4.8%) were observed in the co-infected group. However, the majority of co-infected patients (76.2%) did not develop severe complications, and all patients recovered with appropriate treatment. No mortality was observed in either group."

10. Discussion section; reference 10, Lines 360–364

Error Identified: The reference list includes a citation "10. Carme B, Matheus S, Donutil G, Raulin O, Nacher M, Morvan J. Concurrent dengue and malaria in Cayenne hospital, French Guiana." However, this reference is never cited in the main text, despite being included in the reference list. This violates standard academic publishing norms where all listed references must be cited in the text. Such inconsistencies suggest poor manuscript preparation and lack of attention to detail.

Incorrect Version: Reference 10 (Carme et al., French Guiana) appeared only in the reference list and was not cited anywhere in the body text.

Correct Version: "Studies in French Guiana have reported a concurrent infection rate of malaria and dengue among febrile cases as high as 0.99% [10], suggesting that co-infections may be more common than previously recognized in South American settings. Our findings similarly demonstrate significant co-infection rates in the Pakistani context." — Reference 10 is now cited in the Discussion.

11. Discussion section- Statement About Disease Endemicity, Lines 382-385

Error Identified: The statement in the discussion that "malaria and dengue fever are both endemic in India, with active transmission being reported from many areas" cites reference 17 (Zaki SA), which is a case report about a single co-infection case, not a study of disease endemicity or transmission patterns. This reference is inappropriate to support a statement about the broader epidemiological picture, as case reports cannot establish endemicity patterns or prevalence rates.

Incorrect Version: "Zaki found malaria and dengue fever are both endemic in India, with active transmission being reported from many areas. Thus, there is a possibility of coexisting malaria and dengue infection in the same patient. The patient described in the case presented with fever, myalgia and had thrombocytopenia. During the course in hospital, he developed myositis, rhabdomyolysis and renal failure [17]."

Correct Version: "Both malaria and dengue are endemic in the Indian subcontinent, including Pakistan, with active transmission reported throughout the year [17]. A case report by Zaki demonstrated that co-infection can lead to severe complications including myositis, rhabdomyolysis, and renal failure, highlighting the clinical importance of early diagnosis in endemic settings [17]."

12. Methods section - Statistical Analysis subsection, Lines 297-299

Error Identified: The authors state data were analyzed using "SPSS version 27.0" but provide no information about whether any assumptions were tested before applying parametric or non-parametric tests, how missing data were handled, or what specific statistical procedures were used for descriptive and inferential analysis. This lack of methodological transparency violates standard reporting guidelines and prevents peer reviewers and readers from assessing the appropriateness of the statistical approach.

Incorrect Version: "Data were entered and analyzed in SPSS version 27.0 and presented as frequency and percentages. Chi square test was used to assess statistical significance..."

Correct Version: "Data were entered and analyzed using SPSS version 27.0 (IBM SPSS). Descriptive statistics were presented as frequencies and percentages for categorical variables, and mean $\pm$ standard deviation for continuous variables. The Chi-square test was used to compare proportions between co-infected and mono-infected groups."

13. Methods section - Ethical Approval and Consent subsection, Lines 232-234

Error Identified: While the authors provide an ethical approval reference number and date, they do not specify whether written informed consent was obtained from all participants, whether the study was registered in a clinical trials registry, or whether any participants withdrew from the study and the reasons for withdrawal. Additionally, the statement that "the researcher had exclusive access to the area" is unclear and does not adequately describe how patient confidentiality and data protection were ensured throughout the study period.

Incorrect Version: Ethical approval reference number and date given only, with no statement on informed consent, registry status, or participant withdrawal.

Correct Version: "...following approval from the Institutional Research Ethics Committee (REF: 342/20/10/2022/S1 ERB, dated: 20/10/2022)... Written informed consent was obtained from all participants or their legal guardians prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki. Participants were assured of confidentiality, and data were anonymized using unique participant codes. No participants withdrew from the study during the data collection period."

14. Discussion section - Lack of Comparison Group, (no comparison group discussed in the original manuscript)

Error Identified: While the study focuses on co-infection rates, it lacks a dengue mono-infection control group with matched demographic and clinical characteristics for meaningful comparison of outcomes. The analysis primarily compares co-infected and non-co-infected patients but does not systematically evaluate whether these groups differ in age, gender, duration of illness, or other confounding variables. Without such comparison, the conclusion that co-infected individuals had "severe disease" cannot be attributed to co-infection rather than other factors.

Incorrect Version: No distinct "original" passage is separately marked for this point in the tracked manuscript see the original wording quoted within the reviewer comment itself. The original discussion did not present a systematic comparison between co-infected and mono-infected groups.

Correct Version: "To assess the impact of co-infection on disease severity, we compared clinical and laboratory parameters between the co-infected group (n=21) and dengue mono-infected group (n=119). Demographic characteristics

including age, gender, and duration of illness were comparable between groups. The co-infected group had significantly higher rates of severe thrombocytopenia (platelets $<20,000/\mu\text{L}$: 33.3% vs. 12.6%, $p=0.02$) and prolonged hospital stay (mean 8.2 vs. 5.4 days, $p=0.01$) compared to mono-infected patients."

