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Editorial **Open Access**

Plagiarism Behind The Closed Door

Iqbal Hussain Udaipurwala

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Peer reviewer and editor occupy a position of extraordinary privilege during the process of scientific publication.[1] They are entrusted with manuscripts that may contain years of experimental labor, unique datasets, or groundbreaking theoretical insights well before these ideas reach the public record.[2] While their role is outlined as a service to science, the balance of power between these gatekeepers and the authors is many a times ambiguous. Author as a rule has to abide rigorous standards including plagiarism report and disclosure of conflict of interest etc. However, reviewers and editors by contrast, operate largely unseen, only bounded by professional norms rather than systematic scrutiny.[3,4] Thus scientific and specially medical publishing might rest on a fragile social contract. Author submit his most innovative work to journal with the expectation that it will be reviewed fairly, kept confidential, and will be judged on merit. Reviewer and editor serve as a caretaker and custodian of this scientific process and trusted to protect its integrity while guiding knowledge into the public domain.[5] Yet, the history has shown that not all gatekeepers act honorably and instances are reported where reviewer or editor had stolen idea, data, or even entire passage from the unpublished manuscripts.[6] Unlike plagiarism by the author, which is often detected through software and investigated by the journal, editorial misconduct frequently occurs in silence, hidden behind the confidentiality of peer review. A young researcher may lose recognition for his new discovery and his career may be hindered. At one end, this asymmetry facilitates candid and honest feedback and scientific confidentiality while on the other hand, it may create fertile ground for misconduct. Reviewer can delay evaluation, to get time for his own experiment or to harvest idea for enriching his own research program or may even undermine competitors by issuing biased recommendation. Editors, endowed with unilateral power to reject submissions, may suppress manuscript that conflict with his interest and later incorporating elements into his own work. The lack of transparency in this process makes detection extraordinarily difficult.

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Plagiarism in peer review process is not a monolith rather it may manifest in several distressing ways.[7,8] Direct textual plagiarism occurs when reviewers or editors copy passages, tables, figures or verbatim from the confidential submissions. Far more insidious is idea appropriation where the theft involves hypothesis, methodology or dataset rather than words itself. As the ideas can be paraphrased and integrated into a new project, thus proving its actual ownership a challenging task. For early-career researcher, this theft is devastating as many years of conceptual development will be lost if a senior academician rushes a plagiarized paper for early publication. Another abuse involves editorial exploitation, as editor can terminate submissions without peer review. There are documented cases of editors rejecting manuscripts only to later publish strikingly similar work themselves or with close collaborators. Such conduct not only damages the credibility of a journal but also undermines the collective trust on editorial process. Finally, silent collaboration represents another understated breach where a reviewer shares manuscript with colleagues or laboratory member without consent. While often rationalized as a way to seek assistance, it simultaneously seeds new projects, effectively crowdsourcing stolen intellectual property. Together, such misconduct represents a betrayal of scientific trust where a conventional plagiarism only effects an individual paper, reviewer and editorial misconduct weakens confidence in the infrastructure of scholarly publishing.

The implications of reviewer and editorial plagiarism extend far beyond individual victims. At the personal level, authors particularly graduate students, postdoctoral fellows, and early-career academicians suffer irreparable harm, losing credit for their ideas that can derail their career, diminish prospects for funding and erode professional reputation. At the general level, misconduct corrodes the trust upon which science depends and if a researcher fears his ideas will be stolen during peer review, he may withhold his most innovative work. This attitude will definitely delay the dissemination of discoveries and suppresses creativity. Once the community loses faith in peer review, the legitimacy of medical publishing as an enterprise is threatened.

Despite its gravity, reviewer and editorial plagiarism often escapes detection as most plagiarism detection software such as iThenticate or Turnitin routinely detects similarity in published work only. Peer review confidentiality, while essential to protect author's right, also shields gatekeepers

from scrutiny. Proving editorial or reviewer misconduct is challenging as the text overlap can be identified but the idea adoption is elusive and intellectual property law offers limited protection for unpublished manuscripts. Even when plagiarism is suspected, a junior researcher may hesitate to accuse influential reviewer or editor, fearing retaliation or damage to his career.[9] Many cases become evident only after publication of suspiciously similar study that appear months or even years later.

To protect the integrity of medical publishing, systemic reforms are needed such as:

- Ø Open peer review: Publishing reviewer name and report, as some journals already do, makes it harder for reviewer to secretly appropriate ideas.[10]
- Ø Timestamped submissions: Preprints and block-chain timestamping provide verifiable proof of priority. An author who can publicly archive his work before submission create a digital trail that can expose idea theft later on.
- Ø Reviewer declaration: Journals should require explicit agreements from reviewers affirming that they will not use privileged information for personal gain. Due to massive increase in scientific publication in the last decade, for journal editors it is often difficult to find a suitable reviewer who can timely summit his review.[11] For this reason the editor might send a manuscript to multiple reviewer in the hope to make review process quickly. Because of this practice chance of leakage of scientific data is more.
- Ø Editorial oversight boards: Independent committee must be established by every journal who could review allegations of misconduct, ensuring that editors are not shielded from accountability by their positions.
- Ø Training and education: Regular ethics workshops for editors and reviewers must be organized that would emphasize the seriousness of plagiarism in peer review.
- Ø Sanctions: Misconduct should lead to permanent bans from editorial board and professional societies, and findings should be made public to deter others.
- Ø Protection of the whistleblower: Safe and confidential channel is essential to allow author to report suspected misconduct of the editorial board or reviewer without fear of retaliation.[12]
- Ø Password-protected and non-editable manuscript: Journals could consider sending manuscripts to reviewers in password-protected, non-editable formats to prevent unauthorized saving, copying, or sharing of content. Reviewers would access the manuscript only through the journal's secure online portal, where annotations and tracked changes could be made directly within the system without the ability to download or replicate the file.

These modifications demand cultural as well as procedural change because the reviewer or editorial misconduct must not be treated as an isolated case, rather it should be considered as a systemic risk to the credibility of medical publishing. As the scientific or academic culture is now increasingly defined by funding, prestige, and authorship, the attraction to exploit privileged access is real. If the author has to uphold rigorous standards, then reviewer and editor must also be held for equal standard of transparency and responsibility. The medical publishing community must act decisively as the above-mentioned reforms are no longer optional, they are essential. The choice is simple either confront this misconduct with urgency, or risk the collapse of credibility in medical publishing.

Authors Contribution:
Iqbal Hussain Udaipurwala: Conception, writing, literature search, proof reading

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Original Article **Open Access**

Effectiveness of Non-Hormonal Treatment on Moderate to Severe Premenstrual Syndrome: A Double Blind Randomized Control Trial

Haleema Sadia, Nadia Zahid, Gulfreen Waheed, Sana Navid

Abstract

Objective: This study aimed to evaluate the effectiveness of calcium and vitamin D supplementation compared with placebo in reducing premenstrual symptom severity among female university students.

Study design and Setting: A double blind, randomised, placebo controlled, parallel trial was conducted involving 100 females aged 18 to 40 years diagnosed with PMS at the Department of Gynecology and Obstetrics, Avicenna Medical College Hospital, Lahore

Methodology: Participants were randomly divided into two equal groups: one received vitamin D (50,000 IU every two weeks) plus calcium (1,000 mg daily), and the other received a placebo for 12 weeks. Premenstrual symptoms were assessed using the Premenstrual Symptoms Screening Tool Adolescent (PSST A). Chi square, Student t test, and repeated measures ANOVA were applied for analysis using SPSS version 23.

Results: The calcium plus vitamin D group (mean age 25.7 ± 1.53 years) showed significant improvements in anger or irritability, anxiety or tension, and reduced interest in work ($p = 0.04, 0.03, 0.001$). Overeating or food cravings improved ($p < 0.001$), and physical symptoms and work efficiency improved at 6 months ($p = 0.04, 0.01$).

Conclusion: Calcium plus vitamin D supplementation significantly alleviated emotional and physical PMS symptoms and improved work efficiency compared with placebo.

Keywords: Calcium; Premenstrual Syndrome; Randomized Controlled Trial; Vitamin D; Women's Health

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INTRODUCTION

Premenstrual syndrome (PMS) is a combination of physically and psychologically observable signs of discomfort within the luteal phase of menstrual cycle. Such experiences normally cause significant distress and functional impairment amongst the affected individuals who normally show improvement of symptoms during the onset of menstruation.[1] Empirical findings confirm that prevalence rate of PMS in the world is about 50 % among women at childbearing age.[2]

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Though in most cases the symptomatology is mild and moderate, severe ones that can interfere with the day-to-day functionality are registered in 2.5-3 percent of patients. Women who attend the university, especially, show an increased rate of PMS.[1-3]

PMS is typified by mood alteration, stress, and anxiety, three of the most widespread symptoms in a range of around 200. Concomitant symptoms such as emotional imbalances, like stress, anxiety, insomnia, headaches, fatigue, changes in mood, emotional sensitivity and variations in libido are not uncommon, whereas alterations in the appetite, constipation, Nausea, tenderness of breasts or swelling, acne during the menstrual period, exhaustion, as well as pain or discomfort in the joints and muscles make up the respective somatic manifestation.[4] According to the criteria most regularly found in the literature, the primary complaint should include signs of serious emotional difficulties, in order to be eligible to fulfill diagnostic criteria of PMS.[4,5]

The aetiology of PMS remains unknown.[1] It is believed that PMS is not a singular disorder but rather a collection of symptoms with biological origins, encompassing psychological and social components. Consequently, both pharmacological and non-pharmacological treatments have been explored.[6] Treatment strategies generally focus on alleviating symptoms and minimizing the impact of PMS

on daily activities. Pharmacological approaches often involve combinations of diuretics, painkillers, antihistamines, antidepressants, and anti-anxiety medications targeting specific symptoms.[1]

More focus has recently been placed on alternative therapies, mostly derived from clinical experience, that attempt to lessen the frequency and intensity of PMS symptoms via as-yet-unidentified mechanisms. These include dietary changes like primrose oil or high-carb diets, which have drawn more attention, and supplementing with minerals including calcium, vitamin D, magnesium, vitamin E, and vitamin B6.[7]

Serum calcium and vitamin D levels have been observed to vary across the menstrual cycle, with numerous studies indicating a significant deficiency in women experiencing premenstrual syndrome (PMS) compared to those without the condition.[8] Calcium plays a vital role in neuromuscular transmission and hormonal balance, while vitamin D contributes to the regulation of inflammatory responses and neurotransmitter activity, both of which are implicated in PMS pathophysiology.[9] Supplementation with calcium and vitamin D has been associated with improvements in mood stability, reduction in anxiety and depressive symptoms, and alleviation of physical discomfort such as bloating and fatigue during the luteal phase.[10,11] Despite global research supporting their therapeutic potential, limited data exists from Pakistan evaluating the clinical efficacy of these nutrients in managing PMS symptoms. Given their roles in modulating endocrine and immune function, calcium and vitamin D supplementation may offer a safe, non-hormonal approach for symptom relief.[12] Therefore, the objective of the current study is to investigate, in a local setting, if combined calcium and vitamin D supplementation can lessen the intensity of PMS in women.

METHODOLOGY

The sample size of the study was determined via WHO sample size calculator of health studies; which relies on the formula of calculating a proportion with a given level of absolute precision. The assumptions were: confidence level of 95%, expected proportion of the population of 50% and an absolute precision of 10 percent (0.10).

Based on these parameters, a total sample size of 100 participants was calculated with 50 participants being assigned to each group by randomly choosing them. This was found to be a sufficient size to give a reasonable statistical power to find significant differences between the intervention and placebo groups. This research was a double-blind, randomised clinical trial conducted between March 25th, 2025 to August 25th, 2025. The study population comprised female aged 18–40 years with premenstrual syndrome (PMS), reporting in the Department of Gynecology and obstetrics, Avicenna Medical College Hospital, Lahore, Pakistan. Inclusion criteria encompassed participants aged 18–40 years with moderate to severe PMS, enrolled at Avicenna Medical College Hospital, and willing to participate in the trial. Exclusion criteria included individuals exhibiting symptoms of malnutrition or requiring calcium+vitamin D supplementation; those presenting with severe malnutrition; symptoms of systemic diseases such as sepsis, haemodynamic instability, or acute meningitis; diarrhoea (defined as three or more watery stools in the preceding 24 hours); known intolerance or sensitivity to calcium+vitamin D or calcium+vitamin D containing compounds; smoking; exposure to stressful situations; or a history of mental illness.

Participants were randomly assigned to two groups of equal size: One group received vitamin D supplementation at a dose of 50,000 IU every two weeks along with a daily intake of 1,000 mg of calcium, whereas the comparison group was administered a placebo under the same conditions for 12 weeks. Participants' symptoms were assessed at baseline, one month, three months, and six months following the commencement of the study. To allocate participants equally into the two groups, with 50 participants assigned to each group. By using a double-blind approach, the study reduced bias by guaranteeing that neither participants nor researchers knew the group assignments.

In order to participate in the study, individuals had to read and sign an informed consent form before it started. Demographic data, such as age, occupation, marital status, and level of education, were gathered and documented at the time of enrolling. In this study, the severity of PMS was evaluated using the Premenstrual Symptoms Screening Tool (PSST) questionnaire. The PSST consists of 19 questions that are separated into two sections: 14 items in the first segment cover emotional, somatic, and behavioural symptoms, and 5 questions in the second section assess how these symptoms affect participants' daily life. This tool was developed by McMaster University in Canada.[13] Participants completed the questionnaire at baseline, as well as one month, three months and six months after the study commenced. The Ethics Committee of Avicenna Medical College in Lahore, Pakistan, gave the study ethical approval

Table 1 Bifurcation of demographic characteristics with respect to intervention and control groups.

Variables	Categories	Calcium + Vitamin D group 50 (50.0%)	Control group 50 (50.0%)	p-value
Age (years)	Mean ± SD	25.7 ± 1.53	24.9 ± 1.79	0.21
Education	Primary	4 (8.0)	6 (12.0)	0.08
	Secondary	17 (34.0)	19 (38.0)	
	Graduation	21 (42.0)	22 (44.0)	
	Masters	8 (16.0)	3 (6.0)	
	Students	19 (38.0)	16 (32.0)	
Occupation	Homemaker	7 (14.0)	12 (24.0)	0.11
	Working women	24 (48.0)	22 (44.0)	

Table 2 Bifurcation of Psychological & Behavioural Symptoms (Mean ± SD) with respect to intervention (calcium + vitamin D) and control groups.

Variables	Categories	Treatment modalities		p-value
		Calcium + Vitamin D group 50 (50.0%)	Control group 50 (50.0%)	
Anger/irritability				0.67
	Mean ± SD	3.43 ± 0.12	3.37 ± 0.12	
Anxiety/tension				0.52
	Mean ± SD	3.60 ± 0.13	3.46 ± 0.11	
Tearful/increased sensitivity to rejection				0.71
	Mean ± SD	3.83 ± 0.13	3.77 ± 0.09	
Depressed mood/hopelessness				0.05
	Mean ± SD	3.43 ± 0.12	4.01 ± 0.07	
Difficulty concentrating				1.01
	Mean ± SD	4.12 ± 0.12	4.12 ± 0.06	
Fatigue/lack of energy				0.31
	Mean ± SD	3.76 ± 0.10	4.02 ± 0.11	
Overeating/food cravings				0.67
	Mean ± SD	3.19 ± 0.12	3.28 ± 0.15	
Insomnia				0.07
	Mean ± SD	3.50 ± 0.11	3.83 ± 0.13	
Hypersomnia				0.03
	Mean ± SD	3.63 ± 0.14	4.01 ± 0.10	
Feeling overwhelmed or out of control				0.48
	Mean ± SD	3.45 ± 0.15	3.59 ± 0.13	

Table 3 Bifurcation of Functional, Social & Physical Impairment Indicators (Mean ± SD) with respect to intervention (calcium + vitamin D) and control groups

Variables	Categories	Treatment modalities		p-value
		Calcium + Vitamin D group 50 (50.0%)	Control group 50 (50.0%)	
Decreased interest in work activities				0.12
	Mean ± SD	3.81 ± 0.13	4.06 ± 0.08	
Decreased interest in home activities				0.08
	Mean ± SD	3.68 ± 0.11	3.92 ± 0.10	
Decreased interest in social activities				0.51
	Mean ± SD	3.50 ± 0.10	3.59 ± 0.11	
Physical symptom (breast tenderness, headaches, muscle pain, bloating, and weight gain)				0.52
	Mean ± SD	3.21 ± 0.11	3.10 ± 0.11	
School or work efficiency				0.68
	Mean ± SD	4.30 ± 0.16	4.37 ± 0.12	
Relationship with friends, classmates				0.73
	Mean ± SD	3.56 ± 0.10	3.48 ± 0.14	
Relationship with family				0.39
	Mean ± SD	3.92 ± 0.11	3.81 ± 0.09	
Social life activity				0.06
	Mean ± SD	3.62 ± 0.12	3.74 ± 0.06	
Home responsibility				0.47
	Mean ± SD	3.91 ± 0.13	3.80 ± 0.07	

Table 4A Bifurcation of post treatment PSST-A components mean score with respect to intervention (Calcium + Vitamin D) and control groups.

Variables	Categories	Calcium + Vitamin D 50 (50%) mean ± SD	Control group 50 (50%) mean ± SD	p-value*	p-value for**	
					Treatment effect	Time effect
Anger/irritability					0.02	0.48
	After 1-month	3.64 ± 0.60	3.95 ± 0.62	0.04		
	After 3-month	3.52 ± 0.41	3.91 ± 0.74	0.03		
	After 6-month	3.03 ± 0.39	3.90 ± 1.01	0.001		
Anxiety/tension					<0.001	0.85
	After 1-month	3.78 ± 0.88	3.81 ± 0.90	0.01		
	After 3-month	3.64 ± 0.59	3.77 ± 0.84	0.04		
Tearful/increased sensitivity to rejection					0.83	0.47
	After 6-month	3.20 ± 0.47	3.80 ± 0.87	0.001		
	After 1-month	4.16 ± 0.47	4.33 ± 0.95	0.03		
	After 3-month	3.95 ± 0.52	4.29 ± 0.95	0.01		
Depressed mood/hopelessness					0.03	0.22
	After 6-month	3.68 ± 0.41	4.31 ± 0.84	0.02		
	After 1-month	4.07 ± 0.38	4.12 ± 0.77	0.04		
	After 3-month	3.82 ± 0.52	4.08 ± 1.26	0.02		
Difficulty concentrating					0.58	0.36
	After 6-month	3.04 ± 0.51	3.97 ± 0.91	0.001		
	After 1-month	4.01 ± 0.52	4.14 ± 0.96	0.003		
	After 3-month	3.83 ± 0.41	4.12 ± 1.09	0.001		
Fatigue/lack of energy					0.77	0.67
	After 6-month	3.08 ± 0.79	4.07 ± 0.68	0.002		
	After 1-month	4.15 ± 1.00	4.54 ± 1.10	0.08		
	After 3-month	4.06 ± 0.48	4.51 ± 0.86	0.03		
Overeating/food cravings					<0.001	0.40
	After 6-month	3.89 ± 0.41	4.49 ± 0.74	0.001		
	After 1-month	3.73 ± 0.78	4.02 ± 0.84	0.001		
	After 3-month	3.57 ± 0.49	3.98 ± 0.97	0.001		
	After 6-month	3.18 ± 0.31	4.01 ± 0.79	0.001		
Insomnia					0.48	0.98
	After 1-month	3.85 ± 0.66	4.07 ± 0.65	0.05		
	After 3-month	3.42 ± 0.60	4.09 ± 0.73	0.001		
	After 6-month	3.12 ± 0.20	4.08 ± 0.89	0.02		
Hypersomnia					0.97	0.29
	After 1-month	4.00 ± 0.62	4.14 ± 1.01	0.01		
	After 3-month	3.72 ± 0.48	4.08 ± 0.94	0.001		
	After 6-month	3.07 ± 0.52	4.12 ± 0.78	0.001		
Feeling overwhelmed or out of control					0.28	0.93
	After 1-month	3.94 ± 0.57	4.17 ± 0.77	0.02		
	After 3-month	3.78 ± 0.38	3.99 ± 1.26	0.01		
	After 6-month	3.55 ± 0.07	3.97 ± 1.09	0.01		

SD (standard deviation), *ANCOVA test, **repeated measure ANOVA test

Table 4B Bifurcation of post treatment PSST-A components mean score with respect to intervention (Calcium + Vitamin D) and control groups.

Variables	Categories	Calcium + Vitamin D 50 (50%) mean ± SD	Control group 50 (50%) mean ± SD	p-value*	p-value for**	
					Treatment effect	Time effect
Decreased interest in work activities					0.42	0.23
	After 1-month	3.82 ± 0.52	4.05 ± 0.91	0.003		
	After 3-month	3.59 ± 0.40	3.92 ± 1.12	0.012		
	After 6-month	3.11 ± 0.02	4.01 ± 0.90	0.001		
Decreased interest in home activities					0.28	0.38
	After 1-month	3.96 ± 0.53	4.08 ± 0.92	0.02		
	After 3-month	3.87 ± 0.37	4.02 ± 1.09	0.001		
	After 6-month	3.64 ± 0.22	3.99 ± 0.84	0.01		
Decreased interest in social activities					0.17	0.85
	After 1-month	4.15 ± 0.50	4.24 ± 0.88	0.001		
	After 3-month	3.76 ± 0.45	4.20 ± 1.03	0.001		
	After 6-month	3.81 ± 0.42	4.21 ± 1.09	0.001		
Feeling overwhelmed or out of control					0.28	0.93
	After 1-month	3.94 ± 0.57	4.17 ± 0.77	0.02		
	After 3-month	3.78 ± 0.38	3.99 ± 1.26	0.01		
	After 6-month	3.55 ± 0.07	3.97 ± 1.09	0.01		
Physical symptom (breast tenderness, headaches, muscle pain, bloating, weight gain)					<0.001	0.48
	After 1-month	3.62 ± 0.65	3.77 ± 1.19	0.24		
	After 3-month	3.54 ± 0.63	3.73 ± 0.94	0.05		
	After 6-month	3.22 ± 0.15	3.76 ± 1.12	0.04		
School or work efficiency					0.67	0.04
	After 1-month	4.42 ± 0.61	4.31 ± 1.10	0.03		
	After 3-month	4.31 ± 0.79	3.92 ± 1.25	0.02		
	After 6-month	4.05 ± 0.38	3.55 ± 0.92	0.01		
Relationship with friends, classmates and coworkers					0.003	0.62
	After 1-month	3.92 ± 0.51	3.80 ± 0.87	0.02		
	After 3-month	3.90 ± 0.62	3.60 ± 1.09	0.001		
	After 6-month	3.93 ± 0.22	3.18 ± 0.08	0.03		
Relationship with family					0.18	0.03
	After 1-month	4.38 ± 0.47	4.25 ± 0.67	0.03		
	After 3-month	4.35 ± 0.34	4.09 ± 0.86	0.001		
	After 6-month	4.40 ± 0.26	3.63 ± 0.74	0.01		
Social life activity					0.78	0.79
	After 1-month	4.01 ± 0.49	3.89 ± 0.81	0.001		
	After 3-month	4.02 ± 0.51	3.55 ± 0.97	0.02		
	After 6-month	4.01 ± 0.52	3.15 ± 1.08	0.001		
Home responsibility					0.05	0.36
	After 1-month	4.38 ± 0.47	4.05 ± 0.67	0.01		
	After 3-month	4.19 ± 0.61	4.06 ± 0.82	0.001		
	After 6-month	3.98 ± 0.24	3.84 ± 0.86	0.001		

SD (standard deviation), *ANCOVA test, **repeated measure ANOVA test.

(IRB/Avic/OB-Gyn/2025/101) in compliance with the Declaration of Helsinki's tenets.

Statistical analysis: All quantitative data were expressed as mean ± standard deviation (SD). The chi-squared test was employed to compare percentages or frequencies of parameters between the two groups. Continuous variables were compared between the groups using the independent Student's t-test. Analysis of covariance (ANCOVA) was utilised to compare the mean scores of PSST-A components between the groups, adjusted for baseline scores, across the specified time points. Additionally, In order to determine a change over time on the PSST-A component scores between the two participant groups, a repeated-measures analyses of variance (ANOVAs) were utilized. The present research used a p-value of less than 0.05 as statistically significant. The analysis of the data was carried out with the help of IBM SPSS v. 23 statistical program.

RESULTS

The mean age was slightly higher in the calcium + vitamin D (25.7 ± 1.53 years) compared to the control group (24.9 ± 1.79 years), with a p-value of 0.14, indicating no statistically significant difference. Regarding education levels, participants were categorised as primary, secondary, graduates, or master's degree holders. In the calcium + vitamin D group, 8.0% had primary education, 34.0% secondary, 42.0% were graduates, and 16.0% held master's degrees. In comparison, the control group included 12.0% with primary education, 38.0% secondary, 44.0% graduates, and 6.0% with master's degrees. The p-value for education was 0.08, indicating no significant difference between the groups. Occupational distribution showed a statistically significant difference (p = 0.001) between the two groups. Among the calcium + vitamin D group, 38.0% were students, 14.0% were homemakers, and 48.0% were working women. In the control group, 32.0% were students, 24.0% were homemakers, and 44.0% were working women as shown in Table 1.

In addition, in Table 2 and Table 3 across most variables, no statistically significant differences were observed between the groups. The mean scores for anger/irritability were 3.43 ± 0.12 in the calcium + vitamin D group and 3.37 ± 0.12 in the control group (p = 0.67). Similarly, scores for anxiety/tension were 3.60 ± 0.13 and 3.46 ± 0.11, respectively (p = 0.52). Increased sensitivity to rejection had scores of 3.83 ± 0.13 and 3.77 ± 0.09 (p = 0.71). A borderline significant difference was noted in depressed mood/hopelessness, with the calcium + vitamin D group scoring 3.43 ± 0.12 compared to 4.01 ± 0.07 in the control group (p = 0.05). Scores for decreased interest in work activities were 3.81 ± 0.13 in the calcium + vitamin D group and 4.06 ± 0.08 in the control group (p = 0.12), while scores for decreased interest in home activities were 3.68 ± 0.11 and 3.92 ± 0.10, respectively (p = 0.08). Difficulty concentrating showed identical mean scores of 4.12 ± 0.12 for the calcium + vitamin D group and 4.12 ± 0.06 for the control group (p = 1.01).

Furthermore, fatigue/lack of energy had mean scores of 3.76 ± 0.10 in the calcium + vitamin D group and 4.02 ± 0.11 in the control group (p = 0.31). Overeating/food cravings were scored at 3.19 ± 0.12 and 3.28 ± 0.15, respectively (p = 0.67). Insomnia had near-significant differences, with scores of 3.50 ± 0.11 in the calcium + vitamin D group and 3.83 ± 0.13 in the control group (p = 0.07), while hypersomnia showed a significant difference with scores of 3.63 ± 0.14 and 4.01 ± 0.10 (p = 0.03). Other variables, such as feeling overwhelmed or out of control, physical symptoms, school or work efficiency, relationships with friends or family, social life activity, and home responsibilities, did not exhibit statistically significant differences. Notably, social life activity had scores of 3.62 ± 0.12 in the calcium + vitamin D group and 3.74 ± 0.06 in the control group (p = 0.06). For anger/irritability, the calcium + vitamin D group showed significant improvement at all-time points (1, 3, and 6 months) with p-values of 0.04, 0.03, and 0.001, respectively, while the control group did not show similar results (p-value = 0.02 for treatment effect). Anxiety/tension also improved significantly in the calcium + vitamin D group, with p-values <0.001 at 1, 3, and 6 months. In contrast, tearful/increased sensitivity to rejection had no significant treatment effect but showed time-dependent changes (p-value = 0.02 for treatment effect). For depressed mood/hopelessness, the calcium + vitamin D group exhibited improvement after 6 months (p = 0.001), compared to the control group, which showed no significant effect across time. Decreased interest in work activities improved for the calcium + vitamin D group over time (p = 0.001), while fatigue/lack of energy did not show significant changes as shown in Table 4A and Table 4B. Notably, overeating/food cravings had a significant treatment effect (p < 0.001) for the calcium + vitamin D group at all three time points, while physical symptoms such as breast tenderness, muscle pain, and headaches improved significantly at 6 months (p = 0.04) for the calcium + vitamin D group, as compared to the control. Work efficiency also improved significantly at 6 months in the calcium + vitamin D group (p = 0.01), showing a treatment effect. Overall, the calcium + vitamin D group showed positive outcomes across many of the PSST-A components, especially emotional symptoms and work efficiency, whereas the control group had less significant improvement over time as shown in Table 3.

DISCUSSION

One of the most common conditions affecting women of reproductive age is premenstrual syndrome (PMS).[13-14] In contrast to a placebo, the present study presented that calcium + vitamin D supplementation improved all PSST-A questionnaire parameters. This improvement was only shown during the 1st month of the study, even though the placebo group also showed lower scores following the intervention. Previous research has established the positive effects of a

placebo[15], and some studies indicate that the placebo response can significantly affect results, especially in trials that target psychological symptoms or pain management.[16]

Potential effect of calcium and vitamin D supplements in modifying inflammatory pathways associated with premenstrual syndrome (PMS) is becoming increasingly acknowledged.[17] By affecting the cyclooxygenase and nuclear factor pathways, vitamin D has been demonstrated to decrease the creation of pro-inflammatory mediators like prostaglandins and cytokines through its regulatory effect on gene expression and immunological regulation.[18] This anti-inflammatory effect can help lessen the physical discomfort that is frequently linked to PMS, such as breast tenderness, muscular soreness, and fatigue.[19] A sufficient intake of calcium has also been linked to better physical function and less pain during the luteal phase. Calcium is also essential for neurotransmitter release and muscle contraction.[20]

Changes in serotonergic transmission are believed to be responsible for several emotional and behavioural symptoms of PMS, including low mood, irritability, anxiety, sleeplessness, and concentration difficulties.[21] The effects of vitamin D in mood stabilisation and emotional balance may be explained by its important involvement in serotonin synthesis and regulation. Additionally, vitamin D supports circadian rhythm and sleep quality, which are frequently disturbed in people with PMS, by influencing the production of melatonin.[22]

The pathophysiology of PMS has also been linked to oxidative stress; it is indicated that those who are impacted have higher levels of free radical activity and a reduced capacity for antioxidant defence.[23] Because of its antioxidant-like qualities, vitamin D may aid in lowering oxidative stress and restoring redox equilibrium. In a similar vein, calcium takes part in cellular signalling pathways that preserve physiological homeostasis under oxidative conditions.[24-25] These mechanisms collectively imply that calcium and vitamin D supplements may provide a non-hormonal, safe means of reducing the psychological and physical symptoms of moderate to severe PMS.

The current study's findings are consistent with a prior systematic review by Abdi et al. (2019), which suggests that taking supplements of calcium and vitamin D or following a diet naturally high in these nutrients may help restore physiological serum levels and subsequently lessen the severity of premenstrual syndrome symptoms.[7] The observed improvement in both physical and emotional dimensions among participants receiving the intervention supports the therapeutic potential of these micronutrients in PMS management. These findings reinforce existing recommendations advocating for calcium and vitamin D as an affordable, well-tolerated, and accessible non-hormonal strategy for alleviating PMS-related discomfort. Their role in modulating neurotransmitter function, hormonal balance, and inflammatory responses further strengthens the case for their inclusion in non-pharmacological treatment protocols for moderate to severe PMS.

This study's strengths include its double-blind design, which minimised bias. However, limitations include potential individual, personality, and genetic differences among participants, which were somewhat controlled by random sampling. Additionally, certain PMS confounders, including relationship status, lifestyle characteristics, and physical activity, were not taken into consideration in this study. Additionally, serum calcium and vitamin D levels were not measured before and during the intervention period in this study, which could have provided more accurate information about the physiological alterations linked to supplementation.

CONCLUSION

In conclusion, calcium and vitamin D supplementation emerged as a simple, accessible, and low-cost non-hormonal intervention that demonstrated measurable improvement in the symptoms of premenstrual syndrome (PMS). The findings of this study add to the increasing amount of data demonstrating the importance of these nutrients in PMS treatment. While hopeful, the findings are only a first step in determining the therapeutic benefit of vitamin D and calcium in this situation. To validate these results across larger and more varied groups, more research is necessary. Future research ought to look into the underlying physiological processes, figure out the best supplementation amount and duration, and evaluate the long-term effects of consistent use on PMS symptoms.

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Authors Contribution:
Haleema Sadia: Introduction, abstract, literature review, data collection, result
Nadia Zahid: Abstract, literature review and results
Gulfreen Waheed: Dissuasion, literature review, data collection
Sana Navid: Literature review data collection

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Original Article **Open Access**

Distinguishing Aplastic Anemia from Hypoplastic Myelodysplastic Syndrome in Children: A Morphological and Ancillary Study

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Abstract:

Objective: Distinguishing hypoplastic myelodysplastic syndrome (hMDS) from aplastic anemia (AA) in children is challenging. This is because of their overlapping clinical and morphological features. This study aimed to identify morphological and ancillary parameters that differentiate these two conditions.

Study Design and Setting: Cross sectional study conducted at Department of Pediatric Medicine and Oncology at Children Hospital and Institute 0f Child Health, Multan.

Methodology: We conducted a study of 220 consecutive children (<16 years) with bone marrow failure syndromes between 10th October, 2024 and 10th October, 2025. Clinical, hematological, morphological, flow cytometric (CD34+%), and cytogenetic data were recorded. Morphology was assessed by two independent hematologists, with discrepancies resolved by consensus and cytogenetic correlation. The final diagnosis, based on consensus, was used as the gold standard for diagnostic accuracy. Statistical tests included the Shapiro-Wilk test for normality, t-test, Mann-Whitney U test, ÷², Fisher's exact test, and binary logistic regression to identify predictors of hMDS. Diagnostic accuracy was calculated with 95% confidence intervals.

Results: Median platelet count was significantly higher in hMDS compared to AA. The study identifies megakaryocytic dysplasia, abnormal cytogenetics, and elevated CD34+% as critical markers differentiating hypoplastic MDS from aplastic anaemia in children. Diagnostic accuracy was highest for abnormal cytogenetics (99.2% specificity), with CD34+ =1% and megakaryocytic dysplasia showing strong diagnostic predictive value.

Conclusion: A combination of megakaryocytic dysplasia, abnormal cytogenetics, and elevated marrow CD34+% robustly differentiates hMDS from AA in children. In resource-limited settings, morphology-first assessment supplemented by targeted ancillary testing can optimize diagnosis.

Keywords: Aplastic Anemia, Bone Marrow Examination, Hypoplastic Myelodysplastic Syndromes

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INTRODUCTION:

Bone marrow failure syndromes constitute an important group of paediatric haematological disorders associated with considerable morbidity and mortality, particularly in resource-limited settings such as Pakistan. Distinguishing aplastic anaemia (AA) from hypoplastic myelodysplastic syndrome (hMDS) is especially challenging in children due to overlapping clinical and morphological features. The global annual incidence of paediatric AA is estimated at 2–4 per million, with higher rates reported in South Asia, likely related to environmental, infectious, and genetic factors.[1] In Pakistan, the lack of national registries and variable diagnostic resources hampers accurate epidemiological assessment; however, tertiary centres report an increasing burden of marrow failure cases, with up to 30% suspected to represent clonal disorders such as hMDS.[2] This underscores the need for locally applicable diagnostic criteria.

Aplastic anaemia is characterised by pancytopenia with a hypocellular bone marrow, typically without significant dysplasia or cytogenetic abnormalities, and may be

idiopathic or secondary to infections, drugs, toxins, or inherited marrow failure syndromes. In contrast, hypoplastic MDS, although less frequent in children, is defined by marrow dysplasia, cytopenias, and frequent cytogenetic abnormalities despite hypocellularity, and carries a higher risk of progression to acute myeloid leukaemia.[3]

The clinical overlap—manifested by fatigue, pallor, bleeding, and recurrent infections—complicates timely and accurate diagnosis. While peripheral counts and bone marrow morphology remain initial tools, histological subtleties and evolving molecular techniques have emerged as critical to precise classification.[4]

Several studies have explored the diagnostic utility of bone marrow features, immunophenotyping, and cytogenetics in distinguishing AA from hMDS. A multicentre European cohort demonstrated that certain morphologic parameters such as megakaryocytic dysplasia and increased CD34+ blasts could distinguish hMDS from AA with high specificity. Similarly, research in India reported that up to 40% of cases initially diagnosed as AA were later reclassified as hMDS upon cytogenetic and histopathological review. Despite these advances, discrepancies remain regarding diagnostic thresholds, interpretation variability, and the limited paediatric-specific data.[5] Furthermore, most available studies have originated from high-resource settings, employing advanced diagnostic platforms that are not routinely accessible in lower-income countries.[6] In Pakistan, where access to comprehensive immunohistochemistry, flow cytometry, and cytogenetic facilities is inconsistent across public hospitals, reliance on bone marrow biopsy findings remains critical.[7] However, there is a paucity of local data validating the diagnostic accuracy of histo-morphological criteria in this population.[8]

This context presents a rationale to evaluate the diagnostic yield of bone marrow findings in differentiating AA from hMDS specifically in Pakistani children. Unlike previous descriptive audits, this study aims to critically evaluate marrow morphology using predefined criteria and correlate findings with confirmatory ancillary testing to delineate true diagnostic boundaries.[9,10]

Currently, no paediatric studies from Pakistan have systematically compared bone marrow histomorphology in AA and hMDS using structured diagnostic criteria. Available international literature may not account for regional differences in disease biology, nutritional influences, consanguinity-related genetic syndromes, or infectious triggers. This study, therefore, addresses a crucial evidence gap in local paediatric haematology by evaluating diagnostic patterns within the confines of existing clinical practice and available diagnostic infrastructure.

This study was designed to identify and quantify the diagnostic performance of key morphological and ancillary features—specifically megakaryocytic dysplasia, cytogenetic abnormalities, and marrow CD34+ cell percentage—in differentiating hMDS from AA in paediatric patients. By establishing evidence-based diagnostic thresholds and effect sizes, we aim to provide a practical framework that is applicable in both well-resourced and resource-limited haematology laboratories.

The objective of this study is to determine the diagnostic accuracy of bone marrow findings in differentiating aplastic anaemia from hypoplastic myelodysplasia in children below the age of 16 years. The secondary objective is to identify specific morphological features that reliably correlate with either diagnosis. It is hypothesised that a combination of marrow cellularity, dysplastic features, and blast quantification can improve diagnostic precision even in settings without advanced laboratory support.

METHODOLOGY:

A cross-sectional study was conducted in a hospital-based, single-centre setting at the Department of Paediatric Haematology and Oncology, The Children's Hospital and The Institute of Child Health, Multan. The duration of the study spanned one year, from 10th October 2024 to 10th October 2025. A non-probability consecutive sampling technique was employed to recruit participants who fulfilled the inclusion criteria during the study period.

Sample size was calculated using the World Health Organization (WHO) sample size calculator. The calculation was based on a confidence level of 95%, a margin of error of 5%, and a reported prevalence of hypoplastic myelodysplastic syndrome among bone marrow failure cases in children at 17.33%, as observed in a 2021 study by Fattizzo et al.[11] The estimated sample size was 220 children.

All children under 16 years of age presenting with peripheral blood pancytopenia and undergoing bone marrow examination for suspected marrow failure were included in the study after obtaining informed consent from parents or guardians. Patients with a known diagnosis of inherited bone marrow failure syndromes, such as Fanconi anaemia or Diamond-Blackfan anaemia, or those currently receiving chemotherapy or immunosuppressive therapy were excluded from the study.

Data were collected using a structured proforma through review of patient records, clinical assessment, and laboratory findings. Sociodemographic variables included age (categorised into <5, 5–10, and 11–16 years), gender (male, female), area of residence (urban, rural), and parental consanguinity (yes, no). Clinical data collected included duration of symptoms, presence of pallor, fever, petechiae, hepatosplenomegaly, and transfusion history. Laboratory parameters included haemoglobin concentration, total leucocyte count, absolute neutrophil count, platelet count, reticulocyte count, serum ferritin, serum vitamin B12, serum folate, and parvovirus B19 serology. Bone marrow assessment included aspirate and trephine biopsy findings: cellularity,

dysplastic changes in erythroid, myeloid, and megakaryocytic lineages, presence of blasts, CD34+ cell percentage, and cytogenetic results.

Thresholds for laboratory categorisation were based on established international guidelines. Haemoglobin <10 g/dL, total leucocyte count <4 × 10?/L, platelet count <100 × 10?/L, and absolute neutrophil count <1.5 × 10?/L were used as cut-off values according to WHO haematological reference ranges for children. Bone marrow cellularity <30% was defined as hypocellular, based on European Working Group on MDS classification criteria. CD34+ cell percentage =1% was considered elevated. Dysplasia in =10% of any lineage was defined as significant. Parvovirus B19 positivity was assessed by ELISA (Bio-Rad, France), and cytogenetic analysis was performed using G-banding techniques with metaphase karyotyping (Cytovision, UK).

Normality of continuous variables such as age, haemoglobin, total leucocyte count, and platelet count was assessed using the Shapiro-Wilk test. Age and haemoglobin were found to be normally distributed and were presented as mean ± standard deviation (SD). Independent t-test was applied for comparison of normally distributed continuous variables (age, haemoglobin) between the two diagnostic groups. Mann–Whitney U test was applied for non-normally distributed variables (platelet count, neutrophil count). Categorical variables such as gender, presence of dysplasia, and bone marrow cellularity were compared using the chi-square test.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarise the data. Frequencies and percentages were calculated for categorical variables including gender, dysplastic features, cytogenetics, and CD34+ expression. Mean and standard deviation were calculated for normally distributed continuous variables such as age and haemoglobin. Median and interquartile range were computed for non-normally distributed continuous variables such as platelet count and reticulocyte count. Comparative analysis was conducted using the chi-square test for categorical variables (gender, marrow dysplasia, cytogenetics) and independent t-test or Mann–Whitney U test for continuous variables (age, haemoglobin, platelet count), depending on distribution. A p-value of <0.05 was considered statistically significant.

Ethical approval was obtained from the Institutional Review Board of The Children's Hospital and The Institute of Child Health, Multan (198/ERC/2024). Informed consent was obtained from parents or legal guardians of all participating children. Confidentiality and anonymity were maintained throughout the study. All procedures were carried out in accordance with the ethical principles outlined in the Declaration of Helsinki.

RESULTS

A total of 220 children were included in the study, of whom 130 were diagnosed with aplastic anaemia and 90 with hypoplastic myelodysplastic syndrome. The mean age was 10.1 ± 3.0 years, with a comparable age and gender distribution between the two groups. Haemoglobin and neutrophil counts did not differ significantly between diagnoses.

Platelet count was the only quantitative haematological parameter that differed significantly, with lower values observed in aplastic anaemia compared to hypoplastic MDS ($p = 0.002$). Among diagnostic markers, dysplastic megakaryocytes demonstrated the highest overall diagnostic accuracy (80.5%), with high specificity (94.6%) and positive predictive value (88.5%). CD34+ expression =1% and abnormal cytogenetics showed excellent specificity (97.7% and 99.2%, respectively) and high positive predictive value, although sensitivities were lower.

Overall, these findings highlight the diagnostic utility of bone marrow morphology, particularly when supplemented by limited immunophenotyping and cytogenetic analysis, in differentiating aplastic anaemia from hypoplastic myelodysplastic syndrome in children.

Normality of continuous variables was assessed using the Shapiro–Wilk test to guide the choice of descriptive statistics and inferential tests. Accordingly, group comparisons for continuous variables were performed using *[t-test / Mann–Whitney U]*.

The Table 1 shows a comparison of continuous variables between children diagnosed with aplastic anaemia (n = 130) and hypoplastic myelodysplasia (n = 90). Variables are grouped based on their distribution status, with normally distributed variables presented as mean ± SD and non-normally distributed variables shown as median (IQR).

This table demonstrates that while age and haemoglobin levels did not differ significantly between groups ($p > 0.05$), platelet count showed a statistically significant difference, with higher median levels in hypoplastic MDS ($p = 0.002$). Neutrophil counts were not significantly different. These findings underline the diagnostic importance of platelet levels in distinguishing between the two marrow failure syndromes.

The Table 2 shows the distribution of categorical variables among both diagnostic groups, with statistical comparison conducted using chi-square or Fisher's exact test depending on assumptions. Variables include gender, parental consanguinity, presence of clinical features (e.g., petechiae, hepatosplenomegaly), and bone marrow findings (e.g., cellularity, dysplasia, cytogenetics).

This table demonstrates that dysplastic changes in megakaryocytes, presence of blasts =5%, and abnormal cytogenetics were significantly more common in the

Table 1. Comparison of Continuous Variables between Aplastic Anaemia and Hypoplastic MDS Groups (n = 220)

Variable	Aplastic Anaemia (n = 130) Median (IQR)	Hypoplastic MDS (n = 90) Median (IQR)	Test Used	p-value
Age (years)	10.0 (8.0 – 12.0)	10.5 (8.0 – 13.0)	Mann–Whitney U	0.201
Haemoglobin (g/dL)	8.4 (7.6 – 9.2)	8.6 (7.9 – 9.3)	Mann–Whitney U	0.343
Platelet Count ($\times 10^9$/L)	60 (36 – 88)	82 (46 – 120)	Mann–Whitney U	0.002
Neutrophil Count ($\times 10^9$/L)	0.83 (0.38 – 1.57)	0.95 (0.51 – 1.70)	Mann–Whitney U	0.392

Independent t-test used for normally distributed variables (Age, Haemoglobin);
uMann–Whitney U test used for non-normally distributed variables (Platelet, Neutrophil);

Table 2. Distribution of Categorical Variables between Aplastic Anaemia and Hypoplastic MDS Groups (n = 220)

Variable	Aplastic Anaemia n (%)	Hypoplastic MDS n (%)	Test Used	p-value	OR (95% CI)
Gender (Male)	74 (56.9)	49 (54.4)	Chi-square	0.720	0.91 (0.54–1.54)
Parental Consanguinity	88 (67.7)	43 (47.8)	Chi-square	0.006	0.43 (0.24–0.76)
Splenomegaly	21 (16.2)	36 (40.0)	Chi-square	<0.001	3.39 (1.85–6.23)
Dysplastic Megakaryocytes	7 (5.4)	54 (60.0)	Fisher's exact	<0.001	26.7 (11.0–64.7)
Blasts =5%	4 (3.1)	30 (33.3)	Fisher's exact	<0.001	15.1 (5.0–45.5)
Abnormal Cytogenetics	1 (0.8)	25 (27.8)	Fisher's exact	<0.001	48.4 (6.4–364.2)
CD34+ =1%	3 (2.3)	21 (23.3)	Fisher's exact	<0.001	12.4 (3.6–42.5)

**Chi-square or Fisher's exact test applied depending on assumptions;*
p-values < 0.05 considered statistically significant.

Table 3. Logistic Regression Model for Predictors of Hypoplastic MDS (n = 220)

Predictor Variable	Adjusted OR	95% CI	p-value
Platelet Count (per 10?/L increase)	1.02	1.01–1.04	0.011
Dysplastic Megakaryocytes (Yes vs No)	21.3	8.7–52.1	<0.001
CD34+ =1% (Yes vs No)	14.6	4.1–51.5	<0.001
Abnormal Cytogenetics (Yes vs No)	44.9	9.1–220.8	<0.001

Multivariate logistic regression adjusting for age, gender, and splenomegaly

Table 4. Diagnostic Accuracy of Key Bone Marrow Features in Differentiating Hypoplastic MDS from Aplastic Anaemia (n = 220)

Bone Marrow Feature	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy % (95% CI)
Dysplastic Megakaryocytes	60.0 (48.9–70.3)	94.6 (88.7–97.6)	88.5 (77.0–94.8)	77.4 (70.3–83.2)	80.5 (74.5–85.4)
CD34+ =1%	23.3 (15.0–34.1)	97.7 (92.9–99.4)	87.5 (69.0–95.7)	64.8 (58.1–71.1)	67.3 (60.8–73.2)
Abnormal Cytogenetics	27.8 (18.6–39.1)	99.2 (95.3–99.9)	96.2 (80.4–99.9)	66.5 (59.8–72.6)	70.0 (63.6–75.7)

PPV = Positive Predictive Value, NPV = Negative Predictive Value.
All values derived using confirmed diagnosis of hypoplastic MDS as reference standard

hypoplastic MDS group ($p < 0.001$). Parental consanguinity and splenomegaly also showed group differences. These categorical features highlight histomorphological markers relevant for diagnosis.

The Table 3 shows the results of binary logistic regression assessing predictors of hypoplastic MDS versus aplastic anaemia. Variables included in the model were those found significant in univariate analysis, including platelet count, dysplastic megakaryocytes, CD34+ expression, and abnormal cytogenetics. Odds ratios (OR) with 95% confidence intervals (CI) and adjusted p-values are provided.

This table demonstrates that the presence of megakaryocytic dysplasia (OR 21.3), CD34+ =1% (OR 14.6), and abnormal cytogenetics (OR 44.9) were strong independent predictors of hypoplastic MDS. These markers offer valuable diagnostic discrimination and warrant clinical consideration.

The Table 4 shows the diagnostic accuracy of key bone marrow features—dysplastic megakaryocytes, CD34+ cell expression (=1%), and abnormal cytogenetics—in

distinguishing hypoplastic myelodysplasia from aplastic anaemia. Each marker was assessed for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy using confirmed diagnosis as the reference.

This table demonstrates that dysplastic megakaryocytes had the highest overall diagnostic accuracy (80.5%) with a strong balance of sensitivity (60.0%) and specificity (94.6%). Abnormal cytogenetics showed the highest specificity (99.2%) and PPV (96.2%), while CD34+ =1% yielded a high PPV (87.5%) despite lower sensitivity. These findings support their clinical value in the diagnostic work-up of paediatric marrow failure.