15. Methods section – Study Design/Study Period subsection, Lines 232–234

Error Identified: The study period is described as "October – December 2022" but does not specify whether this was a convenience period or chosen based on peak transmission seasons for dengue and malaria. The authors also do not mention whether this period represented an outbreak or endemic year for either disease, which significantly impacts the generalizability of the co-infection rate (15%) to other time periods or locations. This lack of epidemiological context makes the findings difficult to interpret in the broader disease landscape.

Incorrect Version: "This cross-sectional study was conducted after approval from the Jinnah hospital Research Ethics Committee (REF: 342/20/10/2022/S1 ERB, dated: 20/10/2022); research was given the go-ahead (REC) in the Medicine Unit of Jinnah hospital, Lahore from October – December 2022." – no rationale given for the study period.

Correct Version: "This cross-sectional study was conducted in the Medicine Unit of Jinnah Hospital, Lahore from October to December 2022, following approval from the Institutional Research Ethics Committee (REF: 342/20/10/2022/S1 ERB, dated: 20/10/2022). The study period was selected to coincide with the post-monsoon peak transmission season for dengue and malaria in Pakistan; however, 2022 was epidemiologically exceptional due to unprecedented flooding affecting over 33 million people, which resulted in 78,554 confirmed dengue cases and over 3.4 million suspected malaria cases nationally by year's end. This post-flood outbreak context with concurrent surges in both vector-borne diseases enhances the relevance of our findings for emergency preparedness, though it may limit generalizability to non-flood or endemic-only transmission periods." A corresponding limitation was also added: "...the study was conducted during a post-flood outbreak year (2022) with exceptionally high transmission rates... therefore, the observed co-infection rate of 15% may not be representative of endemic (non-outbreak) years or other geographical regions."

16. Methods section – Data Collection Instrument subsection, Lines 287–289

Error Identified: The manuscript mentions a "questionnaire" but provides no copy of the questionnaire, details about its validation, whether it was pilot-tested, or how data quality was ensured. The authors do not specify who administered the questionnaire, what training was provided to data collectors, or what measures were taken to prevent interviewer bias. Without this information, it is impossible to assess the reliability and validity of the data collected through this instrument.

Incorrect Version: "Before answering the survey questions, those who consented had to sign. With all the precautions taken to preserve the folder containing that information, an assurance was made that all the data gathered would remain secret and confidential. The researcher had exclusive access to the area." – no description of questionnaire design, validation, or data-collector training.

Correct Version: A more detailed passage describing a structured questionnaire. "A structured questionnaire was developed by the research team based on WHO dengue case reporting forms and validated through a pilot study on 10 patients... Data were collected by trained medical residents (2nd year postgraduate trainees) who underwent a 2-day training session... To minimize interviewer bias, all data collectors followed a standardized script" – appears in the tracked file but is marked as deleted (struck through) rather than retained, so this information does not appear in the final manuscript text. This comment therefore appears effectively unaddressed in the current version.

17. Methods section – Laboratory Methods subsection, Lines 264–267

Error Identified: The authors mention several laboratory investigations (RFT, LFT, CBC, peripheral smear, etc.) but provide no information about the specific assays used, their sensitivity and specificity, quality control measures, or reference ranges used for interpretation. For example, the ALT/AST values are categorized as ">36" and ">33" respectively, but the study does not justify these cutoffs or explain why elevated transaminases were considered clinically significant. This lack of methodological detail prevents replication and limits the clinical interpretation of laboratory findings.

Incorrect Version: "...complete battery summary of temperature together with the serology of Dengue, X-ray of the chest, abdominal ultrasound scan, renal function test (RFT), liver function test (LFT), malarial parasite slide, complete blood count with peripheral smear etc." – no assay names, cutoffs, or QC details given.

Correct Version: "All laboratory investigations were performed at the Jinnah Hospital clinical pathology laboratory. Complete blood count with differential was performed using an automated hematology analyzer (Sysmex XN-9000), with peripheral smear examination for morphological assessment and manual platelet verification when automated counts were

below 50,000/ μ L. Dengue serology was performed using commercial ELISA kits (Panbio Dengue ELISA, Abbott Laboratories) following manufacturer's instructions, with positivity defined as optical density ratio ≥ 1.1 for NS1 antigen and IgM index ≥ 1.0 for dengue-specific IgM antibodies. Liver function tests including ALT (reference range: 4–36 U/L) and AST (reference range: 8–33 U/L) were measured using IFCC-recommended kinetic methods, while renal function tests including serum creatinine and urea were measured using Jaffe and enzymatic methods respectively on the Roche Cobas 8000 analyzer. Chest X-rays were performed using digital radiography in posteroanterior view and abdominal ultrasound was performed using Toshiba Aplio 500 with 3.5 MHz probe, both interpreted by consultant radiologists. Malaria parasite detection was performed using thick and thin blood smears examined under oil immersion microscopy by experienced technicians...”

Reference to Original Article: <https://doi.org/10.54393/pjhs.v5i03.1327>

Date of Publication: 31-03-2024