DISCUSSION:

This study evaluated bone marrow histomorphological and ancillary features to distinguish aplastic anaemia from hypoplastic myelodysplastic syndrome in children under 16 years of age. Significant differences were observed in platelet count, megakaryocytic dysplasia, CD34+ cell expression, and cytogenetic abnormalities, all of which were more frequent in hypoplastic MDS. Multivariate analysis identified abnormal cytogenetics, CD34+ positivity, and dysplastic megakaryocytes as independent predictors, supporting the diagnostic utility of bone marrow morphology, particularly in resource-limited settings.

Dysplastic megakaryocytes and increased blasts were significantly more common in hypoplastic MDS, consistent with established EWOG-MDS diagnostic criteria.[12] Abnormal cytogenetics showed a strong association with hypoplastic MDS, reinforcing its clonal nature. The presence of elevated CD34+ cells further supported this distinction, reflecting expansion of immature progenitor populations in clonal marrow disorders.[13,14] Neutrophil and haemoglobin levels did not differ significantly between groups, indicating limited diagnostic value of cytopenias alone.[15,16]

The biological overlap between aplastic anaemia and hypoplastic MDS arises from shared features of marrow hypocellularity and pancytopenia; however, their underlying pathophysiology differs, with immune-mediated progenitor cell destruction in aplastic anaemia and clonal stem cell dysfunction in hypoplastic MDS.[17,18] Accurate distinction is therefore essential, as treatment strategies diverge substantially, particularly regarding immunosuppression versus stem cell transplantation.[19,20]

The structured, prospective design, adherence to WHO and EWOG-MDS criteria, and use of multivariate analysis strengthen the validity of the findings.[21] Clinically, this study provides a pragmatic, morphology-based diagnostic framework supplemented by minimal ancillary testing, offering valuable locally relevant evidence for paediatric marrow failure evaluation in Pakistan and similar low-resource settings.[22]

Low sensitivity occurs because hypoplastic MDS does not show all diagnostic features in every patient, especially in early disease. Bone marrow samples may also be small or patchy, which can miss abnormal cells. Technical limits and strict cut-off values are used to avoid wrongly diagnosing aplastic anaemia as MDS, but this reduces sensitivity. In this setting, tests with high specificity are still useful when findings are interpreted together.

Single centre study with a relatively small sample size are notable limitations of the study. Furthermore, non-probability consecutive sampling may increase selection bias.

CONCLUSION:

The present study was conducted to evaluate the diagnostic accuracy of bone marrow findings in distinguishing aplastic anaemia from hypoplastic myelodysplastic syndrome in children under the age of sixteen years. The findings demonstrated that certain marrow-based features, including dysplastic megakaryocytes, presence of CD34+ blasts, and cytogenetic abnormalities, were significantly more prevalent in children with hypoplastic MDS. Platelet count was also found to be a differentiating parameter, showing higher values in the hypoplastic MDS group compared to those with aplastic anaemia.

The inclusion of diagnostic accuracy metrics for key bone marrow features reinforces their clinical utility in differentiating hypoplastic myelodysplastic syndrome from aplastic anaemia. Dysplastic megakaryocytes demonstrated the highest diagnostic accuracy, while abnormal cytogenetics and CD34+ expression offered excellent specificity and predictive value. These findings highlight the value of a structured, morphology-based approach particularly in resource-constrained settings where rapid, reliable diagnosis is essential for timely and appropriate therapeutic decisions.

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Zulfiqar Ali Rana: Critical Analysis, final approval
Arif Zulqarnain: Data Analysis
M Kamran Adil: Data Collection
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Original Article **Open Access**

Mean Healing Time of Autologous PRP on Wounds in Terms of Split-Thickness Skin Graft Adhesion and Complications as Compared to Conventional Fixation Technique

Sadia Khan, Danish Almas, Asad Ashraf, Rimsha Irfan, Ali Muhammad

Abstract

Objective: To compare mean healing time and complication rates in patients undergoing Split thickness skin grafting with autologous PRP versus conventional fixation methods.

Study Design and Setting: Two groups comprising of 50 patients (Total 100) in each undergoing split thickness skin grafting were formed, Group A (PRP infiltration prior to STSG) and Group B (STSG with conventional fixation). Mean healing time and graft take were the primary outcomes; infection, seroma, hemorrhage, and graft loss were the secondary events.

Methodology: Non-probability consecutive sampling was used in a quasi-experimental study at PNS Shifa Hospital's Plastic Surgery Department. One hundred patients with open wounds aged 18 and 60 years were randomly divided into two groups by lottery method: Group B had STSG with conventional fixation, while Group A received autologous PRP infiltration prior to STSG. Mean healing time and graft take were the primary outcomes; infection, seroma, hemorrhage, and graft loss were secondary events.

Results: Mean healing time for Group A was 9.88 ± 1.56 days, substantially faster than that of Group B (mean 11.92 ± 2.68 days, $p < 0.001$). The PRP group's graft success rate was higher (85.17±9.83) than the control group (72.63±14.57). Group A experienced significant decrease in complications such infection, seroma, and haematoma.

Conclusion: In patients undergoing STSG, autologous PRP significantly reduced the healing period and increased graft success while lowering postoperative complications. It provides a biologically active substitute for traditional fixation techniques.

Key words: Autologous PRP, Conventional Fixation, Haematoma, Seroma, Split Thickness Skin Graft

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INTRODUCTION:

Skin grafting is the cornerstone of reconstructive surgery which provides long-lasting soft tissue coverage for severe injuries and other skin defects. Split-thickness skin grafting (STSG), although regularly performed, frequently leads to prolonged hospital stays and numerous dressing changes.[1] STSG is frequently used to treat challenging wounds such as burns, venous leg ulcers, and diabetic foot ulcers. Split skin grafting is the most popular treatment used in the area of plastic surgery to resurface wound beds. Hemostasis and the skin graft's adherence to the wound bed are two factors that affect the success of the procedure, while local vascularity and wound microbiology are also important. Although epinephrine soaks can be used to produce hemostasis on the wound bed before skin grafts are applied, this procedure has both systemic and local adverse effects. A skin transplant is typically quilted to the wound bed to minimize shearing and seroma beneath it, and it is secured to the wound borders using sutures, staplers, yano acrylate glue, or fibrin glue. However, the operational time and cost were increased by these strategies.

A Cochrane systematic review found that skin grafting may accelerate healing in venous leg ulcers when combined with the standard care.[2] The microbiological environment, local blood supply, and adhesion to the wound bed are some of the variables that affect graft success. Aiming to anchor the graft and avoid fluid buildup, traditional fixation techniques like sutures or staples can be expensive and time-consuming.[3] In wound healing, autologous platelet-rich plasma (PRP) has become a biologically active adjuvant. By providing nutrient-rich plasma straight to the wound bed, PRP improves graft anchoring, encourages inosculation, and significantly speeds up the healing process.[4] Growth factors such PDGF, IGF-1, EGF, VEGF, and TGF-â are released by platelets and promote angiogenesis, collagen production, and epithelial regeneration.[5] The use of autologous platelet-rich plasma (PRP) in several facets of tissue regeneration and wound healing has gained attention in recent years.[6] PRP, which is an autologous concentration of platelets in a tiny amount of plasma, is vital for tissue regeneration and repair because it contains a variety of growth factors and bioactive proteins. Among these are vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-â (TGF-â), and epidermal growth factor (EGF). PRP's potential to improve the graft's initial adherence due to its high fibrin content and the subsequent revascularization process due to its broad array of growth factors provides the theoretical foundation for its use in skin grafting. According to recent studies, PRP can improve haemostasis, decrease scarring, increase collagen synthesis, encourage angiogenesis, and speed up endothelial and epithelial regeneration .[7] PRP has logistical and financial benefits in addition to biological ones, especially in environments with limited resources. PRP is inexpensive and biocompatible because it is made from the patient's own blood, reducing the possibility of immunogenic reactions and the spread of infection.[8] Its preparation is relatively easy, and it doesn't require sophisticated infrastructure to be incorporated into standard surgical processes. Because of these characteristics, PRP is particularly useful in public hospitals and tertiary care facilities, where high patient volumes and budgetary constraints necessitate scalable, effective solutions.[9] When infilterated before traditional graft fixation, PRP acts as a biologically active enhancer to improve graft function and healing. Chronic wounds present serious obstacles to healing and rehabilitation, especially in burn and diabetic patients.[10] PRP may increase graft take, shorten healing times, and lower complication rates during STSG surgeries, which would ultimately result in less hospital stays and resource usage. Apart from its therapeutic value, PRP is in line with worldwide trends in regenerative and individualized medicine. Because it is autologous, it minimizes donor site morbidity and improves patient safety while supporting customized treatment plans.[11] Additionally, the incorporation of PRP into surgical workflows indicates a move away from mechanical fixation and toward biologically enriched techniques that maximize recovery. PRP stands out as a flexible, evidence-based solution that support current methods and enhances patient outcomes as surgical specialties use regenerative adjuncts more frequently.[12] There is a dearth of local data assessing PRP's function in surgical wound treatment, especially when split-thickness skin grafting (STSG) is involved, despite encouraging global data. To accurately reflect local patient demographics, clinical practices, and institutional capabilities, region-specific research are required. The purpose of this study is to provide regional data comparing traditional fixation with autologous PRP infiltration in STSG patients. The results could direct future clinical practice and aid in the integration of PRP into regular wound care protocols.

METHODOLOGY:

This Quasi experimental study was carried out from 15th may 2025 to 14th august 2025 in the Plastic Surgery Department of PNS Shifa Hospital in Karachi, Pakistan. Ethical approval was obtained from the institutional review board ethical with IRB No.BUHS-IRB #192/25. Patients who required split-thickness skin grafting (STSG) for soft tissue defects between 18 to 60 years age of both gender were included. Immunosuppressive treatment, bleeding problems, systemic infections, serious systemic diseases, and wounds exposing major arteries, nerves, or bone were all excluded.[16] These standards were chosen in light of earlier research assessing the safety of PRP and the results of wound healing.Non-probability consecutive sampling was utilised to recruit participants, and the lottery method was used to randomly allocate them to two groups. The sample size was calculated by using the mean±SD of complete healing time 37.9±14.3 in PRP/ thrombin gel group and 73.7±50.84[10] in control group using open Epi Software for taking the power of test = 80% and confidence interval 95%.[13] Previously published data comparing PRP and traditional fixation methods served as the basis for this computation.The study was open-label, and blinding was not possible because the patient and the operating surgeon could see the obvious differences in the intervention approaches. In compliance with ethical guidelines, all participants provided written informed permission prior to enrollment and group assignment.Clinical outcomes were assessed by impartial clinicians who were not involved in the intervention in order to reduce evaluation bias. Autologous platelet-rich plasma (PRP) was administered to the wound bed in Group A before grafting, whereas Group B got standard Split thickness skin graft (STSG) without PRP.

Autologous PRP was prepared in the outpatient department using two-step centrifugation technique.10-20ml of venous blood sample was drawn and transferred into sterile tubes containing anticoagulant . Tubes were placed in centrifuge machine for first cycle of spinning. Cycle was performed at 3000 rpm and spined for 10 minutes .This cycle separated

plasma and buffy coat from red blood cells resulted in distinct layering. Yellow coloured plasma was at upper half of tube , thin white coloured buffy coat was in middle and dark red coloured layer containing red blood cells was at the bottom of the tube. Plasma and buffy coat were collected in other sterile bottles containing anticoagulants and placed in centrifuge machine for second cycle. This time machine was set at 4000 rpm and spined for 5-7 minutes . This separated platelet rich plasma from platelet poor plasma. PRP could be seen by colour difference which was dark yellow coloured and at bottom of the tube. Upper Platelet poor plasma layer was discarded and platelet rich plasma was carefully aspirated using a syringe for infiltration into the wound. PRP was infiltrated into wound bed 15 minutes before split thickness skin grafting. A dermatome was used to harvest Split thickness skin grafts (STSG), which were then secured with staples or sutures. In addition to applying standard postoperative dressings, patients were observed for graft take and post operative complications. Successful graft take and mean healing time were primary outcomes while complications including infection, seroma development, and graft loss were secondary outcomes.

RESULTS:

A total of 100 patients were included, evenly divided between the PRP (n = 50) and Conventional (n = 50) groups. The overall a mean age of the study participants in current study was 36.2±1.1 years with the duration of diseases before treatment was 21.7±15.2, hospital stay in days was 6.9±2.4. Mean graft take was 78.9±14.6 beside the mean Healing time 10.9±2.4 days. Table 1. Male were 55 (55%) and female were 45 (45%). Out of 100 only 33 (33%) acquired the wound site infection, while 33 (33%) had Hematoma, and 46 (46%) had Seroma. Most common site of wound was left 11 (11%) and right foot 11 (11%). Table 2 and Figure 1. In current study autologous PRP significantly improved graft success and reduced post operative complications. The incidences of infection 10 (10%) were in PRP group while in conventional group it was 23 (23%) having the significant statistical association with p= 0.005. Length of hospital stay were categorized into two group detailing as stay of <=7 days and > 7 days for statistical analysis. 45 (45%) study participants of PRP groups had hospital stay of less than 7 days while only 27 (27%) in conventional group stayed in hospital for <= 7 dyas having the showed the significant statistical link with p= 0.001. Seroma and haematoma development were not associated with the groups. Table 3 and Figure 1. Additionally, the PRP group's healing period was substantially shorter than the Conventional group's, with a mean of 9.88 ± 1.56 days against 11.92 ± 2.68 days (p <.001), indicating a quicker recovery and lower morbidity. Importantly , the PRP group's mean graft take was greater (85.17 ± 9.83%) than the conventional group's (72.63 ± 14.57%), confirming PRP's ability to improve graft integration. Table: 04.

Table 1. Mean and standard deviation of quantitative variables

Variable	Mean±SD
Age (Years)	36.2±1.1
Duration of Disease (Days)	21.7±15.2
Hospital Stay (Days)	6.9±2.4
Healing time (Days)	10.9±2.4
Graft Take (Percent)	78.9±14.6

Table 2: Mean and standard deviation of quantitative variables

Variable	Percentages
Gender	
Male	55 (55%)
Female	45 (45%)
Infection	
Yes	33 (33%)
No	67 (67%)
Seroma	
Yes	46 (46%)
No	54 (54%)
Hematoma	
Yes	33 (33%)
No	67 (67%)
Hospital Stay	
<=7 Days	72 (72%)
>7 Days	28 (28%)
Wound Site	
Abdomen	3 (3%)
Back	4 (4%)
Left Arm	2 (2%)
Left Arm	1 (1%)
Left Axilla	4 (4 %)
Left Flank	1 (1%)
Left Foot	11 (11%)
Left Forearm	4 (4%)
Left Hand	5 (5%)
Left Leg	9 (9%)
Left Shoulder	1 (1%)
Left Sole	1 (1%)
Left Thigh	4 (4%)
Right Palm	1 (1%)
Right Arm	4 (4%)
Right Axilla	2 (2%)
Right Foot	11 (11%)
Right Forearm	6 (6%)
Right Hand	6 (6%)
Right Leg	8 (8%)
Right Palm	1 (1%)
Right Shoulder	2 (2%)
Right Thigh	3 (3%)
Scalp	4 (4%)

DISCUSSION:

This study shows that autologous PRP significantly improved graft success and reduced post operative complications. The incidences of infection (20% vs. 46%), seroma (36% vs. 56%), and haematoma (24% vs. 42%) were all lower with PRP than with traditional therapy. PRP's fibrin-rich composition, which produces an instant biological adhesive effect, is responsible for this rapid adherence. Similar results were shown by Kakudo et al, who reported improved skin graft adhesion when PRP was given to the wound bed prior to graft insertion. They suggested that PRP's fibrin aids in anchoring the graft to the wound bed and reduces micro-motion, which is harmful to graft take. Particularly useful in anatomically difficult areas where traditional dressings might not offer the best graft-recipient contact is this instant adherence.[14]

Table: 3. Association of complications and age with PRP and Conventional group

Variables	PRP group	Conventional Group	p-Value
Gender			
Male	27 (27%)	28 (28%)	0.5
Frmale	23 (23%)	22 (22%)	
Infection			
Yes	10 (10%)	23 (23%)	0.005*
No	40 (40%)	27 (27%)	
Seroma			
Yes	18 (18%)	28 (28%)	0.035
No	32 (32%)	22 (22%)	
Hematoma			
Yes	12 (12%)	21 (21%)	0.04
No	38 (38%)	29 (29%)	
Hospital Stay			
<=7 Days	45 (45%)	27 (27%)	0.001*
>7 Days	05 (05%)	23 (23%)	

Figure 1: Frequency of complications in both groups

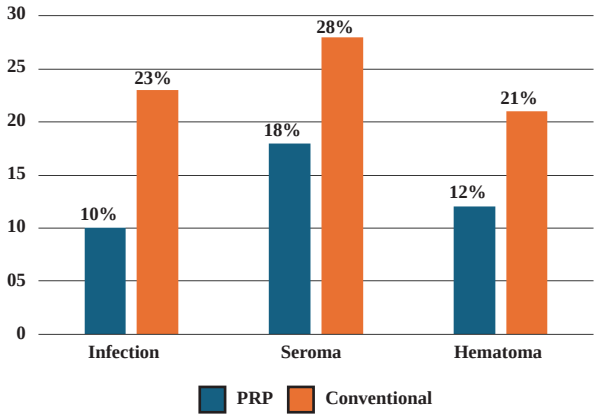

Table: 04. Association of two groups with Healing time and graft take comparison

Outcome	PRP Group (mean ± SD)	Conventional Group (mean ± SD)	p-Value
Healing time (days)	9.88 ±1.56	11.92±2.68	< .001
Graft take (%)	85.17 ±9.83	72.63±14.57	< .001
Duration of disease (days)	21.28±17.26	22.12±12.95	.785

According to the study conducted by Faizan Rahim et al at Sialkot concluded that autologous PRP treatment demonstrated superior efficacy in promoting graft adhesion compared to conventional fixation that are in line the results of current study. [15] Autologous platelet-rich plasma (PRP) is significantly more effective at healing wounds than conventional dressings, according to a different study by Shakoor, S. et al. PRP-treated wounds showed improved granulation tissue growth, quicker epithelialization, and improved patient satisfaction. PRP is a beneficial supplement to wound care since its physiologically active components aid in tissue regeneration. [16] Another study by Sara Mubeen et al. at the Mayo Hospital in Lahore found that microneedling with insulin is more effective in treating acne scars than microneedling with platelet-rich plasma. All skin types benefit from this combined procedure, which is affordable and causes less post-inflammatory hyperpigmentation. Additionally, because it doesn't require advanced abilities, doesn't require an IV line, and takes less time, this innovative combo method is convenient for both patients and doctors.[17]

The superior graft takes percentages observed in the PRP group 85% compared to conventional group 72%. highlight the sustained beneficial effects of PRP on graft survival. PRP influences wound healing in a number of ways, which can be linked to this increased graft take.[6] Growth factors including fibroblast growth factor (FGF) and VEGF in PRP encourage angiogenesis, which speeds up the graft's revascularization.[15] This guarantees proper oxygenation and nourishment, both of which are essential for graft survival.[17] Furthermore, fibroblasts, keratinocytes, and endothelial cells proliferate and migrate in response to growth factors like PDGF and EGF, which speeds up wound healing and graft integration.[18] Reduced scar formation has also been linked to the TGF-â found in PRP, which may improve cosmetic results.[19] Our results are consistent with several studies in the literature that have shown that using PRP can improve graft take rates and shorten healing times. In a related study, Maghsoudi et al. examined diabetic foot ulcers and found that using PRP improved graft take rates and sped up recovery.[20] Overwhelming inflammation can harm the graft, and reducing it helps increase graft success. These complex processes cooperate to improve graft take and reduce problems. These results not only confirm the biological effectiveness of PRP but also highlight its usefulness in surgical procedures. PRP provides a scalable option that improves graft results without requiring sophisticated equipment in high-volume public hospitals where cost

containment and quick recovery are crucial. PRP may have an impact on patient-reported outcomes like pain, mobility, and happiness in addition to its biological and logistical benefits.[21] Although pain scores and scar quality were not fully evaluated in this study, the observed decrease in hematoma and seroma production may indirectly improve patient comfort and cosmetic results. These outcomes along with PRP's affordability and simplicity of integration, are increasingly acknowledged as crucial endpoints in surgical recovery. Patients in the PRP group reported anecdotal evidence of less discomfort during dressing changes and an earlier return to walking, most likely as a result of quicker epithelialization and less inflammation. Although not explicitly measured in this study, these subjective benefits should be investigated further in subsequent studies utilizing validated patient-reported outcome measures (PROMs). Furthermore, PRP's function in regulating the local immune response may have outcomes that go beyond graft acceptance, possibly affecting tissue remodeling and long-term scar quality. PRP may lessen hypertrophic scarring and increase pliability in grafted areas, especially in burn victims, according to new researches. Future research may be able to quantify these impacts by using objective scar assessment instruments like the Vancouver Scar Scale. [5]

The results of this investigation support PRP's useful benefits in standard reconstructive procedures. Its function as a biologically active enhancer that improve conventional grafting techniques is supported by the statistically significant decrease in healing time and complication rates. Crucially, the PRP group's better graft take and lower infection rates point to a more stable wound environment that promotes early epithelialization. These results are particularly important in high-volume surgical facilities where reducing hospital stays and dressing frequency can alleviate resource shortages. PRP's viability in public hospitals is further supported by its autologous origin and ease of processing. Furthermore, cost-effectiveness studies contrasting PRP with negative pressure wound therapy or synthetic sealants would offer insightful information for institutional decision-making. PRP stands out as a physiologically active, patient-derived adjunct that bridges the gap between cost and effectiveness as the field of regenerative surgery develops, making it a viable contender for wider adoption in reconstructive protocols across a variety of clinical contexts. Because it is autologous, it lowers the danger of immunogenicity and fits nicely with the global movement toward regenerative, individualized treatment.[22] Additionally, using PRP into STSG regimens may enhance resource use, shorten hospital stays, and decrease the frequency of dressings. Biologically active adjuncts like PRP may become routine practice as wound care advances, particularly in situations where traditional fixation techniques are constrained by anatomical or financial limitations. Even at the end of the first week following surgery, Venter et al. and Pallua et al. found decreased complications and improved graft take rates with PRP administration.[23,24]

The much lower incidence of complications in the PRP group—such as graft infection, seroma, and hematoma formation—highlights and supports the clinical efficacy and preventative advantages of PRP against factors that usually endanger or compromise graft take. The haemostatic and anti-inflammatory properties of PRP, which together create a more stable and favourable environment for wound healing, are primarily responsible for this positive result. Thromboxane A2, a strong mediator that promotes strong platelet aggregation and causes vasoconstriction, is released by PRP's concentrated platelets. This significantly reduces intraoperative and postoperative bleeding as well as the risk of hematoma development.[25] Additionally, a variety of anti-inflammatory cytokines found in PRP actively modulate, regulate, and temper the wound bed's inflammatory response, limiting excessive inflammation that may otherwise hinder graft integration.[26] Crucially, immunosuppressive therapy—which is typically required in allogeneic or donor-derived applications to prevent immunological rejection—is eliminated by PRP's autologous origin, which is obtained exclusively from the patient's own biological material. Additionally, it streamlines the preparing process by avoiding the need for lengthy, labor-intensive, and resource-intensive donor screening procedures. Without adding any further immunological risk or regulatory complication, this intrinsic compatibility makes PRP a more versatile, adaptive, and widely applicable treatment alternative across a variety of clinical contexts. [27]

Although the outcomes of this study are promising, it is important to recognize a few limitations. The sample size was sufficient to show statistical significance in primary outcomes, but it restricts the findings' applicability to larger populations and a variety of clinical contexts including different health care systems and patient care models. Because the study was carried out at a single tertiary care facility, institutional biases pertaining to patient demographics, postoperative care procedures, and surgical technique may have been introduced. Although the study population's homogeneity reduces confounding from systemic disorders, it also limits its application to patients with more complicated medical profiles or comorbidities.

Conclusions about long-term efficacy or delayed problems were further limited by the study's lack of long-term follow-up and absence of standardized patient-reported outcome measures.Future studies should incorporate multicenter trials with bigger, more diverse populations, uniform PRP methods, and longer follow-up times in order to confirm and expand these findings. These investigations would improve external validity and offer a more thorough grasp of PRP's function in various surgical settings.

CONCLUSION:

This study found that in surgical reconstruction, autologous PRP greatly enhanced graft take and sped up wound healing. When compared to traditional fixation therapy, PRP was linked to a shorter hospital stay, a quicker healing period, and a lower risk of infection, seroma, and hemorrhage.

Furthermore, incorporating PRP into surgical procedures may lessen the requirement for systemic antibiotics, diminish the frequency of dressings, and reduce reliance on expensive synthetic sealants. In public hospitals, where large patient numbers and tight budgets necessitate scalable solutions, these operational benefits are especially beneficial. PRP is a useful addition to traditional grafting procedures since it lowers postoperative morbidity and resource consumption, supporting clinical quality and institutional sustainability.

Its capacity to lower problems and encourage early epithelialization may also result in better scar quality, less frequent dressings, and increased patient comfort. More multicenter trials with bigger sample numbers and longer follow-up times are highly advised in order to validate these results and look at long-term benefits across different patient groups. Future studies should also examine how PRP affects cosmetic results, patient satisfaction, and how effective it is in comparison to other biologic or synthetic graft enhancers. PRP stands out for its biological potency, ethical soundness, and economic viability as surgical specialties use regenerative adjuncts more frequently. Because of its autologous origin and ease of production, it can be widely used in a variety of therapeutic settings and is in line with global developments in personalized medicine. To fully characterize PRP's therapeutic spectrum and maximize its use in reconstructive surgery, future studies should examine its role in complex wound beds, irradiated tissues, and immunocompromised patients.

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Danish Almas: Supervisor and sample collection, Bench Work
Asad Ashraf: Data collection and literature review
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Original Article **Open Access**

Hourly Low-Dose Oral Misoprostol Solution for Induction of Labour at Term: A Prospective Observational Study from a Pakistan

Saba Nadeem, Iqra Aslam, Samreen Akram, Salma Jabeen, Irum Manzoor

Abstract:

Objectives: To evaluate the effectiveness and short-term safety of an hourly 20 µg oral misoprostol solution protocol for induction of labour (IOL) in primigravid term pregnancies at a Pakistani tertiary center.

Study design and setting: Prospective observational study conducted in the Department of Gynecology & Obstetrics, Sadiq Abbassi Hospital / Quaid-e-Azam Medical College, Bahawalpur, from 21-Nov-2024 to 21-May-2025.

Methodology: Primigravida with singleton, cephalic, 37–42-week gestations, Bishop score >5, and reactive CTG were enrolled; women with prior uterine surgery or other contraindications to vaginal birth were excluded. Misoprostol 200 µg was dissolved in 200 mL of water; 20 mL (20 µg) was given orally every hour until adequate uterine activity or a maximum of 10 doses. Oxytocin was started if contractions became inadequate after active labour onset.

Results: One hundred women were included (mean age 27.20 ± 3.62 y; mean gestation 38.65 ± 1.51 weeks; mean estimated fetal weight 2511.05 ± 265.42 g). Mean pre-induction Bishop score 6.32 ± 0.98 improved to 7.43 ± 1.65 at 6 h. The mean induction-to-delivery interval was 12.43 ± 3.21 h; the mean misoprostol doses were 5.52 ± 1.62. Vaginal birth within 24 h occurred in 79/100 (79%; 95% CI 71–87). Oxytocin augmentation was required in 28% and meconium-stained liquor occurred in 18%.

Conclusion: Hourly 20 µg oral misoprostol solution achieved high 24-h vaginal-delivery rates with generally reassuring short-term outcomes within recorded parameters in primigravid women at term in this tertiary-care Pakistani cohort. Larger comparative studies are warranted.

Keywords: Cesarean Section, Labor, Induced, Misoprostol, Pakistan, Pregnancy, Term

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INTRODUCTION:

Induction of labour (IOL) is undertaken in approximately 20–30% of pregnancies worldwide to reduce maternal or fetal risks when continuing the pregnancy is no longer beneficial.[1] Because the likelihood of vaginal birth after IOL depends strongly on cervical favorability, the Bishop score remains an important predictor that guides method selection.[2]

Multiple pharmacologic and mechanical approaches to IOL are available, including prostaglandins (dinoprostone, misoprostol) administered orally, vaginally, or buccally/sublingually; transcervical balloon catheters; amniotomy; oxytocin; and various combinations.[3,4] In resource-constrained settings, agents that are inexpensive, heat-stable, and easy to administer are especially valuable.[1,3] Misoprostol, a synthetic prostaglandin E1 analogue, meets many of these criteria, and major guideline bodies endorse its judicious use for IOL in appropriately selected women, typically excluding those with a prior uterine scar, and with adequate fetal and uterine monitoring.[4,5] Recent international guidelines from the World Health Organization (WHO) and American College of Obstetricians and Gynecologists (ACOG) explicitly recognize oral misoprostol as an acceptable option for cervical ripening/induction with appropriate monitoring and locally approved protocols.[6,7]

The oral route of misoprostol offers practical advantages for both patients and health systems. Compared with vaginal

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administration, oral dosing may reduce the need for repeated vaginal examinations, facilitate ambulation and mobility, and allow more responsive titration of dose according to uterine activity and fetal status. In addition, pharmacokinetic and protocol data support re-dosing at approximately 1–2-hour intervals to achieve steady stimulation without excessive peaks in uterine activity. Accurate micro-dosing can be achieved by dissolving a 200-µg tablet in 200 mL of water to yield a 1 µg/mL solution; measured aliquots permit delivery of very low doses with minimal wastage and consistent preparation at the bedside.[4] Contemporary dosing aids from the International Federation of Gynecology and Obstetrics (FIGO) also summarize low-dose oral regimens and emphasize safety considerations (for example, avoiding buccal/sublingual routes for viable pregnancies).[8]

Evidence supporting low-dose oral misoprostol includes prospective cohort studies and randomized trials conducted across diverse populations and clinical settings. The PROBAAT-II multicenter randomized controlled trial found that oral misoprostol was comparable to a Foley catheter in terms of effectiveness and safety during term inductions, reinforcing its role as a viable cervical ripening and induction strategy.[5] Beyond device comparators, solution-based regimens have been evaluated: an Indian series using an oral misoprostol solution reported vaginal birth within 24 hours in roughly 80% of cases, suggesting timely efficacy with acceptable safety.[9] Furthermore, randomized comparisons of hourly titrated versus two-hourly static oral misoprostol regimens have indicated favorable outcomes with carefully titrated protocols, supporting the biological plausibility and clinical utility of small, repeated oral doses.[10,11] A 2021 Cochrane Review focused on low-dose oral regimens (initial dose ?50 ìg) and concluded that oral misoprostol probably improves key outcomes versus several comparators while reducing hyperstimulation compared with vaginal misoprostol.[12]

Despite this growing international experience, oral misoprostol solution has not been widely adopted across many Pakistani labour wards. Potential barriers include variability in local protocols, concerns about standardization of solution preparation, staffing and monitoring requirements, and limited availability of local outcomes data to guide context-specific implementation.[3,4] In settings where cesarean section capacity is constrained and the burden of referral is high, a simple, low-dose oral protocol that achieves high rates of timely vaginal birth while maintaining safety would be valuable for patients and providers alike.[1,10] Generating local evidence is therefore essential to address uncertainties about effectiveness, dosing logistics, and near-term maternal and neonatal outcomes within our practice environment.

The objective of the study was to evaluate, in a tertiary-care Pakistani setting, the effectiveness and short-term safety of an hourly 20 µg oral misoprostol solution protocol for the induction of labour in primigravid term pregnancies. Specifically, we assessed the rate of vaginal birth within 24 hours as the primary outcome, and we described the induction-to-delivery interval, need for oxytocin augmentation, and selected maternal and neonatal events as secondary outcomes.

METHODOLOGY:

A prospective observational study was conducted in the Department of Obstetrics & Gynecology at Sadiq Abbassi Hospital/Quaid-e-Azam Medical College (QAMC), Bahawalpur, Pakistan. The study period was six months from 21 November 2024 to 21 May 2025. Consecutive eligible women presenting to the labour ward during this period were invited to participate. Protocol approval was granted by the Institutional Review Board, QAMC (ERC No.: 310/DME/QMC Bahawalpur). The study complied with the Declaration of Helsinki and ICH-GCP; participation was voluntary, and patients could withdraw at any time without impact on care. Written informed consent was obtained from all participants before enrollment. No procedures commenced before consent was signed and witnessed.

Eligibility was predefined. Primigravid women of any age with singleton, cephalic pregnancies at 37+0 to 42+0 weeks were included. We required a Bishop score >5 at presentation with a reactive cardiotocograph/non-stress test, consistent with contemporary guidance that recommends misoprostol use in appropriately selected term, singleton, vertex pregnancies with reassuring fetal status.[6-8,12] Exclusions comprised any contraindication to vaginal birth (placenta previa, placenta accreta spectrum, antepartum hemorrhage of uncertain origin, non-cephalic or unstable lie, multiple pregnancy, estimated fetal weight >4 kg, prior uterine surgery including caesarean, myomectomy, or metroplasty), non-reassuring baseline CTG, hypersensitivity to prostaglandins, or refusal of consent. Exclusion of a prior uterine scar and non-reassuring fetal status follows WHO, ACOG, and FIGO recommendations for safe use of oral misoprostol in viable pregnancies.[6-8,12] After consent, prespecified variables were recorded on a case record form: maternal age, gestational age, booking status, estimated fetal weight, and baseline Bishop score. General, abdominal, and pelvic examinations were performed by a consultant obstetrician. To minimize inter-observer variation, the same examiner reassessed the Bishop score at 6 hours when feasible. Ultrasound was used to confirm dating, amniotic fluid, placental location, and estimated fetal weight. Induction was carried out using an oral misoprostol solution at 1 µg/mL. A 200 µg tablet was dissolved in 200 mL of drinking water, and the bottle was inverted before each withdrawal. A dose of 20 mL (20 µg) orally every hour was administered until adequate uterine activity occurred or a maximum of 10 doses (200 µg total) was reached. The prepared solution was stored at room temperature and discarded after 24 hours. Adequate uterine activity was defined as =3 contractions per 10 minutes, each

=30 seconds. The next dose was withheld for tachysystole (>5 contractions per 10 minutes), any prolonged contraction (>2 minutes), or fetal heart rate (FHR) abnormalities. Active labour was defined as regular painful contractions with cervical dilatation =5 cm (local protocol). No further misoprostol was given once active labour began. Oxytocin augmentation was initiated after active labour onset if contractions fell below 3 per 10 minutes (lasting <20 seconds) or if cervical progress was inadequate for 4 hours. The infusion was started at 2 mU/min and increased every 30 minutes to a maximum of 20 mU/min, titrated to uterine response. During misoprostol administration, intermittent CTG was used with 15–20 minutes of monitoring after each dose. This approach aligns with World Health Organization recommendations for low-risk term inductions in settings where continuous cardiotocography is not feasible, provided that facilities for escalation to continuous monitoring and emergency operative delivery are available. Thereafter, monitoring followed hospital protocol: intermittent auscultation every 30 minutes in the latent phase and continuous monitoring in active labour. Maternal pulse, blood pressure, temperature, and uterine activity were charted hourly on the Labour Care Guide. Decisions for lower-segment caesarean section (LSCS) were made by the consultant obstetrician. Indications included non-reassuring FHR or suspected fetal compromise, failed induction (no active labour after 10 doses and/or 24 hours from first dose), arrest disorders in active labour, and other emergencies (e.g., cord prolapse, severe bradycardia). All indications were recorded.

The primary outcome was vaginal birth within 24 hours of the first misoprostol dose. Secondary outcomes were total vaginal birth rate (any interval), induction-to-delivery interval (hours), change in Bishop score from baseline to 6 hours, number of misoprostol doses, need for oxytocin augmentation, mode of delivery, maternal adverse events (tachysystole; hyperstimulation defined as tachysystole with FHR change; postpartum haemorrhage >1000 mL or transfusion; maternal fever =38 °C), and fetal/neonatal outcomes (meconium-stained liquor; Apgar at 1 and 5 minutes; Apgar <7 at 5 minutes; NICU admission; perinatal death).

The sample size was calculated using the single-proportion sample size formula $n = Z^2 \cdot P \cdot (1-P)/d^2$, where P = 0.805 for vaginal birth =24 h, Z = 1.96 (95% confidence), d = 0.08, and Q = 1-P = 0.195, giving n = 93.4.[9] A target of 100 participants was set to allow for attrition and protocol deviations. Data were recorded contemporaneously on paper forms and double-entered into a password-protected SPSS v24 database. Weekly range and logic checks were performed. Normality was assessed with the Shapiro–Wilk. Normally distributed continuous variables are reported as mean ± SD; skewed variables as median (IQR). Categorical variables are presented as n (%) with 95% confidence intervals for key proportions. The primary outcome (?24-hour vaginal birth vs not) was compared across prespecified subgroups (age category, gestational age category, estimated fetal weight category, oxytocin augmentation, meconium) using ÷² or Fisher's exact tests. Continuous variables were compared using a t-test or Mann–Whitney U as appropriate. A two-sided $p < 0.05$ was considered significant. Analyses followed an intention-to-treat approach, with all enrolled women included. Missing data were handled by complete-case analysis. Outliers were verified against source records before the database lock. This was an observational, non-randomized, unblinded study. Randomization, allocation concealment, and masking were not applicable.

RESULTS:

One hundred eligible primigravid women were enrolled during the study period; all received the protocol and were followed through delivery. There were no post-enrolment exclusions and no losses to follow-up.

Participant age ranged 18–40 years (mean 27.20 ± 3.62); 72% were 18–30 years. Mean gestational age at induction was 38.65 ± 1.51 weeks (68% at 37–39 weeks; 32% at 40–42 weeks). The mean estimated fetal weight (EFW) at assessment was 2511.05 ± 265.42 g; 52% had EFW =2500 g. Table 1 shows the baseline maternal and pregnancy characteristics of the study participants. Baseline Bishop score averaged 6.32 ± 0.98 and increased to 7.43 ± 1.65 at 6 h after the first misoprostol dose (mean change +3.11 points). Women received a mean of 5.52 ± 1.62 hourly 20-µg misoprostol doses before the protocol was stopped for adequate uterine activity or progression to active labour. The mean induction-to-delivery interval was 12.43 ± 3.21 h. Table 2 shows the labour process measures, including changes in Bishop score, induction-to-delivery interval, and misoprostol doses administered. Oxytocin augmentation after misoprostol was required in 28% of women. Meconium-stained liquor was documented in 18%. Mean 1- and 5-min Apgar scores were 8.32 ± 1.23 and 8.96 ± 1.02, respectively. Additional maternal complications (tachysystole, postpartum hemorrhage) and neonatal outcomes (NICU admission, Apgar <7) were not systematically recorded in the dataset available for analysis. Table 3 shows the maternal and neonatal outcomes following induction with oral misoprostol solution. Prespecified maternal adverse events, including tachysystole, uterine hyperstimulation, postpartum haemorrhage, and neonatal intensive care unit admission, were not systematically recorded in the available dataset and are therefore not reported. Vaginal delivery within 24 h of the first misoprostol dose, the prespecified primary endpoint, occurred in 79 women (79%; 95% CI 71–87%). Twenty-one women (21%; 95% CI 13–30%) underwent caesarean delivery (LSCS) under protocol criteria (failure to deliver within 24 h and/or clinical indications). No instrumental vaginal deliveries were recorded separately. Table 4 presents the mode of delivery and the primary

outcome, along with 95% confidence intervals. Table 5 shows the distribution of indications for LSCS among the 21 patients who underwent caesarean delivery. In this prospective cohort of 100 primigravid term women induced with an hourly 20-µg oral misoprostol solution, 79% (95% CI 71–87) achieved vaginal birth within 24 hours, and 21% (95% CI 13–30) delivered by caesarean section. The mean induction-to-delivery interval was 12.43 h, the mean number of misoprostol doses was 5.52, and the Bishop score improved from 6.32 at baseline to 7.43 at 6 hours. Oxytocin augmentation was used in 28%, and meconium-stained liquor occurred in 18%. Neonatal status was generally reassuring (Apgar 1 min 8.32; 5 min 8.96). There were no post-enrolment exclusions or losses to follow-up; some prespecified maternal and neonatal safety endpoints were not systematically recorded.

DISCUSSION:

In this prospective observational cohort of 100 primigravid women at term (37–42 weeks) with unfavorable cervices (baseline Bishop 6.32 ± 0.98), an hourly 20-µg oral misoprostol solution regimen achieved vaginal birth within 24 h in 79% of participants. The mean induction-to-delivery interval was 12.43 ± 3.21 h, the Bishop score improved by around 3 points at 6 h, 28% required oxytocin augmentation after active labour onset, and meconium-stained liquor was observed in 18%. Neonatal status was reassuring with mean 1- and 5-min Apgar scores of 8.32 ± 1.23 and 8.96 ± 1.02, respectively.

Induction of labour is one of the most common procedures being done in labour rooms. Various mechanical and pharmacological methods are used to start labour. Mostly vaginal prostaglandins are licensed for the induction of labour in term pregnancies with a viable fetus in various countries. But these vaginal prostaglandins (PGE2) are expensive, require temperature maintenance, and hence make them inappropriate for poor resource settings in developing countries like ours. Hence pocket-friendly, heat-stable, and freely available options and regimens are required.

Misoprostol is a synthetic analogue of prostaglandin E1, which has gastric and mucosal protective effects. It is widely used in oral form by physicians for patients with acid peptic disease or gastric ulcers. It is also prescribed as a safety agent in people who chronically use painkillers for osteoarthritis or other reasons.[10] Furthermore, misoprostol also exhibits uterotonic properties, i.e., it stimulates the contractions of the smooth muscles of the uterus, hence making it a principal part of the bundle approach to PPH management. It also, on the other hand, contracts smooth

Table 1. Baseline Characteristics (n=100)

Characteristic	Category	N	%	Summary (mean ± SD)
Maternal age (y)	18–30	72	72.0	27.20 ± 3.62
	31–40	28	28.0	
Gestational age (weeks)	37–39	68	68.0	38.65 ± 1.51
	40–42	32	32.0	
Estimated fetal weight (g)	=2500	52	52.0	2511.05 ± 265.42
	>2500	48	48.0	

Table 2. Labour Process Measures (n=100)

Variable	Mean ± SD
Bishop score, baseline	6.32 ± 0.98
Bishop score, 6 h	7.43 ± 1.65
Induction-to-delivery interval (h)	12.43 ± 2.21
Misoprostol doses administered	5.52 ± 1.62
Apgar score, 1 min	8.32 ± 1.23
Apgar score, 5 min	8.96 ± 1.02

Table 4. Mode of Delivery and Primary Outcome (n=100)

Outcome	N	%	95% CI
Vaginal delivery =24 h			71–87
• Normal	74	74.0	
• Instrumental:	05	5.0	
Forceps	03	3.0	
Vacuum	02	2.0	
Caesarean delivery (LSCS)	21	21.0	13–30

Table 5. Causes of Caesarean Section (n = 21)

Cause	N	%
Non-progress of Labour	8	38.1%
Suspicious CTG	5	23.8%
Fetal Bradycardia	4	19.0%
High head	2	9.5%
Refusal to further trial of labour	2	9.5%

Table 3. Maternal and Neonatal Outcomes (n=100)

Outcome	N	%	Notes
Maternal			
Oxytocin augmentation	28	28.0	Initiated for inadequate contractions/progress per protocol.
Fetal/neonatal			
Meconium-stained liquor	18	18.0	Any grade.
Apgar 1 min (mean ± SD)	—	—	8.32 ± 1.23
Apgar 5 min (mean ± SD)	—	—	8.96 ± 1.02

muscles in the myometrium while facilitating the relaxation and effacement of the cervix, resulting in the onset and progress of labour.[11] It helps bring changes in cervical consistency, making it soft and favorable for labour. PGE1 in both oral and vaginal routes can be used for IOL and cervical ripening.[13,14] The dose depends on the parity, period of gestation, and Bishop score. PGE1 oral dosage may cause nausea, abdominal pain, dyspepsia, vomiting, and fever.[10] Additionally, it may cause hyperstimulation, uterine rupture, fetal bradycardia, and fetal demise on the extreme.

Owing to its mechanism on uterine receptors, it is widely used in various routes for the induction of labour and termination of pregnancy for various reasons. It can be given by oral, vaginal, cervical, sublingual, and buccal routes commonly, but its use in the form of oral solution is limited and is still not endorsed by many Hospital protocols. Oral misoprostol solution has a high likelihood of achieving a normal vaginal delivery within 24 hours of IOL. In this study, 79% patients delivered vaginally within 24 hours of induction by oral misoprostol solution. In another study by Deshmukh et al, in India, vaginal delivery was successful in 80.5% women induced with ORAL PGE1 solution. 31% women required oxytocin aid to augment labour and achieve vaginal delivery. 3% of the babies were admitted to the NICU due to meconium, but the Take-home baby rate was 100%.[9]

Antil et al designed a randomized study for IOL. 54 women received titrated oral misoprostol and 52 women received intravenous oxytocin for induction.[15] Induction to delivery interval was shorter in the misoprostol arm than in the oxytocin arm, but the active phase was of the same duration in both groups. In addition, Asokan et al.[16] conducted a comparative study of titrated oral misoprostol solution and oxytocin in 280 term pregnant showed that induction to delivery time was quicker in the misoprostol group 10.1±6.1 than in 12.9±5.4 oxytocin group.

Also, Pambet et al did a randomized controlled trial of 760 term pregnant women, which exhibited similar results in favor of misoprostol solution for IOL.[17] Yenuberi et al an RCT of 83 pregnant women with pre-labour rupture of membranes, reflects that women delivered in 8.4 hours receiving misoprostol as compared to 9.45 hours in the women who received oxytocin for IOL.[18] However, the active phase of labour was the same in both groups. The facts in favor of induction with misoprostol are also favored and supported by homogenous studies like Aalami-Harandi et al a randomized clinical trial of 285 term pregnant women, showing a shorter stretch of labour in the misoprostol group by about 2 hours.[19]

Misoprostol in literature is also compared with mechanical methods of IOL. A Dutch multicenter trial published with facts and figures on the safety of misoprostol to the Foley catheter for IOL.[5] Low-dose misoprostol (25 ìg) when compared to higher doses (50 ìg) also demonstrates more safety by exhibiting a lower number of instrumental deliveries and fewer babies going to NICU, which supports our personal experience too.[20] Aalami-Harandi et al also reinforced the similar promising results of successful IOL with misoprostol leading to normal vaginal delivery when studied in comparison to oxytocin.[19] Similarly, Wasim et al. also discovered a higher proportion of normal vaginal deliveries in the patients receiving oral misoprostol than the dinoprostone given by vaginal route.[21] Across these comparative studies, oral misoprostol use was associated with lower caesarean section rates compared with published data from alternative induction methods; however, such associations should not be interpreted as causal. Das et al study also suggests more operative deliveries in the oxytocin and dinoprostone groups.[22,23]

Oral misoprostol, therefore, is an attractive option for induction protocols in labour suites in developing countries because of its safety, feasibility, and efficacy. The dose is minimum, so avoid hyper-stimulation leading to fetal bradycardia, hence minimizing the chances of operative delivery. Furthermore, the use of oral misoprostol solution is more practical because it avoids multiple vaginal examinations for dose repetition only. Multiple vaginal examinations may be uncomfortable and painful for patients, and if done in patients with ruptured membranes, may be a source of infection; and oral route avoids this inconvenience.[24] It keeps the patient mobilized, also helping labour.[25] Hence, the results of various international studies coincide with our findings, supporting the feasibility of oral misoprostol solution for IOL. However, given the observational design of the present study, these findings should be interpreted as associations rather than evidence of causation.

Strengths of this study include a clearly defined, low-dose hourly protocol; standardized Bishop scoring; intermittent CTG with post-dose monitoring and continuous monitoring in active labour; and complete follow-up for the primary outcome in 100 consecutively enrolled primigravid women. Important limitations must be acknowledged. In addition to the absence of a concurrent control group and potential confounding from clinician-directed oxytocin augmentation in 28% of participants, several prespecified maternal and neonatal safety outcomes—including tachysystole, uterine hyperstimulation, postpartum haemorrhage, and NICU admission—were not systematically captured. This incomplete safety ascertainment limits the strength of conclusions regarding comparative safety and underscores the need for cautious interpretation of reassuring neonatal findings. The single-center design may also limit generalizability beyond similar resource-constrained tertiary units.

Where prostaglandins or mechanical methods are hard to maintain, a 20µg hourly oral misoprostol solution, with strict

monitoring and clear stopping rules, may improve access to timely induction and reduce unplanned C-sections in low-resource settings. Guidelines (WHO, FIGO) support such adapted protocols when safety measures (fetal monitoring, emergency C-section capacity) exist.

Studies should compare hourly versus 2-hourly dosing and misoprostol versus alternatives (oxytocin, Foley catheter, dinoprostone), with a safety and cost analysis. Cluster trials or stepped-wedge designs could assess real-world use in South Asian public hospitals. Existing trial data (Iran, Kenya, U.S.) support feasibility and sample-size planning.

This single-center, prospective observational design lacked a concurrent control group; clinician-directed oxytocin augmentation in 28% of participants may have introduced confounding; the study was not powered for infrequent safety endpoints; capture of some prespecified maternal adverse events was incomplete; and external generalizability may be limited to comparable resource-constrained tertiary units

CONCLUSION:

Hourly low-dose (20 µg) oral misoprostol for induction of labour at term achieved a 79% vaginal birth rate within 24 hours in our primigravid cohort, with generally reassuring short-term maternal and neonatal outcomes. The regimen appears feasible in this setting; however, larger comparative studies with comprehensive safety monitoring are needed before wider adoption.

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Authors Contribution:
Saba Nadeem: Concept & Design of study, revisiting critically, data analysis, final approval of version
Iqra Aslam: Drafting, Revisiting critically, data collection and analysis
Samreen Akram: Drafting, literature search & references, data collection and analysis
Salma Jabeen: Drafting, revisiting critically, data collection and analysis
Irum Manzoor: Drafting, revisiting critically, data collection and analysis.

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Original Article **Open Access**

Expression of Vascular Endothelial Growth Factor (VEGF) in Individuals with Squamous Cell Carcinoma of Esophagus

Aisha Jamil, Maria Tasneem Khattak, Shams ul Hadi, Maria Khan, Sidra Mashal, Iqbal Muhammad Khan

Abstract

Objective: The aim of the study was find out the vascular endothelial growth factor (VEGF) expression in individuals with esophageal squamous cell carcinoma.

Study Design and Setting: The current prospective study was carried out at the department of Histopathology, Rehman College of dentistry / Rehman Medical Institute (RCD/RMI) from July 2024 to December 2024 after taking approval from the ethical board of the institute.

Methodology: A total of 53 esophageal squamous cell carcinoma samples were collected and placed at -80ºC. For culturing, humidified five percent carbon dioxide in air was used for cells in monolayer culture at 37°C. Esophageal squamous cell carcinoma tissue samples that were kept at -80°C and EC9706 cells were used to extract total RNA. Gel electrophoresis was used to assess the quality of the extracted RNA. Immunohistochemistry, RT-PCR and in situ hybridization were used to find out the VEGF expression. Data was analyzed using SPSS version 16.

Results: Vascular endothelial growth factor was expressed and secreted by EC9706 cells, confirmed by RT-PCR, in situ hybridization and immunohistochemistry staining. Using in situ hybridization, out of 53 cases with esophageal squamous cell carcinoma, 39(73.5%) had positive immunohistochemistry for VEGF. The VEGF positive rate for both metastatic and non-metastatic lymph node patients was 91% (20/22) and 61.2% (19/31) respectively. A significant difference observed in the VEGF expression between the lymph node-positive and node-negative groups ($p<0.05$).

Conclusion: This study concluded that in individuals with esophageal squamous cell carcinoma, expression of VEGF is an important and helpful prognostic factor.

Key words: Expression, vascular endothelial growth factor, Squamous cell carcinoma, esophagus

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INTRODUCTION

In terms of incidence esophageal cancer ranks seventh in the world accounting for 604,000 new cases & 544,000 deaths each year.[1] The two most prevalent histologic subtypes of esophageal cancer, esophageal squamous cell carcinoma (ESCC) & esophageal adenocarcinoma (EAC), have somewhat different incidence rates. The prevalence of these cancer depend on the location and the economic conditions of a country.[2] Although ESCC incidence has lately decreased it still accounts for almost half of all new ESCC cases worldwide[3] According to statistics on cancer epidemiology, dietary carcinogen exposure, alcohol consumption, tobacco use, and micronutrient deficiencies will all contribute to ESCC [4]. Other suspected risk factors include chewing betel quid, eating pickled vegetables, and consuming extremely hot food and drinks[1] Lymphangiogenesis is a critical phase in tumor advancement and metastasis. Prior research has shown that tumors actively stimulate the formation of their own lymphatic networks that interface with adjacent lymphatic veins.[2] The conveyance of tumor cells via lymphatic capillaries is the predominant mechanism for early dissemination, with cancer propagation occurring via

afferent lymphatics along established drainage pathways. [1] Two VEGF family members, VEGF-C and VEGF-D, are recognized as natural ligands for VEGFR-3 and have previously been linked to lymphangiogenesis. [4]

A variety of cytokines are secreted by carcinoma cells, and these cytokines have an impact on the cells' properties. One of the important cytokines is VEGF.[5] It is believed that VEGF plays significant functions by directly promoting the migration and proliferation of endothelial cells as well as by triggering a number of proteinase activities that break down the surrounding matrix tissues. Recent research on VEGF expression in esophageal carcinoma explains how VEGF influences angiogenesis in esophageal squamous cell carcinoma, which leads to poor prognoses and cancer growth.[6] According to evidence, angiogenesis and lymph angiogenesis are promoted by the high expression of the vascular endothelial growth factor. Angiogenesis is an inherent feature of all cancers, contributes to their aggressiveness and proliferation, and is a prerequisite for metastatic development. [7] Around 50% of esophageal cases of cancer in China are of this subtype, which has a comparatively high prevalence among individuals in South America, South Africa, Iran, and China.[8] Despite significant advancements in diagnostic and treatment methods over the last three decades, the prognosis for esophageal cancer remains dismal, with 5-year rate of survival ranging from 10% to 13%.[2] One of the primary reasons for the poor prognosis is lymph node metastasis. It might be the most significant prognostic variables and is more often seen in ESCC compared to tumors in other areas of digestive tract .[3] The exact processes behind the onset and advancement of LNM in ESCC are unclear, nevertheless. Angiogenesis and lymphangiogenesis are significantly influenced by vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) .[6] Among them is VEGF-C, which has been identified as an angiogenic and lymphangiogenic growth factor. It starts the related signal transduction pathway by binding to the VEGFR-3 and VEGFR-2 receptors.[9] In a number of tumor forms, including expression of ESCC and VEGF-C has direct association with clinicopathological characteristics.[4-10] The prognosis and clinicopathological characteristics of ESCC have been tightly linked to the VEGF-C expression in tumor tissues.[11] One of the most serious forms of gastrointestinal cancer is esophageal squamous cell carcinoma (ESCC), which has a comparatively high risk of spreading even in its early stages. Specifically, one of the most significant prognostic variables is the metastasis of lymph node.[1] To encourage metastasis to the lymph nodes and beyond, tumor cells exploit the lymphatic vascular system. [1] Tumor-induced lymphangiogenesis often serves as the first stage of tumor spread and encourages metastasis to local lymph nodes. One important predictive factor for the development of human cancer types is lymph node metastasis. According to reports, two components of the vascular endothelial growth factor (VEGF) family, VEGF-C and VEGF-D, stimulate lymphangiogenesis in addition to angiogenesis on lymphatic endothelial cells via the VEGF receptors (VEGFR)-2 and VEGFR-3. [3] These receptors promote lymphatic metastasis in addition to controlling lymphangiogenesis. [4] Furthermore, it was recently found that tumor cells express VEGF-C and VEGFR-3, both of which have been suggested as a marker for lymphatic endothelial cells. These expressions are linked to the invasion, metastasis, and progression of cancer cells. The functions of lymphangiogenesis and the VEGF-C/VEGFR-3 axis have been studied in a number of prior research. A significant contributor to nodal metastasis, lymphangiogenesis is also a predictor of prognosis for a number of carcinomas of the stomach, esophagus, cervix, prostate, colorectum and Lung. [6-12] Few findings exist on the VEGF-C expression in lymph fluid , despite the fact that serum VEGF-C has recently shown significance on both diagnostic and prognostic level.[8-11] Similarly the present study was carried out to determine the VEGF expression in individuals with esophageal Squamous cell carcinoma.

METHODOLOGY

The current prospective study was carried out at the department of Histopathology, Rehman College of dentistry / Rehman Medical Institute (RCD/RMI) from July 2024 to December 2024 after taking approval from the ethical board of the institute. The ethical approval number for our study was RMI-REC/Ethical Approval/CPSP synopsis/42. The inclusion criteria for our study were all the ESCC patients of both the gender and all ages, without surgical management and distant metastasis. The exclusion criteria were all the patients with other type of carcinoma patients and patients treated with chemotherapy and radiation therapy before surgery. The overall sample size in our study was 53 based on the WHO sample size calculator. All the Individuals who had an incomplete resection were excluded from our study. A total of 53 esophageal squamous cell carcinoma samples were collected from the patients admitted in the Rehman Medical Institute Peshawar and placed at -80^{o}C. None of the patients had ever had chemotherapy or radiation treatment. Experienced pathologists clearly categorized each specimen in to grade I, II and grade III. The EC9706 human esophageal cancer cell line was obtained from the institute's research lab. For culturing, humidified five percent carbon dioxide in air was used for cells in monolayer culture at 37°C. RPMI-1640 medium was used to cultivate the cells. Esophageal squamous cell carcinoma tissue samples that were kept at -80°C and EC9706 cells were used to extract total RNA using the TRIzol Reagent. Gel electrophoresis was used to assess the quality of the extracted RNA, and the A260/280 ratio was used to assess the RNA's concentration and purity. The primer pairs used in PCR to amplify vascular endothelial growth factor and internal controls (â-actin) in all reaction were according to the previous study.[8] According to Chen et al., staining was done in tissue sections (6 ìm thick) and

the cell slides ready for hybridization.[9] Immunohistochemistry was also done according to the previous study.[9] After being stored in 10% neutral buffered formalin for 8 to 48 hours, each sample was dehydrated using xylene and alcohol. Paraffin was used to encase the dried samples. The MaxVision two-step method was used for immunohistochemical staining. Slices of tissues measuring 4 µm were cut out. Following an hour of baking at 65 °C, the slices were deparaffinized by using xylene and then ethanol gradient was used for rehydration. To inhibit the activity of endogenous peroxidases, the slices were exposed to 0.3% H2O2 for 10 minutes. Then, for VEGF-C, survivin, and Ki-67, antigen retrieval was performed under high-pressure circumstances utilizing pH 6.0, 0.01 M citrate buffer. For VEGFR-3, the retrieval was performed under conditions of high temperature employing pH 9.0 EDTA. The samples were washed three times with phosphate-buffered saline for three minutes after being allowed to settle at room temperature. The sections were incubated with the secondary antibody at 37 °C for 15 minutes after being treated with the primary antibody for an hour. After five minutes of DAB staining, the slices were counterstained for one minute with hematoxylin. Neutral gum was used to secure the slides. Instead of using the primary antibodies, PBS buffer was used to incubate the negative controls. A blinded study of the stained slides was performed by two pathologists. The color of the brownish-yellow cellular staining was positive. The lack of significant color intensity fluctuation relative to the backdrop was a defining feature of negative staining. Light microscopy was used to observe staining. After identifying the area with the highest staining intensity at low magnification (50×), 10 visual fields were examined at high magnification (400×). Each patient sample's staining of 100 cells was assessed. As previously mentioned, a semi-quantitative scoring system was used to assess staining for VEGF-C, VEGFR-3, and survivin.[9] The intensity of certain stains was used as the basis for scoring. 0 represents no staining; 1 represents light staining; 2 represents moderate staining; and 3 represents severe staining. The following semi-quantitative method was used to determine the percentage of positive cells amongst all the cells counted: Zero is negative; one is 1% to 10% positive; eleven is to 50% positive; and three is above 50 percent positive. The immunohistochemistry score was finally calculated by combining the intensity and percentage evaluations. A score of =3 on immunohistochemistry was considered positive. The following is the breakdown of the final immunohisto-chemistry scores: 5 to 7 are fairly positive (++); 8 to 9 are highly positive (+++); and 3 to 4 are mildly positive (+). The percentage of Ki-67-positive cells amongst all tumor cells was used to assess Ki-67 staining. Data was analyzed using SPSS version 16. Data analysis was done using the Student's t-test or the Chi-square test. Statistical significance was defined as values having a $P < 0.05$.

RESULTS

A total of 53 patients were included in this study out of which 27 patients were male and female patients 26. The mean age was 59.4 (44-76 years). Vascular endothelial growth factor was expressed and secreted by EC9706 cells, confirmed by RT-PCR, in situ hybridization and immunohistochemistry staining. For VEGF, in cytoplasm of EC9706, the brown positive stained granules were found**.** figure 1. Using in situ hybridization. It was discovered that the cytoplasm of the EC9706 cells contained VEGF mRNA (blue-purple granules) as shown in figure 2. RTPCR revealed positive bands of VEGF mRNA in EC9706 cells. When at least thirty percent of the tumor cells exhibited vascular endothelial growth factor immunoreactivity, this was referred to as positive staining.[11] Out of 53 cases with esophageal squamous cell carcinoma, 39(73.5%) had positive immunohistochemistry for VEGF. The VEG positive rate for both metastatic and non-metastatic lymph node patients was 91% (20/22) and 61.2% (19/31) respectively. A significant difference observed in the VEGF expression between the lymph node-positive and node-negative groups (p?0.05). In esophageal squamous cell carcinoma participants, immunohistochemistry revealed that the lymph node-involved group had significantly greater VEGF expression than the node-negative group. Reverse transcriptase -PCR identified VEGF-C mRNA in tumor tissues in 31 out of 53 esophageal squamous cell carcinoma patients. The lymph node-involved group's expression of VEGF differed significantly from that of the involved group ($P<0.01$). Using RT-PCR, the lymph node-involved group's expression of VEGF- mRNA was noticeably greater than that of the lymph node-noninvolved group. In situ hybridization for VEGF mRNA was found to be positive in 25 out of 53 cases of esophageal cancer. In contrast to the non-metastatic lymph node group (4 of 31; 12.9%), VEGF positive staining was observed in majority of patients with metastatic lymph nodes (19 of 22; 95.40%). When comparing the carcinomas with lymph node metastases to those without, the staining was much greater in the former group ($P<0.01$). The group with lymph node involvement had substantially greater levels of VEGF-C mRNA expression than the group with and without involvement of lymph node, according to ISH technique. VEGF levels were not substantially linked with age, sex, or pathological grade as described in table 1.

DISCUSSION

In light of the expanding understanding of the molecular pathways that govern tumor life, the pursuit of prognostic indicators has become the most dynamic areas in studying cancer. In order to determine the prognosis of patients with solid cancers, efforts are now being made to find molecular biological markers. To link markers to survival, for example, parameters related to cell cycle, development, or apoptosis have been studied.[1-3] It has been shown that the production

Table 1 Correlation between the clinical factors and the VEGF expression by 3 methods in squamous cell carcinoma of esophagus

Features	N	mmunohistochemistry			in situ hybridization			RT-PCR		
		(+)	(-)	P Value	(+)	(-)	P Value	(+)	(-)	P Value
Gender										
Male	27	21	6	> 0.05	17	10	> 0.05	14	13	> 0.05
Female	26	17	9		14	12		11	15	
Lymph node metastasis										
Positive	22	20	2	> 0.05	20	2	< 0.01	22	0	< 0.01
Negative	31	19	11		4	27		11	21	

Figure 1.In the cytoplasm of EC9706, the brown positive staining granules for VEGF

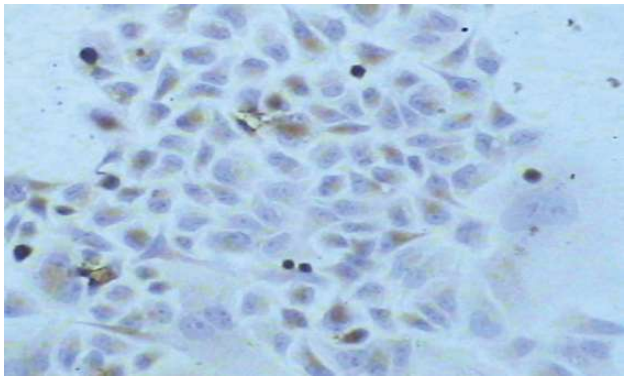
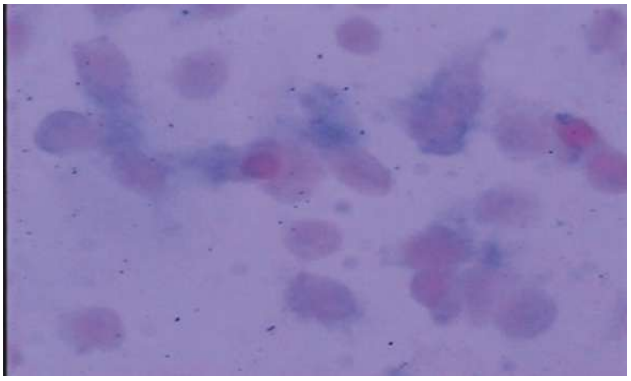


Figure 2. Cytoplasm of the EC9706 cells contained VEGF mRNA (blue-purple granules)



of VEGF, a key angiogenic factor, promotes the development and maintenance of a vascular network that promotes tumor growth and metastasis in a variety of human cancers and cell lines.[9] VEGF expression is highly associated with poorer outcomes in cancer patients, according to a large and growing body of research.[9]

On the basis of literature study, there is no published data about VEGF expression in esophageal cancer in the literature. The authors thus investigated microvessel density and VEGF expression in 53 primary esophageal squamous cell carcinomas in order to elucidate the relationship between angiogenesis and disease clinical characteristics. The prognosis and clinicopathological characteristics of ESCC have been tightly linked to the VEGF-C expression in tumor tissues.[11] Few findings exist on the VEGF-C expression in lymph fluid , despite the fact that serum VEGF-C has recently shown significance on both diagnostic and prognostic level.[8-11] Only the members of the VEGF family ("PlGF, VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E") are distinct growth factors for vascular endothelial cells. Lymphangiogenesis is induced due to VEGF-C.[12] Transgenic mice's skin has been demonstrated to show lymphatic endothelial proliferation due to its overexpression, suggesting that VEGF contributes to the maintaining of the lymphatic endothelium.[13] In experimental tumors, overexpression of these factors transgenes demonstrated a clear link between lymphangiogenesis and lymph node metastases.[14] VEGF-C expression and lymph node metastases are strongly positively correlated, according to the majority of clinical research.[6-9] VEGF-C stimulates the proliferation of tumor cells, which is associated with the expansion of lymphatic capillaries around tumors and the spread of cancer inside the lymphatic system. The metastasis of lymph nodes is intimately linked to the production of VEGF-C in tumor cells.[15] Using reverse ploymerase chain reaction, in situ hybridization, and immunohistochemistry, all of the EC9706 cells in the current investigation showed positive expression of Vascular endothelial factors. The outcomes were consistent with the invasive nature of the highly metastatic EC9706 cell line. Furthermore, the results of this investigation showed that in squamous cell carcinoma of esophagus patients, VEGF expression was positively correlated with lymph node metastasis. VEGF-C protein and mRNA expression and metastasis in squamous cell carcinoma of esophagus were revealed to be strongly correlated by immunohisto-chemistry, in situ hybridization, and Reverse transcriptase polymerase chain reaction. The findings aligned with those of earlier publications. [8-12] There was no significant correlation found between age, gender, or disease grade and any of the VEGF-C tissue expressions. These findings contrast from those of Onogawa et al.[16] This causes the growth and proliferation of new lymphatic capillaries, which in turn increases the likelihood of lymph node metastases in animal models. As per specific investigations,[17-21] lymph node metastasis and levels of VEGF-C in primary tumors are correlated. Additionally, it has been found that

individuals with some malignancies that express high amounts of VEGF-C have worse prognoses in comparison to tumors that express decrease levels of VEGF-C. Expressions of VEGF-C are not always associated with lymphatic involvement or the advancement of cancer, according to certain research[17-21]Anyhow these doubts, a treasure of data from clinicopathologic and experimental research supports the clinical targeting of the VEGF-C/VEGFR-3 lymphangiogenic signaling system. This will take precedence in the future.[22]. RT-PCR techniques may amplify the RNA from a small number of contaminating cells, masking tumor-specific changes.[23] There is no site-dependent differential expression of VEGF-C detected by RT-PCR analysis. However, ISH and IHC can detect intra-tumor heterogeneity in expression and pinpoint the cellular source.

Small sample size and single centre nature of the study were the main limitations of the study. To fully understand the relevance of these two biomarkers in ESCC, more research into the molecular mechanisms linking them and their roles in angiogenesis and metastasis is required.

CONCLUSION

In human squamous cell carcinoma of esophagus, vascular endothelial growth factor expression may trigger lymphangiogenesis. The expression of VEGF and lymph node metastases were closely related. This study concluded that in individuals with esophageal squamous cell carcinoma, expression of VEGF is an important and helpful prognostic factor.

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Aisha Jamil: Data collection, article writing
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Original Article **Open Access**

Comparison of Colostomy Reversal Outcomes in Paediatric Patients with Enhanced Recovery after Surgery vs. Traditional Care Protocol

Salman Ali, Hamza Sohail, Tahir Shahzad Nawaz Babar, Anum Manzoor, Ismael Asif, Sayed Elyas

Abstract

Objective: Comparing postoperative outcomes, particularly hospital length of stay (LOS), between paediatric patients undergoing colostomy reversal following Enhanced Recovery After Surgery (ERAS) and Traditional Care Protocol (TCP).

Study Design and Setting: This randomized clinical trial (RCT) was conducted at the Children's Hospital & Institute of Child Health, Faisalabad.

Methodology: Sixty paediatric patients (aged 2–13 years) who underwent colostomy reversal were enrolled in the study, over a period of three months from the date of commencement. patients were recruited using a non-probability consecutive sampling technique and were subsequently randomized into the ERAS group (n = 30) or the TCP group (n = 30). Categorical variables, such as gender and diagnosis, were summarised as frequencies and percentages.

Results: The study was completed by all sixty randomised patients, with a mean age of 6.78 ± 0.43 years, and 51.7% were male. The ERAS group had a significantly shorter mean hospital length of stay (5.3 ± 0.8 days) compared with the TCP group (7.1 ± 1.1 days; $p < 0.001$).

Conclusion: The application of the Enhanced Recovery After Surgery (ERAS) protocol in paediatric colostomy reversal resulted in a shorter hospital stay and earlier commencement of oral intake, without increasing postoperative complications compared to the Traditional Care Protocol (TCP).

Keywords: Anorectal malformation, Colostomy, Hirschsprung disease

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INTRODUCTION

Enhanced Recovery After Surgery (ERAS) is an integrated perioperative protocol that employs evidence-based interventions acting synergistically to produce an overall positive impact on patient outcomes. Multiple studies refer to this as the pathway of enhanced recovery. These proven perioperative components, when applied in combination, considerably enhance outcomes.[1] Procedures that involve prolonged presurgical fasting, chronic with delayed ambulation, and delayed oral resumption cause morbidity in 15 to 20 percent of stoma reversal cases, which can be improved by ERAS protocols.[2]

Over the past 20 years, Enhanced Recovery After Surgery (ERAS) has transformed postoperative care for adults through its evidence-based, multidisciplinary approach. However, its role in paediatric surgery is yet to be widely recognised. The ERAS concept emphasises optimising every stage of a paediatric patient's surgical journey before, during, and after the surgery, to promote faster recovery and reduce complications. The goal is to preserve regular bodily functions while reducing surgical stress. Preoperative counselling to prepare patients and families, nutritional optimisation to hasten recovery, and standardised pain management and anaesthesia protocols to ensure comfort

and safety are the essential elements of Enhanced Recovery After Surgery (ERAS). It also highlights the importance of early mobilization, the prudent use of antibiotics to avoid infection, and mechanical bowel preparation when required. Together, these measures reduce hospital stays, improve patient outcomes, and improve overall quality of surgical care for both adults and, increasingly, children.[3]

Through patient-centered strategies, ERAS protocol integrates evidence-based interventions aimed at reducing postoperative complications, standardising perioperative care, and accelerating recovery. By alleviating discomfort and enabling an earlier return to regular activities, it has also been demonstrated to improve Paediatric patient satisfaction, which is a significant development in contemporary perioperative care.[4,5]

Enhanced Recovery After Surgery protocol is a set of scientifically validated interdisciplinary approaches that aim to improve perioperative treatment and surgical outcomes. Many previous studies in adult colorectal surgery have shown that using ERAS protocol improved post-surgical recovery by reducing physiological stress from the surgical procedure and increasing early recovery and nutrition. Patients treated with the protocol of ERAS had faster recovery times due to fewer complications after surgery and better pain control using multimodal analgesia. As a result, hospital stays were shorter, decreasing the cost of healthcare and improving resource utilisation. Additionally, the ERAS protocol encourages patient interaction and education, which enhances the overall satisfaction level with the surgical procedure. The efficacy of the protocol of ERAS in colorectal surgery has driven its adoption in other surgical specialities, highlighting its ability to change traditional perioperative care protocol into a more efficient, patient-centred paradigm.[6]

A colostomy is the formation of an opening of the large bowel onto the surface of the abdomen for the excretion of faecal matter. In paediatric surgery, colostomy formation is often a damage control measure, such as in cases of Anorectal Malformation (ARM) or Hirschsprung's disease (HD), or a means of faecal diversion, such as in severe cases of peri-anal injuries.[7] Reversal of colostomy is a common treatment in Paediatric surgery that restores bowel continuity following a temporary colostomy. However, generally secure, it has a significant risk of complications. These include infection of wounds, anastomotic leak, bowel obstruction, incisional hernia, and postsurgical ileus. The probability of complications differs according to the child's nutritional health, chronic disease, time of colostomy, and surgical method. Careful perioperative evaluation, excellent technique of surgery, and appropriate postsurgical care are required to reduce risks and assure successful recovery after the colostomy reversal procedure in Paediatric patients.[8] The decision to undergo a colostomy procedure depends on various factors, including the extent of the underlying illness, the individual's overall health, and the potential for complications. Colostomy is a life-saving procedure for preterm/critically unwell infants, but it comes with problems.[9] A study conducted in Pakistan revealed that before surgical procedures for diseases like Hirschsprung's disease and anorectal malformation are undertaken, risks involved in the development of a colostomy should be taken into account. With careful surgical procedures and appropriate nursing assistance, complications can be avoided.[10]

This study was designed to compare the hospital length of stay (LOS) between paediatric patients undergoing colostomy reversal under Enhanced Recovery after Surgery (ERAS) and Traditional Care Protocols (TCP).

METHODOLOGY

The Paediatric surgery department of the Children's Hospital & Institute of Child Health, Faisalabad, conducted this single-centre, randomised clinical trial. This study was approved by the institutional review board (IRB) under registration no. 696/CH and ICH/FSD, and all study participants' parents/guardians provided written informed consent (IC). The randomized clinical trial number for this study was NCT07206836. The study began in August 2025 and culminated in October 2025. The sample size was calculated by using the Formula for comparing the two means:

$= 2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2/\Delta^2$.
In this formula,
$Z_{1-\alpha/2} = 1.96$ (two sided $\alpha = 0.05$)
$Z_{1-\beta} - 0.84$ (Power = 80%)
$\sigma = 1.265$ (SD)
$\Delta = 7.26 - 3.77 = 3.49$ (Means difference)

The World Health Organisation sample size calculator was used to compare two means, with á = 0.05 and a power of 80%. Based on the expected mean hospital stay of 3.77 days in the ERAS group and 7.26 days in the TCP group, and assuming a standard deviation of 1.265, the hypothetical minimum sample size was calculated to be 2 patients per group. Therefore, a total of 60 paediatric patients (30 in each group) were included using a non-probability consecutive sampling technique to account for variability and potential missing data, as the estimated minimum sample size was considered too small given the assumptions.

Children aged between 2 and 13 years, of either gender, who were scheduled for elective colostomy reversal were included in the study. Exclusion criteria included the presence of significant cardiac, endocrine, spinal, or haematological disorders, and a history of more than one abdominal surgery.

Study participants were randomised 1:1 to either the ERAS protocol or TCP using a computer-generated randomisation technique. Study participants and doctors could not be blinded because the interventions were not kept secret. The data analyst, however, was unaware of the group assignment.

Paediatric surgeons with at least 5 years of post-fellowship experience performed all surgical procedures.

Postoperative LOS, or the number of days between surgery and the time of discharge, was the study's main outcome. Criteria for this included being afebrile for 24 hours, being able to tolerate solid food, having adequate pain relief with oral painkillers, and passing stool. Additional clinical observations included the number of days required to start oral feeding and the incidence of postoperative complications like prolonged ileus, anastomotic leak, infection of the wound, and vomiting.

In the ERAS group, the protocol included limited preoperative bowel preparation a day prior to the surgery with two per-rectal (or distal colostomy loop) enemas administered 12 hours apart, oral antibiotics, laxatives, and restriction of diet to only clear fluids. Intake of clear fluids was permitted up to three hours preoperatively. Intraoperatively, a caudal epidural block for analgesia and minimal bowel handling were employed. Postoperatively, multimodal opioid-sparing analgesia, removal of the nasogastric tube within 48 hours, early enteral feeding with oral rehydration solution, and gradual advancement to a tolerated diet were implemented.

In the TCP group, the protocol involved three days of mechanical bowel preparation that comprised the following: daily administration of laxatives and distal colostomy-loop or rectal enema, restriction of the diet to clear fluids only, and oral antibiotics. Postoperatively, routine opioid analgesia was used; the nasogastric tube was kept in situ for a minimum of three days, with the patient-maintained nil per os. Enteral feeding was initiated after nasogastric tube removal, typically on postoperative days three to four.

A pre-designed proforma was used to collect all the data, and IBM SPSS version 27.0 was used for analysis. Age and hospital length of stay are examples of continuous variables that are displayed as mean and standard deviation. Frequencies and percentages were found for categorical variables. The independent samples t-test was used to compare the mean hospital stay which was the primary outcome, between the ERAS protocol and the Traditional Care Protocol groups. The analysis used stratification to control age, gender, and diagnosis as effect modifiers to account for potential confounders, and an independent t-test was used post-stratification.

RESULTS

Table 1 shows the preoperative characteristics of the 30 participants in each of the ERAS and TCP. The mean age of the ERAS group was 6.7 ± 0.4 years, while that of the TCP group was 6.9 ± 0.5 years ($p > 0.05$). There were 16 males and 14 females in the ERAS group, and 15 males and 15 females in the TCP group. Anorectal malformation was identified in 40.0% of patients in the ERAS group and 43.3% in the TCP group. Hirschsprung's disease was diagnosed in 53.3% of the ERAS group and 50.0% of the TCP group. Other causes of colostomy formation were observed in a small proportion of patients.

As seen in Table 2, ERAS group had a significantly shorter mean hospital length of stay, 5.3 ± 0.8 days, as compared to TCP group, 7.1 ± 1.1 days, p-value less than 0.001.

DISCUSSION

A study conducted by Bhasker et al. showed that the ERAS group had a significantly shorter postsurgical hospital stay, averaging 3.7 days vs. 7.2 days for traditional care protocol. Only one child in the group of ERAS had difficulties, whereas 9 cases were reported in the group of TCP that developed some complications; however, none required surgical intervention. Additionally, 1 patient in the ERAS group needed antiemetics. These findings indicated that the group of ERAS protocol had substantially decreased stay in hospital and postsurgical problems or complications, enhancing recovery and decreasing the requirement for extra medication when compared to the general care pathway.[1]

A study conducted by Suliman et al. revealed that colostomy development and closure in Paediatrics are associated with a high risk of problems, involving bleeding, retraction, stenosis, prolapse, infections, and stoma closure concerns like anastomotic leaks and bowel obstruction. These issues are more common in Paediatrics than in the older population and can impair their growth and general quality of life (QoL).

Table 1: Participants' baseline characteristics

Variable	ERAS Group (n=30)	TCP Group (n=30)	p-value
Age in years	6.7 ± 0.4 years	6.9 ± 0 .5 years	> 0.05
Distribution of Gender (Male/Female)	16 / 14	15 / 15	> 0.05
Diagnosis			
1. Anorectal malformation	12 (40.0%)	13 (43.3%)	>0.05
2. Hirschsprung disease	16 (53.3%)	15 (50.0%)	>0.05

Table 2: Clinical outcomes comparison across both groups

Outcomes	ERAS Protocol Group (n=30)	TCP Group (n=30)	P-value
Duration of Hospital stay (days)	5.3 ± 0.8 days	7.1 ± 1.1 days	< 0.001

Understanding the incidence and associated risk/risk factors are critical for better surgical planning and post-surgical care. The results emphasise the importance of standardised management measures and enhanced assistance for families in order to decrease morbidity and improve outcomes. In general, this analysis provides information to help clinicians improve their practice and impact future Paediatric surgery guidelines.[11] Formation of colostomy and the subsequent closure in children are complicated surgical procedures that are associated with a high risk of postsurgical complications, resulting in morbidity. Infection of wounds, stoma prolapse, bowel obstruction, electrolyte imbalance, and delayed healing are all potential complications. The high occurrence of such complications emphasises the requirement for enhanced perioperative care protocols, like the ERAS protocol. ERAS protocol highlights validated approaches such as effective pain management, early feeding to children, early mobilisation, and minimal fasting durations to promote faster healing and prevent complications. These standardised interventions, which standardise care and focus on the child's overall physiological recovery, can shorten stay in hospital, lower costs related to healthcare, and enhance surgical outcomes. As a result, the introduction of standardised perioperative care protocol is crucial to ensuring safer and quicker recovery in children undergoing colostomy-based procedures.[12]

In the present study, the demographic characteristics of Paediatric patients in the ERAS and TCP groups were almost similar, decreasing potential confounding variables. The mean age of paediatric patients and the gender distribution of paediatric patients were also comparable, highlighting a well-balanced group. The primary surgical conditions, such as anorectal malformation and Hirschsprung disease, were also similarly distributed among both groups. This homogeneity in basic characteristics implies that any observed problems in postsurgical outcomes, like recovery time, complication proportions, and/or length of hospital stay, were most likely caused by perioperative care measures rather than variations in patient characteristics. Such comparability improves the internal reliability of the research by confirming that the impact measured is reflective of the protocol under consideration rather than demographic or diagnostic differences.

Implementation of structured perioperative care pathways in paediatric colorectal surgery has been shown to improve measurable outcomes, even when applied to younger age groups.[13] A meta-analysis conducted by Loganathan et al. included several studies with a high number of Paediatric patients. The outcomes showed that paediatric patients maintained under an ERAS protocol started tolerating enteral diet earlier and progressed to intake of age appropriate full diet faster than those receiving traditional care. Furthermore, the demand for opioid-based analgesics was significantly reduced in the ERAS group, indicating better postsurgical satisfaction and pain management. The period of hospitalisation was also significantly reduced, indicating a faster general recovery. Notably, the incidence of postsurgical complications and hospital readmissions were similar between groups, indicating that the extended recovery method improves recovery measures without raising clinical risk factors.[14] According to a meta-analysis including 2112 adult patients, early initiation of oral feeding following bowel surgery was associated with shorter duration of hospital stay.[15] According to another meta-analysis of four RCTs including 186 cases, early initiation of feeding in children following anorectal anastomosis supported early bowel function recovery, reduction in hospital stay, and reduction in the incidence of surgical infection, without increasing postoperative complications.[16]

Regarding postoperative morbidity, our findings revealed no significant difference in complication rates between the ERAS and TCP groups. The incidence of postoperative vomiting, wound infection, and anastomotic leak was low and comparable between groups. This observation supports the safety of ERAS in paediatric colostomy reversal, alleviating concerns that accelerated recovery might compromise patient outcomes. The favourable safety profile of ERAS has been consistently reported across multiple studies. The ERAS Society's recommendations for paediatric colostomy closure emphasise a significant reduction in surgical stress and the potential for lower complication rates.[17] Additionally, a meta-analysis of ten studies involving 1,298 patients demonstrated that enhanced recovery protocols in paediatric colorectal surgery reduce intraoperative fluid administration (through judicious use), postoperative opioid requirements, bowel recovery time, time to oral intake, hospital readmissions, length of stay, and overall healthcare costs.[18]

The success of the ERAS protocol can be attributed to the synergistic effect of its components, of which two major components are: opioid-sparing multimodal analgesia, and early commencement of enteral feeding. Multimodal analgesia effectively manages postoperative pain without opioids. A literature analysis and anecdotal data revealed that opioid-sparing multimodal analgesia is just as effective (or even slightly more) than opioid-based treatments in treating postoperative pain without the use of opioids.[19]

On the other hand, a review found that paediatric patients who were given early enteral nutrition had fewer post-surgical complications and faster recovery as compared to those who received delayed feeding. Early oral feeding was associated with lower complications related to infection and septic events, proposing improved immune and bowel recovery. Additionally, it allowed for an earlier return of bowel function and a shorter hospital stay, highlighting its function in accelerating recovery. These outcomes add to the increasing body of evidence that providing early nutritional support in paediatric surgical care is both safe

and beneficial.[20]

A retrospective case-control study was conducted by Dipasquale et al. (2022), which revealed that 61 procedures in 33 paediatric patients with inflammatory bowel disease assessed the effectiveness of the ERAS protocol versus the traditional care protocol. The results showed that the intervention of ERAS protocol resulted in a considerable decrease in surgical complication proportions and faster recovery of bowel function. Paediatric patients who were managed with the ERAS protocol had better surgical outcomes, with shorter hospital stays, and faster return to daily life activities. These findings show the effectiveness and safety of ERAS in paediatric inflammatory bowel surgery, promoting its increased adoption to improve recovery and minimise morbidity in this patient group.[21]

In a study, it was found that the ERAS protocol significantly lowers the length of stay in the hospital and shortens recovery duration following colostomy reversal in paediatric patients. There has been no rise in complications or readmissions in hospitals, indicating that it is a safe protocol, with improved inflammatory, metabolic, and dietary recovery characteristics. Reduced expenses and increased parental satisfaction indicate that the ERAS protocol is a better surgical management protocol than the traditional care protocol.[22]

Our study has a few limitations that should be acknowledged. For instance, because the study was conducted in a single child medical center, the outcomes may be limited in their relevance to other children's hospitals due to differences in surgical procedure techniques, patient populations, and healthcare facilities. Secondly, while the sample size was enough for evaluating the primary objectives, it may have been insufficient to uncover uncommon or infrequent complications. Thus minimising certain adverse events. Additionally, the study did not observe readmission rates or late postoperative problems, which are important markers of the long-term effectiveness and safety of the ERAS protocol. The lack of such follow-up data makes it difficult to have a complete understanding of the protocol's long-term effectiveness. To further solidify the evidence foundation, new multicenter studies with large sample sizes, greater follow-up durations, and standardized ERAS components are required to improve external validity and confirm consistency across clinical settings.

CONCLUSION

In this study, we compared the findings of paediatric patients operated under ERAS protocol to those paediatric patients who were operated under TCP protocol for colostomy closure. Both groups had similar baseline characteristics, like age, gender distribution, and primary diagnoses, e.g., anorectal malformation and Hirschsprung's disease, confirming their comparability. The findings revealed that the ERAS treatment procedure resulted in a significantly better postsurgical recovery than the standardised technique. Patients treated with the ERAS protocol had a shorter stay in the hospital, as compared to TCP. It indicates faster recovery and earlier discharge from the hospital. The improved outcomes can be attributed to the multidisciplinary, scientifically proven techniques integrated into the ERAS protocol, including improved pain management, early feeding and early mobilisation, all of which reduce surgical stress and promote physiological balance.

By emphasising patient-centered and focus on recovery care, the ERAS protocol helps to improve clinical effectiveness, minimise hospital stays, and increases satisfaction of paediatric patients. The protocol's organized approach standardises perioperative therapies, minimises clinical variability, and promotes collaboration across surgical anaesthesia and nursing teams.

Application of the ERAS protocol in paediatric patients having colostomy closure greatly enhances recovery as compared to standard treatment. These findings promote the broad adoption of the ERAS protocol in paediatric surgical practices, as it improves recovery, decreases stay in hospitals, and is an excellent resource utilisation. Additional research studies are needed to validate these outcomes and improve the ERAS components for implication in various surgical procedures and patient demographics.

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Original Article **Open Access**

Efficacy of Topical Insulin Eye Drops In Dry Eye Disease

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ABSTRACT

Objective: To seesee(ASSESS/ EVALUATE)evaluate the treatment efficacy of topical insulin eye drops in patients suffering from dry eye disease (DED) by assessing improvement in corneal epithelialization, conjunctival hyperemia and corneal staining assessed before and after 3 months of therapy.

Study Design and setting: Prospective analytical study, Department of Oophthalmology, Combined Military Hospital Lahore from January-June 2025.

Methodology: A total of 390 patients with dry eye disease received topical insulin drops 1 U/ml, one drop in each eye to be taken 6 hourly for a total duration of 3 months. Primary variables studied were improvement in epithelial defects, corneal staining and hyperemia by comparing before and after 3 months of topical insulin therapy.

Results: Median hyperemia grade before therapy was 3.00 (1.00) before therapy and it was 1.00 (0.00) when assessed after treatment at 3 month follow-up ($p<0.001$). Similarly, median corneal staining grade showed median scores of 9.00 (1.00) before therapy and scores were 5.00 (2.00) at the 3 months follow-up after end of topical insulin treatment ($p<0.001$). Corneal epithelialization defect was improved by 50% in patient with mild, moderate and severe grading score before therapy.

Conclusion: We conclude that topical insulin can be recommended as an effective first line management option in patients with dry eye disease improving hyperemia, corneal staining and epithelial defects.

Key Words: Dry, disease, eye, insulin, topical

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INTRODUCTION

Dry eye disease (DED) also known as keratoconjunctivitis sicca is a disease affecting the tear film of the eye covering the epithelial surface of the cornea and the conjunctiva.[1] The tear film is a thin layer of fluid responsible for a multitude of function including lubrication, ensuring a smooth surface for refraction, preventing infection, inflammation and desiccation while ensuring oxygenation and nourishment to the eye.[2] The two main causes for DED are reduced tear film production or increased evaporation. The 2017 TFOS DEWS II report defines DED as a disease in which inflammation, hyperosmolarity, and neurosensory abnormalities play central roles in pathogenesis. Associated signs and symptoms include discomfort, itching, corneal epithelial damage, loss of visual acuity and increased frequency of infections. The reported worldwide prevalence for DED ranges from 5-50% depending upon patient age, population demographics and geographical area.[3]

DED is broadly classified into two main subtypes including aqueous-deficient dry eye, resulting from inadequate tear secretion (often due to lacrimal gland dysfunction), and evaporative dry eye, which arises from excessive tear evaporation, frequently related to meibomian gland dysfunction. These subtypes may coexist, contributing to a mixed disease presentation. The underlying pathophysiology for the disease involves a complex interaction between local hyperosmolarity, tear film instability, neurosensory abnormalities and ocular surface inflammation.[4] Clinically, DED presents with symptoms

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such as foreign body sensation, burning, stinging, fluctuating vision, and ocular fatigue. Diagnostic evaluation incorporates both subjective symptom assessment (e.g., Ocular Surface Disease Index) and objective tests such as tear breakup time (TBUT), Schirmer test, tear osmolarity measurement, and ocular surface staining with fluorescein, lissamine green, or rose bengal.

Risk factors aggravating the condition include increasing age, female gender, environmental exposures, prolonged digital device usage and autoimmune diseases. [5] Gap in literature shows that despite a high number of patients presenting with the condition, there have been no standard treatment guidelines and decision for therapy endpoints. [6] Secondly, novel non-invasive treatment options including insulin like growth factors (IGFs), autologous serum, topical fibronectin and hemoderivative products require further conclusive studies to add them to standard treatment regimens.

Topical insulin has emerged as a potential therapeutic agent in ocular surface disorders, including Dry Eye Disease (DED), particularly in cases associated with epithelial healing defects. Insulin, beyond its systemic metabolic functions, exerts trophic effects on epithelial cells, promoting proliferation, migration, and differentiation. These properties are crucial in restoring corneal epithelial integrity and tear film stability in DED. Insulin receptors are expressed on corneal and conjunctival epithelial cells.[7] Upon topical application, insulin activates the PI3K/Akt and MAPK signaling pathways, enhancing cell survival, cytoskeletal remodeling, and wound healing.[8] Additionally, insulin may modulate inflammatory responses by reducing pro-inflammatory cytokine expression (e.g., IL-1β, TNF-α), thereby attenuating the inflammatory cycle characteristic of DED. For DED, especially in diabetic patients with impaired corneal innervation and tear secretion, topical insulin has been proposed to enhance epithelial health, improve tear film quality, and reduce symptoms. Insulin in the topical form is closely associated with IGFs and is proposed to be effective in improving corneal inflammation and damage associated with DED. [9] The presence of insulin receptors in the epithelium of the cornea and presence in the tear film have advocated its use. [10]

While early results are promising, topical insulin is not yet a mainstream therapy for DED. Most studies are small-scale or focused on secondary dry eye in specific contexts (e.g., diabetic keratopathy). Long-term safety data are limited, and optimal dosage regimens remain to be standardized. The rationale of our study is to evaluate the treatment efficacy of topical insulin eye drops in patients suffering from dry eye disease (DED) to formulate treatment guidelines for patients with DED presenting in our setup.

METHODOLOGY:

This prospective analytical study was carried out at the Department of Ophthalmology, Combined Military Hospital, Lahore from January – June 2025 after approval from the ethical review board of the institute vide letter no 635/2025. Sample size was calculated keeping the confidence interval at 95%, power of test at 80% with anticipated population prevalence for dry eye disease at 50%.[11] Minimum sample size came out to be 383 patients according to WHO calculator. We included 390 patients in our final study protocol as per the inclusion criteria furnished keeping margin for lost to follow-up.

Inclusion criteria included patients of both genders, ages between 18-65 years of age presenting with dry eye disease and not responding to conventional therapies (intensive lubrication, bandage soft contact lenses etc.) taken for at least 4 weeks.

Exclusion criteria included patients with infectious etiology, keratitis of infective origin, acute chemical or thermal injury and trauma to the eye, patients on other therapies for DED, patients lost to follow-up or patients who non-consented to be included in the study.

The study method included all patients according to the inclusion criteria furnished. All patients were thoroughly counselled about the study protocol before induction in the study group. All participants agreed to and ensured regular follow-up in the OPD (outpatient department) as per the study design for monthly visits for a total duration of 3 months. After inclusion in the study protocol, patient's details including age, weight, gender, and duration of disease were recorded by a resident ophthalmology unaware of the study protocol on a proforma and submitted to the analysis team daily at the end of the OPD. Prior to starting topical insulin therapy, baseline ocular parameters were recorded in all patients. Corneal epithelial defects were assessed using fluorescein staining and slit lamp examination and repeated on follow-up visits monthly and degree of improvement in all patients was recorded till the end of the study protocol at 3 months.

All patients received topical insulin drops 1 U/ml, one drop in each eye to be taken 6 hourly for a total duration of 3 months. Patients with worsening condition of the eye after 4 weeks with no improvement were excluded from the study protocol to be shifted to alternate therapies.

Corneal staining in all patients was assessed using the NEI (National Eye Institute)/Industry workshop scale using fluorescein staining. The cornea was divided into five zones (central, superior, nasal, inferior and temporal). Each zone was graded from 0-3, 0= no staining, 1= mild (few, scattered punctate spots), 2= moderate (more numerous, large punctate spots), 3= severe (coalescent staining or epithelial defect). Final grading scores for all zones was calculated and total score out of 15 was noted at the start and end of the study period to see improvement. [12] **Hyperemia** in all patients was assessed using the Efron Grading Scale, with increasing hyperemia from 0-4, 0= Normal (no hyperemia), 1= Trace

(slight redness), 2= Mild (obvious but not severe), 3= Moderate (marked, more widespread), 4= Severe (intense, deep red). Values before and after completion of treatment at 3 months were recorded and endorsed. [13] Epithelial defect size was graded using Bron's A1–A3 area classification, which stratified corneal involvement according to the proportion of the surface affected by fluorescein staining. A1: represented mild area involvement and was defined as staining affecting less than one-third of the total corneal surface, corresponding to a small, focal epithelial defect or a limited cluster of punctate lesions. A2: denoted moderate involvement, with one-third to two-thirds of the corneal surface affected, reflecting a larger but still non-diffuse epithelial defect distributed across multiple quadrants. A3: indicated severe or extensive involvement, characterized by staining over more than two-thirds of the corneal surface and consistent with a large, near-diffuse epithelial defect involving most of the cornea.

All data collected over 3 months duration was then submitted to the final analysis team unaware of the study outcomes or the protocol to prevent bias and ensure blinding. [14]

Primary variables studied were improvement in epithelial defects, corneal staining and hyperemia by comparing before and after 3 months of topical insulin therapy. Demographic data including age, weight and gender were statistically described in terms of meanSD, frequencies, and percentages when appropriate. Normality for continuous variables was checked and was in the normal range. Values for corneal staining and hyperemia using the mentioned scales were expressed as median (IQR) and compared before and after therapy using the Mann-Whitney U test. Chi-square test and Fisher Exact was used to compare frequency variables for corneal epithelization in patients with mild, moderate and severe damage as appropriate. A p value of 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0

RESULTS:

A total of 420 patients were assessed for eligibility with 10 not meeting the inclusion criteria and 15 declining to give consent to be included in the study. 5 patients were lost to follow-up, and a total of 390 patients were analyzed in the final study protocol assessment. Mean age of patients in the study group was 47.7611.34 years and mean weight was 74.705.40 kg. Gender distribution revealed 104 (26.7%) males and 286 (73.3%) females in the study group. Mean duration of disease was 8.551.52 weeks in the study group (Table-1).

Study of primary variables showed that median hyperemia grade before therapy as assessed by the Efron scale was 3.00 (1.00) before therapy and it was 1.00 (0.00) when assessed after treatment at 3 month follow-up (p<0.001). Similarly, median corneal staining grade as assessed by the NEI scale showed median scores of 9.00 (1.00) before therapy and scores were 5.00 (2.00) at the 3 months follow-up after end of topical insulin treatment (p<0.001). Grade of corneal epithelialization defect assessed before treatment was mild in 138 (35.4%) patients, moderate in 161 (41.3%) patients and severe in 91 (23.3%) patients in the study group. After 3 months of therapy, improvement was seen in 107 (27.4%) patients in the mild defect group, 82 (21.0%) patients in the moderate defect group and 63 (16.2%) patients in the severe defect group (p<0.001) (Table-2).

DISCUSSION:

The study concluded that topical insulin can be recommended as an effective first line management option in patients with dry eye disease. At the end of therapy with topical insulin drops, patients had significant improvement in disease associated hyperemia, corneal staining and more than 60% patients had significant improvement in corneal epithelialization defect.

Figure No 1: Phases of the Study

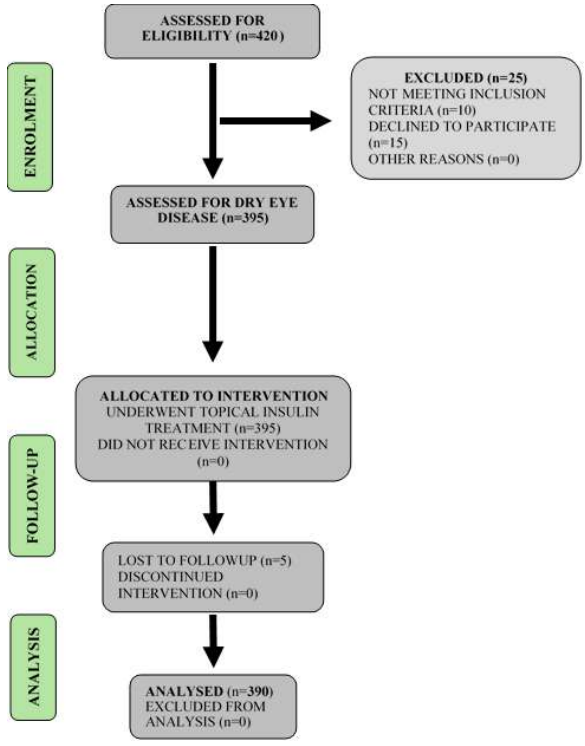

Table No 1 Demographic and Clinical Characteristics (N=390)

Variable	Topical Insulin Therapy Group (n=390)
Mean age (years)	47.76±11.34
Mean weight (kg)	74.70±5.40
Gender	
Male	104 (26.7%)
Female	286 (73.3%)
Mean duration of disease (weeks)	8.55±1.52

Table No 2 Ocular Vairables Compared Before and after Treatment (N=390)

Variable	Before therapy (n=390)	After therapy (n=390)	P value
Median Hyperemia Grade (Efron Scale) (0-4)	3.00 (1.00)	1.00 (0.00)	<0.001
Median Corneal Staining Grade (Nei Scale) (0-15)	9.00 (1.00)	5.00 (2.00)	<0.001
Frequency Of Improvement In Corneal Epithelialization Defect N (%)			
Mild	138 (35.4%)	107 (27.4%)	<0.001
Moderate	161 (41.3%)	82 (21.0%)	
Severe	91 (23.3%)	63 (16.2%)	

Comparison of our study results with local and international literature shows that in a study carried out by Burgos Blasco et al, the authors concluded accelerated corneal healing in patients receiving topical insulin drops at 1 IU/ml three times a day with observable improvements in fluorescein staining and ocular surface disease index. This is in line with results of our study with improvement in both the Efron as well the NEI scores for grading of hyperemia and corneal staining respectively.[15] In another study done by Zhang et al, the authors concluded beneficial outcome in patients with dry eye disease suffering from diabetes mellitus. They concluded that insulin in the topical form has the ability to modulate cellular metabolism and reduce ocular inflammation with improvements in corneal epithelialization defects as well as improvement in visual acuity. [16] This is in line with our study results with improvement seen both for the ocular inflammation as well as surface defect. Although not classic DED, multiple studies in epithelial defects, recurrent erosions, neurotrophic keratopathy, and post-vitrectomy diabetics consistently report faster epithelialization and good tolerance supporting the biologic plausibility for DED where epithelial stress/inflammation dominate. Case series in refractory or severe DED have demonstrated significant reductions in corneal staining and hyperemia within three months, though results may be confounded by concomitant treatments like cyclosporine or autologous serum. The therapy appears well tolerated, with negligible systemic absorption at ophthalmic doses.

In a recent systemic review and analysis, Andrade et al concluded from various randomized controlled trials and observation studies that topical insulin is very effective in improving epithelial regeneration and reduces tear film breakup time in patients with moderate to severe DED. [17] This is in confirmation of our results in which more than 50% patients in each of the mild, moderate and severe category showed a statistically significant improvement in corneal defects after the 3 months treatment period. While similar results have been reported by using autologous serum in patients with DED, a study by Krolo et al concluded that topical insulin offers easier preparation and potentially fewer immunological complications. [18]

Local studies done on the subject show that in a study carried out by Balal et al at Jinnah Postgraduate Medical Center, Karachi, topical insulin three times a day led to significant improvements in fluorescein staining and Schirmer's test scores after 6 weeks of use. One potential drawback is the lack of standard formulations for insulin in the country at present posing a challenge for widespread adoption. [19] Another local study done by Khilji et al concluded promising results in improving ocular parameters in patients suffering from neurotrophic keratopathy and diabetics suffering from dry eye disease confirming results of our study. [20]

The limitations are that the study is single center only. Long term safety profile optimized standard regimens and quality controlled delivery still remain a hurdle in widespread adoption and require further literature to recommend a broader adoption.

CONCLUSION:

We conclude that topical insulin eye drops can be recommended as an effective first line management option in patients with dry eye disease improving hyperemia, corneal staining and epithelial defects.

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Authors Contribution:
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Junaid Afsar: Conception, design, analysis and interpretation of data

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Original Article

Open Access

Diagnostic Accuracy of Twinkling Artefect in Diagnosis of Ureteric Calculus Keeping Non-Contrast CT as A Gold Standard

Naveed Hussain, Usman Shakil, Sana Sharif, Mohammad Uzair, Nosheen Sadiq, Muhammad Saeed

ABSTRACT

Objective: To determine the diagnostic accuracy of the twinkling artifact on Doppler ultrasound using non-contrast CT as the gold standard for detecting ureteric stones.

Study Design & Setting: This cross-sectional diagnostic accuracy study was conducted at the Department of Radiology, a tertiary care hospital, from 2 October 2021 to 1April 2022.

Methodology: A total of 141 patients with clinically suspected ureteric colic were enrolled. All underwent Doppler ultrasound followed by Non contrast enhanced CT. Findings of twinkling artifact were recorded and compared with Non contrast enhanced CT outcomes. Diagnostic parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. Subgroup analysis was performed based on age, gender, and stone size.

Results: The mean age was 38.59 ± 9.97 years; 55.3% were male. The twinkling artifact was observed in 94 (66.7%) patients. Non contrast enhanced CT confirmed ureteric stones in 81 (57.4%) cases. Sensitivity, specificity, PPV, NPV, and overall accuracy of the twinkling artifact were 90.1%, 93.3%, 94.8%, 87.5%, and 91.5%, respectively. Stratified analysis showed diagnostic accuracy above 89% across all subgroups.

Conclusion: The twinkling artifact on Doppler ultrasound demonstrated excellent diagnostic accuracy and can be considered a reliable, radiation-free alternative to Non contrast enhanced CT for detecting ureteric stones.

Keywords: Accuracy, Doppler ultrasound, Non contrast enhanced CT, Sensitivity, Specificity, Twinkling artifact, Ureteric stones

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INTRODUCTION

Ureteric calculi are a most common cause of colicky abdominal and acute flank pain. Various factors are contributing in recurrent formation of ureteric calculi with various composition. Contributing factors may include environmental conditions such as hot climate and humid weather as well as metabolic causes. Urinary tract calculi remain a significant contributor to morbidity worldwide. Symptoms of ureteric colic or acute flank pain may vary, ranging from asymptomatic mild dull ache to severe colicky abdominal pain that may require hospitalization with adverse outcome like altered renal function and infection secondary to obstructive cause.[1] Urolithiasis, or renal tract stones i.e. in kidney, ureter and urinary bladder, affect between 2% to 3% of the Western population. The majority of stones seen in the urinary system are composed of calcium, with 35% being calcium oxalate, 10% being calcium phosphate, and 35% being a combination of the two. Recurrent formation of urinary tract stone causes adverse effect on quality of life due to severe colic episodes disturbing daily routine activities.[2] Urolithiasis from recent decades is becoming more common; its average prevalence has increased from 3.25 percent in the 1980s to 5.64 percent in the 1990s. Due

to progressively increasing incidence of urolithiasis globally, it estimates cost impact in billions in America and European countries.[3] There is alarmingly rise in incidence of indoor and outdoor patients presented with renal and ureteric symptoms. Many a time patients decline consultation due to unawareness and financial impact and presented with adverse complication of urosepsis and renal failure. Twelve percent of Pakistanis suffer from urolithiasis, and thirty-one point four percent of those people reported experiencing acute flank pain.[4]

Radiology comprises multimodality specialty including X-ray or plain radiograph, Ultrasonography, CT scan and MRI. Prompt and accurate diagnosis of urinary tract calculi is essential for effective clinical management. The choice of diagnostic imaging plays a pivotal role in identifying the presence, number, location, and size of calculi, and density or composition of stone which subsequently guides therapeutic decisions.[5] ultrasonography is initial investigation of choice for acute abdominal colic, despite of multiple modalities in radiology, abdominal radiograph is preferred in some setups, for ureteric calculi. Ultrasound being safe, easily accessible, cost effective and showing no harmful teratogenic effects on pregnant women and fetus is preferred over CT scan. Currently, noncontrast computed tomography (NCCT) is widely recognized as the gold standard for detecting ureteric stones due to its high sensitivity (94–100%) and specificity (92–100%). Non contrast CT scan provides rapid, non-invasive and detailed anatomical visualization, identifying even not only radio dense but also radiolucent stones and other differential diagnoses of acute abdominal pain especially to rule out acute appendicitis .[6] However, CT imaging comes with certain limitations, notably radiation exposure, high cost, limited accessibility in some settings, and potential nephrotoxicity if contrast is used and competency of operator and CT technician, though not applicable on Non contrast CT scan.[7]

In recent years, twinkling artifact, a phenomenon observed on color Doppler ultrasound, has been studied for its potential to enhance the diagnostic accuracy of sonography in detecting urinary tract calculi.[8] The twinkling artifact appears as a rapidly alternating mixture of red and blue signals posterior to a strongly reflective surface such as a calculus, mimicking turbulent flow. This artifact results from intrinsic machine noise interacting with rough surfaces like stones and is more prominent than acoustic shadowing in many cases.[9] It has been suggested that this doppler finding may allow detection of stones that are otherwise not visible on grayscale imaging. According to Rahmouni's 1996 description of twinkling artefact on colour Doppler ultrasonography, this phenomenon is caused by a highly reflective material.[10]

Ureteric calculi are frequently encountered in emergency settings, yet diagnosis using ultrasound remains limited due to low sensitivity. Incorporating the twinkling artifact on Doppler ultrasound may significantly enhance detection rates of ureteric stones without exposing patients to radiation. While international studies have shown promising results, local data in Pakistan remains scarce, and twinkling artifact is underutilized in routine practice. This study will fill a research gap by validating its diagnostic accuracy against Non contrast CT scan in a Pakistani population. The findings may promote safer, costeffective, and accessible imaging protocols in low-resource settings. Moreover, it may help reduce unnecessary CT usage, especially in vulnerable groups.

METHODOLOGY:

This descriptive cross-sectional study was conducted at the Tertiary care hospital, Department of Radiology, PNS Shifa, Karachi over a period of six month from 2- Oct-2021, to 1-Apr-2022.

The sample size was calculated using a calculator, based on formula reference proposed by Buderer [11], taking into account the reported sensitivity and specificity of the twinkling artifact on Doppler ultrasound in diagnosing ureteric calculus as 91.2% and 95.7%, respectively.[12] The prevalence of acute flank pain was taken as 31.46%, with a margin of error of 7% for sensitivity and 4% for specificity, at a 95% confidence level, resulting in an estimated sample size of n = 141.[13] A non-probability, consecutive sampling technique was used for the selection of study participants.

Inclusion criteria: Patients aged between 18 to 60 years, of either gender, presenting with acute ureteric symptoms or acute flank pain of less than 72 hours duration and who underwent both color Doppler ultrasound (for twinkling artifact) and non-contrast CT within 24 hours were included.

Exclusion criteria: Patients were excluded if they had a history of ureteric stone surgery or those who has known or already diagnosed for ureteric stone, patients who has solitary kidney, acute or chronic renal failure, renal failure (serum creatinine >1.5 mg/dL), symptoms of urinary tract infection (?10 WBCs/HPF or nitrite positive), or were pregnant (confirmed by â-hCG).

Consent and IRC: The research was approved by ethical review committee of PNS Shifa hospital

(ERC/2023/RAD/05). All patients who fulfilled the inclusion criteria and visited the outpatient or inpatient departments of PNS Shifa, Karachi, and were referred to the Radiology Department for KUB ultrasound, were considered for inclusion.

Informed consent: was obtained after explaining the purpose and nature of the study in simple and understandable language.

Data collection was initiated after the approval of the synopsis by the Research Department of the College of Physicians and Surgeons, Pakistan. Patients were assured of confidentiality and their right to withdraw at any time without providing a reason. Each patient subsequently underwent

Doppler ultrasound performed by a trained, competent consultant radiologist. The findings of KUB ultrasound were then confirmed with non-contrast CT (NCCT), as defined in the operational definitions, in order to assess the diagnostic accuracy of the twinkling artifact observed on Doppler ultrasound. All collected data were recorded on a pre-designed proforma.

Data were entered and analyzed using SPSS version 26.0. Mean and standard deviation were calculated for quantitative variables such as age and stone number and size. If the data were not normally distributed, median was used. Frequencies and percentages were calculated for qualitative variables such as gender, and findings on Doppler ultrasound and non-contrast CT. A 2×2 contingency table was used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of the twinkling artifact. Effect modifiers such as age, gender, and stone size were controlled through stratification. Post-stratification, diagnostic accuracy was recalculated using a 2×2 table.

RESULTS

As shown in Table 1, the mean age of the study population was 38.59 ± 9.97 years. Patients who were aged = 40 years were 76 (53.9%), while those patients aged > 40 years were 65 (46.1%). The majority of participants were male with a frequency of 78 (55.3%), whereas 63 (44.7%) were female. Various sizes of stone were recorded in study. The mean stone size was 6.54 ± 3.37 mm. Stones measuring = 6 mm were observed in 80 (56.7%) cases, while stones > 6 mm were present in 61 (43.3%) patients included in study.

As shown in Table 2, the twinkling artifact on Doppler ultrasound was present in 94 (66.7%) of patients, while it was absent in 47 (33.3%) cases. In comparison, ureteric stones on non-contrast CT were identified in 81 (57.4%) patients, and were absent in 60 (42.6%) cases included in study.

As shown in Table 3, among the 141 patients part of our study, twinkling artifact on color Doppler ultrasound was present in 73 (51.8%) true positive (TP) cases where ureteric stones were confirmed on Non contrast CT scan, and 4 (2.8%) were false positive (FP) with no stone on Non contrast CT scan. Conversely, 8 (5.7%) were false negative (FN) where the twinkling artifact on color Doppler ultrasound was absent but stone was present on Non Contrast Computed Tomography (NCCT), while 56 (39.7%) were true negative (TN) with no stone detected on both Doppler ultrasound and non-contrast CT scan (NCCT).

As shown in Table 4, the twinkling artifact on Doppler ultrasound in patient with ureteric colic included in study demonstrated a sensitivity of 90.1% (95% CI: 83.6%–96.6%) and a specificity of 93.3% (95% CI: 87.0%–99.7%) in detecting ureteric and renal stones. The positive predictive value (PPV) was 94.8% (95% CI: 89.8%–99.8%), while the negative predictive value (NPV) was 87.5% (95% CI: 79.4%–95.6%). The overall diagnostic accuracy of twinkling artefect on color Doppler ultrasound was 91.5% (95% CI: 86.9%–96.1%), and the prevalence of ureteric stones based on Non contrast CT scan findings was 57.5% (95% CI: 49.3%–65.6%).

The diagnostic accuracy of the twinkling artifact on Doppler ultrasound was also assessed in across different stratified groups using Non contrast CT scan as the gold standard. In individuals aged = 40 years (n = 76), sensitivity was 88.1%, specificity was 91.2%, and overall accuracy was 89.5%, whereas in those aged > 40 years (n = 65), sensitivity increased to 92.3%, specificity to 96.2%, and accuracy to 93.8%. Among males (n = 78), sensitivity was 90.9%, specificity 94.1%, and accuracy 92.3%, while in females (n = 63), sensitivity was 89.2%, specificity 92.3%, and accuracy 90.4%. For patients with stones = 6 mm (n = 80), the sensitivity was 88.1%, specificity 92.1%, and accuracy 90.0%, whereas those with stones > 6 mm (n = 61) demonstrated higher sensitivity (92.3%), specificity (95.5%), and accuracy (93.4%). These results indicate consistently high diagnostic performance across all subgroups, with relatively better outcomes in older patients and those having larger stones.

DISCUSSION

Ureteric stones are a common cause of acute abdominal colic and flank pain and urinary obstruction mostly due to calculus, requiring prompt and accurate diagnosis to avoid its lethal complications like pyonephrosis, acute and chronic renal failure and chronic renal scarring secondary to obstructive cause and urinary retention. For the detection of ureteric calculi various diagnostic means of radiology are

Table 1: Baseline Characteristics of Study Population (n = 141)

Variable	Category	Mean ± SD / n (%)
Age	Mean±SD	38.59 ± 9.97
	= 40 years	76 (53.9%)
	> 40 years	65 (46.1%)
Gender	Male	78 (55.3%)
	Female	63 (44.7%)
Stone Size (mm)	Mean±SD	6.54 ± 3.37
	Stone = 6 mm	80 (56.7%)
	Stone > 6 mm	61 (43.3%)

Table 2: Frequency of Findings on Imaging Modalities (n=141)

Imaging Finding	Present n (%)	Absent n (%)
Twinkling Artifact on Doppler Ultrasound	94 (66.7%)	47 (33.3%)
Ureteric Stone on Non-Contrast CT	81 (57.4%)	60 (42.6%)

Table 3: Diagnostic Accuracy of Doppler Ultrasound Using Non-Contrast CT as Gold Standard (n = 141)

Doppler Ultrasound Findings	NCCT Present	NCCT Absent	Total
Twinkling Artifact Present	73 (51.8%)TP	4 (2.8%)FP	77 (54.6%)
Twinkling Artifact Absent	8 (5.7%)FN	56 (39.7%)TN	64 (45.4%)
Total	81 (57.4%)	60 (42.6%)	141 (100.0%)

Table 4: Diagnostic Performance of Twinkling Artifact on Doppler Ultrasound (n = 141)

Diagnostic Parameter	Percentage (%)	95% Confidence Interval
Sensitivity	90.1%	83.6% – 96.6%
Specificity	93.3%	87.0% – 99.7%
Positive Predictive Value (PPV)	94.8%	89.8% – 99.8%
Negative Predictive Value (NPV)	87.5%	79.4% – 95.6%
Overall Accuracy	91.5%	86.9% – 96.1%
Prevalence	57.5%	49.3% – 65.6%

utilized varies from setup to setup. Most commonly and easily accessible means of early detection of urinary tract stone in emergency setup and assessment of complications with grey scale and Doppler ultrasound scan is widely used due to cost effective easily accessible in majority of setups. Noncontrast computed tomography (NCCT) is considered the gold standard for detecting ureteric stones due to its high sensitivity and specificity for detection of number, sizes, location and density of stone and complication of obstructive stone on urinary tract system. However, its limitations include radiation exposure, and higher costs. Doppler ultrasound, particularly the detection of the twinkling artifact, offers a non-invasive, cost effective and radiation-free alternative. The twinkling artifact appears as a rapidly alternating color signal behind a reflective object, such as a calculus.[14] Assessing the diagnostic accuracy of this artifact compared to Non contrast CT scan is essential for establishing its clinical utility in routine emergency evaluations.

The current study aimed to assess the diagnostic performance of the twinkling artifact (TA) on Doppler ultrasound in detecting ureteric calculi, using non-contrast CT (NCCT) as the gold standard. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of the Twinkling Artifects, in our study were found to be 90.1%, 93.3%, 94.8%, 87.5%, and 91.5%, respectively. These values indicate a high diagnostic reliability of Doppler ultrasound in identifying ureteric stones. Our findings were consistent with those of Abid et al. (2021), who reported slightly higher sensitivity (91.2%), specificity (95.7%), Positives Predictive Value (98.7%), Negative Predictive Value (75.2%), and accuracy (92.2%), suggesting strong agreement in terms of overall performance of Twinkling Artifects.[13]

Comparing further, Tariq et al. (2024) observed a remarkably high sensitivity of 99.3% and specificity of 92.0% for Twinkling Artifects, with an overall accuracy of 92.97%, reinforcing the role of color Doppler as a first-line imaging modality. Their study also noted that the diagnostic yield of

Twinkling Artifects, was slightly greater than grey-scale ultrasound (GSU) and comparable to CT KUB.[14] On the contrary, Khan (2024) documented a sensitivity of 90.4% similar to ours but reported lower specificity (73.9%), positive predictive value PPV (88.7%), positive predictive value NPV (77.2%), and diagnostic accuracy (85.3%). This discrepancy could be attributed to sample differences or operator variability.[15] Similarly, Memon et al. (2021) found a high sensitivity (92%) but very low specificity (44%) and NPV (50%) for Twinkling Artifects, resulting in a much lower diagnostic accuracy of 70%, which is significantly inferior to our findings.[19]

Some studies, however, have also reported lower sensitivities and overall diagnostic performance. For instance, Adel et al. (2024) found the sensitivity of Twinkling Artifects, to be 54.3%, specificity 94.7%, PPV 93.2%, and NPV 60.5%, with an overall diagnostic accuracy of 71.5%. These results indicate that although Twinkling Artifects, can strongly confirm the stone presence (high PPV and specificity), it may fail to detect all true positive cases (low sensitivity).[16] Similarly, Shuja et al. (2025) reported a sensitivity of 71.5%, specificity of 96.4%, positive predictive value (PPV) of 98.2%, and a comparatively low negative predictive value of 55.2%. The high positive predictive value and specificity in these studies suggest Twinkling Artifects, is reliable for confirming a diagnosis when positive, but a negative Twinkling Artifects, may not confidently rule out stones unlike our study, which reported a higher NPV (87.5%).[20]

Other studies such as Hanafi et al. (2019) and Lalchan et al. (2022) also corroborated the high specificity and positive predictive value of Twinkling Artifects.[17] Hanafi et al. showed a sensitivity and accuracy of 94%, and a positive predictive value (PPV) of 100%, slightly better than our values, while Lalchan et al. reported sensitivity of 85.8%, specificity 80%,

positive predictive value (PPV) 97.1%, negative predictive value (NPV) 42.1%, and accuracy 85.2%, all generally lower than our results.[17,21] Arshad et al. (2021) found the diagnostic accuracy of Twinkling Artifects, to be only 68%, with a sensitivity of 75.6%, specificity 46.1%, positive predictive value (PPV) 80%, and negative predictive value (NPV) 40%, highlighting significantly inferior outcomes. These variations across studies might be due to differences in stone location, size, ultrasound settings, operator skills, and study populations.[18] Rasul et al. in his study reported the sensitivity of twinkling artifact 84%, with sensitivity 95% and specificity 56%, PPV 92%, and NPV 68%, with diagnostic accuracy of 89%.[22] Rashid et al study showing sensitivity 90.4%, specificity 73.9%, negative predictive value 77.2%, positive predictive value 88.7%, and diagnostic accuracy 85.3% of Doppler ultrasound for twinkling artifact.[23]

This study utilized a well-defined gold standard Non contrast CT scan (NCCT) for evaluating diagnostic performance. The sample size was adequate to detect statistically meaningful differences across subgroups. Stratified analysis by age, gender, and stone size provided detailed insight into diagnostic accuracy. However, being a single-center study may limit generalizability. Operator dependency and variability in ultrasound quality may affect reproducibility. Additionally, inter-observer variability was not assessed, which could influence diagnostic consistency.

Only single radiologist performed ultrasound and reported non enhanced CT scan of patient included in study independently, hence interobserver reliability could not be established.

CONCLUSION:

Doppler ultrasound with the twinkling artifact showed high sensitivity and specificity for detecting ureteric stones in patients presented with abdominal pain or acute renal colic. It may serve as a reliable, safe, cost effective, rapidly available and non-invasive alternative to Non contrast CT scan (NCCT) in appropriate clinical settings for management of abdominal and urinary tract symptoms. Incorporating the use of color Doppler ultrasound for abdominal pain or renal pain into routine practice could reduce harmful effects of radiation exposure and healthcare costs.

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Authors Contribution:
Naveed Hussain: Substantial contributions to conception and design alongwith acquisition of data
Usman Shakil: Acquisition analysis and interpretation of data
Sana Sharif: Literature review
Mohammad Uzair: Revising it critically for important intellectual content
Nosheen Sadiq: Literature review
Muhammad Saeed: Discussion

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Original Article **Open Access**

Association of Hypocalcemia and Elevated Parathyroid Hormone with Delayed Tooth Eruption in Children. A Cross-Sectional Study from a Pediatric and Dental Cohort

Shakil Ahmed Shaikh, Sidra Jabeen, Aqeela Memon, Kulsoom Jawed, Muhammad Hanif, Hira Saeed Khan

Abstract

Objectives: This study aimed to evaluate the association between biochemical parameters and stunted odontogenesis in children attending dental and pediatric clinics.

Study design and setting: This cross-sectional study was conducted at the dental OPD of LUMHS, Jamshoro, Sindh**.**

Methodology: After approval from the research ethics committee (DREC/113, dated 17/06/24), this study was conducted among 250 children aged 2–16 years, from 1st July 2024 to 31 December 2024. Clinical assessment included dentine scoring and evaluation of delayed tooth eruption. Biochemical analysis measured serum calcium, PTH, vitamin D, magnesium, sodium, potassium, iron, folic acid, calcitonin, urea, and creatinine. Comparative analysis, ANOVA, and regression were performed using SPSS, with significance set at $p < 0.05$.

Results: Delayed tooth eruption was observed in 88.4% of participants. Mean serum calcium was below normal (7.98 ± 1.10 mg/dL), with elevated mean PTH (18.90 ± 22.78 pg/mL). Children with delayed eruption had lower calcium levels ($p = 0.001$) and higher PTH levels ($p = 0.021$) than those without delay. Regression analysis revealed a positive linear relationship between PTH and serum calcium ($y = 7.38 + 0.03x$, $R^2 = 0.429$).

Conclusion: This study highlighted that disturbances in mineral metabolism, particularly hypocalcemia and compensatory PTH elevation, are associated with delayed tooth eruption and dentine defects.

Keywords: Dentine Score, Hypocalcemia, Parathyroid Hormone, Tooth Eruption,

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INTRODUCTION:

Tooth eruption is not simply about breaking teeth through the gums but is an exceptionally modified physiological process that relies on the harmonious relationships of hormones, mineral metabolism, and appropriate nutrition. The timing and sequence of tooth eruption are influenced by genetic, environmental, nutritional, and endocrine factors. Deviations from normal eruption patterns, particularly delayed tooth eruption, may serve as early indicators of underlying systemic or metabolic disorders and have been associated with functional, nutritional, and psychosocial consequences in children. Among them, the parathyroid hormone (PTH) played a critical role in maintaining the stable calcium level in the bloodstream, which is very important in the formation of healthy enamel and dentine during the development of teeth. PTH performs this by attracting calcium in the bones, as it enables the kidneys to retain calcium.

Studies have demonstrated that children who lack adequate calcium or vitamin D can have delayed tooth eruption, brittle enamel or dentin problems, which are symptoms of underlying nutritional or metabolic problems, especially in children who grow up. Calcium is a fundamental mineral

required for skeletal growth and dental mineralization. Adequate serum calcium levels are essential for the formation of enamel and dentin, as well as for the remodeling of alveolar bone that allows normal tooth eruption. Hypocalcemia during childhood has been linked to impaired bone mineralization, delayed skeletal maturation, and abnormalities in dental development. Endocrine regulation of calcium homeostasis is primarily mediated by parathyroid hormone (PTH), which increases in response to low serum calcium levels to maintain mineral balance. Chronic hypocalcemia often results in elevated PTH levels, a condition known as secondary hyperparathyroidism. Elevated PTH alters bone turnover by increasing osteoclastic activity, which may disrupt normal alveolar bone dynamics and interfere with the eruption pathway of teeth. While the skeletal effects of hypocalcemia and secondary hyperparathyroidism are well established, their specific impact on dental eruption has not been adequately investigated, particularly in pediatric populations.

Previous studies examining delayed tooth eruption have largely focused on local dental factors, genetic syndromes, or nutritional deficiencies, with limited attention to biochemical and hormonal contributors.4 The dental manifestations of calcium and PTH imbalance may therefore be under-recognized, leading to missed opportunities for early diagnosis of metabolic disorders. Understanding the association between serum calcium levels, PTH concentrations, and delayed tooth eruption could provide valuable insights for both pediatricians and dental practitioners.

Earlier literature has documented that the timing of tooth eruption can be influenced by systemic conditions that disturb normal growth and mineralization. Research in pediatric endocrinology has shown that inadequate calcium availability during early childhood interferes with dentine and enamel formation and may slow the eruptive process. Experimental and clinical studies have also demonstrated that sustained elevation of parathyroid hormone, often secondary to chronic hypocalcemia, alters bone turnover and the resorptive activity required for normal eruption of teeth. In addition, population-based studies have reported a higher frequency of delayed eruption among children with nutritional deficiencies, particularly in regions where vitamin D insufficiency is widespread. Despite these observations, many studies have assessed dental findings or biochemical abnormalities in isolation, leaving limited evidence on their combined effect.

These visible dental changes often indicate underlying nutritional or metabolic issues, particularly in growing children. It is also important to introduce complementary foods at the appropriate time, and the World Health Organization proposes starting at approximately six months. Postponing this step or leaving it too long with the help of exclusive breastfeeding may increase the probability of calcium and vitamin D deficiency. But the impact of various weaning methods and nutritional cultures on the biochemical indicators of children and on the formation of teeth has not been studied in South Asia, such as Pakistan.

To fill this gap, our study focused on children visiting the Dental Outpatient Department and Pediatric Ward at Liaquat University of Medical & Health Sciences (LUMHS). We set out to explore the relationship between serum calcium and PTH levels and delayed tooth eruption and dentine defects, and examine the influence of other nutrients and minerals, such as magnesium, sodium, potassium, iron, folic acid, vitamin D, and calcitonin, on dental health.

METHODOLOGY:

The data were collected as a cross-sectional analytical study at the Dental outpatient department (OPD) and pediatrics ward of Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, between 1st July 2024 and 31st December 2024. The purpose of the study was to examine the association between the biochemical parameters, such as serum calcium, parathyroid hormone (PTH), and other micronutrients, and odontogenesis stunting in children. There were 250 children aged 2-16 years who were visiting the dental OPD or pediatric clinics. The sampling criteria of children were non-probability consecutive sampling. The inclusion criteria included: Children with reported delayed tooth eruption or dentine defects, and who were available to have their blood sampled and parental consent. Exclusion criteria were: Children with known systemic illnesses that would impair calcium metabolism (e.g., chronic kidney disease, rickets because of genetic disorders). Past medical history of bone or tooth mineralization affecting drugs. The clinical examination involved Recording Age and gender, and nutritional status, which was measured by obtaining Body Mass Index (BMI) and Mid-Upper Arm Circumference (MUAC). Dental checkup conducted by trained pediatric dentists to check: Tooth eruption status (Delayed/Normal, according to standard eruption charts) and Dentine involvement measured on a scale of 0 (no defect) to 4 (severe defects). Biochemical Analysis Venous blood samples were taken and tested as follows: Serum calcium (mg/dL), Parathyroid hormone (PTH) (pg/mL), Serum magnesium, sodium, potassium, iron, folic acid, vitamin D, and calcitonin, Urea and creatinine to measure renal functioning. All tests were performed on the standard analysis using automated systems in the hospital lab. The data were typed and computed in the SPSS software (version 23.0). Participant demographics, biochemical parameters, dentine scores, and weaning practices were summarised through descriptive statistics (mean ± SD, frequencies, and percentages). Comparative studies were made by Independent t-tests to compare biochemical parameters in children with and without delayed eruption. ANOVA was used to test the differences in weaning. The dependence between PTH and serum calcium (as a regression equation and R2) was evaluated by

the use of correlation and regression analysis. The issue was established as $p < 0.05$.

RESULTS:

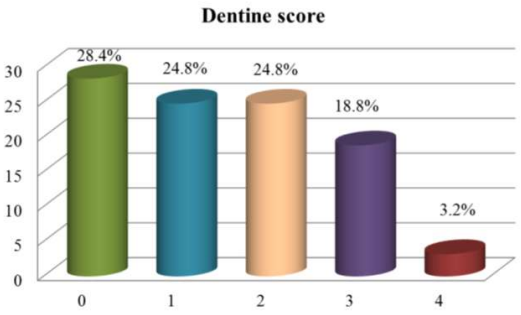
Table No. 01: The age of the children studied was 5 to 15 years, with the mean age of the children being 9.34 +- 3.45 years. The anthropometric evaluation showed an average body mass index (BMI) of 17.29 +- 2.78 /m2, and the mean Mid-Upper Arm Circumference (MUAC) was 14.89 +- 3.92 cm, and oddly enough, the growth patterns in terms of body mass index and Mid-Upper Arm Circumference are generally lean and quite typical of this age group. Biochemical examination showed a mean level of serum calcium was 6.89 +- 1.20 mg/dL below the normal range of pediatric level, and a mean of Parathyroid hormone (PTH) concentration was 10.89 +- 2.87 pg/mL. Mean levels of serum sodium and potassium were 135.00 +- 3.31 mmol/L and 3.23 +- 0.69 mmol/L, respectively, were almost at the lower end of the normal range and the mean level of magnesium was 1.65 +- 0.43 mg/dL. Renal markers of function indicated a mean urea level of 30.65 +- 12.05 mg/dl and a mean creatinine of 0.32 +- 0.12mg/dl, which were within normal pediatric limits. Also, the average serum level of iron was 133.80 +- 3.32mg/dl, folic acid was 3.43 +- 0.83 ng/mL, and vitamin D was very low at 1.89 +- 0.54 ng/mL

Graph No. 1 indicates that the dentine scores were between 0 and 4, and this represented the different levels of dentine involvement. The greatest percentage of the children (28.4) had a dentine score of 0, which implies that no evidence of dentine defects was detected. The scores of 1 and 2 were both standard, with 24.8 percent of children having each score, which are considered mild dentine changes in almost half of the sample. A dentine score of 3, which was more severe dentine changes, was found in 18.8 percent of the participants. The proportion of children with the most severe dentine involvement of 4 was the lowest at only 3.2% Graph No. 2: Study of the pattern of tooth eruption in the study participants showed that there was a significantly high percentage of delayed eruption. A total of 250 children were found to have delayed tooth eruption, with only 221 children (88.4%) having delayed eruption, with only 29 children (11.6) showing no delay. Graph No. 3: Study of the pattern of tooth eruption in the study participants showed that there was a significantly high percentage of delayed eruption. A total of 250 children were found to have delayed tooth eruption, with only 221 children (88.4%) having delayed eruption, with only 29 children (11.6) showing no delay. These results indicate that the delayed eruption of teeth was a significant clinical observation in the cohort of the study. The present high frequency can indicate that it is related to some underlying disturbances in mineral metabolism, nutritional deficiencies, or hormonal causes. Table No. 2, the comparative analysis of the biochemical parameters of children with and without delayed tooth eruption, indicated the significant difference in the main indicators of mineral metabolism. The mean serum calcium level (7.97 +- 0.50 mg/dL) of children with delayed eruption (n = 29) was found to be lower than that of those without delay (8.09 +- 1.16 mg/dL), and the difference between them was statistically significant ($p = 0.001$). Also, the mean parathyroid hormone (PTH) level (21.11 +- 24.35 pg/mL) was significantly higher in the delayed eruption group ($p = 0.021$), although it was also significantly higher in the non-delay group (9.11 +- 2.62 pg/mL). Though there was no significant difference between means of serum magnesium levels between groups ($p = 0.065$), children with delayed eruption were found to have higher mean serum iron levels (122.21 +- 10.91 ug/dL) than those with no delay (97.78 +- 31.76 ug/dL), which was significantly different ($p = 0.001$). The differences in the levels of folic acid and vitamin D did not make a significant difference between the two groups ($p = 0.674$ and $p = 0.563$, respectively).

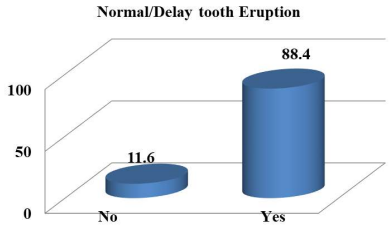
Table 01: Descriptive Analysis of Study Population

Variable	Mean ± SD
AGE	9.340 ± 3.45
BMI	17.29 ± 2.78
MUAC	14.89 ± 3.92
SERUM CALCIUM	6.89 ± 1.2
PARATHYROID HORMONE	10.89 ± 2.87
SODIUM	135.00 ± 3.31
POTASSIUM	3.23 ± 0.69
MAGNISUM	1.650 ± 0.43
UREA	30.65 ± 12.05
CREATNINE	0.32 ± 0.12
IRON	1.33.80 ± 3.32
FOLIC ACID	3.43 ± 0.83
VIATMIN D	1.89 ± 0.54

Graph 01: Dentine Score of the Participants



Graph 2: Delayed Tooth Eruption



Graph 3: Relationship between Parathyroid Hormone and Serum Calcium

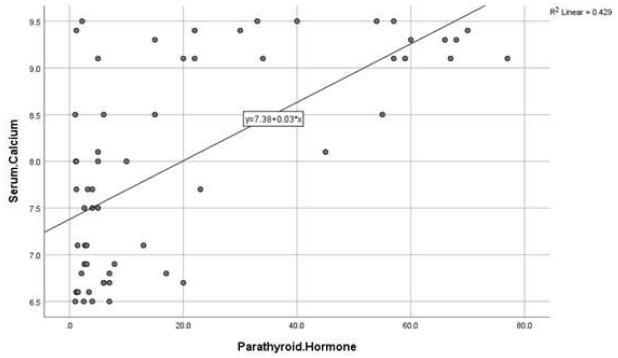


Table 2: Biochemical Variables and Delayed Tooth Eruption

Variables	Delay Eruption	N	Mean	Std.	p-value
Serum calcium	Yes	29	7.966	.5012	0.001
	No	221	8.086	1.1592	
Parathyroid hormone	Yes	29	21.106	24.3460	0.021
	No	221	9.106	2.6186	
Serum magnesium	Yes	29	1.745	.4306	0.065
	No	221	1.751	.3313	
Serum Iron	Yes	29	122.207	10.9067	0.001
	No	221	97.783	31.7632	
Folic acid	Yes	29	9.328	2.5112	0.674
	No	221	7.352	2.6772	
Vitamin D	Yes	29	37.655	3.4875	0.563
	No	221	35.801	4.0571	

DISCUSSION:

This study evaluated how mineral metabolism disruptions are linked to the retarded eruption of teeth among children between the ages of 5-15 years. The average serum calcium concentration of the participants (6.89 +- 1.20 mg/dL) was lower than the normal pediatric range. Conversely, the average parathyroid hormone (PTH) level (10.89 +- 2.87 pg/mL) was a sign of the body adjusting itself to calcium homeostasis by compensatory mechanisms. The results are in line with this latest research, which has reported that chronic hypocalcemia, frequently coupled with either subclinical or overt vitamin D deficiency, causes a considerable amount of alteration to odontogenesis and tooth eruption in children.

The average serum vitamin D content in the present study (1.89 -0.54 ngs/mL) was significantly low, and this is in line with the national and global data showing that a large proportion of children in South Asia. Vitamin D deficiency and this deficiency triggers PTH to be released and resultantly mineralization process, without which children cannot have their dentine and enamel erupt and form normally.

The anthropometric measurements of our cohort, such as BMI (17.29 +- 2.78kg/m2) and MUAC (14.89 +- 3.92 cm), reflected fairly lean and not severely malnourished patterns of growth. This implies that macronutrient levels are possibly okay, but there is a problem with the specific micronutrient deficiencies, especially calcium and vitamin D, which are potentially causing stunted odontogenesis. The rest of the biochemical parameters, sodium, potassium, magnesium, urea, and creatinine, were within normal ranges, which ruled out the possibility of any significant renal or systemic disease leading to a secondary effect on mineral metabolism.

These results highlight the role of early biochemical screening and specific nutritional interventions. The current research has been associated with the effectiveness of vitamin D and calcium supplementation in correcting the state of hypocalcemia and dental outcomes in children at risk. Public health policies that emphasize dietary education, regular pediatric screening, and fortified food programs can help decrease the rate of mineral metabolism disorders and associated effects on oral health.

The frequencies of dentine scores in this group of people give invaluable information about the clinical presentation of the disturbance of mineral metabolism and nutritional deficiencies in other groups of work. Although a dentine score of 0 (perfect dentine) is shown by 28.4% of the children, almost half of them had mild defects (scores 1 and 2, 24.8 and 24.8, respectively), and a considerable proportion of respondents had moderate (score 3, 18.8) and severe tooth defects (score 4, 3.2). This trend is generally in agreement with the other studies that have found a correlation between differences in the status of calcium and vitamin D and the degree of dentine and enamel hypomineralization.

The moderate to severe dentine defects seen in more than one-fifth of the children imply that alterations in mineral homeostasis, e.g. hypocalcemia and hypovitaminosis D recorded in the biochemical analysis, may have a direct effect on dentine matrix formation and mineralisation.4 and the relatively high prevalence of mild dentine changes might be due to chronic subclinical deficiencies or marginal hormone imbalances, e.g. high levels of parathyroid hormone (PTH) as seen in the study, and this would adverse .

These results highlight the complexity of the etiology of dentine defects, which concerns not only those at the systemic nutritional level, but also the local developmental processes. Their afterthought is the significance of screening and early intervention on the dietary habits because even slight or moderate changes in the dentine may predispose the children to caries, sensitivities, and long-term dental-related complications.

The fact that there was a significantly high proportion of delayed tooth eruption in this cohort, with 88.4% of the participants affected by the condition, brings to attention the importance of the possibility of systemic factors influencing the dental development of children. This is an

excessive frequency because the frequency normally reported in population-based studies is between 6 and 15 per cent, implying that kids who visit these dental outpatient and pediatric clinics are a very vulnerable population. This observation is consistent with the biochemical evidence of the study that proved that there was a high level of hypocalcemia, serious vitamin D deficiency, and high levels of parathyroid hormone (PTH). These interruptions may damage the activity of odontoblasts and mineralisation of enamel, slowing down eruption.

Besides, the risk has been suggested to be increased by the combined effect of chronic hypovitaminiosis D and secondary hyperparathyroidism, which has been reported to be the cause of delay in tooth eruption and dentofacial malformation in various children's studies.18 The nutritional contribution to the risk, due to the adequacy of nutrition in dental follicle formation and eruption pathway resorption, is further suggested by the borderline BMI, MUAC, and low folic acid levels of the sample. The nutritional contribution to the risk, due to the adequacy of nutrition in dental follicle formation and eruption pathway resorption, is further suggested by the borderline BMI, MUAC, and low folic acid levels of the sample.

Altogether, these results point to the conclusion that delayed eruption is not a local dental problem only, but it is likely to be a manifestation of systemic disturbances in mineral metabolism and nutrition. This highlights the significance of interdisciplinary screening, such as the use of biochemical measures, in the assessment of pediatric patients with a delay of eruption, in order to detect and treat possible reversible systemic factors.

The fact that the regression equation as $y = 7.38 + 0.03x$, has a coefficient of determination $(R2) = 0.429$, suggests that about 42.9 percent of the variation in the level of serum calcium can be explained by the difference in the level of parathyroid hormone among the study participants. This observation conforms to known physiological mechanisms where PTH is central in ensuring calcium homeostasis by enhancing bone resorption, renal calcium reabsorption, and the stimulation of vitamin D activation. The given trend, in which the increase in serum calcium was observed to be correlated with the increased levels of PTH, is indicative of a compensatory mechanism expected of secondary hyperparathyroidism, which is usually activated by chronic cases of hypocalcemia or vitamin D deficiency

The biochemical parameters comparison between children who experience delayed tooth eruption and those who do not gives additional support to the fact that mineral metabolism disruptions are the factors that contribute to the odontogenesis stunting. True to their name, children with delayed eruption showed a much lower average serum calcium level (7.97 +- 0.50 mg/dl) and much higher average parathyroid hormone (PTH) levels (21.11 +- 24.35 pg/ml), respectively, with p-values (0.001, 0.021) of 0.001 and 0.021. Such results are also aligned with the physiological process in which chronic hypocalcemia stimulates secondary hyperparathyroidism, whereby PTH release is augmented to reestablish calcium homeostasis. Although high levels of PTH may also stimulate bone resorption and alter the eruption cycles of dental follicle tissues, this may disrupt normal tooth development.

Interestingly, the mean levels of serum magnesium did not significantly differ, but the delayed eruption group had strongly elevated serum iron levels ($p = 0.001$). This is contrary to certain reports in which iron deficiency is associated with delayed eruption. This could be due to an increase in serum iron levels that could be related to dietary habits, supplementation, or inflammatory processes, but further research is needed to bring an understanding to this relationship.

The differences in the folic acid and vitamin D levels between groups were not statistically significant. Nevertheless, the overall average vitamin D content was significantly low in the cohort, in line with hypovitaminosis D as a background factor. The reported biochemical pattern supports the idea that a delay in eruption in the pediatric population is multifactorial, although reduced serum calcium and compensatory PTH raise seems to be the primary mechanisms that disrupt the eruption of teeth and mineralisation promptly.

The results highlight the clinical relevance of early biochemical evaluation in children with delayed eruption that allows specific interventions, including calcium and vitamin D supplementation, to bring the eruption on track and possibly enhance the dental outcomes.

The cross-sectional design limits causal inference between mineral imbalance and delayed tooth eruption. As the study was conducted at a single center using non-probability sampling, the findings may not be generalizable to the broader pediatric population. Dietary intake, sun exposure, socioeconomic status, and supplementation history were not assessed and may have acted as confounding factors. Biochemical parameters were measured at a single time point, which may not reflect long-term mineral status. In addition, dental eruption was assessed clinically without radiographic confirmation, which could have affected measurement precision.

CONCLUSION:

This cross-sectional study demonstrates that delayed tooth eruption in children is strongly associated with disturbances in mineral metabolism, particularly hypocalcemia accompanied by elevated parathyroid hormone levels. The high prevalence of delayed eruption observed in this cohort underscores that dental developmental delay is not merely a local oral finding but often reflects underlying systemic and biochemical imbalance. The consistent finding of low serum calcium with compensatory PTH elevation supports

the role of secondary hyperparathyroidism in altering normal odontogenesis and eruption pathways.

Although severe hypovitaminosis D was common across the study population, its lack of significant difference between children with and without delayed eruption suggests that calcium–PTH dynamics play a more direct role in eruption timing than vitamin D status alone in this setting. The presence of mild to severe dentine defects in a substantial proportion of participants further reinforces the impact of chronic mineral imbalance on dentine formation and mineralization.

Taken together, these findings highlight the importance of integrating biochemical evaluation into the assessment of children presenting with delayed tooth eruption. Early identification of hypocalcemia and related hormonal changes may allow timely nutritional and medical interventions, potentially improving dental development and broader skeletal outcomes. Interdisciplinary collaboration between pediatricians and dental practitioners is essential to address these reversible systemic factors and to reduce long-term oral health complications in vulnerable pediatric populations.

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Shakil Ahmed Shaikh: Critical Analysis, final approval
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Aqeela Memon: Data Collection
Kalsoom Jawed: Data Analysis
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Hira Saeed Khan: Write up, data analysis

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Original Article **Open Access**

Relationship between Vitamin D Level and Recurrent Wheezy Chest in Pediatric Patients

Ikram Ullah, Sabir Khan, Zia Muhammad, Muhamamd Shabir, Aimal Khan. Arooj Khan

Abstract

Objective: To determine the association between serum vitamin D deficiency and recurrent wheezy chest in children aged 6-36 months.

Study Design and Setting: This case-control study was conducted at the Department of Paediatrics. Khyber Teaching Hospital, Peshawar, from August 2024 to February 2025.

Methodology: Seventy children (35 cases with =3 wheezing episodes in the last year; 35 age-matched controls without wheeze) were evaluated. They were enrolled after excluding those with chronic lung disease, allergies, or recent vitamin D supplementation. Serum 25-OH-vitamin D <20 ng/mL defined deficiency. The sample size was calculated to have 80% power and an á = 0.05. Data was analysed with IBM SPSS 25.0; an independent t-test and X2 test were applied; association was quantified by odds ratio (OR) with CI 95%.

Results: Mean age was 16.7 ± 7.0 D in cases (18.8 ± 5.9 ng/mL) was lower than in controls (23.6 ± 5.8 ng/mL; p = 0.001). Vitamin D deficiency was present in 66% cases versus 37% controls (p = 0.017). Children with deficiency had 3.24-fold higher odds ratio of recurrent wheeze (95% CI 1.28-8.21; p = 0.013).

Conclusion: Vitamin D deficiency is significantly associated with recurrent wheezy chest in early childhood. Screening and supplementation may decrease the wheezing burden in this age group.

Keywords: Paediatrics, Vitamin D deficiency, wheezing

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INTRODUCTION:

Childhood respiratory diseases caused by viruses can be classified in many ways depending on the primary manifestations, like acute bronchochiolitis, viral infections of the lower respiratory tract (LRTA), acute viral bronchitis, viral pneumonia, persistent, transient, or nonspecific and /or virally induced wheezing, and asthma exacerbation.[1] Wheezing in children is an acute breathing symptom marked by whistling during breathing, which most usually occurs while exhaling.[2] Wheezing is usually caused by obstruction or narrowing of the respiratory passages and can be related to a variety of conditions, including mild viral infections and long-term diseases such as asthma.[3] Wheezing in children is most usually caused by viral infections in the form of colds, but wheezing can be caused by environmental factors such as allergies to compounds in the environment, parental smoking, and atmospheric pollution.[4] Repeated wheezing over time is known as recurrent wheezing, and it is particularly concerning because wheezing can be a sign of developing asthma or other long-term respiratory difficulties in children. To effectively treat wheeze and prevent recurring episodes, it is vital to identify the underlying conditions that cause wheezing.[5] Recurrent wheeze in children has been linked to an interaction of genetic, environmental, and immunologic factors.[6] Wheezing is more common in children from allergic or asthmatic families, implying an underlying propensity.[7] Allergens in the environment, like dust mites, cat dander, and pollen, irritants such as secondhand smoking, and indoor pollutants

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cause wheezing by inflaming and hyperreactivity of tissues in the respiratory tract.[8]

The epidemiological data show that wheezing is reported in nearly 30% of children 3 years of age and significantly affects their overall health status [9]

The pathophysiology of recurrent wheezy chest is complex, and its mechanism is related to multiple immunological and environmental factors. The common causes of wheezing are asthma, viral bronchiolitis, and allergic airway diseases; however, acute respiratory tract infections are the most frequent cause. In infancy and early childhood, viruses can trigger various respiratory conditions, including viral bronchitis, bronchiolitis, pneumonia, and asthma exacerbations.[10]

While working on recurrent wheezy chest, nutritional status has been given attention as a leading risk factor. The researchers have more specifically focused on the significance of vitamin D as a modulator of immune response and respiratory health and found it as a pivotal immunoregulatory molecule.[11]

Numerous immune cells have vitamin D receptors. When 1, 25-dihydroxyvitamin D attaches to its receptor, it starts an immunological cascade and preserves the delicate equilibrium between humoral (Th2) and cellular (Th1) immune responses. Thus, Vitamin D boosts innate immunity (through macrophage function) by promoting bacterial elimination and regulating adaptive immunity (through lymphocyte regulation) to reduce inflammation. Vitamin D deficiency can, thereby, affect the Th1/Th2 cytokines balance and increase autoimmunity. Enhancing the immune defence of Vitamin D by enabling macrophages to produce antimicrobial peptides, particularly cathelicidin, ultimately helps to fight respiratory pathogens [12]

Vitamin D appears essential for good lung function, while recent studies have repeatedly shown a robust connection between it and overall respiratory well-being, especially in children worldwide. The implications of this deficiency have now been mentioned, extending beyond skeletal health, and it is linked to a range of chronic and acute illnesses related to respiration, including infections, asthma exacerbations, and recurrent wheezy chest.[13]

Considering these results, the study on the protective effect of vitamin D levels in recurrent wheezing of the chest is an area of interest for further research. This is particularly crucial in our area where vitamin D deficiency is widespread among children, and there is a significant number of pediatric patients presenting with wheezing chest. The purpose of this study was to look at the connection between vitamin D insufficiency and recurrent wheezy chest in children, with a particular emphasis on the relationship between vitamin D levels and recurrent wheezy chest. The results of this study will help our paediatricians treat children who frequently have chest wheezing episodes.

METHODOLOGY:

This case-control study was conducted over 6 months from August 2024 to February 2025 at the Department of Paediatrics, Khyber Teaching Hospital, Peshawar, Pakistan. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the hospital with Reference No. 747/DME/KMC, ensuring compliance with ethical standards for human research.

The sample size was calculated using OpenEpi software, based on anticipated proportions of vitamin D deficiency among pediatric patients aged 6 months to 3 years with and without recurrent wheeze. Assuming a prevalence of vitamin D deficiency of 73.8% in children with recurrent wheeze (Group 1) and 39.34% in those without in Group 2, with a two-sided á = 0.05 and 80% statistical power, the minimum required sample size was calculated to be 35 participants in each group.

A total of 70 children aged 6 months to 3 years were included using consecutive sampling.

Formula:

$N = (Z_{1-a/2}v(2p(1-p)) + Z_{power}v(p1(1-p1)+p2(1-p2))^2/(p1-p2)^2$

In this formula

$\bar{p} = (0.738 + 0.3934)/2 = 0.5657$

$Z_{1-á/2} = 1.95$

$Z_{power} = 0.841$

After computing the values, 31.3 study participants per group were found. Sample size should be a whole number; we rounded it up to 32 per group (total 64). 35 per group is conservative and reasonable, which is why we selected 35 per group (70).

The case group comprised 35 children with a history of recurrent wheezing, defined as three or more wheezing episodes in the past year, each lasting longer than 24 hours. Diagnosis was confirmed through clinical examinations and parental or medical history. The control group consisted of 35 children, age-matched with no prior history of wheezing. Children with pre-existing pulmonary conditions, documented allergic diseases, or recent vitamin D supplementation (within the past 3 months were excluded from the study. Written informed consent was taken from the parents or legal guardians of all study participants before enrollment.

In the study, detailed demographic and clinical data were collected for each study participant, including age, sex, nutritional status, and relevant medical history. A comprehensive physical examination was performed, with special attention to respiratory outcomes.[14] Venous blood samples (2mL) were collected under aseptic conditions to measure serum 25-hydroxyvitamin D [25(OH)D] levels using chemiluminescent immunoassay. Vitamin D deficiency was defined as serum 25(OH)D levels <20 ng/mL, in accordance with the Endocrine Society guidelines. [15]

Data was analysed using IBM SPSS 25.0. Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed data were presented as mean and standard deviation (SD), while non-normally distributed data were presented as median and interquartile range (IQR). Frequencies and percentages were found for categorical variables. Differences between groups were assessed using the independent samples t-test for continuous variables. The association between vitamin D deficiency and recurrent wheeze was quantified using odds ratios with 95% CI. A p-value of less than 0.05 was considered statistically significant.

DISCUSSION

Vitamin D is crucial for immune system regulation and pulmonary health conditions, and deficiency has been associated with causing wheezing in children under five. A study conducted in Pakistan by Naseem and her team revealed that an increased prevalence of deficiency of vitamin D and deficiency in wheezing children, with 27.4 percent deficient and 30.5 percent insufficient. This was most probably attributed to improvement in outdoor games and sunlight exposure in young children, which resulted in greater vitamin D production. His gender variation, in which males had a higher proportion of adequate vitamin D while females had a higher proportion of insufficient vitamin D, can be attributed to differences in outdoor games, clothing and exposure to sunlight. Socioeconomic factor status was a distinct variable of status in vitamin D, with pediatrics in poorer families having the highest proportion of deficiency due to inadequate dietary intake, minimal exposure to light, and limited access to medical centers.[16]

Naseem et al.'s [16] study outcomes revealed that a mean vitamin D concentration of 26.93 ± 9.36 ng per mL, with 27.4 percent deficient, 30.5 percent insufficient, and 42.1 percent sufficient. This study was recommended by Pechanha et al., [17] finding that pediatric patients who wheeze have a higher prevalence of 57.3 percent of vitamin D deficiency or insufficiency. Another study, Khan et al.[18], found that 73.8 percent of pediatric wheezers had insufficient vitamin D levels, with a mean concentration of 16.87 ± 4.9 ng per mL, considerably lower than controls 27.23 ± 3.1 ng per mL, with a p-value of 0.001. A study conducted by Prasad et al.[19] found that wheezing in children with vitamin D deficiency was more severe, with only 23 percent having levels below 5 ng per mL. This can be attributed to variation in geographic regions, exposure to sunlight, dietary patterns, and vitamin D metabolism among people. Contrary to this study, where 42.1 % of pediatrics had an optimal vitamin D concentration, Pechanha et al.[17] observed lower rates in children who are not wheezing. This can be caused by differences in the criteria applied to define deficiency in these studies, as well as differences in the concentration calculation techniques.

Our study found that low socioeconomic status was a strong predictor of recurrent wheezing condition, showing that those children who are from economically not good backgrounds are far more likely to have recurring episodes than those children who belong to higher socioeconomic family backgrounds. Contrary to this, the breastfeeding period, when categorised as less than 1 year vs. one year or more than one year, did not demonstrate a statistically meaningful association with recurrent wheeze within this study, indicating that variables other than infant feeding habits may play a more crucial role in this condition. In the study conducted by Naseem et al.[16], children from low-income families had the highest prevalence of vitamin D deficiency, 55.9%, while children from high-income families had better vitamin D status, 87.5 % with a significant p-value of 0.001. This study is comparable to a study conducted by Pecanha et al.[17] who found that vitamin D deficiency was substantially associated with environmental pollution and lower socioeconomic status of children. Furthermore, a study conducted by Prasad et al.[19] emphasised that exclusive breastfeeding after 6 months, as well as delayed initiation to complementary feeding after 6 months, predicted vitamin D insufficiency and higher wheeze risk indirectly. Low consumption of vitamin D-containing foods, as well as reduced access to health-based services in low-income households, can help explain these outcomes.

Age differences in vitamin D status were also found in a study conducted by Naseem et al. 16 study, where infants

Table 1: Demographics of the Study Participants (n=70)

Demographic Variable	Study Group (n=35)	Control Group (n=35)	p-value
Age (Mean ± SD) months	16.23 ± 6.66	17.14 ± 7.38	0.581
Gender			
Male n (%)	16 (45.7%)	18 (51.4%)	0.814
Female n (%)	19 (54.3%)	17 (48.6%)	
Socioeconomic Status			
High n (%)	8 (22.9%)	6 (17.1%)	0.463
Medium n (%)	14 (40.0%)	13 (37.1%)	
Low n (%)	13 (37.1%)	16 (45.7%)	
Breastfeeding (Mean ± SD) months	13.77 ± 5.48	14.54 ± 4.90	0.528

Figure 1: Gender Distribution in Study & Control Groups

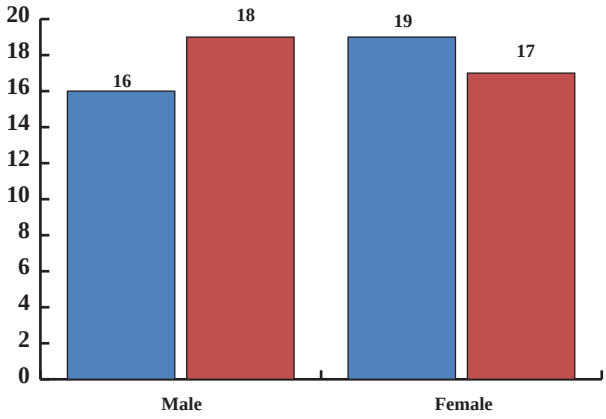

Table 2: Status of Vitamin D Levels and Deficiency (n=70)

Parameter	Study Group (n=35)	Control Group (n=35)	p-value
Vitamin D Level (Mean ± SD) ng/mL	18.77 ± 5.89	23.59 ± 5.78	0.001
Vitamin D Deficiency (<20 ng/mL)			
Yes n (%) No n (%)	23 (65.7%) 12 (34.3%)	13 (37.1%) 22 (62.9%)	0.017

Table 3: Univariate Analysis of Factors Associated with Recurrent Wheezy Chest

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Vitamin D Deficiency	3.24	1.28 - 8.21	0.013
Low Socioeconomic Status	3.50	1.23 - 9.97	0.019
Breastfeeding <12 Months	1.17	0.47 - 2.89	0.735

and children aged from two to three years had a higher percentage, 35.4% than children aged 4-5 years, who had a higher percentage than children aged 2 to 3 years (59.6%) with p=0.003. Another study conducted by Hodiatska et al.[20] found that children aged 6 months to 3 years of age had a 75 percent prevalence of vitamin D deficiency, which was associated with an exponential rise in wheezing recurrence with an odds ratio (OR= 4.3 with a 95% confidence interval 2.75 to 6.86 and with a significant probability value. This represents that young children are more vulnerable because of less dietary intake, less outdoor activities during this duration, increased infections related to the hospital, and thus less exposure to light.

The children in our study were approximately 16.7 months old, with ages ranging from 6 to 36 months. The sample consisted of approximately the same number of males (34) and females (36). Laboratory analysis revealed that the study group's vitamin D levels were considerably lower than those of the control groups (18.77±5.89 ng/ml vs. 23.59 ± 5.78 ng/ml, p=0.001). In a similar vein, the study group experienced a considerably greater prevalence of vitamin D deficiency than the control group (66% vs. 37%, p=0.017). The authors concluded that using vitamin D supplements could help prevent COVID-19. Additionally, the data indicated a high correlation between repeated wheezy chest and vitamin D deficiency (OR = 3.24, 95% CI: 1.28-8.21, p = 0.013). Additionally, the data indicated a high correlation between repeated wheezy chest and vitamin D deficiency (OR = 3.24, 95% CI: 1.28-8.21, p = 0.013).

The likelihood of recurrent wheeze in preschoolers who needed corticosteroid dosages was connected to vitamin D insufficiency in a previous study on the subject conducted in the United States by Beigelman A. 264 children, whose average age was 35 months, participated in the study. The children who had vitamin D levels below 20 ng/ml had more frequent and severe wheezing episodes. Keeping blood vitamin D levels over 20 ng/ml may reduce the likelihood of exacerbations in young children, according to the study's findings.[21]

Khan compared children with recurrent wheeze to age-matched controls to investigate the relationship between vitamin D levels in the blood and recurrent wheezing in kids as young as three years old. Children who frequently wheezed in their chest had much lower vitamin D levels than a control group, according to an Indian study (73.8% vs. 39.34%, p=0.001). These results strongly showed that recurring wheezy chests in young children are associated with vitamin D insufficiency.[18] Osman NS et al.[22] looked at the link between the frequency and intensity of wheezing episodes and the serum vitamin D levels of preschool-aged children who reported having RWC. 53% of participants with 100 children who had at least three recorded wheezing episodes in the past year had low vitamin D levels (32% deficient, 21% insufficient). Compared to children who did not have adequate vitamin D, those who did had fewer symptoms of wheezing in their chests (p<0.025). Vitamin D levels, recurrent wheezing episodes, and the severity of asthma were found to be significantly inversely correlated (r=-0.334, p=0.001).

El fiki OA et al.[23] worked on the subject in preschool children with a mean age of 3.63±1.1 years. The results showed that children with daytime symptoms of wheezing had significantly lower mean vitamin D levels compared to those without it (9.37±2.75 ng/mL Vs 15.59±6.23 ng/mL, p<0.001). Similarly, patients with nighttime awakenings showed markedly lower vitamin D levels than those without it (12.18±5.54 ng/mL vs 21.45±0.07 ng/mL, p<0.001). A similar strong association was also found between Vitamin D levels and recurrent wheezing in a study performed in

Pakistan by Hussain M et al (13.90±4.63 ng/mL Vs 25.90±7.57 ng/mL, p= 0.02).[24]

In 2024, a study conducted by Feketea G. involved 40 children with wheezing and 16 individuals without any respiratory issues. The findings revealed that children with recurrent wheezing had significantly lower levels of vitamin D compared to those who had experienced wheezing for the first time and those without any wheezing. The research findings indicated that a higher prevalence of vitamin D deficiency was observed in individuals with recurrent wheezing, implying a substantial association between vitamin D and the recurrence of wheezing.[25] Our results are consistent with previous studies in this area and demonstrate a strong association between vitamin D levels and repeated wheezing in children under the age of 3 years. This study's limited sample size was one of its main limitations. Future studies involving more participants will validate these preliminary findings in our local population.

The case-control design indicates an association, but not causation, between vitamin D deficiency and recurrent wheeze. The single-centre sample size may restrict the applicability of the findings. The results could be affected by residual confounding from unmeasured factors such as sunlight exposure, dietary habits, and atopy history. The definition of recurrent wheezing was based on parental recall and clinical history, which is prone to reporting bias. A single measurement of serum vitamin D might not accurately represent the participants' long-term vitamin D levels.

CONCLUSION

This study highlights that a lack of vitamin D is a significant risk factor for recurring wheezy chest in early childhood. Furthermore, a low socioeconomic position was recognised as a significant contributor to the disease. These findings highlight the need to take nutritional and socioeconomic factors into account when treating pediatric respiratory health issues. Screening for vitamin D deficiency in young infants with recurrent wheeze, combined with public health initiatives that address nutritional support for at-risk populations, could be critical strategies for reducing the burden of wheezing disorders in this vulnerable age group.

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Authors Contribution:
Ikram Ullah: Conceptualization, final review, final investigation
Sabir Khan: Writing and review of manuscript
Zia Muhammad: Review and editing
Muhamamd Shabir: Data Collection
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Arooj Khan: Data acquisition and editing

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Depression, Anxiety, and Stress in Beta Thalassemia Patient in Comparison to Siblings

Ahsan Ali Shaikh, Muhammad Ahmad, Khurram Fayyaz, Inshal Jawed, Abu Huraira Bin Gulzar, Saira Zubair

Abstract

Objective: Our study assessed psychological outcomes and health-related quality of life (HRQoL) in transfusion-dependent â-thalassemia patients as compared to their siblings in Pakistan, and identified whether stress and the frequency of transfusions are independent predictors of physical functioning in thalassemia patients.

Study Design and Setting: This analytical cross-sectional survey was conducted at PNS Shifa Hospital, Karachi (January-July 2025).

Methodology: 70 patients aged between 7 and 25 years of confirmed â-thalassemia major, intermedia, or minor were enrolled. Standardized scales have been used: PHQ-9, GAD-7, PSS-10, and SF-12. Mann-Whitney, Kruskal-Wallis, t-tests, and ANOVA were used where appropriate, and a hierarchical linear regression modeled predictor of PCS-12.

Results: The study included 70 patients with transfusion-dependent thalassemia (mean age, 13.4±2.67; 58.6% males), with 78.6% of them having â-thalassemia major. No significant difference was found between the psychological outcomes of the patients as compared to their siblings ($p > 0.05$). The higher the frequency of transfusion, the higher the depression, anxiety, stress, and the lower the mental HRQoL($p<0.05$). In multivariable analyses, stress had an independent relationship to lower PCS-12 (beta=-0.383, $p=0.009$). Perceived stress (beta= -0.511, $p<0.001$) and worse mental HRQoL (beta= -0.433, $p<0.001$) explained 42.7 percent of the variance in PCS-12. When stress was entered alone, it accounted for 27 percent of PCS-12 variance (0.607, $p<0.001$).

Conclusion: Transfusion-related perceived stress appears to be the strongest psychosocial determinant of physical functioning, which undermines mental HRQoL. Moreover, the patients and their families were affected equally. Thus, stress-sensitive care models are required in addition to biomedical monitoring in Pakistan.

Keywords: beta-Thalassemia, Mental Health, Physical Health, Psychological outcomes

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INTRODUCTION

The β-thalassemia, the set of recessive inherited diseases of globin-chain production, remains a significant global health burden in spite of the progress in transfusion medicine and chelation therapy.[1] According to the World Health Organization (WHO), it is estimated that over 40,000 infants are born with thalassemia annually, with the vast majority of them having β-thalassemia major or intermedia.[2] A recent Global Burden of Disease study demonstrated that, over the past 30 years, the disability-adjusted life-years (DALYs) caused by thalassemia have decreased relatively little compared with other inherited anemias, highlighting the clinical and social burden of extended survival.[2] The geographical distribution of β-thalassemia is clumped around the so-called thalassemia belt, which includes some of the Mediterranean, Middle East, South-East Asia, and Indian subcontinent areas historically under malaria selective pressure. Worldwide, the percentage of carriers is about 1.5, with an estimated 60,000 infants born annually with the disease. So far, more than 350 HBB gene mutations have been reported, of which only twenty mutations contribute to 80 percent of the cases.[3] The burden is not

only in iron overload and endocrine dysfunction, but the need to attend hospitals regularly, treatment exhaustion, and stigma compromise quality of life and exert pressure on already weak health systems, particularly in low-resource countries.[4] Approximately 5-7% of the population, or more than ten million individuals, are carriers of a β-thalassemia mutation, and about 5000-6000 children with transfusion-dependent β-thalassemia are born each year.[3] Unlike the other countries in the neighborhood, which have introduced mandatory premarital screening, prevention programs in Pakistan are patchy and province-specific. Consequently, pediatric and adolescent thalassemia units in large cities are permanently overcrowded, whereas families in rural areas have to travel considerable distances to access safe blood and deferoxamine. Transfusion intervals in publicly funded centers are as low as every two weeks to reach hemoglobin targets, and this imposes repeated direct and indirect costs on households with an average monthly income of less than US$120.[3] There is no established national thalassemia prevention or registry system in Pakistan despite the high carrier rate (57 percent) and the estimated 5,000-6,000 births per year of transfusion-dependent 8-thalassemia. This disjointed landscape has led to NGOs such as the Patients Welfare Association (established in Karachi Civil Hospital) to step in to offer regular transfusions and some chelation services at no cost, albeit to a small group of needy patients.[3] Nonetheless, national guidelines pay almost no attention to psychological screening or social support based on biomedical endpoints of pre-transfusion hemoglobin and serum ferritin.[5]

Psychosocial outcomes-related information is scarce in South Asia. Although literature on Mediterranean and Southeast Asia has associated thalassemia with depression, anxiety, and poor health-related quality of life (HRQoL), cultural issues in Pakistan (such as extended families, consanguineous marriage, and gendered caregiving expectations) reduce its utility. Studies that are available tend to combine children and adults.[6] They infrequently stratify by transfusion burden and rarely measure perceived stress, which has a robust predictive association with physical health. Small qualitative reports from Pakistan suggest that the frequency of hospital visits, rather than genotype or ferritin levels, is the most disruptive factor for families, but these observations remain unquantified.[7] South Asian psychosocial data is limited, but a recent survey revealed that siblings of thalassemia patients develop mild-to-moderate levels of psychological stress, with anxiety and depression being notably common, indicating that the general care model should deal with the health of the family as a whole and not the affected individual.[8]

In this background, we carried out a cross-sectional study in Karachi to compare depression, anxiety, perceived stress, and HRQoL between transfusion-dependent β-thalassemia patients and their siblings. Our hypothesis was that perceived stress, as opposed to conventional disease measures, would best predict physical functioning and that reduced transfusion interval would worsen psychological distress in the patient and their family. In contrast to traditional markers (e.g., hemoglobin, ferritin), perceived stress, as assessed by measures such as the PSS, has been shown to have strong correlations with biological stress, mental health outcomes, and even immune and aging processes, thus supporting its utility as an indicator of physical functioning.[9] We hope to inform family-centered, stress-sensitive models of thalassemia care in Pakistan by producing locally relevant evidence.

METHODOLOGY

This was an analytical cross-sectional survey aimed at evaluating the psychosocial outcomes in β-thalassemia patients. The study was in accordance with the STROBE recommendations on observational studies.[10] The protocol was approved by the Ethical Committee PNS Shifa (ERC/2024/Paeds/133). All procedures conformed to the Declaration of Helsinki.[11] And, the data were de-identified before it left the institution for analysis. We filtered through the registry PNS Shifa and contacted people who matched the eligibility criteria. We aimed at the age group 7 to 25 years, especially encompassing late childhood and early adulthood.

The inclusion criteria were as follows: All of the patients had to be hematologically confirmed beta-thalassemia major, intermedia, or minor according to the lab reports, having a transfusion interval of 12 weeks or less during 12 months or more. Reference range of hemoglobin was set to =9 g/dL -1 at the index visit (to reduce the transient fatigue effects).[12] The patient or their parents must have the capacity to read the Urdu language or English, or to undertake an assisted interview.

Patients were excluded if they had any acute febrile illness, obvious cardiac failure, uncontrolled endocrine disease, or a known congenital or acquired cognitive delay. These conditions could introduce self-reported bias when evaluating the mental-health scores.[12] The data collection was conducted from 12-Jan-2025 to 30-July-2025 at the PNS Shifa Karachi, which is a leading care center for thalassemia patients and serves to provide transfusion and chelation therapies to the patients.

We powered the study to detect a moderate association between perceived stress (PSS-10) and physical HRQoL (SF-12 PCS), specifying ñ = 0.35 a priori. Prior work shows stress–physical HRQoL correlations that are small in healthy student samples (e.g., r ˜ -0.20), but moderate in caregiver and chronic-disease contexts (e.g., r ˜ -0.36 to -0.58), placing 0.35 within the observed mid-range. Sample size (two-sided á = 0.05; power = 0.80) was computed for a correlation test using Fisher's z and verified in GPower 3.1.[13]

A research nurse screened potential participants on the transfusion list of the day. Eligible individuals (and parents of underage individuals) were provided with an information

sheet after phlebotomy and pre-transfusion observations, and written consent (and assent in those under 18 years) was received in a confidential counselling cubicle. Self-administered questionnaires were used; illiterate respondents had their items read aloud word-for-word by the nurses to prevent interpretive bias. The mean completion time was 15 min. Clinical data (genotype and transfusion frequency) were extracted from the electronic record on the same day.

Health-related quality of life (PCS-12, MCS-12) was treated as a continuous variable to quantify overall physical functioning. This was the main endpoint for group comparisons and for regression models examining predictors of physical health. PCS-12 evaluates physical health, specifically physical activity, bodily pain, general health, and role-physical. While MCS-12 focuses on mental health, i.e., vitality, social functioning, role-emotional, and mental health. All of the 12 questions are combined using a published scoring algorithm and yield norm-based scores in the form of mean (SD), where a higher score is better, while scores below 50 reflect worse-than-average health relative to norms. Depression (PHQ-9) analyzed the depression symptoms based on nine questions, each scored between 0 ("not at all") to 3 ("nearly every day"). Finally, scores are summed (0–27). A higher score means more depressive symptoms. According to the conventional bands, 0–4 is regarded as minimal, 5–9 as mild, 10–14 as moderate, 15–19 as moderately severe, and 20–27 as severe. Anxiety (GAD-7) was used to evaluate the anxiety burden using the seven items, each scored 0–3; the total range is 0–21, where higher totals mean greater anxiety. Clinically relevant readings included 5 (mild), 10 (moderate), and 15 (severe). Perceived stress (PSS-10) measured the stress that is evaluated based on how unpredictable or overwhelmed a person feels. It is based on the 10-score items, each ranging from 0-4 ("never" to "very often") with a total score of 0-40. A value of lower than 14 is considered low, between 14 and 26 (moderate), and higher than 27 as high.

All of the analyses were pre-specified and performed as two-sided tests at the level of significance of á =0.05. Continuous data (age; PHQ-9, GAD-7, PSS-10; SF-12 component scores) were described as mean (SD), if they were normally distributed, and as median (IQR) where they were skewed; categorical data (sex, marital status, thalassemia phenotype, transfusion interval categories) were presented as percentages, n (%). The Shapiro-Wilk test, QQ plot, and histograms were used to analyze the distribution of the data. For normal data, parametric tests were utilized (independent-samples t or one-way ANOVA) while for skewed or non-normal data, non-parametric tests (Mann-Whitney U or Kruskal-Wallis or Chi-square) were employed accordingly.

We used hierarchical linear regression to model PCS-12 (continuous) as a predictor of physical functioning to determine independent predictors of physical functioning. Predictors were added in conceptually sequential blocks: Block 1, demographics; age (years), and sex (M/F); Block 2, clinical load; thalassemia phenotype (dummy-coded with beta-thalassemia minor as reference), and transfusion interval (coded by weekly intervals); Block 3, psychological variables; PHQ-9, GAD-7, PSS-10, and MCS-12. Standardization of psychological predictors was done to bring the coefficients to a similar scale. Assumptions of the models (linearity, normality of the residuals, homoscedasticity, and multicollinearity) were thoroughly tested and found acceptable. We present standardized β coefficients, 95% CIs, p-values, and model fit (adjusted R^2). Data management, assumption diagnostics, and analysis were all carried out in IBM SPSS Statistics, version 25 (IBM Corp.).

RESULTS

Seventy transfusion-dependent β-thalassemia patients (age 7–25 y; mean 13.4 ± 2.67) and 40 accompanying siblings (mean age 15.5 ± 4.3 y) were enrolled. Males accounted for 58.6% of patients and 53.5% of siblings. Most patients had β-thalassemia major (78.6%), while siblings were unaffected. Nearly all participants in both groups were unmarried. Patients most often received transfusions every four weeks (52.2%), with intervals ranging from two to twelve weeks. Baseline sociodemographic characteristics were broadly comparable between patients and siblings [Table 1, 2].

Depression, anxiety, and stress scores were low to moderate across both groups. Among patients, mean PHQ-9 was 3.37 ± 3.47, GAD-7 was 3.58 ± 3.01, and PSS-10 was 13.91 ± 4.74. Siblings showed a similar pattern: 86.1% reported minimal depressive symptoms, 74.4% minimal anxiety, and 67.4% moderate stress. Comparison testing (Fisher's Exact) showed no statistically significant differences between

Table 01: Demographic characteristics of the â-Thalassemia patients

Demographics	â-Thalassemia Patients N (%)	Siblings N (%)
Gender		
Female	29 (41.4)	20 (46.5)
Male	41 (58.6)	23 (53.5)
Age, mean (SD)	13.4 (2.67)	15.5 (4.3)
Marital status		
Married	4 (6)	5 (11.6)
Single	66 (94)	38 (88.4)
Type of Thalassemia		
B Thalassemia Minor	5 (7.1)	-
B Thalassemia Intermediate	10 (14.3)	-
B Thalassemia Major	55 (78.6)	-
Frequency of Transfusions		
Every 2 weeks	6 (8.7)	-
Every 3 weeks	9 (13)	-
Every 4 weeks	36 (52.2)	-
Every 5 weeks	17 (24.6)	-
Every 12 weeks	1 (1.4)	-

Table 03: Mann-Whitney U test was used to evaluate the relation between Gender, age, and psychological state (PHQ-9, GAD-7, PSS scores, MCS-12, PCS-12). While the Kruskal-Wallis test was used to find the association of age, gender, psychological state with the Type of â-Thalassemia and frequency of transfusions. The table shows the reported p-values

Categories	Age	PHQ-9	GAD-7	PSS	MCS 12	PCS-12
Gender	0.211	0.559	0.758	0.943	0.95	0.335
Type of β-Thalassemia	0.968	**0.034***	0.211	**0.013***	0.875	0.928
Frequency of Transfusions	0.463	**0.041***	**0.025***	**0.008***	**0.007***	0.757

Student t test was used to evaluate the difference of means for gender in PCS-12

One way ANOVA was used to evaluate the difference of means based on thalassemia type and number of transfusions

* P-value is significant ($\alpha = 0.05$)

Table 02. Comparison of Psychological Outcomes in â-Thalassemia Patients vs. Siblings

Categories	â-Thalassemia Patients N (%)	Siblings N (%)	p-value
Stress (PSS-10)			
Low stress	25 (35.7)	14 (32.6)	0.31*
Moderate stress	41 (58.6)	29 (67.4)	
Anxiety (GAD-7)			
Minimal anxiety	47 (67.1)	32 (74.4)	0.43*
Mild anxiety	16 (22.9)	7 (16.3)	
Moderate anxiety	4 (5.7)	4 (9.3)	
Depression (PHQ-9)			
Minimal depression	57 (81.4)	37 (86.1)	0.86*
Mild depression	8 (11.4)	4 (9.3)	
Moderate depression	4 (5.7)	1 (2.3)	
Moderately severe depression	1 (1.4)	1 (2.3)	

*****Fisher's Exact Test was used to evaluate any difference between the two groups

Table 04: Multiple linear regression models predicting PCS-12 based on the predictors: Gender, Type of thalassemia, Number of Transfusions, Depression, Anxiety, Stress, and MCS-12 scores

Model 1 (Adjusted R-squared= .07)	â-coefficient	P-value
Gender	0.02	0.908
Type of â-Thalassemia	-0.13	0.374
Number of Transfusions	-0.11	0.488
Depression	-0.12	0.458
Anxiety	0.06	0.724
Stress	-0.38	**0.009***
Model 2 (Adjusted R-squared= .43)		
PHQ-9 scores	-0.02	0.871
GAD-7 scores	-0.1	0.448
PSS score	-0.51	**<0.001***
MCS-12	-0.43	**<0.001***
Model 3 (Adjusted R-squared= 0.27)		
PHQ-9 score	0.07	0.619
GAD-7 scores	0.05	0.743
PSS score	-0.61	**<0.001***

patients and siblings across depression, anxiety, stress, or HRQoL domains (all $p > 0.05$) [Table 2]. This indicates that the psychosocial burden extends beyond patients to their siblings.

No significant sex differences were observed among patients in depression, anxiety, stress, PCS-12, or MCS-12 (all $p > 0.05$). Across thalassemia major, intermedia, and minor, depressive symptoms ($p = 0.034$) and perceived stress ($p = 0.013$) differed modestly, but no significant group differences were seen for anxiety, PCS-12, or MCS-12. This suggests that while clinical phenotype influences distress modestly, the overall psychosocial profile of patients still mirrors that of their siblings. Among patients, shorter transfusion intervals were associated with higher depression ($p = 0.041$), anxiety ($p = 0.025$), stress ($p = 0.008$), and lower mental HRQoL ($p = 0.007$). PCS-12 did not differ significantly ($p = 0.757$). These findings reinforce that the psychosocial burden in patients arises more from treatment intensity than from disease biology alone. [Table 3]

Regression modeling showed that stress was the only independent predictor of poorer PCS-12 in patients ($\beta = –0.383$, $p = 0.009$). When psychological variables were entered together, perceived stress ($\beta = –0.511$, $p < 0.001$) and lower MCS-12 ($\beta = –0.433$, $p < 0.001$) explained 42.7% of the variance. Importantly, this aligns with the comparative findings: although siblings were clinically unaffected, they reported similar stress levels, highlighting stress as a shared determinant of functioning within thalassemia families [Table 4].

DISCUSSION

Our study found no difference between the psychological outcomes of the patients and their siblings. This lies in parallel to the results of Ajij M et al. 2015. They reported that thalassemia patients and their siblings scored significantly lower in the environment when compared to the control.[14] Similarly, another study highlighted that patients with transfusion-dependent thalassemia go through significant mental burden as well as economic stress. They stressed the

need for improved HRQoL care in order to have better outcomes and reduce the emotional stress bear by this group.[15] Similarly, Lodhi et al. conducted a 2025 cross-sectional study in Bhopal. They included 95 siblings of multi-transfused Thalassemia Patients aged 2 to 18, and found that more than half reported moderate perceived stress on the PSS-C, whereas low stress in the rest. Most importantly, internalizing symptoms (e.g., anxiety, depression) were positive in at least one third of them, with smaller percentages indicating attention and externalizing issues. Moreover, advanced age was a predictor of increased likelihood of internalizing pathology. Therefore, we can conclude that the siblings of transfusion-dependent thalassemia patients are not just passive observers but demonstrate measurable stress and internalizing symptoms and should be considered a vulnerable population that needs family-centered psychosocial interventions.[8]

Our study observed that both transfusion-dependent patients and their siblings had moderate stress with minimal depression and anxiety. It was consistent with the literature on chronic illnesses. As Pawlowski et al. found, people with long-term conditions experienced a higher perceived stress regardless of official psychiatric diagnosis, placing stress as a marker of perceived burden unrelated to disease.[16] In the thalassemia context, this is reflective of the constant anxiety over the availability of safe blood, the pain of accessing a vein, and hospital logistics, which are felt by both patients and their siblings visiting the care facilities. Smith et al. further emphasized the situation by reporting that the caregivers of chronically ill children never take a sigh of relief, and the anticipatory vigilance that the Pakistani siblings experience by missing school, witnessing repetitive blood transfusions, and internalizing the worsening socioeconomic remuneration of the family.[17] The concept analysis put forth by Davis elucidated stress as overload, unpredictability, and loss in coping confidence, exactly the factors that prevail in the lives of transfusion-dependent families, where uncertainties of monthly transfusions and financial toxicity dominate everyday household life.[18] Therefore, the stress scales can measure total allostatic load of the family, and the syndromal batteries are simply under-sensitive in such a cultural and developmental environment. We can infer then that the management of thalassemia cannot be patient-centered; there is the psychosocial imprint of stress on the siblings that can only be addressed with the transition to being family-centered in thalassemia transfusion programs.

Our findings indicate that shorter transfusion intervals had a consistent adverse impact on all depression, anxiety, and stress measures and MCS-12, although physical functioning (PCS-12) was largely unaffected. This implies that among those who undergo frequent transfusions, a psychosocial trace is more likely to be attributed to the logistic disturbances than to somatic deterioration. Sobota et al. (2011) found comparable results in the Thalassemia Longitudinal Cohort of adolescents and adults with transfusion-dependent thalassemia who had a considerably lower score in SF-36 mental domains than U.S. norms, with the degree of treatment intensity serving as an important predictor of impairment.[19] Among our cohort, the same pattern was found: the greater the number of transfusions per month, the clearer a decline of mental well-being was, even without any significant changes in the physical health status.

Transfusion days required an almost ten-hour investment of patients' and caregivers' time, with associated patient and caregiver fatigue, anticipatory anxiety, and caregiver strain. Notably, these destabilizations affect siblings as well, who have to miss school, wait long hours at hospitals, and bear the costs involved and the emotional burden of frequent visits. The association between frequency of transfusion, economic burden, and deterioration of HRQoL in Bangladeshi patients further confirmed our interpretation that psychosocial stress is enhanced by treatment burden in South Asia, a resource-limited region.[20] Collectively, these results position the frequency of transfusion as both a biomedical imperative and a stress-amplifier at the family level. The anticipation, pain, and disruption fuel moderate stress (but not much in the way of syndromal anxiety or depression) in patients. To siblings, this similar exposure to the disruptors means the same feelings of stress, balancing the anticipated patient-sibling disparity. Therefore, although transfusions continue to be life-saving, the psychosocial opportunity cost is high, and there is a need to intervene at a systems level, either through longer transfusion intervals, day-care models, which disrupt less, or family-centered psychosocial interventions at transfusion units.

Depressive symptoms and perceived stress were significantly less distinct in our cohort; in-between β-thalassemia phenotypes, however, there were no significant differences in PCS-12 or MCS-12. This is in agreement with Scalone et al. (2008), who observed that health-related quality of life was inferior in all phenotypes, and differences were minimized after adjusting for transfusion modality and chelation adherence.[21] Genotype, although clinically important in the administration of transfusions and iron collection risks, does not seem to be a useful surrogate measure of psychosocial burden. Despite reduced morbidity overall, β-thalassemia intermedia, due to less-routine transfusions, has a different multi-organ comorbidity burden-imposed by relative iron overload and hypercoagulability-with high rates of extramedullary hematopoiesis, skeletal deformity, and diffuse spleno-/ hepatomegaly; these long-term and unpredictable morbidities have a significant psychosocial burden.[22] In agreement with this, adults with transfusion-independent β-thalassemia intermedia report lower HRQoL than regularly transfused thalassemia major (TM), a fact that has been ascribed to shorter time since diagnosis and a higher multiplicity of complications - an

effect that may reflect on the uncertainty of care as being more disruptive than the intensity of regimented care.[23]

Our data indicate that the psychological outcomes are influenced more by the environment in which the family lives with the transfusion-dependent child than by genotype. This finding aligns with those of regional studies, including Ansari et al. (2014) in Iran, which identified that access to care and adherence to chelation and socioeconomic issues predicted mental-health outcomes much more than phenotype.[24] The findings that large genotype-specific differences in psychosocial scales are absent indicate that this is not a measurement factor but rather emphasize the involvement of the system-level stressors to which all phenotypes are exposed. In relation to policy and clinical pathway, it means that to carry out psychosocial screening should be uniform across all phenotypes of thalassemia (and not concentrated on major disease) as the patients and their siblings possess similar stress levels regardless of genotype.

In our study, we did not find any significant association between males and females in terms of depression, anxiety, stress, or HRQoL scores. This is consistent with the previous literature indicating that the gender impact in thalassemia is irregular and frequently weakened when clinical components are adjusted. A study by Sobota et al. (2011) found that the overall HRQoL among females in the Thalassemia Longitudinal Cohort is lower than in males, and those differences become insignificant after controlling for the severity of the disease itself.[19] Consistent with the findings of Scalone et al. (2008), gender was not an independent predictor of quality of life among Italian patients after considering the effects of chelation adherence and complications.[21] Ansari et al. (2014) also demonstrated no significant between-gender disparities in psychosocial measures in a regional cohort of Iran.[24] Collectively, these results indicate that the prevailing factors determining psychosocial outcomes in transfusion-dependent thalassemia are treatment intensity and clinical burden, and not biological sex.

Lastly, our sample showed low depression and anxiety scores with moderate stress. As reported earlier, in thalassemia, symptoms may be aggravated with time, possibly as a result of accumulated complications, changing social roles, and chelation fatigue, thus showing a clustering effect over time.[25] In this respect, every individual passes through a pre-transition period whereby the structured support from family, colleagues, and transfusion facility staff can help buffer the stress and cope with it better during regular transfusions. Longitudinal follow-up during the years of transition can also be significant to elucidate the paths and prevention windows. Frequent transfusions elevate perceived stress and erode mental HRQoL; stress, in turn, is the proximate predictor of diminished physical functioning. Genotype and sex are secondary once treatment intensity and service exposure are in view.

Psychosocial needs are yet to be addressed in the low-resource transfusion centers in Pakistan. Our results indicate that it is the measure of stress, not the measure of depression or anxiety, that best predicts functioning and that siblings do share this invisible load. Short stress screening could be incorporated at transfusion visits, low-cost counseling could be provided, and family-centered support models could be created, which can help in reducing this disruption. Multicentric, longitudinal studies in the future are needed in order to inform scalable, culturally sensitive interventions in a wide variety of Pakistani contexts.

Our study has several limitations. One, it had a cross-sectional design and measured the quality of life at one point in time. And patients came from one public day-care center, so the results may not be generalizable across Pakistan. Second, the sample size was limited, and some subgroups were small (e.g., β-Thalassemia intermedia, and minor). This limits power for detecting subtle differences by sex or genotype, and it widens confidence intervals. Third, our reliance on self-reported scales (PHQ-9, GAD-7, PSS-10, SF-12) introduces bias as these scales are only screening tools and do not make clinical diagnoses. Our study could not account for several confounding factors, like annual transfusion volume, pre-transfusion haemoglobin, serum ferritin level trends, chelation type, adherence/compliance of patients, endocrine complications, splenectomy status, pain scores, sleep quality, or family income. Fourth, our study also had selection bias. We enrolled patients based on convenience sampling, i.e., those who attended the day-care unit and were well enough to complete questionnaires. Moreover, our regression treated effects as additive and linear; we did not test interactions (e.g., stress × transfusion interval), so more complex relationships might be missed. Finally, we could not include qualitative interviews. Numbers tell us that stress matters; they do not tell us which parts of the care journey are most stressful.

CONCLUSION:

Our paper reports that Transfusion Dependent β-thalassemia patients show no difference in psychosocial burden in comparison with their siblings, with perceived stress as the key indicator of strength in physical functioning and HRQoL. Contrary to the depression or anxiety scores, which were much lower when measured in stress, the scores were high enough, and they alone significantly worsened the physical health. The frequency of transfusion added to this burden, highlighting how treatment logistics and not genotype or sex have the most significant impact on mental well-being. These results recontextualize the task of thalassemia care as an issue of an individual on a family scale, with disclosure of siblings as a vulnerable, yet frequently ignored, category. To achieve this, it is critical to integrate stress-sensitive screening and psychosocial support into transfusion programs to go beyond survival, to dignified survivorship in a low-resource setting.

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Original Article **Open Access**

Efficacy of Intrathecal Dexmedetomidine on Post-operative Pain Relief in General Surgical Cases

Muhammad Salman Maqbool, Fahad Zubair, Kainat Irshad, Hozaifa Iqbal

Abstract

Objectives: To compare the efficacy of intrathecal bupivacaine combined with dexmedetomidine versus bupivacaine alone in providing postoperative analgesia for patients undergoing general surgical procedures under spinal anesthesia.

Study design and setting: A single-blind interventional study was conducted by the Anesthesiology Department at Farooq Hospital (ASMC), Rawalpindi, from January 16th to December 25, 2024.

Methodology: After ethical approval from the Research Advisory Committee of Akhtar Saeed Medical College, Rawalpindi,60 patients (placed in ASA classes I-III) undergoing elective general surgical cases in spinal block were enrolled and randomized into two groups (by lottery method). Group A received intrathecal 1.5 mL hyperbaric bupivacaine 0.75% (15 mg) alone, while Group B received the same dose of bupivacaine with 5microgram dexmedetomidine. Standard ASA monitoring, preloading with isotonic crystalloids, and spinal anaesthesia at the L3–L4 level were employed using a 26-G spinal needle. Hemodynamic parameters, adverse effects and need for rescue analgesia were documented. Statistical analysis done by SPSS v26(with $p<0.05$ as significant).

Results: Demographic parameters (age, weight, BMI) were comparable between groups. Mean postoperative analgesia duration was significantly longer in the dexmedetomidine group (20.18 ± 3.48 h) compared to group B (11.78 ±1.64 h, $p < 0.05$). The dexmedetomidine group required fewer rescue opioid doses, reflecting an opioid-sparing effect.

Conclusions: Intrathecal dexmedetomidine to bupivacaine in spinal anaesthesia for general surgical cases significantly prolongs the postoperative analgesia period.

Keywords: Bupivacaine, Bromage scale, Dexmedetomidine, Lumbar puncture, Postoperative rescue analgesia

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INTRODUCTION

Spinal anaesthesia is one of the most frequently used anaesthetic approaches applied during surgery, and it provides surgical anaesthesia for lower abdominal, urological, cesarean sections, and orthopaedic surgeries, compared to general anaesthesia. It is a type of regional block in which a local anaesthetic drug is administered in the subarachnoid space.

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Spinal anaesthesia results in a block of autonomic, motor, and sensory function in the lower body.[1] General contraindications to spinal anaesthesia include the patient's refusal, coagulopathy, infection at the site of drug administration, stenotic valvular disease and increased intracranial pressure.[1] Most common injection site is either L3-4 or L4-5 interspace, and the local anaesthetic agent most commonly employed is bupivacaine; others include lidocaine, procaine, tetracaine and ropivacaine.[2]

Bupivacaine is an amide-type local anaesthetic that works by blocking voltage-gated sodium channels that propagate action potentials in nerve terminals.[2]Bupivacaine may be used alone, or other drugs can be added as adjuvants, like sufentanil, dexmedetomidine, fentanyl, epinephrine, morphine, midazolam, dexamethasone and clonidine, are added to enhance the duration of block density and for postoperative analgesia.[2]The commonly used agent as an adjunct is dexmedetomidine.[3]Dexmedetomidine is a new drug that has specificity in the targets: presynaptic alpha-2 adrenoreceptors located in the dorsal horn of the spinal cord, which causes analgesia by means of changing the intensity of synthesis of neurotransmitters.[3]

Dexmedetomidine is also administered as premedication and as an accessory in routine general anaesthesia regimen,

it acts by binding to adrenoceptors at the locus ceruleus level, and it works as an analgesic, anxiolytic and as a sedative agent.[4] These effects may be the effect of either systemic absorption/ vascular redistribution to higher brain areas, or as a result of cephalad migration in intrathecal dexmedetomidine adjuvant use.[5] Thus, dexmedetomidine administration intravenously or intrathecally prolongs spinal anaesthesia and enhances postoperative analgesia.[6]

The effectiveness of Dexmedetomidine has been noted to provide relief of postoperative pain when combined with Bupivacaine in general surgical patients. Its use with Bupivacaine also curtails the possibility of neurotoxicity.[5] It causes dose-related sedation, anxiolysis, and analgesia (spinal and supraspinal sites) with no respiratory depression, alpha-2 agonists are found to decrease anaesthetic needs, and due to their sympatholytic action, they provide hemodynamic stability during the intraoperative period.[4]The Dexmedetomidine has been further evaluated in the context of sedation and treating delirium in ventilated patients in intensive care units, as well as for procedural sedation and as an adjunct infusion during general anaesthesia, which controls emergence agitation and prevents postoperative delirium and cognitive dysfunction.[7] In a study conducted by Ayesha Shahid and colleagues in monitoring hemodynamic stability(pulse, blood pressure) for up to five minutes following endotracheal intubation, comparing lignocaine with dexmedetomidine, they noted intravenous dexmedetomidine superiority in comparison to lignocaine in the prevention of laryngoscopy pressor response.[8]

In another randomized controlled trial by Ayesha and colleagues in parturients undergoing cesarean delivery using bupivacaine 0.5% 12mg alone and with dexmedetomidine 4ug observed onset of pain postoperatively they noted that mean onset of pain in dexmedetomidine group was 364±35.6 minutes in comparison to 179 minutes in plain bupivacaine group. They concluded that dexmedetomidine as adjuvant had better efficacy in controlling postoperative pain in first six hours.[9]

Dexmedetomidine also has good analgesia with the least drug interaction. Administration of dexmedetomidine decreases the risk of shivering in postoperative anaesthetized patients. A study by Riaz, Iqbal & Salman Haider has found that this combination improves pain relief, prolongs analgesic effect, decreases opioid intake, and increases patient satisfaction. One of the main advantages of dexmedetomidine is it can increase analgesic duration. Only patients receiving bupivacaine usually need rescue analgesics at about 7 hours post-subarachnoid block. But after the addition of dexmedetomidine, the analgesic duration increases considerably, usually lasting 9 hours or longer.[10]

The postoperative pain is a major surgical complication, which can lead to morbidity, longer hospital stays, financial burden, and various complications, including respiratory in addition to psychological complications. In a study on postoperative pain outcome after surgery, they inferred that almost half of the patients suffered moderate to severe intensity of pain with a high rate of opioid consumption.[11]

The safety profile of this combination is also excellent. Notably, dexmedetomidine does not result in a higher rate of side effects like hypotension or bradycardia; furthermore, patients administered dexmedetomidine have a lower rate of side effects. Neonatal outcomes of health are unchanged, further attesting to the safety of this combination for surgical patients [8,9,10]

Clinical trials uniformly show that the addition of dexmedetomidine extends postoperative analgesic duration by about 2 to 3 hours, postpones the first demand for rescue analgesics, and dramatically minimizes pain score intensity as well as total opioid use over the initial 24 hours following surgery.[4] The reason why it is effective is that its mechanism of action as a selective alpha-2-adrenergic agonist increases spinal analgesia by blocking pain transmission at the dorsal horn and amplifying the action of local anaesthetics. At therapeutic doses (usually 5 microgram), intrathecal dexmedetomidine also possesses an excellent safety profile with low chances of hemodynamic instability or side effects like nausea, vomiting, or shivering. But higher doses have the risk of causing transient bradycardia or hypotension. A second significant advantage of dexmedetomidine is its opioid-sparing activity. Patients receiving this combination receive fewer rescue doses of opioids after the operation than those in the bupivacaine-alone group.[3,4] This decrease in opioid intake serves to reduce opioid-related side effects and results in better overall recovery. Additionally, maternal satisfaction is greater in the dexmedetomidine group with sustained pain relief and less need for supplementary analgesics. The enhanced comfort and less use of opioids allow for a generally improved postoperative course.[3]

It is imperative from the above discussion that adequate control of post-operative surgical pain is a cornerstone in patient management. The rationale for the study conducted was combining dexmedetomidine with bupivacaine intrathecally, to assess its effectiveness on improving the quality of analgesia post-operatively in patients undergoing general surgical procedures without openly increasing adverse effects, in comparison to Bupivacaine alone. As fewer studies have been conducted involving general surgical procedures (under sub-arachnoid block), this study combines orthopaedic, urological, gynaecological and infra-umbilical general surgical procedures in a teaching private hospital. Primary outcomes included postoperative analgesia duration and opioid requirement; secondary outcomes evaluated hemodynamic stability and incidence of adverse effects. This study will assess a method to improve post-operative analgesia following a subarachnoid block.

METHODOLOGY

The Research Advisory Committee and Institutional Review Board, Akhter Saeed Medical College, Private Limited, Rawalpindi Campus, Main Murree Expressway, Bahria Golf City, Rawalpindi, endorsement was taken vide letter number (RAC-14-6-23),15th June 23, for this study. Statistical Kingdom calculator was used for calculation of sample size using t-distribution; with a margin of error; 0.04, a confidence level; 0.96 (Z-score of 2.29), and a standard deviation of 0.29, resulting in 60 patients. A total of 60 patients, planned for elective infra-umbilical surgical procedures randomly divided into 2 groups by employing computer-generated divisions within the electively placed surgical case lists, were divided(n=30) in each study group. Participants were broadly informed about the study and provided consent in written form before registration. The study duration was ten months and was convened at Farooq Hospital, Rawalpindi, from 16th Jan 2024 to 25th December 2024. The inclusion criteria of this single-blind interventional study were piloted with random sampling methodology for both genders, for elective surgery under sub-arachnoid block incorporating departments of surgery/ urology/orthopaedics and gynaecological patients (aged 28 to 55 years), and belonging to ASA class I and II or ASA III(medically controlled co-morbid states) were included in accordance with the foregoing conducted studies.[9,10,12] The exclusion criteria included, as per various study guidelines included patients with cardiac disease, liver and kidney disease, coagulopathy, emergency procedures and those who did not give consent.[9,10] Proper preoperative informed verbal consent was done before the surgery, and written informed consent was obtained after explaining the procedure to the patient. Patients were also informed about the procedure to be performed, the technique being employed, and the risks and possible benefits, in clear terms so that they could make a better decision regarding participation in research. In both groups, patients were prepared as per ASA guidelines. Patients were unaware of the group allocation. In both groups, patients were prepared as per ASA guidelines.[12] However, after being taken into the main operating theatre, emergency drugs were prepared, monitors were attached (electrocardiograph, capnograph, pulse oximetry and non-invasive blood pressure), an intravenous large-bore line was inserted, and patients were preloaded with crystalloid solutions, which was followed by a spinal block at L3–L4 interspace with a 26-G Quincke spinal needle in both groups. A consultant anesthesiologist performing spinal block also participated in the research, was not aware of group allocation, whereas another senior registrar anesthesiologist prepared medication to be placed intrathecally and was not part of the research outcome and also did randomization of research patients into 2 groups, thus endorsing unbiased handling of the study. In group A, 1.5 mL hyperbaric bupivacaine 0.75% 15 mg was used, and in group B, 1.5 mL hyperbaric bupivacaine 0.75% 15 mg plus 5 microgram dexmedetomidine medication was used in the study. In both research groups, hemodynamic parameters (systolic, diastolic, heart rate, SpO2) were recorded preoperatively and every 5 minutes for 50 minutes post-block. Adverse hemodynamic effects (hypotension, bradycardia), use of anti-cholinergic and vasopressors noted. The hemodynamic monitoring was continued, and the need for rescue analgesia was documented in the Post-Anaesthesia Care Unit. Hypotension was defined as systolic blood pressure of less than 90 mmHg and treated by phenylephrine 50 microgram increments. Bradycardia was defined as a heart rate of less than 50 beats per minute, and was treated with atropine 0.01 mg/kg. Supplemental oxygen was given via face mask to all patients to maintain O2 saturation of about 98%. Sedation scores in Group A, but specifically in B, were noted because of the sedative properties of dexmedetomidine in the intraoperative and postoperative period. All the patient data was noted on the anaesthesia proforma, and the confidentiality of the patients was ensured. The Paired sample t-test was used with a confidence interval of 95% (to seek significance) for analysis of the study variables in both groups, with a p-value greater than 0.05. SPSS v.26 was used for statistical analysis.

RESULTS

The average age in years of bupivacaine patients (group A) is 42.12 ± 13.40, and that of the patients taking bupivacaine with dexmedetomidine (group B) is 42.70 ± 11.09. The average weight of bupivacaine patients was 75.32 ± 7.43 as compared to 73.51 ± 6.85 in patients using bupivacaine plus dexmedetomidine. The average Body Mass Index (BMI) between the patients of group A was 24.13 ± 3.11, and the mean BMI that corresponded to the patients of group B was 23.87 ± 2.84. The average postoperative analgesia in the bupivacaine group was 12.57 ± 2.53 as compared to the average postoperative analgesia in the bupivacaine plus dexmedetomidine group of 20.18 ± 3.48. Zero per cent are the Bupivacaine patients were diagnosed with bradycardia, although non-bradycardia individuals were hundred percent (100%) whereas bupivacaine plus dexmedetomidine patients, owing to bradycardia were 16.7, and non-bradycardia individuals were 85.5. In bupivacaine, 5.4 of patients had hypotension and 93.7 had no hypotension whereas in the case of bupivacaine plus dexmedetomidine, the same was 25% and 75 % respectively. Among the patients of bupivacaine, 90.6 % did not have nausea and 9.4 % had nausea, but with bupivacaine plus dexmedetomidine, 6.4 had nausea and 93.7 were without nausea. In bupivacaine, 6.4 per cent of the patients vomited as compared to 93.7 percent of the patients vomited although in dexmedetomidine plus bupivacaine, there were 3.1 percent and 96.9 percent of the patients who vomited. The ASA grades are depicted in Table 1. The analgesic medications used postoperatively are shown in Table 2. Statistical analysis revealed that there was a marked improvement in relative frequency of

bradycardia in the Bupivacaine plus Dexmedetomidine group 2, when compared to the Bupivacaine alone group 1 with a "p-value of 0.026* and the Lavene test was applied for analysis of variances and the p-value was less than .05(0.228*) showed a significant statistical difference between variances as presented in Table 3. The hemodynamic variables of both groups are presented graphically in Figure 1.

DISCUSSION

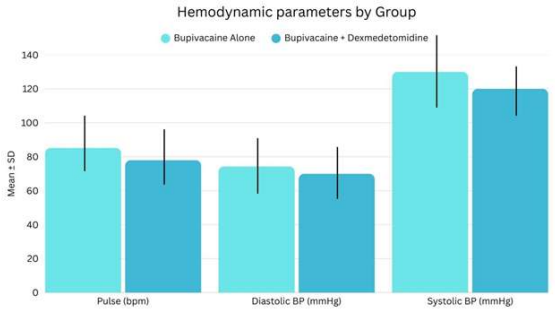
The addition of adjuvants to local anesthetics has gained significant attention these include fentanyl, midazolam, ketamine, etc. but have shorter durations of analgesia, higher incidence of side effects such as pruritus, nausea, vomiting, and respiratory depression, and less consistent prolongation of sensory and motor block in comparison to dexmedetomidine.[13,14,15] A combination that has emerged with promising results is dexmedetomidine combined with bupivacaine, compared to bupivacaine alone.[3] This combination offers a range of clinical benefits as the current research studied postoperative pain following the use of a combination of dexmedetomidine and bupivacaine in spinal anesthesia in general surgical procedures. Dexmedetomidine is an extremely selective agonist, alpha-2-receptor with the property of being sedative, anxiolytic/analgesic. It has been demonstrated that when used as an adjuvant agent to local anesthetics in spinal anesthesia, dexmedetomidine enhances the action of the block by exerting effects both centrally and on the spinal cord as it holds potential in ensuring the best opioid-sparing effects which remain an important subject regarding perioperative care.[4] Bupivacaine, a long-acting amide local anesthetic, is commonly used for spinal anesthesia due to its effective sensory and motor blockade. However, its duration of analgesia, although longer than some other

Table 1: Demographic data (n=30)

Variables		Group A	Group B
ASA classes (frequency/percentage)	Class-1	20/75%	28/62%
	Class-2	9/22%	10/35%
	Class-3	1/2.5%	2/3%

Table 2: Postoperative analgesics data. (n=30)

		Group-A	Group-B
Post op analgesic Used N /%	Opioids	6 / 20%	3 /10%
	NSAIDS	24/80%	27/90%



local anesthetics, is still limited in the context of postoperative pain control.[2] The foundation for combining dexmedetomidine with bupivacaine in our study centers on prolonging and improving the quality of analgesia without significantly increasing adverse effects.

Clinical studies comparing the combination of dexmedetomidine and bupivacaine with bupivacaine alone consistently reveal that the addition of dexmedetomidine leads to a significant prolongation of postoperative analgesia.[1] Patients who receive this combination generally experience a longer duration of pain relief, often double the duration provided by bupivacaine alone. This extension in analgesia means that patients require their first dose of rescue analgesics much later in the postoperative period, ultimately reducing the frequency and total dose of opioid or other analgesic medications administered. Reducing opioid consumption is particularly beneficial in the current medical landscape, where minimizing opioid-related side effects and dependency is a priority, as in our study, fewer patients needed opioids in group B.

When considering patients' postoperative experience, those who receive dexmedetomidine in addition to bupivacaine report significantly lower pain scores across various postoperative time points. This consistent reduction in pain directly correlates with improved patient comfort and potentially quicker overall recovery, and reduces complications such as deep vein thrombosis or pulmonary issues. The lower pain scores and delayed need for additional analgesics contribute to higher satisfaction levels among patients receiving the combination therapy.

From a hemodynamic perspective, concerns often arise regarding the addition of potent adjuvants like

Table 3: Independent Sample t-test results. (n=30)

Variables			Group A	Group B
Bradycardia		Yes Count	0	5(0.026*)
		No Count	32	27
Post-operative analgesia duration	Levene's Test	variances assumed / not assumed	1.482	0.228*

*p < 0.05 is considered statistically significant.
**Calculated by the Independent Sample t-test

dexmedetomidine, given its sympatholytic effects that can potentially lead to bradycardia or hypotension. However, most clinical trials using standard intrathecal doses of dexmedetomidine, typically between 3 and 5 micrograms, demonstrate that while there may be mild decreases in heart rate and blood pressure, these changes are generally clinically insignificant and easily managed. The hemodynamic stability with this combination remains comparable to that observed with bupivacaine alone, which underscores its safety profile for use in a broad patient population.[4,8,9]

Nevertheless, a mild increase in sedation is a noted side effect of dexmedetomidine. This sedative effect is generally well-tolerated and not problematic for most patients; in fact, for some, it may be considered beneficial as it can alleviate perioperative anxiety and contribute to a smoother induction of anaesthesia. Importantly, the incidence of severe adverse effects such as respiratory depression or neurological complications has not been demonstrated to increase with the addition of intrathecal dexmedetomidine. Moreover, the combination has been found to reduce the occurrence of postoperative shivering, nausea, and vomiting the common complications of spinal anaesthesia, which further enhanced patient comfort.[1] From a practical clinical perspective, the dexmedetomidine-bupivacaine combination represents a cost-effective strategy to manage postoperative pain, reducing the reliance on systemic analgesics such as opioids or nonsteroidal anti-inflammatory drugs (NSAIDs), which have their own side effect profiles.[2] The longer duration of analgesia may also translate into shorter stays in recovery units and better allocation of healthcare resources. A meta-analysis study done on (randomized controlled trials), which used dexmedetomidine as an adjuvant to local anaesthetic agents, inferred that motor and sensory block duration was prolonged, along with post-operative analgesia duration. However, there was no significant statistical difference in the incidence of hypotension; they noted that bradycardia per-operatively was transient in nature and easily reversible with intravenous atropine.[16] Patients who receive this combination generally experience a longer duration of pain relief, often double the duration provided by bupivacaine alone.[17] These results were similar to our conducted study. Bradycardia incidence was higher with dexmedetomidine as stated in our study, whereas no significant differences were observed in nausea, vomiting, or other adverse effects, and all hemodynamic (blood pressure) changes were clinically manageable in both groups. As stated earlier that optimal post-operative pain control plays a role in faster recovery. In this context a study done by Thaku SK and colleagues noted that dexmedetomidine markedly extended post-operative analgesic duration. Additionally, extent of intrathecal sensory and motor block was not affected by dexmedetomidine in their study. Furthermore, more hemodynamic stability was not compromised with dexmedetomidine as adjunct.[18]Usage of dexmedetomidine together with bupivacaine increases the length of the postoperative analgesia and lowers opioid usage. In their study, the combination group had a mean analgesia time of 19.18 hours, whereas the single agent bupivacaine used in the other group had a mean analgesia time of 11.78 hours ($p < 0.05$). Patients in the dexmedetomidine group needed less opioid medication within the first 24 hours as well (20.69 mg vs. 10.88 mg in the bupivacaine-only group, $p < 0.05$). In spite of these advantages, the incidences of bradycardia and hypotension were more in the dexmedetomidine comparison group.[18]

In a triple-blind randomized study, assessing the analgesic effect of 0.5% bupivacaine noted that patients' pain perception on a numerical rating scale, duration of analgesic effect and post-op analgesics used. They noted that use of bupivacaine didn't have a superior analgesic value in comparison to placebo in regulating post-operative acute pain.[19]Similar results were inferred in our study. A systematic review study on sub-arachnoid dexmedetomidine as an adjuvant in elective surgical cases. They noted post-op analgesia duration, adverse effects(bradycardia, hypotension, post-op shivering, and nausea pointed out that post-op analgesic duration was prolonged, and had a lower visual analogue scale, nausea and shivering in comparison to placebo.[20]As regards recent advancement in use of centrally acting alpha-2 agonists(dexmedetomidine) in various other clinical settings, such as in the Emergency Department, a study done by Kevin Baumgartner and colleagues pointed out that dexmedetomidine can be used in selected clinical scenarios, as the hemodynamic effects(bradycardia, hypotension) do require medical treatment infrequently.[21]In another recent efficacy study of bupivacaine alone and with dexmedetomidine local wound infiltration at the end of abdominal surgeries after general anaesthesia, showed a marked useful difference in post-operative analgesia effect with the use of the latter combination.[22] A study done by Zulfiqar Ahmed and colleagues to assess clinical effects of dexmedetomidine across regional and general anaesthesia regimens as well as procedural sedation pointed out that it's highly efficacious in reducing general opioid requirement post-operatively, as well as having a stable hemodynamic effect(pulse and blood pressure) and thus good recovery outcome. Their study results were similar to ours, with less opioid requirement post-operatively.[23]

Another randomized, placebo-controlled study tested 60 patients with similar results, i.e. a considerable reduction in the postoperative morphine requirement in those administered with bupivacaine than in those who received ropivacaine ($p = 0.03$). The patients treated with bupivacaine were exposed to less pain during incision and less vomiting in the first six hours after surgery, along with a lower total number of pharmacological analgesia demands.[24]

Apart from prolonging analgesia, the dexmedetomidine-bupivacaine combination has been shown to hasten the onset

of both sensory and motor blockade. This faster onset can be highly advantageous in operative settings by allowing surgical procedures to commence sooner with adequate anaesthesia. In addition, the quality of the block is generally enhanced, displaying a more profound and reliable sensory and motor effect. This enhancement contributes to better intraoperative conditions and reduced patient discomfort during positioning or surgical manipulation.[25]

In summary, the evidence firmly supports the conclusion that the combination of dexmedetomidine and bupivacaine in spinal anaesthesia offers superior postoperative analgesia compared to bupivacaine alone. This superiority is reflected in a significantly prolonged duration of pain relief, faster onset and improved quality of sensory and motor blocks, lower pain scores, reduced need for rescue analgesics, and high patient satisfaction. The safety profile of the combination is acceptable, with stable hemodynamics and only mild sedation and other minor side effects reported. This makes dexmedetomidine an excellent adjunct to bupivacaine in providing enhanced postoperative analgesia in patients undergoing a variety of general surgical procedures under spinal anesthesia and be a valuable addition to multimodal analgesic strategies in surgical care.

Limitations of the study included a smaller sample size, and additional research is needed to confirm the results of our findings.

CONCLUSION

Dexmedetomidine, when added to bupivacaine as an adjuvant in Spinal anaesthesia in general surgical cases, increases the post-op duration of analgesia in comparison to bupivacaine alone.

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Authors Contribution:
Muhammad Salman Maqbool: Concept & Design of Study, Drafting, Revisiting Critically, Data Collection & Analysis, Final Approval of version
Fahad Zubair: Concept & Design of Study, Drafting, Revisiting Critically, Data Collection & Analysis
Kainat Irshad: Drafting, Revisiting Critically, Data Collection & Analysis
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Original Article **Open Access**

Diagnostic Delay in Chronic Inflammatory Rheumatic Diseases Presented to the Tertiary Care Rheumatology Unit in PIMS

Alina Fakhar, Shazia Zammurrad, Uzma Rasheed, Muhammad Sufyan Khan

Abstract:

Objective: To quantify the therapeutic and diagnostic delays among patients with CIRDs in Pakistan.

Study Design and Setting: Cross sectional study. PIMS Hospital Islamabad Rheumatology OPD. Duration 8th June 2025 to 8th September 2025.

Methodology: This cross-sectional study comprised 220 patients. Informed consent was obtained; demographic details like age and sex were noted. All Patients previously diagnosed with conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or similar diseases were selected from various rheumatology clinics and departments over six months. Data collection was done using a structured face-to-face interview which included data on demographic information, age of symptom onset, consultation times, and treatment commencement, dividing delays into diagnostic and therapeutic categories. For the analysis in SPSS v21, Shapiro–Wilk, Chi-square, and Fisher's Exact Test were performed, and the results were presented as the median for continuous variables and percentages for categorical data. A p-value = 0.05 was taken as statistically significant.

Results: A total of 220 participants were included in this study. Among the 220 patients, 40.5% had diagnostic delay exceeded 18 months with only 6.4% diagnosed within 6 months. Patients who visited homeopaths had the highest delay rate (56.1%). Psoriatic arthritis (71.4%) and ankylosing spondylitis (53.8%) had longest delays. Joint pain led to early referral in 54.6%, whereas atypical symptoms caused prolonged delays.

Conclusions: The findings of this study revealed that both diagnostic and therapeutic delays are common in CIRDs in Pakistan, often caused by multiple reasons before reaching a rheumatologist and referral system inefficiencies.

Keywords: Ankylosing Spondylitis, Diagnostic Delay, Psoriatic Arthritis, Rheumatoid Arthritis, and Therapeutic

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INTRODUCTION

The CIRDs represent a major challenge for healthcare; they are group of complex autoimmune diseases, including Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Systemic Lupus Erythematosus (SLE), Inflammatory Bowel Disease-associated Arthritis IBD arthritis, Sjogren's Syndrome, Overlap Syndrome, and MCTD. Diseases under this category characteristically affect the musculoskeletal system in multifaceted ways and have largely been responsible for chronic pain, joint damage, and long-term disability. It usually affects many joints throughout the body at one time but could involve just one joint. Immune cells come into this tissue causing the lining to thicken. These immune cells, along with the cells normally found in the lining, release chemicals that cause the signs of inflammation: swelling, redness and heat. [1,2].

These conditions pose serious health risks and place a significant social and economic strain on patients, families, and the healthcare system. Global health organizations continue to stress the importance of timely diagnosis and treatment in managing CIRDs.

The latest guidelines recommend that patients with suspected disease see a rheumatologist within six weeks of symptom onset to relieve symptoms early and prevent long-term complications.[3] unfortunately, it has generally been difficult to implement this recommendation in LMICs, of which Pakistan is one. This gap in services highlights both the disparity in the access to health care in general and the

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challenges the specialty of rheumatology still faces.[4]

Diagnostic delays in CIRDs are common and multilevel in Pakistan. First, there is a general lack of awareness about rheumatic diseases and their symptoms in patients. Many persons developing early symptoms may not realize the importance of their symptoms and thus procrastinate seeking professional medical help. Added to this is the system structure itself: for instance, the lack of availability of trained rheumatologists makes timely access to specialty care difficult for many patients. In addition, primary care professionals may be unaware or lack the resources to refer their patients appropriately to specialty care, contributing to further delays.[5,6]

Further, many patients in Pakistan first seek alternative therapies rather than waiting for evidence-based treatment protocols. All this can significantly increase the time to diagnosis and the institution of treatment. Therefore, delays in diagnosis not only enhance disease progression but also increase the social and economic burdens on families and the healthcare system. The cause of such delays would need to be identified and understood. That would hopefully lead the policymakers and healthcare providers toward necessary changes in the way training is imparted, resources are utilized, and policies are framed regarding rheumatologic care.[7,8]

Addressing diagnostic delays in CIRDs assumes significance in light of various studies conducted both internationally and regionally. These highlight the trend toward continued prolongation of time awaiting diagnosis across different healthcare settings. In fact, research from India revealed that patients' diagnostic delay ranged from at least 9 months to as long as 3 years, with considerable variation based on the rheumatic disease a patient suffered from. Such findings only cause difficulties to deal with the complexities of CIRDs.[9,10] However, there is still a significant gap in comprehensive data at the local level regarding the nature and extent of these delays, especially from public-sector tertiary care facilities like our own, the Pakistan Institute of Medical Sciences, in Islamabad. Lack of adequate research impacts the understanding of, and limits our power as healthcare professionals to act on, pressing issues affecting our patient population. Therefore, this study was undertaken with the intention of filling in this gap. Focusing on the referral and diagnostic delays among patients presenting to our Rheumatology Unit, we intend to gather critical baseline data that will help healthcare policymakers to design better interventions at improving the quality of rheumatologic care throughout Pakistan. The process of addressing the challenges posed by CIRDs comprehensively is multilevel: it involves collaboration between health practitioners, educators, policymakers, and the communities concerned. As we continue to gather more evidence and data from our study, we hope to enhance our understanding of these delays and propose best solutions that will bridge the existing gaps in care. In doing so, we will have created a healthcare environment in which individuals with CIRDs can receive timely, effective, and compassionate care, improving their quality of life and reducing burdens on families and society at large.

METHODOLOGY

This cross sectional study took place at the PIMS Hospital Islamabad from 8th June 2025 to 8th September 2025, having received approval from the Institutional Review Board (IRB) under reference number F-5/2024(ERRC)/PIMS. To establish our study parameters, an extensive review of existing literature was performed. From this analysis, we determined a sample size of 220 participants utilizing the World Health Organization (WHO) sample size calculator based on the following assumptions: a 95% confidence level, a 5% margin of error, and an estimated prevalence of rheumatic diseases of 17.3%[11], as reported in prior literature.

Inclusion Criteria: The study included patients aged 18 years and above with a confirmed diagnosis of a chronic inflammatory rheumatic disease, who had experienced symptoms for at least six months before diagnosis, and who consented to participate in the interview process.

Exclusion Criteria: Patients were excluded if they had degenerative or non-inflammatory joint conditions (such as osteoarthritis), incomplete or unclear clinical histories, cognitive impairments affecting memory or communication, or if they were unwilling to participate in the interview.

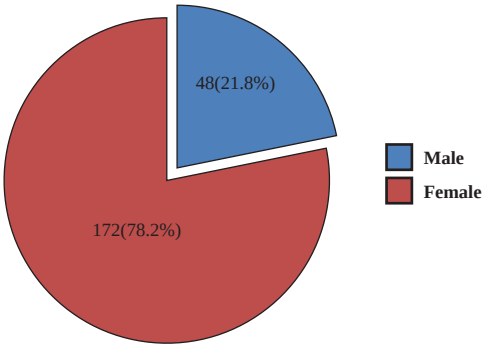
All patients provided written agreement before the enrolment, and their confidentiality was maintained at all levels. The institutional ethics committee's approval was also obtained prior to beginning the study. A total of 220 patients who had already been diagnosed with conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or similar diseases were selected from rheumatology clinics and departments over a period of six months. Information was gathered using face-to-face interviews with each patient, guided by a structured questionnaire prepared specifically for this study. These interviews were conducted by trained staff to maintain uniformity in data collection. The questionnaire included various parts. The first section focused on personal background details such as age, gender, education, and place of residence. The second section inquired the date of first symptom appearance, the time taken to consult a healthcare provider, the number of healthcare professionals consulted prior to final diagnosis, and the duration between the initial consultation and confirmation of the diagnosis. In addition, patients were asked about the interval between diagnosis and the start of specific treatment for CIRDs. This allowed the classification of delays into two major categories: diagnostic delay (time from symptom onset to confirmed diagnosis) and therapeutic delay (time from diagnosis to initiation of appropriate treatment). Both durations were recorded in months for consistency.

Data were analyzed using SPSS version 21. Continuous

Table-1: Baseline Demographic and Clinical Characteristics of the Study Population (n = 220)

	Variables	Median, IQR
	Age	39.00 (32.00-44.00)
		n (%)
Marital Status	Single	32 (14.5%)
	Married	188 (85.5%)
Education Status	No Formal Education	65 (29.5%)
	Primary to Secondary	55 (25.0%)
	Higher Education	100 (45.5%)
Socioeconomic Status	Below 20k	60 (27.3%)
	20,001 to 50,000	128 (58.2%)
	50,001 to 100,00	24 (10.9%)
	100,001 to 200,00	8 (3.6%)
Residence	Rural	75 (34.1%)
	Urban	105 (47.7%)
	Semi Urban	40 (18.2%)
First Symptom	Joint Pains	97 (44.1%)
	Oral Ulcer	27 (12.3%)
	Raynaud's	45 (20.5%)
	Photosensitivity	12 (5.5%)
	Inflammatory back pain	31 (14.1%)
	Rashes	5 (2.3%)
	Neurological signs	3 (1.4%)
Referral Pathway	Hakeem or Homeopathic	66 (30.0%)
	Family Physician	28 (12.7%)
	Medical Specialist	79 (35.9%)
	Orthopedic Surgeon	47 (21.4%)
Setting of First visit	Public	125 (56.8%)
	Private	95 (43.2%)
Initial Symptom to any Physician	Within 6 Months	85 (38.6%)
	6 Months to 12 Months	111 (50.5%)
	12 Months to 18 Months	24 (10.9%)
Initial Symptom to any Rheumatologist	Within 6 Months	17 (7.7%)
	6 Months to 12 Months	54 (24.5%)
	12 Months to 18 Months	74 (33.6%)
	18 Months to 24 Months	56 (25.5%)
	After 24 Months	19 (8.6%)
Diagnostic Delay	= 6 Months	14 (6.4%)
	6 Months to 12 Months	49 (22.3%)
	12 Months to 18 Months	68 (30.9%)
	> 18 months	89 (40.5%)
Final Diagnosis	Ankylosing Spondylitis	39 (17.7%)
	IBD-associated arthritis	3 (1.4%)
	Mixed Connective Tissue Disease	24 (10.9%)
	Overlap Syndrome	8 (3.6%)
	Psoriatic Arthritis	7 (3.2%)
	Rheumatoid Arthritis	69 (31.4%)
	Systemic Lupus Erythematosus	70 (31.8%)

Figure 1: Gender Distribution of Study Population (n=220)



variables, such as age, were assessed for normality using the Shapiro–Wilk test. Since age was not normally distributed, it was summarized as median with interquartile range (IQR). Categorical variables, including gender, marital status, education status, socioeconomic status, residence, first presenting symptom, referral pathway, setting of first visit, diagnostic delay categories, and final diagnosis, were presented as frequencies and percentages. Associations between clinical variables and diagnostic delay as well as referral delay were evaluated using the Chi-square test. Where expected cell counts were less than 5, Fisher's Exact Test was applied to ensure validity of results. All statistical tests were two-tailed, and a p-value = 0.05 was considered statistically significant.

RESULTS

A total of 220 participants were included in this study. Out of the total, 48 (21.8%) were male with the median age of 44.00 (36.50-47.25) years and 172 (78.2%) were female with the median age of 38.00 (31.00-44.00) years. The gender distribution of study population is shown in figure 1.The baseline demographic and clinical characteristics of the study population is shown in Table-I. The association between clinical variables and diagnostic delay in patients with chronic inflammatory rheumatic diseases is shown in Table II. Referral pathway had a strong effect ($p < 0.001$), with the longest delays seen among patients who first visited hakeem or homeopathic practitioners (56.1% had delays >18 months). Those who initially attended public health facilities also experienced significantly longer delays compared to private settings (47.2% vs. 31.6%, $p < 0.001$). The type of first symptom was also significant ($p = 0.018$). Patients presenting with inflammatory back pain (58.1%), rashes (60.0%), and neurological signs (66.7%) had the highest proportion of delays exceeding 18 months, whereas those with joint pains or Raynaud's phenomenon had comparatively shorter delays. Final diagnosis showed a notable association ($p = 0.014$), with psoriatic arthritis (71.4%) and IBD-associated arthritis (66.6%) having the highest rates of prolonged diagnostic delay. Patients with ankylosing spondylitis (53.8%) and overlap syndromes (62.5%) were also commonly delayed, while those with rheumatoid arthritis and systemic lupus erythematosus had relatively earlier diagnoses.

Overall, patients seen first in non-specialist or public settings and those with atypical symptom presentations experienced the greatest diagnostic delays. The association of first symptom and final diagnosis with referral delay is shown in table III. The analysis showed a significant association between first presenting symptom and referral delay ($p < 0.001$). Patients presenting with joint pains were more likely to be referred within 6 months, while those with oral ulcers, Raynaud's phenomenon, photosensitivity, rashes, or neurological signs tended to have longer delays. Similarly, there was a significant association between final diagnosis and referral delay ($p = 0.005$). Rheumatoid arthritis cases were more often referred early, whereas systemic lupus erythematosus, ankylosing spondylitis, and other connective tissue diseases had higher proportions of delayed referrals.

DISCUSSION

Chronic inflammatory rheumatic diseases (CIRDs) affect people across the world by causing rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), inflammatory bowel disease related arthritis, Sjogren syndrome, and several overlap connective tissue disorders that still burden the populations. Although it is a well-established fact that the most promising policies that could be implemented to avoid the irreversible damages of the joints and organs are early diagnosis and the introduction of disease-modifying treatment, the realization of the aforementioned objectives has been identified as a challenge in low- and middle-income countries (LMICs), including Pakistan. Patient factors, provider factors, and system factors that often cause long delays in referring to specialized rheumatologic care occur in these settings.

The most common diagnoses in this study of 220 patients were SLE (31.8%), RA, (31.4%), AS, (17.7%), mixed connective tissue disease (10.9%), overlap syndromes (3.6%), PsA (3.2%), and IBD-associated arthritis (1.4%). These distributions contrast with most international epidemiological data whereby RA has typically comprised of the highest percentage of autoimmune rheumatic diseases. As an example, a recent international survey showed RA prevalence about 0.5-1% globally, which further confirms its superiority among CIRDs. [12] In the same measure, SLE is generally reported at lower frequencies across the globe with the incidence estimates continuing to be significantly lower compared to what is observed in this tertiary-based cohort.[13]

At relatively similar rates (6.4 vs. 5-8%), AS prevalence in this study coincides with recent multinational data indicating an increasing use of the axial spondyloarthritis concept in clinical practice, which is also consistent with the generally low dermatologic-rheumatologic collaboration pathway in terms of their relative frequency and thus selective presentations.[14] The 14.5% collectively percentage of mixed

Table-2: Association between Clinical Variables and Diagnostic Delay in Patients with Chronic Inflammatory Rheumatic Diseases (n = 220)

Variables		Diagnostic Delay				Total	p-Value
		< 6 Months	6-12 Months	12-18 Months	> 18 months		
Referral Pathway	Hakeem or Homeopathic	4 (6.1%)	16 (24.2%)	9 (13.6%)	37 (56.1%)	66 (30.0%)	<0.001
	Family Physician	2 (7.1%)	2 (7.1%)	12 (42.9%)	12 (42.9%)	28 (12.7%)	
	Medical Specialist	2 (2.5%)	15 (19.0%)	35 (44.3%)	27 (34.2%)	79 (35.9%)	
	Orthopedic Surgeon	6 (12.8%)	16 (34.0%)	12 (25.5%)	13 (27.7%)	47 (21.4%)	
Total		14 (6.4%)	49 (22.3%)	68 (30.9%)	89 (40.5%)	220 (100.0%)	
Setting of First visit	Public	5 (4.0%)	16 (12.8%)	45 (36.0%)	59 (47.2%)	125 (56.8%)	<0.001
	Private	9 (9.5%)	33 (34.5%)	23 (24.2%)	30 (31.6%)	95 (43.2%)	
Total		14 (6.4%)	49 (22.3%)	68 (30.9%)	89 (40.5%)	220 (100.0%)	
First Symptom	Joint Pains	11 (11.3%)	29 (29.9%)	23 (23.7%)	34 (35.1%)	97 (44.1%)	0.018
	Oral Ulcer	0 (0.0%)	3 (11.1%)	15 (55.5%)	9 (33.3%)	27 (12.3%)	
	Raynaud's	0 (0.0%)	12 (26.7%)	16 (35.6%)	17 (37.8%)	45 (20.5%)	
	Photosensitivity	1 (8.3%)	2 (16.7%)	3 (25.0%)	6 (50.0%)	12 (5.5%)	
	Inflammatory back pain	2 (6.5%)	2 (6.5%)	9 (29.0%)	18 (58.1%)	31 (14.1%)	
	Rashes	0 (0.0%)	0 (0.0%)	2 (40.0%)	3 (60.0%)	5 (2.3%)	
	Neurological signs	0 (0.0%)	1 (33.3%)	0 (0.0%)	2 (66.7%)	3 (1.4%)	
Total		14 (6.4%)	49 (22.3%)	68 (30.9%)	89 (40.5%)	220 (100.0%)	
Final Diagnosis	Ankylosing Spondylitis	2 (5.1%)	5 (12.8%)	11 (28.2%)	21 (53.8%)	39 (17.7%)	0.014
	IBD-associated arthritis	0 (0.0%)	0 (0.0%)	1 (33.3%)	3 (66.6%)	3 (1.4%)	
	Mixed Connective Tissue Disease	1 (4.2%)	3 (12.5%)	8 (33.3%)	12 (50.0%)	24 (10.9%)	
	Overlap Syndrome	0 (0.0%)	1 (12.5%)	2 (25.0%)	5 (62.5%)	8 (3.6%)	
	Psoriatic Arthritis	0 (0.0%)	0 (0.0%)	2 (28.6%)	5 (71.4%)	7 (3.2%)	
	Rheumatoid Arthritis	10 (14.4%)	24 (34.8%)	13 (18.8%)	22 (31.9%)	69 (31.4%)	
	Systemic Lupus Erythematosus	1 (1.4%)	16 (22.9%)	31 (44.3%)	22 (31.4%)	70 (31.8%)	
Total		14 (6.4%)	49 (22.3%)	68 (30.9%)	89 (40.5%)	220 (100.0%)	

Table 3: Association of First Symptom and Final Diagnosis with Referral Delay

Variables		Referral Delay			Total	p-Value
		< 6 Months	6-12 Months	12-18 Months		
First Symptom	Joint Pains	53 (54.6%)	38 (39.2%)	6 (6.2%)	97 (44.1%)	<0.001
	Oral Ulcer	6 (22.2%)	16 (59.3%)	5 (18.5%)	27 (12.3%)	
	Raynaud's	11 (24.4%)	32 (71.1%)	2 (4.4%)	45 (20.5%)	
	Photosensitivity	4 (33.3%)	7 (58.3%)	(8.3%)	12 (5.5%)	
	Inflammatory back pain	9 (29.0%)	13 (41.9%)	9 (29.0%)	31 (14.1%)	
	Rashes	1 (20.0%)	3 (60.0%)	1 (20.0%)	5 (2.3%)	
	Neurological signs	1 (33.3%)	2 (66.7%)	1 (33.3%)	3 (1.4%)	
Total		85 (38.6%)	111 (50.5%)	24 (10.9%)	220 (100.0%)	
Final Diagnosis	Ankylosing Spondylitis	11 (28.2%)	19 (48.7%)	9 (23.1%)	39 (17.7%)	0.005
	IBD-associated arthritis	0 (0.0%)	3 (100.0%)	0 (0.0%)	3 (1.4%)	
	Mixed Connective Tissue Disease	10 (41.7%)	12 (50.0%)	2 (8.3%)	24 (10.9%)	
	Overlap Syndrome	2 (25.0%)	5 (62.5%)	1 (12.5%)	8 (3.6%)	
	Psoriatic Arthritis	2 (28.6%)	3 (42.9%)	2 (28.6%)	7 (3.2%)	
	Rheumatoid Arthritis	42 (60.9%)	24 (34.8%)	3 (4.3%)	69 (31.4%)	
	Systemic Lupus Erythematosus	18 (25.7%)	45 (64.3%)	7 (10.0%)	70 (31.8%)	
Total		85 (38.6%)	111 (50.5%)	24 (10.9%)	220 (100.0%)	

connective tissue disease and overlap syndromes is also higher than most international data, and thus may be due to selective referral of complex auto.[15]

There was a high level of diagnostic delay in this study: 40.5 percent of the patients were delayed more than 18 months, whilst only 6.4 percent of the patients managed to get a diagnosis within 6 months as recommended.[16, 17] The delays in these cases are greater than those observed in more recent European studies of early arthritis initiatives, with shorter referral times and early-arthritis clinics significantly shortening diagnostic times. Likewise, these results confirm that diagnostic inefficiencies are present in all areas where there are no established rheumatology pathways.[18, 19]

It has consistently been demonstrated that early diagnosis and DMARDs early start have significant positive effects on outcomes in the long-term across CIRDs. Recent studies have found again that use of DMARD early - even in the first 12 weeks of symptoms - is associated with reduced radiographic progression and improved functional outcome.[20] and similar findings were also found in this data whereby failure to use DMARD early is a significant contributor to morbidity in Pakistan over the long run.

Referral pathways were very important towards delays experienced in this population. Patients who initially used other non-medical providers incurred the longest delays, which is consistent with the regional literature that indicates that early use of non-medical providers is often associated with significant delays in the diagnosis process.[21,22] On top of this, patients who sought the services of the public-sector facilities in the first instance had much longer delays as compared to those who visited the non-medical services, which is indicative of structural constraints, workforce deficits, and long chains of referrals typically reported in LMIC healthcare systems.

Another important determinant was the nature of the first presenting symptom. Prospective referral of patients with classic rheumatologic manifestations, like joint pain, was comparatively earlier whereas; oral ulceration, neurological manifestations, rashes, or Raynaud's phenomenon resulted in a long delay. This has been noted in qualitative European research, where indeterminate or unusual symptoms frequently resulted in repeat assessment by non-experts before they were referred to a specialist. The result of this tendency is that axial spondyloarthritis is regularly mistaken with mechanical back pain in general practice.[23]

The disease-specific analysis revealed that persons with PsA and AS had the highest delayed recognition and systemic referral, which is also in line with recent reports in Turkey, South America, and the COMOSPA initiative, which attribute a high level of delay to low disease awareness, lack of specific biomarkers, and misattribution of symptoms to non-inflammatory diseases.[24] This analysis also indicates that both delay recognition and inefficient use of systems are major challenges in early diagnosis of both diseases.

Taken together, these results highlight the fact that delays in diagnosis are major contributors to poor clinical outcomes and increased economic and social costs. These delays will need a multifaceted intervention related to the health system in Pakistan: educational programs in the population, physician training on primary care, universalized referral protocols, and Better Avenue of access to rheumatologists. Other models demonstrate that organized early-arthritis centers, referral algorithms via the digital, and tele-rheumatology initiatives are capable of eliminating delays in a way that can be used in our study to inform equivalent reforms in Pakistan.

Another aspect that is required is the urgency of national registries and multicenter collaboration to measure diagnostic and treatment delays in a more effective way. Those systems do not only enable policymakers to recognize population-specific barriers, keep track of trends, and assess the effects of interventions. Raising awareness to the general population, reinforcing primary care education, and increasing access to specialists are all crucial ways of increasing patient outcomes and decreasing long-term disability due to CIRDs.

This study had several limitations. It focused solely on one tertiary care hospital, which may limit generalizability to other regions of Pakistan. Data on the onset of symptoms and the dates of consultations were based on the patient's memory, which may have been inaccurate. The study only included patients who went to rheumatology clinics, which could have left out those who were not diagnosed or treated elsewhere. The limitations of the healthcare system, the availability of physicians, and patient health literacy were not thoroughly investigated. Additionally, the sample size was relatively small, and the study did not account for other potential confounding variables. Future research should aim to explore a broader spectrum of contributing risk factors through larger, more comprehensive studies.

CONCLUSIONS

This research indicates a high diagnostic and therapeutic delay in the case of patients with chronic inflammatory rheumatic conditions, such as rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. These delays not only the cause of delay in the initiation of the correct treatment but also result in disease progression, irreversible joint destruction, and reduced quality of life. The results highlight the imperative of raising public and professional awareness for the early signs of these conditions, since diagnosis of diseases to rheumatologists on time can significantly enhance outcomes. Building up primary healthcare systems, equipping general practitioners with the training to recognize early disease markers, enhancing access to specialist services and advanced facilities are key steps in reducing diagnostic delay. In addition, patient education on disease control and early medical consultation should be emphasized. Specialized

research must identify specific delay barriers to early diagnosis and investigate interventions that can decrease delays in different healthcare environments. Early and precise diagnosis with immediate treatment initiation continues to be the guideline for better prognosis and quality of life in rheumatic patients.

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Alina Fakhar: Study design, data collection
Shazia Zammurrad: Literature Review, Data collection, final
Uzma Rasheed: Literature Review, Proof Reading
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Original Article **Open Access**

Effect of Septoplasty versus Septoplasty with Turbinate Reduction for Relief of Nasal Obstruction due to Deviated Nasal Septum

Aiman Fatima Naqvi, Muhammad Waqas Ayub, Asim Abbas, Haider Ali, Fizza Batool, Bakhtawar Meraj

Abstract:

Objective: Nasal obstruction has significant impact on life quality, with deviated nasal septum being the third most common cause. This condition involves nasal structural abnormalities that reduce airflow. This study evaluates the comparative effectiveness of septoplasty alone versus septoplasty combined with turbinectomy in patients presenting with a deviated nasal septum.

Study Design and Setting: This was a prospective, randomized comparative study conducted in ENT Department at CMH Hospital Malir. Patients underwent septoplasty with and without turbinectomy.

Methodology: A total of 88 patients underwent septoplasty for a deviated nasal septum. Participants were randomly assigned into two groups, with 44 patients in each. Group A underwent septoplasty alone, while Group B received septoplasty with turbinectomy. The nasal obstruction severity was evaluated using the NOSE score, with a mean preoperative score of (11.16±1.1) for septoplasty and (8.6±1.19) for septoplasty with turbinectomy. Surgical outcomes were assessed one month postoperatively using NOSE scores to compare the effectiveness of both procedures.

Results: Results revealed significant postoperative improvement in nasal obstruction symptoms, with both septoplasty alone and septoplasty with turbinectomy showing relief in symptoms. However, patients who underwent combined procedure experienced greater reductions in nasal blockage, congestion, trouble sleeping, and difficulty breathing during exertion. Statistical analysis confirmed that septoplasty with turbinectomy provided significant symptomatic improvement compared to septoplasty alone ($P<0.05$), emphasizing added benefit of turbinate reduction in improving nasal airflow.

Conclusion: Combining inferior turbinectomy with septoplasty is more effective than performing septoplasty alone in patients with nasal obstruction due to deviated nasal septum.

Keywords: Airway resistance, Nasal obstruction, Nasal septum, Turbinates, Septoplasty, Nasal septal deviation

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INTRODUCTION:

Nasal obstruction refers to the subjective feeling of inadequate airflow through the nasal passages. Nasal obstruction is a highly prevalent condition, experienced by 30 - 40% of the general population, and is most commonly observed by otolaryngologists.[1] Nasal obstruction is known to cause significant impact on quality of life. The studies showed that the prevalence of deviated nasal septum ranges from one-third of the general population to as high as 76%[2] and it is the third most frequent cause of nasal obstruction. In this condition there is structural abnormalities in the bony and cartilaginous parts of the nose that often leads to breathing difficulties, recurrent sinus infections, and sleep disturbances.[3] The much higher prevalence of nasal septal deviation (NSD) had been identified using advanced diagnostic methods, such as CBCT, with rates reaching up to 86.6%.[4]

Among individuals presenting with structural nasal obstruction, accurate evaluation of nasal septal deviation (NSD) poses a significant clinical challenge. Though NSD

is a common anatomical variation, it is often difficult to isolate its precise contribution to nasal airflow impairment and overall symptomatology and the reason of this complexity is the multifactorial nature of nasal obstruction, where other elements such as turbinate hypertrophy, mucosal inflammation, and nasal valve collapse may coexist and complicate the clinical picture. Thus it requires a comprehensive assessment including patient history, physical examination, endoscopic evaluation, and imaging studies, to determine whether NSD is the primary cause of obstruction or merely an incidental finding. Moreover, the subjective nature of nasal blockage symptoms and variability in patient perception further complicate the diagnostic process. Therefore, clinicians must exercise careful examination and utilize a combination of objective and subjective tools to accurately identify the role of NSD in structural nasal obstruction that can guide to appropriate management strategies.

The NOSE scale is a validated and reliable tool for used for subjective evaluation of nasal obstruction symptoms.[5] The NOSE questionnaire is designed to measure the severity of symptoms and the impact of nasal obstruction on patient's quality of life. It provides scores ranging from 0 to 100, with higher scores indicating more severe obstruction. Globally, septoplasty with or without turbinate modification shows significant enhancement in obstructive symptoms at long-term follow-up per both objective and subjective measures.[6] This treatment is widely accepted for structural nasal obstruction. A number of studies have demonstrated the effectiveness of septoplasty, with patient satisfaction rates ranges from 50% to 100%.[7,8]

A study conducted by Harvey RJ, concluded that nearly patients continue to experience nasal obstruction even after experiencing primary septoplasty.[9] A deviated nasal septum is often accompanied with inferior turbinate hypertrophy, that leads to increased airway resistance, particularly involving the contralateral nasal cavity. This may result in persistence of residual symptoms among patients postoperatively, which highlights the importance of addressing turbinate hypertrophy alongside septal deviation to attain optimal surgical outcomes and long-term relief from nasal blockage.

The incomplete correction of the septal deviation is the most common cause of persistent symptoms. However, other factors, such as nasal valve dysfunction, worsening allergic rhinitis, or inadequate treatment of turbinate hypertrophy, may also play a role.[10] Radiological evidence shows that compensatory enlargement of the inferior turbinate on the side opposite the septal deviation significantly increases nasal airway resistance, contributing to obstruction.[11] To address this, turbinate reduction is often performed alongside septoplasty to enhance nasal airflow, alleviate symptoms and enhancing the surgical outcomes and improve nasal airflow.[12] Although both septoplasty and septoplasty with turbinectomy are widely performed, there is a lack of robust comparative studies evaluating their outcomes in terms of nasal airflow, symptom relief, and patient satisfaction. There is insufficient research utilizing objective tools like the NOSE scale to compare the effectiveness of these procedures. Comparing the outcomes of septoplasty alone versus septoplasty with turbinectomy will help determine whether the combined procedure provides superior symptom relief and better long-term results.

METHODOLOGY:

This comparative study with RCT design was conducted at the ENT department of CMH Hospital Malir, Karachi. Duration of study was started from August 2024 to January 2025. Research was approved by the Institutional Review Board (IRB) in accordance with the standards of accepted medical ethics with reference number 11/24/IRB/KIMS.

In this study, patients were enrolled between age 18 and 50 years who presented with nasal obstruction due to deviated nasal septum (DNS), or anterior septal defect (ASD) or inferior turbinate hypertrophy. Participants were excluded with nasal polyps, epistaxis, nasal perforations, facial malformations, chronic sinusitis, and other nasal pathologies. Moreover, patients with a history with again nasal surgery and expecting females were also excluded minimize confounding factors.

The participants were selected using a non-probability purposive sampling method, including all patients who fill full the inclusion criteria during the study period. The sample size was calculated using OpenEpi version 3.0, based on mean NOSE score 11.16 ±1.1 and 8.6 ±1.19 for septoplasty and septoplasty with turbinectomy respectively, 95% confidence interval and 80% study power. The estimated minimum sample size was eight patients, with 4 per group, but a total of 88 patients were included, with 44 in each group to enhance validity of study result.

This study included patients suffering surgical procedure for deviated nasal septum at the ENT department of CMH after obtaining informed consent. Participants were randomly assigned into two groups using the coin toss method. Patients younger than 18 years or those with epistaxis, nasal polyps, chronic sinusitis, facial malformations, nasal perforations, were excluded from the study.

The study Participants were categorized into two groups: Group-A underwent septoplasty, while Group-B received septoplasty with turbinectomy. Surgery performed under general anesthesia.

Septoplasty was performed using either a Killian's incision or a hemitransfixation incision. For Group B, septoplasty was conducted following the same technique as in Group A, with nasal turbinectomy scissors used for turbinate resection and contralateral inferior turbinate was removed. In Group A, the nasal pack was removed after 24 hours,

whereas in Group B, it was removed after 48 hours.

The surgery procedures were completed by specialist otolaryngologist. *Nasal Obstruction Symptom Evaluation Scale (NOSE)* was applied to assess the NOSE score after one month of the surgery. All patients' characteristics were recorded on a proforma like age, gender, disease duration, NOSE score on *Nasal Obstruction Symptom Evaluation Scale***.**

All information was analyzed by using SPSS 20. Descriptive statistics were applied to determine the mean and SD for age, duration of disease, and NOSE score, while numbers and percentages were estimated for gender. To control the potential confounding, the data were stratified based on age, gender, and disease duration.

All participants were informed about the surgery. The surgical procedure was conducted by experienced surgeons. The surgeon was ensuring consistency for performing septoplasty and septoplasty combined with inferior turbinectomy surgical technique, to minimizing the variability. Patients were assigned, one surgeon of the two based on convenience.

To control the postoperative care through all patients. Patients were closely observed after the immediate postoperative period and throughout follow-up visits to measure the healing, for symptom and any possible complications. For clinical evaluation, endoscopic assessments and physical examinations were reported, and patient-reported outcome measurements such as visual analog scales (VAS) and NOSE scores for breathing comfort.

All relevant information reported as surgical notes. Furthermore documented the intra-operative findings, and postoperative meticulously for subsequent finding. This inclusive approach allowed for a strong comparison of outcomes between the two surgical techniques were evaluated and confirmed the findings under reliable clinical observations.

RESULT:

The assessment of demographic characteristics of study participants with deviated nasal septum suffering septoplasty and those suffering septoplasty with turbinectomy. The mean age and standard deviation of patients in the septoplasty group was 23.86 ± 6.13 years, while 30.65 ± 7.90 years in the septoplasty with turbinectomy group which was significantly higher. In the septoplasty group, majority 39 (53.4%) were males, while, 10 (66.7%) patients were female, and 34 (46.6%) were male in the septoplasty with turbinectomy group.

The paired sample t-test was applied to assess the effect of septoplasty on symptom severity in patients with DNS. The result revealed statistically significant progressed across all evaluated symptoms of the following treatment. For nasal blockage/ obstruction, the average score reduced significantly from 1.18 of a mean difference ($P < 0.001$). Similar substantial increased were observed in other symptoms, including nasal congestion/ stuffiness and sleeping trouble, where mean±SD scores reduced from 2.57 ± 0.82 to 1.39 ± 0.66 (difference: 1.18, $P < 0.001$) and from 2.45 ± 0.59 to 1.39 ± 0.75 (difference: 1.07, $P < 0.001$), one-to-one.

A prominent increased was also noted problem in getting enough air through the nose during exertion, with the mean score reducing from 2.39 ± 0.69 to 1.25 ± 0.78 ($P < 0.001$). The most significant improvement was observed in distress breathing through the nose, where the mean score reduced from 2.27 ±0.62 to 0.82 ±0.72, resultant in a mean difference of 1.46 ($P < 0.001$).

Research findings highlight the effectiveness of septoplasty in significantly reducing nasal symptoms and improving

Table-1: Pre-operative vs. Postoperative nose score comparison in septoplasty patients

Septoplasty	Preoperative		Postoperative		Paired t-test	
	Mean	SD	Mean	SD	Mean difference	P value
Nasal obstruction	2.64	0.685	1.45	0.820	1.182	<0.001
Nasal congestion or stuffiness	2.57	0.818	1.39	0.655	1.182	<0.001
Trouble sleeping	2.45	0.589	1.39	0.754	1.068	<0.001
Unable to get enough air through my nose during exercise or exertion	2.39	0.689	1.25	0.781	1.136	<0.001
Difficulty in breathing through my nose	2.27	0.624	0.82	0.724	1.455	<0.001
Total Score	12.3182	2.43781	6.2955	1.87492	6.02273	<0.001

Table-2: Pre-operative vs. Postoperative Nose score Comparison in Septoplasty with Turbinectomy Patients

Septoplasty with turbinectomy	Preoperative		Postoperative		Paired t-test	
Nasal obstruction	2.57	1.02	0.661	0.731	1.545	<0.001
Nasal congestion or stuffiness	2.59	0.89	0.693	0.655	1.705	<0.001
Trouble sleeping	2.55	0.82	0.548	0.582		<0.001
Struggled breathing through the nose during physical activity or exertion.	2.55	0.91	0.548	0.676	1.636	<0.001
Difficulty in breathing through my nose	2.45	0.93	0.589	0.759	1.523	<0.001
Total Score	12.7045	4.5682	1.77292	2.51875	8.13636	<0.001

breathing functionality in deviated nasal septum patients.

The effectiveness of septoplasty combined with turbinectomy in relieving nasal symptoms in patients having DNS by comparing preoperative and postoperative severity scores of symptoms. The outcome of paired t-test showed significant improvement across all assessed characteristics. The significant decrease in score of nasal blockage/ obstruction was observed postoperatively with a mean difference of 1.55 ($P < 0.001$). Similarly, nasal congestion or stuffiness presented a remarked able improvement, with average scores reducing from 2.59 ±0.89 to 0.69 ±0.66, with a mean difference of 1.71 ($P < 0.001$). A statistically significant reduction was also observed in trouble sleeping, where the mean score dropped from 2.55 ±0.82 to 0.55 ±0.58, reflecting a mean difference of 2.00 ($P < 0.001$).

During physical activity or exertion, in struggling to breathe through the nose, the mean score decreased significantly 1.64 ($P < 0.001$). The breathing trouble symptom, through the nose showed considerable improvement, through the mean score decreasing from 2.45 ±0.93 to 0.59 ±0.76, with 1.52 mean score difference ($P < 0.001$). Overall, the total symptom score showed a substantial reduction, declining from 12.70 ± 4.57 preoperatively to 1.77 ± 2.52 postoperatively, with a mean difference of 8.14 ($P < 0.001$).

The postoperative outcomes of septoplasty and septoplasty with turbinectomy were compared using an independent sample t-test. Patients undergoing septoplasty with turbinectomy showed significantly greater improvement in most symptoms, including nasal blockage or obstruction with a mean difference of 0.43 and P value= 0.011, nasal congestion or stuffiness yielding a mean difference of 0.50 and P value= 0.001. The turbinectomy group also showed significant improvement in trouble sleeping with a mean difference of 0.57 and $P < 0.001$ and difficulty getting enough air during exercise or exertion yielding mean difference of 0.34 and $P = 0.031$). For breathing trouble through the nose, no significant difference was observed ($P = 0.474$). The total mean score of symptoms was significantly lower in the turbinectomy group (mean difference: 1.73, $P < 0.001$). Study finding highlighted both procedures are effective in improving nasal symptoms, septoplasty with turbinectomy offers superior postoperative to relief for most symptoms compared to septoplasty alone.

DISCUSSION:

The present study highlights the comparative effectiveness of septoplasty and septoplasty plus turbinectomy in alleviating nasal symptoms among patients with deviated nasal septum (DNS).

The findings of the current study revealed a clear significant clinically improvement in nasal obstruction in patients who suffered with septoplasty. Participants informed consistent postoperative relief in across multiple symptoms like nasal blockage, disturbance in sleep, nasal breathing difficulty, and nasal stuffiness. These outcomes reinforce the well-established role of septoplasty as an effective modality for symptoms origins to a deviated nasal septum. In most of the cases, repositioning of the septum alone appears as satisfactory to restore functional airflow and improvement in day-to-day respiratory comfort.

The present study conclusion is in line with broadly consistent with the studies reported by Sommer et al[13]. and Alotaibi et al.,[14] These researches reported substantial improvements in septoplasty and also proved secondary benefits particularly in nasal blockage, disturbance in sleep, nasal breathing difficulty, and nasal stuffiness

The result from present study, emphasizes the clinical efficacy of both interventions as viable surgical options for patients presenting with a deviated nasal septum together with inferior turbinate hypertrophy. This outcome was determined by systematic evaluation of pre-operative and post-operative symptoms of patients, including nasal obstruction, difficulty in breathing, snoring, sleep disturbances, and overall patient-reported data related to quality of life. There was statistically significant improvement in air flow through nasal passage and reductive in symptoms of obstruction was observed among patients with both surgical approaches. The current research data analysis revealed that patients who underwent septoplasty combined with turbinate reduction, have achieved a superior degree of symptomatic augment than those treated with only septoplasty. This outcome enhanced the attributable to the dual modification of structural deviation and mucosal hypertrophy, which together contribute to nasal airway compromise.

The finding of this study closely aligns with a study reported from Pune, India by Karodpathy et al.,[15] who observed postoperative Nose scale scores improvement across both treatment groups, which is statistically significant and favoring the combined surgical intervention. Their findings are particularly informative like nasal blockage 2.6±0.5 vs 1.68±0.47 *(p<0.001)*, nasal congestion/ stuffiness 2.08±0.49 vs 1.56±0.506 *(p<0.001)*,, trouble sleeping 2.48±0.509 vs 1.76±0.435 *(p<0.001)*,, unable to get enough air through my nose during exertion 1.96±0.454 vs 1.56±0.506 *(p<0.001)*,, and total Nose score 11.16±1.1 vs 8.6±1.19 *(p<0.001)*, while septoplasty alone was effective in correcting deviation of the central nasal framework.

Taken collectively, these results underscore the importance of individualized surgical planning that considers the extent of turbinate hypertrophy in addition to septal deviation. For patients exhibiting substantial turbinate enlargement, the combined procedure may represent a more effective therapeutic strategy, leading to improved functional outcomes and greater patient satisfaction.

The results of present study demonstrate that combine the septoplasty and inferior turbinate reduction provides substantial pronounced relief in postoperative symptoms

like nasal blockage, congestion, troubled in sleeping and struggling in breathing during exertion in patients presenting with nasal obstruction and inferior to a deviated nasal septum complains.

These outcomes of study support the available literature, septoplasty plus turbinate suggest better improvements in longer outcomes compared to septoplasty alone.

Similar randomized study was reported from India by Sharma AR., observed a substantial enhancement in mean NOSE scores. after 1, 3, and 6 months postoperatively follow up (9.4 ±2.62 vs 5.10± 2.46), (6.26± 2.6 vs1.61 ±1.67) and (4.16± 3.11 vs 0.21± 0.41) (*p*= <0.001) respectively in patients undergoing septoplasty with inferior turbinectomy, compared septoplasty alone.[16] This outcome pattern was repeat in present study sample.

Another similar research was found conducted in Iran by Samarei R & Mabarian S.A., which compared at baseline, 6, 12, 24 and 48 months follow up in septoplasty with and without turbinectomy groups using mean NOSE scores 6 to 48 months (67.4 ±22.4 vs 69.0±29.4) (p= <0.001) to (35.0 ±20.8 vs 11.9 ±8.3) (p= <0.001) and VAS scores 7.4 ±23.3 vs 39.2 ±19.2(p=0.013) to 33.9 ±20.3 vs 12.0±11.5(p? 0.001) to evaluate the efficacy of earlier and more meaningful symptom relief in nasal obstruction[17].Both intervention researches revealed the statistically significant arguments on better symptom relief in Septoplasty with turbinoplasty group on all postoperative follow-ups.

For further support of this modality combining inferior turbinate reduction with septoplasty, a systematic review and meta-analysis by Ladjam et al[18], study conclusion established a statistically significant augment in NOSE score compared to septoplasty alone. The marked improvement in nasal blockage and congestion highlights the importance of turbinate reduction in improving nasal airflow. Inferior turbinate hypertrophy, which frequently accompanies DNS, significantly contributes to nasal obstruction. By reducing the turbinate size, septoplasty with turbinectomy decreases mucosal contact and airway resistance, explaining the observed symptomatic relief. Constant findings were reported in a study by Seden N et al., Inferior turbinate ablation combined with septoplasty does not provide any more benefit to the objective and subjective outcomes of patients than septoplasty alone.[19]

The significant reduction in trouble sleeping, with a mean difference of 0.57 and P < 0.001 further highlights the advantages of incorporating turbinectomy. Nasal obstruction is a well-established cause of sleep disturbances, including poor sleep quality and obstructive sleep apnea. The improved symptom scores in our study suggest that restoring nasal airflow through combined surgery positively influences sleep patterns, thereby enhancing overall patient well-being. Similar findings were reported by Mahmoud Elhabashy, who observed a subjective improvement in sleep quality among patients with obstructive sleep apnea and nasal obstruction following intranasal surgery. This effect was more pronounced in patients who underwent inferior turbinectomy alongside septoplasty, with a significant value of 0.003, compared to 0.005 for septoplasty alone.[20]

Though turbinectomy is an effective procedure for relieving nasal obstruction but it may cause complications including pain, bleeding, infection, crusting, nasal edema, and synechiae formation. Late complications may be more significant and include chronic nasal dryness, atrophic rhinitis, persistent crusting, hyposmia, and the development of empty nose syndrome, particularly after excessive or total turbinate removal. The findings of this study suggest that addressing both septal deviation and turbinate hypertrophy provides a more comprehensive solution for nasal obstruction. This aligns with a growing consensus in the literature encouraging for a combined surgical approach among patients with symptoms of nasal blockage due to deviated nasal septum. This study was conducted in CMH Hospital Malir only, which may limit the generalizability of its findings. Therefore, while the combined approach of inferior turbinectomy with septoplasty showed promising results, further studies involving diverse populations and clinical settings are needed to confirm its broader applicability and ensure consistent benefits across varied healthcare contexts.

CONCLUSION:

The findings of current study demonstrate the benefits of combine clinical intervention, turbinectomy with septoplasty on septoplasty alone in patients coming with the nasal obstruction and inferior to a deviated nasal septum complains. These surgical intervention suggest a superior symptomatic relief to nasal airflow impairment i.e., inferior turbinate hypertrophy and septal deviation. Despite the fact septoplasty ruins effective in straightening the nasal septum, while septal may not resolve nasal obstruction when turbinate enlargement persists. Inferior turbinectomy balances septoplasty by surgically tumbling the much of the hypertrophied turbinates, therefore expanding the nasal airway and moderating residual obstruction. Septoplasty having sustained improvement in objective nasal patency and patients subjective interpretations. Remarkably, patients who experienced the combine interventions (turbinectomy plus septoplasty) reported better statistically significant relief to symptoms including sleep disturbances. Moreover this cohesive intervention was related to better postoperative pain satisfaction and reduced the likelihood of necessity revision procedures and improvement in patient's quality of life. Also highlighted the personalized surgical planning with consider both factors septal alignment and turbinate size. Taken as a whole, integrating both procedures offers an augmentation and effective restoring optimum nasal function and long-term symptom resolve.

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Authors Contribution:
Aiman Fatima Naqvi: Idea conception, study design, data collection, analysis and interpretation, literature search, and drafting of the manuscript.
Muhammad Waqas Ayub: Analysis, interpretation, drafting of manuscript and data comparison.
Asim Abbas: Interpretation and critical revision of the manuscript.
Haider Ali: Interpretation, drafting of manuscript and data comparison.
Fizza Batool: Interpretation, and data comparison.
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Original Article **Open Access**

Association of Obesity with Outcomes in Patients with Chronic Kidney Disease

Rameen Aijaz, Bushra Jamil

ABSTRACT

Objective: The present study was designed to clarify the impact of obesity with outcomes among hospitalized patients with chronic kidney disease (CKD).

Study design and setting: A 6 months prospective cohort study from From April to September 2024, which took place in the Department of Medicine, Aga Khan University Hospital, Karachi Pakistan.

Methodology: The patients were enrolled from inpatient and outpatient medical wards of AKUH and 200 hospitalized CKD patients were recruited and divided equally into obese (BMI >30 kg/m²) and non-obese (BMI <30 kg/m²) groups. Baseline characteristics were contrasted, and 30-day in-hospital mortality was assessed. We conducted subgroup analyses for age, sex, diabetes and hypertension. p-values were computed by SPSS version 25 and the results of = 0.05 determined significance.

Results: Compared with non-obese patients, obese patients were younger, more likely to be male, and had a higher mean estimated glomerular filtration rate (eGFR). Diabetes occurred less frequently in the obese group (21% vs 47%) and hypertension was present in both groups. Obese patients had a 7% 30-day mortality compared to 3% for non-obese patients [RR = 2.33 (p =.20)]. The risk of mortality was higher in women, younger individuals and those with diabetes but the associations did not reach statistical significance.

Conclusions: Obesity was significantly associated with increased short-term mortality in hospitalized CKD patients, especially for women and diabetics.

Keywords: Body Mass Index, Diabetes Mellitus, Hypertension, Kidney Disease, Mortality, Obesity

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INTRODUCTION

Chronic kidney disease (CKD) is characterised by change in renal parenchyma, functional or structural that lasts for more than three months and whose estimated glomerular filtration rate (eGFR) is less than 60 ml/min/1.73 m². [1] It is a chronic, progressive and life-threatening disease and considered as one of the primary causes of morbidity and mortality worldwide. CKD has become a global public health problem affecting more than 850 million adults globally. The Global Burden of Disease (GBD) 2019 study found that CKD was responsible for 1.4 million deaths worldwide, and circumscribed it as one of the leading causes of non-communicable disease related death. [2] However, projections from the same study suggest that CKD will be among the top five global causes of death by year 2040. [3] The increasing burden underscores the absolute necessity for early diagnosis, risk factor modification and early intervention to slow disease progression and minimize the detrimental ramifications.

The burden of chronic kidney disease (CKD) is even more worrisome especially in resource constrained countries like Pakistan where early diagnostic infrastructure and facilities for renal replacement therapy are scarce, preventive healthcare systems are less developed. Prevalence of end stage Renal Disease (ESRD) in Pakistan is more than 100, we are fighting with limited resources to combat it. 4 Increased prevalence of diabetes mellitus, hypertension obesity and dyslipidemia are the most common etiological causes for CKD in them. 4 In addition, these conditions frequently coexist with each other to promote a vicious cycle of endothelial dysfunction, glomerular lesions and the progression of kidney and heart disease.

In particular, obesity has been identified as a major but modifiable risk factor for the development and progression of CKD.5Renal injury is also linked to obesity via various pathophysiologic pathways - including glomerular hyperfiltration, enhanced renal plasma flow, and intraglomerular hypertension. 6 These hemodynamic and hormonal effects lead to glomerular hypertrophy and

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increased capillary pressure, favoring mesangial expansion, glomerulosclerosis, and in time progressive renal injury. 7 Moreover, obesity is also associated with systemic inflammation, insulin resistance, oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), which contribute to structural and functional renal damage. 5 Altogether, these portion of mechanisms work together not only in the triggering but also in the rapid progression of CKD among obese individuals.

The body mass index (BMI) is still the most popular anthropometric measure to categorize weight status, and estimate health risks of obesity. It is defined as weight (kg) divided by height (m) squared (kg/m²). Several epidemiological studies have shown that high BMI is associated with unfavorable renal outcomes, in the general population and in patients with established CKD. 6-8 Higher BMI has also been associated with more rapid loss of renal function, higher risk of ESRD, and a higher prevalence of cardiovascular morbidity and mortality. 6 But this correlation is not perfectly linear. Several studies have shown a paradoxial "obesity" survival advantage.[9] This paradox might reflect potential beneficial effects of some degree of adiposity in terms of metabolic reserve, resistance to catabolic stress and better tolerance for acute illness.[10]

However, the association between BMI and clinical outcomes in CKD is paradoxical at some levels and not entirely clear. Differences of follow-up status, patient population, and confounders including inflammation, protein-energy wasting (PEW), and malnutrition might contribute to these inconsistencies. [11-12] In some cohorts, a lower BMI has been linked to an increased risk of death likely representing the adverse effects of malnutrition and systemic inflammation in later stages of CKD while extreme obesity may worsen outcomes due to excessive CV and metabolic burden. Differences in patient population, disease stage, and healthcare system all contribute to the difficulty in interpreting BMI-related mortality trends and emphasize the importance of BMI-and cancer-specific data.

Local pilot studies have found that obesity is associated with poor short-term outcomes in CKD patients who are hospitalized.[1] In one tertiary-care cohort, the 30-day in-hospital mortality rate for obese patients with CKD was approximately 25% vs.10% among non-obese patients. This makes the association between obesity and acute clinical outcomes in CKD quite distinct, probably due to increased cardiovascular stress, impaired immune function or metabolic demand during illness. These findings focuses on the need for more thorough examination to evaluate the prognostic significance of obesity and the slowing of CKD progression in our participants.

Understanding the relationship between BMI and CKD end points has important clinical and public health implications. Accurate identification of obesity-associated risk would also allow specific therapeutic interventions, increasingly personalised nutritional management and treatment strategies. Furthermore, if obesity is found to be beneficial or harmful in specific stages of CKD such clarification would help optimize prognostic formulas and it could affect information provided to patients. The coexistent epidemic of obesity and CKD in Pakistan, as well as other emerging countries is becoming a public health challenge. Factors such as Urbanization, sedentary behaviour and dietary change to high calorie low nutrients food have been precipitants of global rise in obesity and the metabolic syndrome. This change in epidemic represents both a challenge and an opportunity: the expanding CKD at-risk population by limited tools for prevention and management. The effect of obesity on renal outcome in these populations is not well known, and there are little large- or long-term analyses about this association.

METHODOLOGY

This prospective cohort study was conducted in the Department of Medicine at Aga Khan University Hospital (AKUH), Karachi, From April to September 2024, after obtaining ethical approval from the Institutional Ethics Review Committee (ERC No. 2023-8241-24405). The study followed the principles outlined in the Declaration of Helsinki for research involving human participants and was also reviewed and approved as exempt by an independent ethics committee. Additionally, approval was obtained from the College of Physicians and Surgeons Pakistan (CPSP) prior to the commencement of data collection. The duration of the study was six months. All patients received information about the purpose, risks, and potential benefits of the study and provided written informed consent prior to participation. Confidentiality and anonymity of patients were ensured and we used data for research purposes only.

This was a prospective cohort study investigating the relationship between obesity and short-term clinical outcomes, in particular 30-day in-hospital mortality for patients diagnosed with CKD. The patients were enrolled from inpatient and outpatient medical wards of AKUH at the time. Inclusion was limited to adults aged 18 years and older with a documented diagnosis of CKD. Patients with acute renal injury, those in whom malignancy was terminal or who were suffering from other end-stage diseases, pregnant women and patients not wanting to be included in the study were excluded.

Patients with the required body mass index (BMI) were divided into two groups. The body mass index was calculated by dividing weight by the square of height (kg/m ^{2}). The participants were categorized into obese (exposed group) with the BMI of =30kg / m ^{2} and non-obese (unexposed group) with the BMI of <30kg / m ^{2}. The study involved the enrolment of 200 patients with chronic kidney disease (CKD) comprising 100 patients each. Obesity was the main exposure

and 30 days in-hospital mortality was the major outcome. Deaths were validated using hospital records and discharge summaries. Secondary outcomes were length of stay, intensive care unit (ICU) admission, and the need of ventilatory support. Extended stay was one of the indicators (10 or more days in the hospital). The outcome of the study was in-hospital mortality during the 30 days of admission. The hospital electronic medical records were used to validate all the outcomes and were corroborated by the review of the clinical notes of the treating physician.

This study was specifically designed to have a standardized data collection proforma to ensure systematic and comprehensive recording of patient information. The proforma recorded the demographics (age, sex) clinical features (body mass index, blood pressure, and history of comorbidity like diabetes mellitus and hypertension), and laboratory values (serum creatinine and estimated glomerular filtration rate). Diabetes mellitus was determined as fasting plasma glucose 126mg/dl and/or HbA1C 6.5 and hypertension was determined as blood pressure 140mmHg/90mmHg and used antihypertensive medication in the past two weeks. Microsoft Word and Microsoft Excel were used to design the proforma because it could be formatted without any complications, it was easy to input data, and variables were organized in a structured manner. Data on hospital records were collected by trained research personnel and strict checks on quality were observed before they were entered into the statistical analysis software.

Data entry and analysis were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0. Quantitative variables, including age,BMI and GFR were reported as mean ± standard deviation (SD) or median and interquartile range (IQR) according to data distribution. The categorical variables were reported as frequencies and percentages including gender, diabetes, hypertension, and mortality. The chi-square was used to compare categorical outcomes, including mortality among obese and non-obese individuals with CKD. For continuous variables, comparisons between groups were performed utilizing the independent sample t-test.

The relative risk (RR, 95% CI) was used to assess the relationship between obesity and in-hospital mortality. A relative risk above 1 implied a positive relationship between obesity and the outcome. Stratified analyses were used to adjust for possible confounding factors such as age, gender, diabetes mellitus and hypertension. After stratification, Chi-square test was used to test the independent contribution of obesity on mortality within each group. P values less than 0.05 were considered statistically significant for all tests and analyses are 2-tailed.

In brief, the objective of this study was to analyze the relationship of obesity with negative short-term outcomes among patients with CKD in a tertiary care hospital at Karachi. Strict data collection, strict inclusion and exclusion criteria, and proper statistical methodologies guarantee the reliability and validity of the results. By matching obese and non-obese CKD patients on various outcomes including mortality, admission in ICU, duration of hospital stay the study justified to generate a significant evidence on whether obesity exerts any impact on prognosis of CKD patients at the local tertiary care set up.

RESULTS

A total of 200 patients with chronic kidney disease were enrolled and equally divided into obese (n = 100) and non-obese (n = 100) groups. The mean age of obese patients was slightly lower than that of non-obese patients (56.1 ± 15.3 years vs. 58.5 ± 16.6 years). A higher proportion of younger adults aged 18–50 years was observed in the obese group compared to the non-obese group (21% vs. 12%, respectively). Male predominance was more pronounced in the obese group, with males constituting 69% of participants, whereas the non-obese group showed an almost equal sex distribution (49% males and 51% females).

The average GFR was higher in the obese group (16.4 ± 13.8 ml/min/1.73 m^2) than the non-obese population (13.3 ± 9.5 ml/min/1.73 m^2). Diabetes mellitus occurred less in obese (21%) than non-obese patients (47%) but hypertension was present in morbidly obese and non-obese Haitian women (%) vs. 89%, respectively. (Table 1)

The overall 30-day in-hospital death rate was greater in obese patients (7%) than in non-obese individuals (3%), with a relative risk of 2.33 (95% CI 0.61–8.95, p = 0.20). Overweight patients also had slightly longer hospitalization and higher ICU admission and need for ventilatory support, however not statistically different. (Table 2)

Subgroup analysis revealed distinct trends in mortality (Table 3). Among male patients, mortality was observed in younger obese individuals (9.5%), whereas no deaths occurred in younger non-obese men. In the older age group (51–90 years), mortality was higher among obese patients compared with non-obese patients (6% vs. 3%). Deaths were recorded among obese women (6.5%), while no mortality was observed in non-obese women. Among patients with diabetes mellitus (DM), the mortality rate was markedly higher in obese diabetics (14.3%) compared with non-obese diabetics and non-diabetic obese patients combined (2.1%), corresponding to a relative risk of 6.71 (p = 0.09). A similar, though less pronounced, trend was observed among hypertensive patients, with higher mortality in obese hypertensives compared to their non-obese counterparts (5.6% vs. 3.4%).

Although these variations were not statistically significant, the net result suggests that obesity has a potential to be associated with greater short-term risk of in-hospital mortality in CKD, especially for younger populations, females and individuals with diabetes.

DISCUSSION

In the present investigation, we found that obese subjects with chronic kidney disease (CKD) were at increased risk of 30-day in-hospital mortality versus their non-obese counterparts and despite lack of statistical significance. The detrimental effect of obesity seemed to be stronger in women, younger adults and those with diabetes mellitus. Although these sub-groups findings come from limited numbers, they suggest that the relationship between CKD short-term outcomes and obesity may be influenced by demographic, metabolic and clinical factors. These findings underscore that the relationship between adiposity and renal outcomes is complex, driven by a variety of factors related to biology and context.

Our findings are consistent with other existing literature showing that obesity has complex and sometimes paradoxical effects on renal function and global outcome. Inverse obesity and survival in the presence of CKD has also been shown in large population-based cohort studies, with those who are underweight or obese being at higher risk for death, whereas moderate overweight was associated with improved survival.[11,12] This finding, commonly referred to as the "obesity paradox," has been reported primarily among outpatients or dialysis-dependent individuals in which a greater nutritional reserve may have a protective effect against chronic catabolic stress. However, this potential survival advantage may not be seen in hospitalized individuals at a higher level of metabolic sequalae of obesity, where the increased metabolic load associated with obesity may exacerbate systemic inflammation, oxidative stress and multiorgan dysfunction leading to poor short-term outcomes.[13,14]

A notable finding of this study was that obese patients tended to be younger, were predominantly male, and exhibited a lower prevalence of diabetes mellitus compared with non-obese patients. Despite these seemingly favorable baseline characteristics, obese patients experienced higher 30-day mortality than their non-obese counterparts, although previous studies have suggested that a BMI > 30 kg/m² may confer a survival advantage in obese CKD patients within preexisting care populations. These differences could reflect context-dependent metabolic responses: in the acute ill or hospitalized patient, obesity acts not as a nutritional reserve but as a source of metabolic stress. Severity of acute inflammatory load and hormonal imbalance during hospitalization might exacerbate deterioration in insulin resistance, endothelial dysfunction and oxidative damage, all causes of higher mortality.[15,16]

The interaction between obesity and diabetes was especially notable. The mortality in obese diabetics was about seven times higher than in non-obese diabetics, although the difference was not statistically significant, probably because of the small sample size. This phenomenon is in line with emerging evidence that obesity-related CKD progression depends largely on metabolic pathways such as insulin resistance, lipotoxicity and chronic low-grade inflammation rather than hitting the kidney itself.[17,18] Metabolic health improvements, especially with weight loss interventions, have been shown to attenuate CKD progression and cardiovascular risk. The results from Mendelian randomization analyses and post–bariatric surgery cohorts also provide further evidence supporting the renal and

Table 1. Baseline Characteristics of Obese and Non-Obese CKD Patients

Variable	Obese (n=100)	Non-Obese (n=100)
Age (years, mean ± SD)	56.1 ± 15.3	58.5 ± 16.6
GFR (ml/min/1.73 m², mean ± SD)	16.4 ± 13.8	13.3 ± 9.5
BMI (kg/m², mean ± SD)	27.4 ± 2.6	24.1 ± 2.8
Age group 18–50 yrs	21 (21%)	12 (12%)
Male	69 (69%)	49 (49%)
Female	31 (31%)	51 (51%)
Diabetes mellitus	21 (21%)	47 (47%)
Hypertension	90 (90%)	89 (89%)

Table 2. Comparison of 30-Day In-Hospital Outcomes Between Obese and Non-Obese CKD Patients

Outcome	Obese Group (n = 100)	Non-Obese Group (n = 100)	Relative Risk (95% CI)	p-value
Deaths within 30 days	7 (7.0%)	3 (3.0%)	2.33 (0.61–8.95)	0.20
Survivors at 30 days	93 (93.0%)	97 (97.0%)	—	—
Mean hospital stay (days, ± SD)	11.2 ± 5.6	10.4 ± 4.9	—	0.41
ICU admission required	18 (18.0%)	13 (13.0%)	1.38 (0.70–2.74)	0.34
Ventilatory support used	9 (9.0%)	6 (6.0%)	1.50 (0.57–3.96)	0.41

Table 3. Subgroup Analysis of 30-Day In-Hospital Mortality by Age, Gender, and Comorbidities

Subgroup	Mortality (%) in Obese	Mortality (%) in Non-Obese	Relative Risk	p-value
Age 18–50 years	9.5	0	2.95	0.47
Age 51–90 years	6	3	1.85	0.38
Male	7.3	6.1	1.73	0.49
Female	6.5	0	8.12	0.17
Diabetic	14.3	2.1	6.71	0.09
Hypertensive	5.6	3.4	1.64	0.48

cardiovascular benefits of treating obesity-mediated metabolic dysfunction.[19]

A biologically plausible explanation for our findings may be found in the inflammatory pathways that connect obesity with adverse renal outcomes. Previous studies have demonstrated that plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6) are significantly increased in obese patients with CKD, indicating the pathophysiological link among fat mass, inflammation process and renal injury.[13] The present findings support the concept and our obese cohort are worse in the short term despite a lower presence of diabetes indicating that inflammation driven by excess adipose may independently adversely influence outcome in an acute hospital treatment. Obese and overweight women had a higher mortality, although there were no deaths in the normal-weight women; suggesting sex-specific differences in obesity associated risk. Potential factors that contribute include hormonal effects (e.g., estrogen regulation of inflammation), body fat distribution, and sociocultural differences in access to healthcare. In addition, the fact that younger obese deaths tended to occur and no death occurred in age-matched non-obese subjects implies the lagged life benefit from younger age would be cancelled due to obesity in CKD. These findings highlight the necessity for sex- and age-specific studies to determine modifying effects of demographic and metabolic traits on CKD outcomes.[20]

Investigation of multicenter prospective cohorts in the future with imaging-based measures of adiposity (waist circumference, waist-to-hip ratio, visceral fat index) and inflammatory biomarkers would be instrumental in better understanding the causal pathways between obesity, inflammation, and CKD outcomes. Randomized trials focusing on the effect of targeted weight loss, anti-inflammatory agents and metabolic control on renal and cardiovascular end-points are also needed. Detecting patients most at risk from obesity-associated metabolic stress may allow clinicians to work towards more personalized approaches to attenuate these risks and subsequently reduce hazards for CKD survival.

Notwithstanding these insights, there are several limitations to this study. The number of participants was small, and only few subgroups were compared; thus, the statistical power to detect subgroup differences was compromised and confidence intervals were wide. Obesity classification was determined solely by BMI, which does not differentiate between fat mass, lean body mass or visceral fat distribution factors that exert differential impact on cardiometabolic and renal outcomes. Only single-center design may preclude its generalizability to broader CKD populations, especially from remote rural or resource-poor locations. In addition, given that we performed the short-term observational study, long-term outcomes including CKD progression, dialysis initiation or cardiovascular mortality could not be evaluated.

CONCLUSION

It is important to note that obesity was identified as an independent predictor of short-term mortality in CKD patients. These findings suggest that overweight may magnify the adverse effects of CKD through mechanisms including enhanced oxidative stress, inflammation and renal hemodynamics. The exposure effect relation appeared to be greater in women and in diabetics, possibly indicating synergistic interaction between effects of metabolic and hormonal status that would contribute to a more structural renal-cardiovascular end organ damage. These findings underscore the complex relationship between obesity and CKD, and suggest a potential role for tailored interventions aimed at weight reduction, glycemic control, and CVD risk in these subjects. However, conclusions regarding the impact of obesity on mortality in CKD cannot be drawn from this analysis because of limited sample size and short follow-up period; further large multicenter studies with more extended duration of follow-up will still be required to confirm these associations and to elucidate whether obesity represents a modifiable risk factor for mortality in CKD.

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Authors Contribution:
Rameen Aijaz: Study conception, design, data collection, statistical analysis and manuscrtip drafting
Bushra Jamil: Critical review of the manuscript, supervision and final approval for submission

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Original Article **Open Access**

Characteristics of Connective Tissue Diseases Interstitial Lung Diseases (CTD-ILD) Presenting in a Tertiary Care Hospital

Feroz Raza, Faisal Faiyaz Zuberi, Arif ul Islam, Asim Shafeeque

Abstract

Objective: To determine the characteristics of connective tissue diseases–interstitial lung diseases (CTD-ILD) presenting in a tertiary care hospital.

Study design and setting: This descriptive cross-sectional study was conducted at the Department of Pulmonology, Ojha Institute of Chest Disease, Dow University of Health Sciences, Karachi, from 11th February 2025 till 26th July 2025.

Methodology: For 6 months study patients aged 18–80 years diagnosed with ILD on the basis of clinical presentation and radiological features were included. High-resolution computed tomography (HRCT) was performed to confirm ILD, while connective tissue disease diagnoses were based on clinical criteria. Demographic data, clinical features, comorbidities, and HRCT findings were recorded. Data were analyzed using SPSS version 25. Frequencies, percentages, and mean ± SD were calculated. Chi-square test was applied for categorical variables with p = 0.05 considered significant.

Results: Among 54 CTD-ILD patients (mean age 51.9 ± 12.4 years, 70.4% females), rheumatoid arthritis (53.7%) was the most common underlying disease. Honeycombing (87.0%) and septal thickening (75.9%) were the predominant HRCT abnormalities. On stratified analysis, diabetes mellitus (p = 0.026) and smoking (p = 0.021) were more frequent in RA-ILD. Younger patients (18–40 years) more often had IPAF and SLE compared to older patients (p = 0.002).

Conclusion: RA was the main cause of CTD-ILD, with honeycombing and septal thickening as key HRCT patterns. CTD-ILD subtypes were significantly linked to diabetes, smoking, septal thickening, and age.

Keywords: Autoimmune Disorders; Connective Tissue Diseases; Interstitial Lung Diseases; Rheumatoid Arthritis; Systemic Sclerosis.

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INTRODUCTION

Connective tissue diseases (CTDs) are a diverse group of autoimmune diseases characterized by systemic inflammation, immune dysfunction, and multi-organ damage.[1] An important and serious complication, interstitial lung disease (ILD) is responsible for a high level of morbidity and mortality.[2] The development of diagnostic imaging techniques and enhanced clinical awareness, have been responsible for delineating CTD-ILD as a major determinant for prognosis in patients with rheumatic diseases.[3]

CTD-ILD consists in a wide constellation of autoimmune disorders involving the lung parenchyma with both interstitial features and progressive fibrosis.[4] Although the exact pathogenesis of the disease remains unclear, it is thought that autoantibody-mediated injury, genetic predisposition, environmental triggers, and aberrant tissue repair processes are involved in the pathogenesis of the disease.[5] The variety of CTD-ILD makes the diagnosis and treatment quite challenging, since the clinical features, imaging features, and disease courses differ from one CTD to another.

Several systemic autoimmune diseases associate with ILD, such as RA, SSc, SLE, polymyositis/dermatomyositis, Sjögren's syndrome and MCTD.[6] The entity of interstitial pneumonia with autoimmune features (IPAF) has been more recently described in patients with signs of autoimmunity but did not satisfy the complete diagnostic criteria for a specific CTD.[7] Epidemiological studies indicate that ILD occurs in some 15–50% of CTD patients, but prevalence rates differ markedly between ethnic groups.[8]

Rheumatoid arthritis-related ILD (RA-ILD) is the most frequent type, representing a proportion closer to half of

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CTD-ILD in some case series.[9] The most common second type of ILD is associated with systemic sclerosis (SSc-ILD) where there is evidence that a significant subset of SSc patients develop ILD within the disease course.[10] Conversely ILD is rarer in SLE and inflammatory myopathies but is a significant cause of morbidity. This distribution highlights the importance of systematic screening in any autoimmune disease.

High-resolution CT (HRCT) is a game changer CTD-ILD where fine morphology is investigated in detail. The patterns of CTD-ILD are diverse, and NSIP and UIP are the two most frequent patterns encountered in patients with CTD-ILD.[11] NSIP, more commonly seen in SSc and inflammatory myopathies, presents with ground-glass opacities and reticular changes, whereas UIP, which is more commonly associated with RA, is characterized by basal and sub pleural honeycombing. These radiological subtypes are not only descriptive, but also have prognostic significance, with most cases of UIP associated with significantly worse overall survival.

Risk factors for ILD development in CTDs seem to differ from those for the underlying autoimmune diseases alone. It has been noted that smoking, aging and metabolic comorbidities (e.g. diabetes mellitus) increase susceptibility and progression of fibrotic changes.[12] For placebo, diseases such as smoking, which has been found to act synergistically with anti-cyclic citrullinated peptide (anti-CCP) antibodies in generating RA-related PF, are known to contribute to PF occurrence. This crosstalk between environmental exposures and immunological mechanisms underscores the complex etiology of CTD-ILD.

Despite the progress in diagnosis and therapy, important open questions persist. The clinical presentation of CTD-ILD varies considerably, with indolent disease seen at one extreme and fulminant, rapidly progressive fibrosis observed at the other. Management approaches often employ the use of immunosuppressant or antifibrotics, however the ideal therapeutic strategy has not been established as a result of variable populations. In addition, the bulk of the literature is based on Western cohorts, and few studies have documented the spectrum and outcomes of CTD-ILD in resource-limited health care systems. This lack of understanding has limited the relevance of global data to local populations.

In view of the significant impact of CTD-ILD on patient prognosis and the heterogeneity of disease presentation, more studies are warranted to enhance the accuracy of diagnosis and facilitate the individualized management of such patients. The objective of the current study is to assess the clinical and radiological profile of CTD-ILD in patients presenting to a tertiary care teaching hospital, and to provide local evidence to inform strategies for screening and treatment.

METHODOLOGY

This cross-sectional descriptive study was carried out among sample of population in the Department of Pulmonology, Ojha Institute of Chest Diseases, Dow University of Health Sciences (DUHS), Karachi for a duration of 6 months from 11th February 2025 to 26th July 2025. The study was started after the approval of the CPSP and it obtained ethical approval from the Institutional Review Board of DUHS (IRB approval no: IRB-3812-DUHS-Approval-2025/44 Date approval: 10th February 2025). The present study was performed in compliance with the Declaration of Helsinki; written informed consent was given by all participants before inclusion. Involvement in the study was voluntary, and confidentiality of patient information was guaranteed at every point of the process.

The required sample size was determined using the OpenEpi sample size software based on prevalence rate of IPAF (idiopathic pneumonia with autoimmune features) as 3.6% according to Jayasinghe et al.95% CI, and 5% margin of error. Sample size calculation we employed a non-probability consecutive sampling method to obtain the required sample size of 54 patients.

Eligible participants were both male and female adults aged 18-80 years who underwent a clinical evaluation and HRCT and had received the diagnosis of ILD. The diagnosis of ILD was reached by agreement between radiologists and pulmonologists based on clinical history, serological findings, and typical imaging features. Patients declined participation, were incompletely documented clinically and had insufficient imaging files were excluded.

Demographic and clinical data was entered in a predesigned structured proforma. Variables consisted of age, sex, and primary presenting symptoms including dyspnea, cough, joint pain, fatigue and chest pain. Comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, hypothyroidism HF and TIPE were also collected. Baseline smoking status was defined as never, ever (former and current smoking), or current smoker; pack-years were calculated for former and current smokers to estimate the intensity of exposure. Time lapse from illness onset and treatment previous history in stroke where it was possible, were also reported.

All the patients had HRCT of the chest and images were reviewed by highly experienced consultant radiologists specialized in thoracic imaging. Characteristic ILD patterns on HRCT were evaluated, including ground-glass opacities, septal thickening, honeycombing, cystic airspaces and traction bronchiectasis. The information on the localization, distribution and size of these anomalies was recorded for individual subjects. Radiological patterns were classified following accepted international criteria for separating UIP, NSIP, and other more rare subtypes.

Data entry and analysis were done using IBM SPSS Statistics

for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous values such as age and duration of symptoms were expressed as mean ± standard deviation (SD) while categorical values such as sex, comorbidities, smoking history, and radiological findings were reported in frequencies and proportions. Stratification was used to adjust potential effect modifiers (age, sex, comorbidity status and duration of symptoms) in the inferential analysis. The relation between categorical variables was analyzed by Chi-square test or Fisher's exact test where the expected frequency in a cell was <5. Independent sample t-tests or one-way analysis of variance (ANOVA) were used for continuous variables when applicable. We considered a p-value < 0.05 as statistically significant.

All analyses were examined for accuracy and double entry of data was used to provide quality control. Interpretation of the findings took into account potential confounders and the cross-sectional nature of the study. The results may extend the general understanding of clinical and radiologic features of connective tissue disease-related interstitial lung disease (CTD-ILD) and idiopathic pneumonia with autoimmune features in the local population.

RESULTS

A sum of 54 CTD-ILD patients were enrolled in this study. The average age of the group was 51.9 ±12.4 years and the ages varied between 28 -80 years. The majority of the patients were older than 40 years. A marked female predominance presented 38 females (70.4%) and 16 males (29.6%), similar to a female-to-male proportion of >2:1 as observed in other autoimmune diseases in the general population.

RA was the most common underlying connective tissue disease associated with ILD, 29 patients (53.7%), followed by SSc in 10 patients (18.5%). Eight (14.8%) patients had idiopathic pneumonia with autoimmune features (IPAF), while 5 patients (9.3%) with systemic lupus erythematosus and 2(3.7%) with mixed connective tissue disease had MCTD. This relative distribution indicated that RA and SSc together already accounted for almost three fourths of all CTD-ILD in the study population, similarly to previous worldwide trends where both these conditions were most often from CTD-ILD spectrum. (**Table 1**)

On radiological evaluation, the high-resolution computed tomography (HRCT) findings showed honeycombing was the commonest abnormality detected and recorded in 47 (87.0%) patients. Septal thickening was the second most common abnormality (41 patients, 75.9%). GG and traction bronchiectasis were identified in 15 patients each (27.7%); cystic air spaces were relatively rare, found only in four patients (7.4%). Most men also displayed honeycombing and septal thickening indicating the fibrotic character of disease evolution in male IPF. These results also indicate the dominance of UIP-like radiological findings in CTD-ILD patients, particularly those with RA or SSc. (**Table 2**)

Among the CTD-ILD subtypes analyzed by sex, RA was also the most common diagnosis among men and women (56.3% vs 52.6%, p = 0.84). Similarly, the other subtypes like SSc, IPAF and SLE had nearly equal proportions of males and females. This suggests that despite the fact both ILD and CTD have a preponderance for being female predominant among patient with these diseases, the distribution of ILD phenotypes is more balanced within men and women at least after developing the disease. The most common comorbidities were hypertension (22.2%) and DM (17.0%). By various subtypes of CTD-ILD, there were no comorbidities which demonstrated a statistically significant difference (all p > 0.05). Of interest, diabetes mellitus was more common in the RA-ILD group compared with other groups highlighting a relatively increased metabolic burden. Hypertension was highly prevalent among all subtypes that may have more to do with age-related comorbidity rather than disease-specific association. The HRCT findings are analyzed in other CTD-ILD subgroups as well. Most of each subtype had honeycombing and septal thickening (p > 0.05). Ground-glass opacities and traction bronchiectasis were slightly more common in IPAF and SSc, whereas ?ndings of cystic air spaces appeared only occasionally, typically in the setting of end-stage FB. Although not significant, these differences indicate unique mechanisms of lung injury between autoimmune subsets. (**Table 3**) Diabetes mellitus (p = 0.026), smoking history (p = 0.021, septal thickening (p = 0.008) and age group (p= 0.002) were significantly associated with different CTD-ILD subtypes. Diabetes Mellitus occurred in almost a third of cases (RA-ILD) and was mostly observed among those with RA-ILD, likely secondary to chronic systemic inflammation, glucocorticoid therapy and metabolic derangements in RA. Patients with SSc and IPAF also had significantly less smoking history in the cigarettes pack year units than those with RA and SLE, reflecting a well-documented connection between cigarette smoke exposure and inflammation of the lung.

Septal thickening was more disproportionately higher in IPAF, SSc than in SLE, indicating a significant degree of interstitial fibrosis in these diseases. Analysis of age distribution also revealed that younger patients (18–40 years) were more likely to exhibit IPAF and SLE, while the frequency of RA increased with age among 3 group (aged 41–80 years). This result supports the idea that ILD related to autoimmune diseases tend to reflect the age-prevalence of the underlying connective tissue disease.

Other HRCT features including honeycombing, ground-glass opacities, traction bronchiectasis, and cystic air spaces showed no significant difference among subtypes (all p > 0.05), suggesting that radiologic resemblance across CTD-related ILDs is common. The distribution of the findings is shown in **Figure 1.** The study demonstrates rheumatoid arthritis as the predominant cause of CTD-associated ILD in this series followed by NVC, honeycombing and septal

thickening being commonest HRCT findings. Strong relationships with diabetes among son-suman and smoking, and age were observed highlighting the complex role of metabolic and environmental factors in driving ILD development / progression in connective tissue diseases

DISCUSSION

In this study, exclusive of IPAF cases, RA (rheumatoid arthritis) was the most common type of CTD-ILD [1], being followed by SSc (systemic sclerosis), MCTD (mixed connective tissue disease), SLE (systemic lupus erythematosus); and then IPAF. This frequency is in agreement with a number of published series in which RA and SSc were reported as the most frequent autoimmune causes of interstitial lung disease. The observed overall and specific prevalence of RA-ILD may mainly be attributed to high global prevalence of disease, the contributing chronic inflammatory burden of RA, in combination with cumulative exposure to immunosuppressive or disease modifying anti-rheumatic therapies.[13,14,15] SSc occupies the second place in most series, such as ours, which is consistent with the well-established fibrotic nature of this disease and with the initial involvement lung parenchyma presents in its natural history.[15]

Radiologically, in our series honeycombing and thickened septa were the most frequent findings (83% and 72%). Since the UIP pattern, honeycombing is highly prevalent (almost 87 out of 100 patients) in this population we suggest that it was the most common pattern. UIP is commonly accepted as a radiologic and histopathologic pattern in CTD-ILD that has been associated with worse prognosis because it represents established fibrosis. Our results confirm at earlier research, reporting that honeycombing was a significant predictive factor for unfavorable outcome in RA-ILD.[13,14] On the other hand, septal thickening and ground-glass opacities were predominantly associated with NSIP, especially in SSc and IPAF patients and in accordance with previous reports of NSIP texture as a characteristic pattern in SSc-related ILD.[16] This radiographic distinction has therapeutic significance, as UIP typically represents low reversibility with immunosuppression while NSIP generally responds to corticosteroids and disease-modifying immunotherapy.[16]

The comorbidity profile of our series also offers relevant clinical information. Diabetes mellitus was substantially associated with RA-ILD, suggesting that metabolic comorbidities are common in autoimmune diseases and may amplify inflammatory and fibrotic lung pathways.[17] Diabetes leads to microvascular damage and low-grade inflammation,

Table 1. Distribution of CTD-ILD subtypes (n = 54)

Subtype	Frequency (n)	Percentage (%)
Rheumatoid arthritis (RA)	29	53.7
Systemic sclerosis (SSc)	10	18.5
idiopathic pneumonia with autoimmune features (IPAF)	8	14.8
Systemic lupus erythematosus (SLE)	5	9.3
Mixed connective tissue disease (MCTD)	2	3.7

Table 2. HRCT findings among participants (n = 54)

HRCT Feature	Frequency n (%)
Honeycombing	47 (87.0)
Septal thickening	41(75.9)
Ground-glass opacities	15(27.7)
Traction bronchiectasis	15(27.7)
Cystic air spaces	4(7.4)

Figure 1: HRCT features across CTD-ILD subtypes

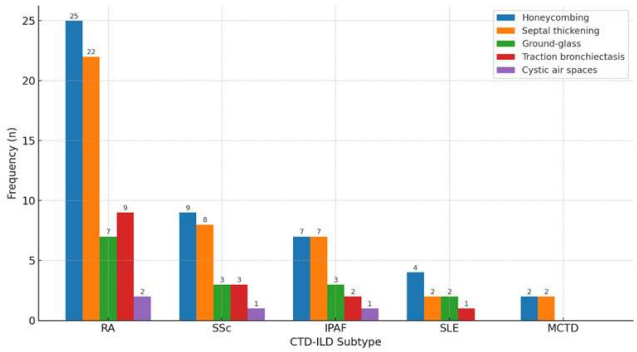

Table 3. Stratified analysis of variables with CTD-ILD subtypes (n = 54)

Variable	RA (n=29)	SSc (n=10)	IPAF (n=8)	SLE (n=5)	MCTD (n=2)	p-value
Gender						
Male (n=16)	9 (31.0%)	3 (30.0%)	2 (25.0%)	1 (20.0%)	1 (50.0%)	0.261
Female (n=38)	20 (69.0%)	7 (70.0%)	6 (75.0%)	4 (80.0%)	1 (50.0%)	
Comorbidities						
Hypertension (n=12)	6 (20.7%)	3 (30.0%)	2 (25.0%)	1 (20.0%)	0 (0%)	0.812
Diabetes mellitus (n=9)	8 (27.6%)	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)	0.026
Hypothyroidism (n=5)	2 (6.9%)	1 (10.0%)	2 (25.0%)	0 (0%)	0 (0%)	0.054
CKD/Heart failure/PE (n=6)	3 (10.3%)	2 (20.0%)	0 (0%)	1 (20.0%)	0 (0%)	0.547
Smoking (n=8)	6 (20.7%)	1 (10.0%)	0 (0%)	1 (20.0%)	0 (0%)	0.021

both described to promote pulmonary fibrosis. The data also underscores the influential role of environment in modulating disease risk as the endemic RA-ILD is statistically linked to tobacco use. Cigarette smoking has been established as a potent trigger of pulmonary autoimmunity, especially in genetically susceptible individuals.[18,19] It drives citrullination of lung proteins and enhances the generation of anti-CCP antibodies, thereby enhancing antigenic damage. These putative mechanisms could also account for the more frequent and severe ILD in smokers with RA in our population. The relationship found between smoking and SLE-ILD is also consistent with previous research suggesting that tobacco exposure enhances oxidative stress and endothelial injury in lupus-related lung disease.

Age-stratified analysis demonstrated that IPAF and SLE were more common among younger patients (18–40 years), while RA-ILD was the main etiology in older patient. This pattern is consistent with previous epidemiological studies regarding the age of presentation in SLE-ILD, which affects usually young females, while RA-ILD tends to occur late in the course of the disease.[20] Differences may be due to differences in immune mechanisms, disease duration and cumulative medication use. In addition, our findings show that ILD secondary to RA is frequently insidious and occurs after many years of systemic inflammation, reinforcing the importance of ongoing pulmonary monitoring in chronic longstanding RA.

Radiologically, traction bronchiectasis and cystic airspaces, and ground-glass opacities were seen in all subtypes without differences between the two groups. This is compatible with the hypothesis that fibrotic remodeling is a downstream, common end-point in CTD-ILD, regardless of the initial autoimmune trigger. Evidence suggests that after parenchymal injury becomes self-sustained, fibroblast activation and extracellular matrix accumulation occur via interdependent cellular pathways.[21] And therefore, while initial histopathologic patterns could be different, advanced fibrosis frequently converges to similar radiographic phenotypes.

From a clinical perspective, our results highlight the need for high-resolution computed tomography (HRCT) to characterize ILD patterns in CTD. Differentiation of UIP and NSIP pattern has important prognostic and therapeutic relationship. UIP often follows a fulminant course and is refractory to immunosuppressive therapy; hence antifibrotic agents such as nintedanib or pirfenidone should be considered after immunomodulation failure. In contrast, patients with NSIP have more potential for reversibility with corticosteroids and steroid sparing agents.[16] Although the classification of MDD into these subgroups largely remains clinical, an early precise diagnosis of subtypes would, consequently, allow the application of individualized treatment strategies and better resource allocation leading to improved clinical outcomes.

In addition, our results also confirm the multifactorial pathogenesis of CTD-ILD. Autoimmune dysregulation, chronic inflammation and vascular injury remain primary drivers, but susceptibility and progression are modulated by genetic and environmental cofactors including smoking, diabetes and age. Immunology has also contributed to a better understanding of the involvement of fibroblast activation pathways, cytokines (e.g. TGF-â as well as IL-6) and extracellular matrix turnover in the pathophysiology of fibrosis.[20] Such observations favor a cross-disciplinary concept of care by including also rheumatologists, pulmonologists and radiologists into the patient management.

Although our results offer valuable regional information, we should consider some study limitations. Our study was conducted in a single tertiary center and might not fully apply to the general CTD-ILD patient population within this geographical area. The sample size was small and might preclude some statistical power to find weaker relationship or further analysis between distinct types of CTD. Additionally, the case-control design does not allow causal inferences for observed risk factors (like diabetes and smoking) on ILD incidence or progression. Furthermore, PFTs and longitudinal follow-up data were not consistently available for correlation of radiographic pattern with lung function decline or mortality. The lack of biomarker and serologic profiling precluded mechanistic interpretation of the immunologic basis for fibrosis, in particular distinguishing between active inflammation and established fibrosis. Notwithstanding these limitations, this work provides pivotal regional data on the spectrum and features of CTD-ILD in South Asia which is poorly represented in global cohorts. This observation highlights the necessity of metacentric prospective studies to validate these patterns, determine regional variability, and generate evidence-based screening guidelines. Subsequent studies using serial imaging, PFT trajectories and biomarker profiling will provide insights into the natural history of disease evolution and response to treatment. In conclusion, this study demonstrates that RA and SSc are still the most common CTDs associated with ILD, where UIP is the principal radiologic pattern related to poor outcomes. Diabetes and smoking are some of the metabolic and environmental agents that seriously affect disease expression, emphasizing the complex contribution of autoimmunity to extrinsic links. Holistic, personalized assessment incorporating clinical, radiological and immunological features is the backbone of enhancing outcome in CTD-ILD.

CONCLUSION:

In this cohort of CTD-ILD, rheumatoid arthritis was the most common underlying disease, followed by systemic sclerosis. Honeycombing and septal thickening were the predominant HRCT findings. Among all variables analyzed, only septal thickening showed a significant variation across CTD-ILD subtypes, being more frequent in systemic sclerosis

and IPAF. No significant associations were observed with gender, comorbidities, or age groups. These findings highlight the heterogeneity of CTD-ILD and emphasize the role of HRCT patterns, particularly septal thickening, in distinguishing subtypes.

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Authors Contribution:
Feroz Raza: Study conception, design, and overall supervision.
Faisal Faiyaz Zuberi: Critical review of the manuscript and final approval for submission.
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Asim Shafeeque: Data verification, analysis support, and critical revision of the manuscript.

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Original Article **Open Access**

Pre-Operative Scoring to Anticipate Intraoperative Difficulty of Elective Laparoscopic Cholecystectomy

Ahmad Yar Khan, Syed Asad Maroof, Muhammad Zarin, Kausar Noor, Muhammad Mazher Irshad, Sheema Gul

Abstract:

Objective: To evaluate the diagnostic accuracy of the Nassar preoperative scoring system in predicting intraoperative difficulty in elective laparoscopic cholecystectomy, using the intraoperative Sugrue score as the reference standard.

Study Design and Setting: A prospective validation study conducted in the Department of Surgery, Khyber Teaching Hospital, Peshawar.

Methodology: A total of 274 patients aged 20–60 years scheduled for elective laparoscopic cholecystectomy were enrolled over six months. Exclusion criteria included prior hepatobiliary surgery, peritonitis, and cholangitis. Preoperative difficulty was assessed using the Nassar scoring system based on clinical and ultrasound findings. Intraoperative difficulty was assessed using the Sugrue scoring system. A Nassar score >6 predicted difficulty. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results: Difficult laparoscopic cholecystectomy (Sugrue score >4) was observed in 16.1% of patients. The Nassar score showed 84.1% sensitivity, 85.6% specificity, 52.9% PPV, and 96.6% NPV. Stratified analysis showed that age >40 years (p=0.008), male gender (p=0.018), and BMI =30 kg/m² (p=0.032) were significantly associated with increased difficulty.

Conclusion: The Nassar preoperative scoring system is a reliable and clinically useful tool for predicting intraoperative difficulty in elective laparoscopic cholecystectomy. Its high sensitivity and NPV make it particularly valuable in ruling out difficult cases, facilitating better surgical planning and resource allocation in resource-limited settings

Keywords: Body Mass Index; Cholecystectomy, Laparoscopic; Risk Assessment; Sensitivity and Specificity; Ultrasonography.

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INTRODUCTION:

The most common operation on the biliary tract is cholecystectomy, which involves surgically removing the gallbladder and is usually recommended for gallstones or inflammation. Laparoscopic cholecystectomy has emerged as the gold standard for treating symptomatic cholelithiasis among the surgical options available. The laparoscopic approach has a number of benefits over the traditional open technique, such as less tissue damage, shorter hospital stays, faster recovery, and improved cosmetic results.[1,2,3]

Despite these advantages, laparoscopic cholecystectomy may still be associated with an increased risk of intraoperative complications. These could include gallbladder perforation, bile leakage, injury to the common bile duct, and harm to nearby structures while surgical instruments are being inserted. Other hazards have also been reported, including the development of adhesions, perihepatic collections, foreign body retention, wound infection, port-site metastases, external biliary fistulas, and in rare instances, cholelithoptysis.[2,4,5] It is important to distinguish intraoperative technical difficulty from postoperative complications, as difficult laparoscopic cholecystectomy refers to increased technical complexity during surgery rather than the occurrence of adverse postoperative outcomes.

Conversion rates to open operations during the early stages of laparoscopic surgery's adoption varied from 2% to 15%; however, as surgical experience has grown, these rates have decreased to approximately 1% to 6%.[3,6] In difficult circumstances, conversion is frequently required to prevent difficulties. Dense adhesions in Calot's triangle, prior upper abdominal surgeries, gallbladder inflammation or gangrene, cholecystoenteric fistulas, and Mirizzi syndrome are some of the factors that can make an operation difficult.[4,7] Numerous preoperative rating systems have been created to help foresee these difficulties. Studies have indicated that one such approach, put out by Nassar et al., has demonstrated promise in forecasting challenging instances, with a sensitivity of 88.2% and a specificity of 73.8%.[5,8-10] Although several preoperative scoring systems, including the Nassar score, have been proposed and validated internationally, their diagnostic performance may vary across populations due to differences in patient characteristics, disease severity, and healthcare settings. Therefore, local validation remains essential before routine clinical adoption.According to one study, 14.6% of laparoscopic cholecystectomies were deemed challenging.[5]

Predicting a challenging laparoscopic cholecystectomy with accuracy can help with improved surgical planning, resource allocation, and patient education. Using the intraoperative Sugrue score as the reference standard, this study aims to assess the diagnostic accuracy of the Nassar preoperative scoring system in identifying challenging laparoscopic cholecystectomy cases. Intraoperative difficulty in laparoscopic cholecystectomy is best assessed using standardized intraoperative grading systems, such as the Sugrue score, which objectively evaluates operative complexity rather than relying solely on conversion to open surgery. By focusing exclusively on elective laparoscopic cholecystectomy, this study aims to determine the diagnostic accuracy of the Nassar score in predicting intraoperative difficulty and to assess its clinical utility for surgical planning and resource optimization.

Using the intraoperative Sugrue score as the reference standard, this study's primary objective is to assess the diagnostic accuracy of the Nassar preoperative scoring system in identifying challenging laparoscopic cholecystectomy cases. As a secondary aim, the study explores associations between patient demographics (age, gender, BMI) and intraoperative difficulty.

METHODOLOGY

Six months after the research summary was approved by Institutional Review Board Khyber Medical College, Khyber Teaching Hospital, ERC number: 661/DME/KMC. This study was carried out as a validation study in the surgery department of Khyber Teaching Hospital in Peshawar from 1st December 2024 to 31st May 2025. Buderer's formula was used to determine the sample size, which was based on the estimated prevalence of difficult laparoscopic cholecystectomy at 14.6%, 88.2%, and 73.8%, with a 10% margin of error and a 95% confidence level. A total of 274 patients were enrolled. The method used was non-probability sequential sampling.

Participants who were scheduled for elective laparoscopic cholecystectomy and were between the ages of 20 and 60 were included. Individuals who had a history of prior hepatobiliary surgery, severe cardiac impairment, cholecystoenteric fistula, peritonitis, or cholangitis were excluded.

Following an explanation of the study's goals, possible risks, and advantages, informed consent was acquired. Age, gender, BMI, place of residence, education, occupation, and socioeconomic position were among the demographic and baseline clinical data that were documented. Every participant had an abdominal ultrasound and a clinical evaluation. One day prior to surgery, a pre-operative Nassar score was determined based on clinical and sonographic observations. Age, gender, ASA classification, primary diagnosis, gallbladder wall thickness, CBD dilatation, pre-ERCP status, and admission type were all included in the Nassar scoring system. Every characteristic was given a score, and a total score higher than six was thought to be indicative of a challenging laparoscopic cholecystectomy.

Under general anaesthesia, the surgeries were carried out by consultant general surgeons who had over five years of experience doing laparoscopic procedures using the usual three-port approach. The Sugrue score, which took into account factors such gallbladder appearance, the extent of distension or contraction, accessibility, infection, and the time required to locate the cystic duct and artery, was determined by intraoperative observations. A challenging laparoscopic cholecystectomy was thought to be confirmed by a Sugrue score higher than 4.

The principal investigator used a standardised proforma to collect data. Every discovery was painstakingly recorded, including the pre- and intraoperative scores.

IBM SPSS version 25 was utilised for data analysis. Depending on the data distribution evaluated by the Shapiro-Wilk test, continuous variables such as age, BMI, Nassar score, and Sugrue score were expressed as means ± standard deviation or median with interquartile range. Frequencies and percentages were used to represent categorical characteristics, including gender, education, domicile, occupation, socioeconomic status, and the incidence of difficult laparoscopic cholecystectomy.

The primary analysis focused on the diagnostic accuracy of the Nassar score against the Sugrue reference standard, calculating sensitivity, specificity, PPV, and NPV. Secondary (exploratory) analyses included stratification by age, gender, BMI, place of residence, education, occupation, and socioeconomic status to assess potential associations with

intraoperative difficulty.

The Sugrue score was used as the reference standard to assess the Nassar score's diagnostic accuracy. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to gauge the effectiveness of the diagnosis. Sensitivity, which was determined as follows, was the Nassar score's capacity to accurately identify patients who had challenging laparoscopic cholecystectomy:

Sensitivity = TP / (TP + FN) × 100

Specificity denoted the ability to correctly identify patients without difficulty:

Specificity = TN / (TN + FP) × 100

Positive predictive value indicated the proportion of patients who tested positive on the Nassar score and were confirmed as difficult intraoperatively:

PPV = TP / (TP + FP) × 100

Negative predictive value referred to the proportion of patients predicted as not difficult who were also confirmed intraoperatively as not difficult:

NPV = TN / (TN + FN) × 100

For this analysis, a 2x2 contingency table was created. Age, gender, BMI, place of residence, education, occupation, and socioeconomic position were additional stratification factors for difficult laparoscopic cholecystectomy. When necessary, the Chi-square or Fisher's exact test was used after stratification, and a p-value of less than 0.05 was regarded as statistically significant.

RESULTS:

The study included 274 patients undergoing elective laparoscopic cholecystectomy. The mean age was 42.8 ± 9.6 years, with 32.8% (n=90) male and 67.2% (n=184) female patients. The mean BMI was 28.4 ± 3.2 kg/m². Regarding place of residence, 58.4% of patients were from urban areas and 41.6% from rural areas. Educational status was distributed as 18.2% primary/none, 43.8% secondary, and 38.0% graduate. Occupation included 51.1% employed and 48.9% unemployed or housewives. Socioeconomic status was low in 29.2%, middle in 54.7%, and high in 16.1% of patients. Median Nassar and Sugrue scores were 5 (IQR: 3–8) and 3 (IQR: 2–5), respectively (Table 1)." Based on the intraoperative Sugrue score (>4), 44 patients (16.1%) out of 274 had a challenging laparoscopic cholecystectomy. A cutoff value of >6 was used to predict difficult laparoscopic cholecystectomy in order to assess the diagnostic accuracy of the Nassar score. A contingency table measuring 2 by 2 was created.

Based on this, the diagnostic accuracy indicators were calculated as follows:

- Sensitivity = 37 / (37 + 7) × 100 = 84.1%
- Specificity = 197 / (197 + 33) × 100 = 85.6%
- Positive Predictive Value (PPV) = 37 / (37 + 33) × 100 = 52.9%
- Negative Predictive Value (NPV) = 197 / (197 + 7) × 100 = 96.6%

Further stratification was performed to evaluate the relationship between patient characteristics and the occurrence of difficult laparoscopic cholecystectomy. Secondary analyses were conducted to explore associations between patient characteristics (age, gender, BMI) and the occurrence of difficult laparoscopic cholecystectomy.

Table 1: Baseline Characteristics of Study Population (n = 274).

Variable	Category / Mean ± SD / n (%)
Age (years)	42.8 ± 9.6
Gender	Male: 90 (32.8%)Female: 184 (67.2%)
BMI (kg/m²)	28.4 ± 3.2
Place of residence	Urban: 160 (58.4%)Rural: 114 (41.6%)
Education	Primary/None: 50 (18.2%) Secondary: 120 (43.8%) Graduate: 104 (38.0%)
Occupation	Employed: 140 (51.1%) Unemployed/Housewife: 134 (48.9%)
Socioeconomic status	Low: 80 (29.2%) Middle: 150 (54.7%) High: 44 (16.1%)
Nassar Score (median, IQR)	5 (3–8)
Sugrue Score (median, IQR)	3 (2–5)

Table 2: Frequency of Difficult Laparoscopic Cholecystectomy

Classification	Percentage (%)	Percentage (%)
Difficult LC (Sugrue > 4)	16.1%	16.1%
Not Difficult LC (Sugrue = 4)	83.9%	83.9%

Table 3: Cross-tabulation of Nassar Score with Sugrue Score

	Sugrue Positive (Difficult)	Sugrue Negative (Not Difficult)	Total
Nassar Positive (>6)	37 (True Positive)	33 (False Positive)	70
Nassar Negative (=6)	7 (False Negative)	197 (True Negative)	204
Total	**44**	**230**	**274**

Table 4: Diagnostic Accuracy of Nassar Score (>6 Cutoff)

Parameter	Value (%)
Sensitivity	84.1%
Specificity	85.6%
Positive Predictive Value	52.9%
Negative Predictive Value	96.6%

Table 5: Stratification of Difficult LC by Demographic Variables

Variable	Category	Difficult LC (n=44)	p-value
Age	<40 years	14 (10.2%)	0.008*
	>40 years	30 (23.4%)	
Gender	Male	21 (23.3%)	0.018*
	Female	23 (12.5%)	
BMI	<30 kg/m²	32 (13.6%)	0.032*
	>30 kg/m²	12 (27.3%)	

DISCUSSION

This study evaluated the diagnostic accuracy of the preoperative Nassar scoring system in predicting intraoperative difficulty during elective laparoscopic cholecystectomy, using the intraoperative Sugrue score as the reference standard. Secondary analyses examining associations between patient characteristics and intraoperative difficulty provide additional clinical context.

According to the Sugrue score, 16.1% of the 274 patients that were included had a difficult laparoscopic cholecystectomy. With a cutoff value greater than 6, the Nassar scoring system showed 84.1% sensitivity, 85.6% specificity, 52.9% positive predictive value (PPV), and 96.6% negative predictive value (NPV).

Although it is a little lower than other worldwide estimates, the prevalence of intraoperative difficulties seen in this study falls within the range documented in comparable studies. A higher percentage of acute and advanced disease cases, such as acute cholecystitis and gallbladder empyema, which were not included in our study population because only elective procedures were taken into consideration, were probably included in Ahmed et al.'s (2025) cohort from a tertiary centre in Ethiopia, which reported a prevalence of 40.2%.[11,12]

The Nassar scoring system's diagnostic performance in this investigation is in good agreement with previous validations. With an AUC of 0.948 and sensitivity of 95.5% and specificity of 96.9%, another study demonstrated a high level of discriminating in a situation with limited resources.[7,14] The usefulness of the scoring system in anticipating operative challenges was further supported by another study, which showed that patients classified as high-risk (score >7) had a significantly higher chance of intraoperative difficulty and conversion to open surgery.[10,15] Given the high NPV of 96.6%, which shows the system's strong usefulness in ruling out challenging instances, our sensitivity and specificity values, albeit being somewhat lower, are still within clinically acceptable levels. Practically speaking, this can simplify operating room scheduling and team allocation in hospitals with limited resources by accurately identifying cases that are unlikely to pose intraoperative difficulties.

Our study's moderate PPV of 52.9% was in line with other recent validations. Due to the relatively low proportion of challenging cases, which has a greater impact on PPV than other performance variables, the PPV was similarly moderate in a prospective analysis with 367 patients, although having acceptable sensitivity.[11,16] While the scoring method can identify the majority of actually difficult cases (as indicated by sensitivity), it will also flag a significant number of cases as tough that turn out not to be, resulting in some over triage. This discovery highlights the difficulty that comes with preoperative prognosis. However, if such over triage results in better readiness and fewer negative outcomes, it might be clinically justified given the potentially severe consequences of intraoperative problems.

A stratified analysis showed that higher BMI, male gender, and advanced age were all substantially correlated with difficulty performing a laparoscopic cholecystectomy. The incidence of difficult surgery was 23.4% for patients over 40 and only 10.2% for patients under 40 (p=0.008). Ahmed et al. found similar results, stating that age above 50 was an independent predictor of problematic LC, most likely due to fibrotic alterations and cumulative inflammatory events in older individuals.[7,17] Additionally, male gender was linked to a higher incidence of difficulties (23.3% vs. 12.5%; p=0.018), which has been a consistent pattern in previous research.

For example, studies[9,18,19] reported a markedly greater difficulty rate in male patients, which they attributed to a higher prevalence of dense pericholecystic adhesions, delayed presentation, and more advanced disease at the time of surgery.

Another important predictor was obesity; patients with a BMI of =30 was more likely to have difficult procedures (27.3% vs. 13.6%; p=0.032). This conclusion is consistent with earlier research that found that higher BMI was associated with impaired visualisation, problems accessing Calot's triangle, and technical issues during port insertion.[8,20] According to research by Farhat et al., BMI is a powerful indicator of conversion and difficulty during laparoscopic cholecystectomy.[8] Therefore, it seems sense to include BMI in scoring models, such as the Nassar system, as it improves their predictive ability.

It should be noted that the intraoperative Sugrue score includes more subjective components like gallbladder appearance, adhesion presence, and time taken to dissect critical structures, whereas the preoperative Nassar score includes clinical and sonographic parameters like gallbladder wall thickness, common bile duct dilatation, and pre-ERCP status. Despite its value, the latter could differ depending on the surgeon's experience and intraoperative judgement, which could affect difficulty rating and cause interobserver differences. However, an intraoperative grading system and a standardised preoperative score offer a formal framework for researching surgical complexity and enhancing results.[14,15]

Our reliance on the Sugrue intraoperative score provides a

more nuanced view of operative difficulty than other studies that used different difficulty benchmarks, such as conversion to open surgery. This is because it captures challenges that may not result in conversion but still present significant intraoperative hurdles. This is particularly important in high-volume facilities because difficult intraoperative situations are still encountered, even though conversions may be uncommon because of skilled surgical teams.

Additionally, the preoperative score cutoff of >6 might not be the best threshold in every population, even if it was chosen based on earlier research, such as that conducted by Nassar et al. To better balance sensitivity and specificity, a receiver operating characteristic (ROC) curve analysis may be helpful in determining the optimal cutoff value for this particular cohort. Finally, even though this study concentrated on difficulty prediction, future investigations should examine whether the application of such grading systems results in better clinical outcomes, including shorter hospital stays, fewer problems, or faster operating times. To determine whether the regular use of preoperative scoring warrants the possible resource allocation related to more aggressively managing high-risk cases, cost-effectiveness assessments would also be necessary.

Despite its strengths, this study has limitations. Exclusion of emergency cases, patients older than 60 years, and those with prior hepatobiliary surgery limits generalizability, particularly to more complex cases. Additionally, the single-centre design and procedures performed by experienced consultants may limit applicability to settings with less surgical expertise.Further multicentre and prospective studies are recommended to validate these findings across diverse patient populations and healthcare settings.

CONCLUSION

This study demonstrates that the Nassar preoperative rating system, which has strong sensitivity, specificity, and an excellent negative predictive value, is a therapeutically useful and dependable tool for predicting intraoperative difficulty in elective laparoscopic cholecystectomy. When used properly, it can improve surgical readiness, aid in patient counselling, and facilitate more effective use of surgical resources, especially in settings with high patient volume or restricted resources. The need of individualised risk assessment is shown by the substantial correlations found between intraoperative difficulties and male gender, age over 40, and obesity. Although the scoring system shows good diagnostic performance, it should be interpreted cautiously because of its modest positive predictive value, which indicates that overestimation of complexity is still possible. To improve predictive thresholds and confirm the system's suitability for larger patient populations, such as emergency and difficult surgical cases, more multicentre study is advised.

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Authors Contribution:
Ahmad Yar: Introduction, Data collection, Result
Syed Asad Maroof: literature review Result
Muhammad Zarin: Result and Discussion
Kausar Noor: literature review, Data Collection
Muhammad Mazher Irshad: Data collection and introduction
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Original Article **Open Access**

Effects of Delayed Skin Closure of Midline Laparotomy Incisions for Peritonitis

Liaqual Ali, Immamuddin Baloch, Javeria Memon, Ahsan Ali, Muhammad Sheeraz, Altaf Hussain

ABSTRACT

Objective: To compare outcomes of delayed versus early primary closure of midline laparotomy wounds in peritonitis.

Study Design and Setting: A randomized controlled trial was carried out during the period from 26th February, 2025 to 30th August, 2025 using consecutive sampling at the Department of Surgery, GMMMC Hospital, Sukkur.

Methodology: After getting ethical approval and consent, eighty patients aged 20-70 years (ASA I-III) were enrolled in this study, undergoing upper midline laparotomy closure for peritonitis. They were randomly placed in Group A (delayed primary closure) and Group B (early primary closure). All were taken up under one team of general anesthesia in the operating theatre. A 15-day follow-up was done for infection and dehiscence of the wound.

Results: Out of 80 patients, the overall wound infection rate was 33.8 %, which was significantly higher in Group B (45 %) compared with Group A (22.5 %); p = 0.033. The incidence of wound dehiscence was higher in Group B as compared to Group A (p = 0.019). Anemia was associated with increased complications, especially early closure. The time taken for surgery was same but blood loss was more with delayed closure (354.10 ± 42.36 ml vs. 305.25 ± 35.46 ml; p < 0.001).

Conclusion: Delayed primary closure of the wound can reduce the incidence of infection and dehiscence in case of peritonitis, although there is a slight increase in blood loss observed.

Keywords: Delayed Primary Closure, Laparotomy, Peritonitis, Wound Dehiscence, Wound Infection.

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INTRODUCTION

Peritonitis is an inflammation of the peritoneal cavity. It can occur as a result of contamination or infection. Peritonitis is a global surgical issue. At the same time, it is considered especially serious in poorer countries. For example, Pakistan suffers from a high burden of peritonitis.[1] The best surgical procedure for generalized peritonitis is midline laparotomy, which allows adequate exploration, source control, and peritoneal lavage.[2] Surgeons face a dilemma between doing the early primary skin closure and delaying it to lower or reduce the incidence of post-operative wound infection. This choice affects patient results, stay in the hospital, and the cost of health care, mainly in developing countries that can't control infection.[3]

The way this is done is through delayed primary closure (DPC) of laparotomy wounds using the deep layer as the first stage. The skin and subcutaneous tissue are open or approximated loosely to facilitate the drainage of the contaminated fluid, which helps in the removal of the bacteria.[4] The total closure of all layers that is done at the termination of the surgery is called early primary closure (EPC). There has been much debate regarding these techniques over time, because there have been contradictory results implicating that it reduces wound infection, dehiscence, and other complications.[5] Even if the EPC supports faster healing time and reduced days in hospital, it has the potential to transmit infection in the contaminated

fields. Because of DPC's potential to increase length of stay and hassle of wound care, the DPC may reduce infection rates by allowing for greater wound drainage and monitoring before closure.[6, 7]

Wound infection after midline laparotomy in cases of peritonitis is still a significant cause of morbidity and mortality in the world. Postoperative complications of 10-30 % have been reported in other studies. Surgical site infections (SSIs) in Pakistan were found at disastrous rates of 20 % to 45% after abdominal surgery due to poor healthcare infrastructure, like congested hospitals, non-sterile environment, and delayed presentations due to socio-economic reasons.[8] Many infections happen due to contaminated or dirty wounds, like peritonitis. It causes longer hospital stays, unnecessary antibiotic use, and makes healthcare costlier. Wound dehiscence is a serious complication that can lead to evisceration. This complication was also found at a significant rate. The data shows that it is commonly associated with factors like infection, poor nutritional condition, and comorbidities. It can include anemia or diabetes, which are commonly found in the community.[9]

In simpler terms, when a dirty wound is closed, a large amount of dirt, bacteria, and necrotic substance gets trapped for the most part in the wound. Thus, they promote infection. In the early phases, the wound was left open to allow it to drain, while the impending infection was treated to ultimately heal.[10] According to the wound classification system by the Centers for Disease Control and Prevention (CDC), this practice aligns with the surgical principles associated with contaminated or dirty wounds. Not all surgeons are persuaded to use DPC in all cases, which is related to the concerns of discomfort in patients.[11]

Multiple international studies have reported that altered timing of wound closure can significantly reduce postoperative infection rates in contaminated abdominal surgeries. Research in countries such as India and South Asia that enjoy a healthcare environment similar to that of Pakistan has all reported a drop in wound infections by approximately 40-50 % in cases of early closure to 15-25 % of cases in cases of delayed closure.[12] The importance of these results is largely due to the connection between the socioeconomic and environmental issues that drive the high rates of infections. In Western countries, however, the literature documents low base-level infection rates and even questions whether closure needs to be postponed, which is suggestive of the difference in the patient population in which the surgery will take place, the surgery environment, and the level of quality of the perioperative care.[13]

METHODOLOGY

A non-probability consecutive sampling technique was used to select randomized controlled trial which was carried out at the Department of Surgery, Ghulam Muhammad Mahar Medical College (GMMC) and Civil Hospital, Sukkur. The time frame was six months as between from 26th February, 2025 to 30th August, 2025. Ethical Review Committee of GMMC/Civil Hospital, Sukkur (ERC No. CMC/RER/217) gave its approval before the beginning of the study. An independent institutional ethics committee granted permission to the research to make sure that ethical standards were met in line with the Declaration of Helsinki. Informed consent was taken in written form during the enlistment of all the participants and privacy of patient information was ensured during the entire study.

Eighty patients (20 to 70 years of both genders) that underwent primary midline laparotomy repair were enrolled. The sample size was estimated with the help of the OpenEpi soft (version 3.01) considering a confidence interval of 95 percent, power of 80 percent and the anticipated rate of wound dehiscence difference between early and delayed closure methods using the published literature of the previous researches (1, 2) in the first place.

Patients, who had primary laparotomy in the midline, and experienced peritonitis as a result of appendicular rupture, perforated peptic ulcer, or bowel injury (traumatic) were included in the study. There were emergency as well as elective laparotomy cases. The participants were eligible provided that their physical status of ASA (American Society of Anesthesiologists) is I–III and they are hemodynamically stable and fit to be put under general anesthesia. Patients were eliminated when they had renal failure, diabetes mellitus, bleeding disorders, chronic liver disease, HIV/AIDS or any other immunocompromised condition, recurrent peritonitis, or were taking long-term corticosteroid treatment.

A pre-designed pro forma was used to record clinical and demographic data, such as age, sex, weight, length of peritonitis, ASA grade, smoking status, anemia, hypertension, and residential location. The lottery method was used to randomly allocate the participants to two groups of equal size (40 individuals) (Group A -Delayed Primary Closure and Group B -Early Primary Closure).

In the first group (Delayed Primary Closure), the peritoneal layer was first stitched followed by loose closure of the musculoperitoneal layer using Prolene sutures. The wound was then stuffed with povidone-iodine impregnated gauze. The tightening of sutures was done slowly on the 5th postoperative day and taken off on the 12th postoperative day.

Group B (Early Primary Closure): The musculoperitoneal layer, fascia, and skin were closed immediately using standard Prolene sutures that were removed on the 8 th postoperative day. The operations were carried out by the same surgical team in all procedures under general anesthesia to reduce the inter-operator variability. All the cases were noted in terms of the duration of operation and intraoperative blood loss. All patients were provided with standard antibiotic

therapy on the initial day of postoperative period and continued up to the time of discharge according to the hospital protocol. The postoperative assessment on the wound was done 48 hours after operation and finally up to 15 days after the surgery to determine the surgical site infections and wound dehiscence as per the hospital post-operative care protocols.

RESULTS

Out of 80 patients who underwent primary closure of the midline laparotomy for peritonitis, 47 (58.8%) were male and 33 (41.3%) were female. The average age of patients was 44.0 ± 12.37 years (Table 1). These patients were equally split into two groups of 40 each. Group A was subjected to delayed primary closure in which the musculoperitoneal layers were closed first, then the fascia and skin were loosely approximated with Prolene sutures, and povidone-iodine-soaked gauze was used to pack the wound. Group B, on the other hand, had early primary closure that was done by closing both the fascia and the skin in interrupted Prolene sutures.

A total of 54 patients (67.5%) were from urban areas, 26 (65.0%) were in the delayed closure group, and 28 (70.0%) were in the early closure group, whereas 26 patients (32.5%) were residing in rural areas, 35.0% from group A and 30.0% from Group B. About their medical history, a smoking history was present in 24 (30.0%). More patients were present in group B (15 patients, 37.5%) rather than in group A (9 Patients, 22.5%). Hypertension was common in 28 patients (35.0%) and was equally common in both groups. Seventeen patients (21.3%) were found to be anemic, more in group A (25.0%) than in group B (17.5%). Eleven patients (13.8%) had no significant past medical history. As per the American Society of Anesthesiologists (ASA) classification, 52 patients (65.0%) were ASA I (normal healthy) with 27 (67.5%) in Group A and 25 (62.5%) in Group B and remaining 28 patients (35.0%) were ASA II (mild systemic disease) including 13 (32.5%) in Group A and 15 (37.5%) in Group B. Thus the two groups were comparable in demographic and clinical characteristics and baseline factors were comparable as per table 1.

Both groups were also evaluated for the duration of peritonitis pre-surgery. The delayed closure group experienced peritonitis for a mean time of 4.53 ± 0.60 days, and the early closure group experienced peritonitis for a mean time of 4.10 ± 0.81 days, as illustrated in Table 1.

Postoperatively, a wound infection developed in 27 patients (33.8%) overall. This was significantly higher in early closure 18 (45.0%), as compared to delayed closure 9 (22.5%). According to the Pearson Chi-Square statistical analysis, the results were statistically significant with p value = 0.033 ($x^2 = 4.53$). It indicates that delayed primary closure is associated with fewer wound infections (Table 2).

The incidence of wound dehiscence, however, was seen in 14 patients (17.5%). However, the incidence was much higher in the early closure group with 11 patients (27.5%), and only 3 patients (7.5%) in the delayed closure group. This difference was also statistically significant ($x^2 = 4.53$, $p = 0.033$). Based on these findings, delayed primary closure may lower the incidence of wound infection and dehiscence in patients undergoing midline laparotomy for peritonitis. Thus, it may enable the surgeon to have an edge over early primary closure in managing contaminated surgical wounds Table 2.

The subgroup analyses showed the effect of delayed primary closure versus early primary closure on wound infection and wound dehiscence across various characteristics. The gender-wise analysis showed that in females, the rate of wound infection was significantly lower with delayed closure that is statistical significance was seen in females, i.e., $p = 0.019$. However, in males, no statistical significance was observed, i.e., $p = 0.312$. It implies that women may benefit the most from delayed closures to reduce post-operative infection. Wound dehiscence showed a similar outcome where fewer events happened in females with delayed closure ($p = 0.041$), while males did not show any significant finding, Tables 3 & 4.

Where a person lives affected their outcome, but it was not a significant difference when analyzed separately for urban and rural groups regarding wound infection. Nevertheless, the study showed that wound dehiscence rates were lower among the urban patients who had delayed closure ($p = 0.029$). Thus, it can be inferred that the urban factors may interact with closure timing to affect wound healing. In rural groups, there were no significant differences, potentially due to limitations of sample size or other contextual factors Tables 3 & 4.

Reviewing the patient's history revealed that anemia was significantly associated with a higher rate of wound infection ($p=0.034$) and also with dehiscence ($p=0.023$) for early closure. It indicates that in case of early closure, anemic patients may be at greater risk of wound complications; hence, surgeons should also consider the preoperative condition during closure techniques. In contrast, the closure groups did not show any statistically significant difference in other histories like smoking and hypertension Tables 3 & 4.

Lastly, assessment based on the American Society of Anesthesiologists (ASA) classification showed trends favoring delayed closure in reducing wound complications, especially in ASA class I patients. Although these results did not reach statistical significance in all analyses, the borderline p-values for wound dehiscence ($p = 0.050$) suggest that healthier patients might also derive benefit from delayed closure (Table 3 & 4). In addition to wound-related outcomes, operative characteristics were analyzed to assess any differences between the delayed and early closure groups.

Table 1. Baseline demographic and clinical characteristics of patients in delayed (Group A) and early (Group B) wound closure groups (n = 80)

Parameters	Total (n=80)	Group A: Delayed Closure (n = 40)	Group B: Early Closure (n = 40)
Sex			
Male	47 (58.8%)	24 (60.0%)	23 (57.5%)
Female	33 (41.3%)	16 (40.0%)	17 (42.5%)
Mean Age (years)		44.0 ± 12.37	
Residence			
Urban	54 (67.5%)	26 (65.0%)	28 (70.0%)
Rural	26 (32.5%)	14 (35.0%)	12 (30.0%)
History			
Smoking	24 (30.0%)	9 (22.5%)	15 (37.5%)
Hypertension	28 (35.0%)	14 (35.0%)	14 (35.0%)
Anemia	17 (21.3%)	10 (25.0%)	7 (17.5%)
No Medical History	11 (13.8%)	7 (17.5%)	4 (10.0%)
ASA Classification			
ASA I	52 (65.0%)	27 (67.5%)	25 (62.5%)
ASA II	28 (35.0%)	13 (32.5%)	15 (37.5%)
Duration of Peritonitis (days)		4.53 ± 0.60	4.10 ± 0.81

Table 2. Comparison of wound dehiscence and infection rates between delayed and early primary closure in midline laparotomy for peritonitis

Outcomes	Categories	Delayed Closure (n = 40)	Early Closure (n = 40)	p-value
Wound Dehiscence	Yes	3 (7.5%)	11 (27.5%)	**0.019***
	No	37 (92.5%)	29 (72.5%)	
Wound Infection	Yes	9 (22.5%)	18 (45.0%)	**0.033***
	No	31 (77.5%)	22 (55.0%)	

The mean operative time was slightly longer in the delayed closure group (123.65 ± 14.44 minutes) compared to the early closure group (121.50 ± 12.08 minutes); however, this difference was not statistically significant (p = 0.472) Table 5.

Intraoperative blood loss was significantly higher in the delayed closure group than in the early closure group. The mean blood loss was 354.10 ± 42.36 ml in the delayed closure group and 305.25 ± 35.46 ml in the early closure group (p < 0.001). This difference of nearly 49 ml suggests that delayed closure patients experienced more bleeding during surgery, which could be related to the condition of the wound or the need for additional surgical measures associated with delayed closure Table 5.

DISCUSSION

The study compared the results of delayed primary closure and early primary closure in patients who had a midline laparotomy operation to repair peritonitis, considering in terms of wound complications, operative parameters, and subgroup differences with respect to demographic and clinical characteristics. The similarities in the various characteristics of the two groups, such as age, gender, comorbidities, and ASA classification, support the internal validity of the comparative analysis.

This significantly reduced wound infection and wound dehiscence observed in the delayed closure group can be compared to a growing body of literature supporting the practice of delayed primary wound closure in dirty or potentially infectious wounds. Delayed closure provides adequate drainage, debride, and improved local infection control before definitive closure, which is perhaps the reason behind the 50% decrease in wound contamination 22.5% vs. 45.0%) and equally lower dehiscence rates (7.5% vs. 27.5%) in this study. These findings are consistent with the prior studies because it was established that delayed closure techniques of contaminated abdominal wounds lead to superior wound healing and lower infection rates.[14]

There were also some significant details provided in the subgroup analyses, including gender-specific benefits of delayed closure. This massive reduction in wound infections and dehiscence among females but not males can be explained by differences in the moods of the skin and connective tissue, hormonal, or wound healing processes that have been previously advanced in the literature.[15] These differences

Table 3. Association of wound infection with patient demographics, clinical history, and ASA classification in delayed and early primary closure groups.

	Wound Infection	Closure		Total	p-value
		Delayed	Early		
Place of Residence					
Urban	Yes	5	11	16	0.107
	N o	21	17	38	
Rural	Yes	4	7	11	0.126
	N o	10	5	15	
Gender					
Male	Yes	8	11	19	0.312
	N o	16	12	28	
Female	Yes	1	7	8	0.019*
	N o	15	10	25	
History					
Smoking	Yes	3	9	12	0.206
	N o	6	6	12	
Hypertension	Yes	3	2	5	0.622
	N o	11	12	23	
Anemia	Yes	2	5	7	0.034*
	N o	8	2	10	
Insignificant	Yes	1	2	3	0.201
	N o	6	2	8	
ASA					
I	Yes	7	12	19	0.099
	N o	20	13	33	
II	Yes	2	6	8	0.150
	N o	11	9	20	

between the genders show that patient-centered surgery is essential because females could gain more in case delayed closure is adopted in high-risk settings.

The statistically significant influence of residence on wound dehiscence was found in urban delayed wound closure patients, but not on infections. This may reflect the enhanced care after an operation and the availability of healthcare centers in the cities, which can aid in the process of identifying and controlling complications earlier.[16] Other factors, such as late presentation or poor compliance phase and environmental differences, may influence the outcome of rural patients; thus, there is a necessity to intervene with specific postoperative interventions among different populations.[17]

It is worth noting that the issue of anemia was critical enough to predispose wound complications in particular situations where early closure was performed. There were higher rates of infection and dehiscence among the anemic patients in the early closure group, which highlights the importance of systemic physiological status in wound healing of the local area. This finding is consistent with the recommendations made by the previous studies,[18,19] which stress the need to improve the patient conditions before the operation, and to use delayed closure in the at-risk population to improve the outcome.

Operative parameters showed that there was no meaningful difference in operative time in the groups, which implies that delayed closure does not add much time to the surgical time, which is a crucial fact to consider when using the resources of the operating room. Nevertheless, the intraoperative hemorrhage discharged in the delayed closure was considerably higher. It could be explained by the fact that the wound environment demands a more detailed debridement and hemostasis before the closure, or, possibly, by a long-term exposure of the tissues to the environment and their manipulation. Agrawal et al. (2017) highlighted similar results, as the risk of bleeding was higher with delayed abdominal surgery closure in case of contamination. In spite of this, the clinical importance of the difference of about 49 ml of the blood loss should be offset against the lower postoperative wound morbidity that is observed in delayed closure.[20]

The ASA trends (classification) indicated that the healthier patients (ASA I) could be helped through delayed closure,

Table 4. Association of wound dehiscence with patient demographics, clinical history, and ASA classification in delayed and early primary closure groups

	Wound Dehiscence	Closure		Total	p-value
		Delayed	Early		
Place of Residence					
Urban	Yes	1	7	8	0.029*
	No	25	21	46	
Rural	Yes	2	4	6	0.250
	No	12	8	20	
Gender					
Male	Yes	2	5	7	0.197
	No	22	18	40	
Female	Yes	1	6	7	0.041*
	No	15	11	26	
History					
Smoking	Yes	2	6	8	0.371
	No	7	9	16	
Hypertension	Yes	1	2	3	0.541
	No	13	12	25	
Anemia	Yes	0	3	3	0.023*
	No	10	4	14	
Insignificant	Yes	0	0	0	---
	No	7	4	11	
ASA					
I	Yes	2	7	9	0.050*
	No	25	18	43	
II	Yes	1	4	5	0.191
	No	12	11	23	

Table 5. Comparison of operative time and intraoperative blood loss between delayed and early primary closure groups

Variables	Groups	N	Mean ± SD	p-value
Operative Time (in minutes)	Delayed Closure	40	123.7 ± 14.4	0.472
	Early Closure	40	121.5 ± 12.1	
Blood Loss (in ml)	Delayed Closure	40	354.1 ± 42.4	0.000*
	Early Closure	40	305.3 ± 35.5	

but the statistical significance was marginal. This concurs with clinical reasoning that patients with fewer systemic comorbidities are capable of wound healing better and could therefore experience more benefit from maximized closure methods [21].

This study yields useful results; however, some limitations should be acknowledged to interpret the findings properly. The relatively limited sample size means the investigators may not be able to detect smaller but clinically important differences between the delayed primary closure and early primary closure groups. Next, the single institution study may limit the applicability of study results to other health care setups of diverse surgical skills, after-surgical protocols, and patient and public demographics. The third issue is that the follow-up period may not have been long enough to observe the late-onset complications related to the wound, for example, incisional hernias or infection of the wound, which becomes chronic. The researchers relied on clinical observation to identify wound infection instead of standard microbiological confirmation, which raised the concern of observer bias. Ultimately, although the groups were matched for demographic and clinical characteristics, unaccounted-for factors such as nutritional status, intraoperative contamination grade, and variations in antibiotic use may have influenced the results. Larger multicenter studies with standardized postoperative monitoring should be undertaken in the future to prove and strengthen these results.

CONCLUSION

The study supports the clinical benefit of delayed primary closure in the treatment of peritonitis wounds in midline laparotomy to avoid wound infections and dehiscence. The subgroup results highlight the need to assess patients individually, taking into account gender, the presence or absence of anemia, and residence, to be able to plan surgical closure. Although an unpromising delay to close could be associated with a slightly greater amount of blood loss, it is compensated with better wound healing rates, justifying its use as the solution of choice in contaminated abdominal surgery. Subsequent multicenter studies involving a larger sample size could help to explain these associations and support the best closure guidelines among varied populations of patients.

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Liaqat Ali: Conception and design of study, data collection, drafting of manuscript, final approval.
Imamuddin Baloch: Study design, supervision, methodology refinement, critical review of manuscript.
Javeria Memon: Data acquisition, literature review, initial drafting of sections.
Ahsan Ali: Methodology guidance, interpretation of results, critical revision.
Muhammad Sheeraz: Data entry, statistical analysis, preparation of tables/figures.
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Original Article **Open Access**

Effect of Preoperative Steroid Injection on Wound Drainage after Modified Radical Mastectomy

Asma Aziz, Muhammad Waqas Arshad, Muhammad Shahzeb Asghar

Abstract

Objective: The aim of this study was to determine the Effect of Preoperative Steroid Injection on Wound Drainage after Modified Radical

Study Design and Setting: The current Quasi-experimental study was carried out at the department of surgery Ibn e siena hospital and research institute Multan and Bakhtawar Ameen Medical and Dental College Multan for a period of six months from January, 2023 -June, 2024 after taking permission from the ethical board of the hospital.

Methodology: A total of 62 females with breast cancer, planned for modified radical mastectomy were included. The patients were assigned computer-generated numbers to form two equal groups, A and B. An hour before to surgery, group A received a 120 mg a day (3 ml) injection of depomedrol, while group B received 3 ml of regular saline. The same consultant surgeon conducted MRM on both groups using the same dissection technique, which is steel scalpel dissection. Two suction drains, one at the breast site and one at the axillary area, were positioned at the end of the treatment. Data was analyzed through SPSS 25.

Results: In our study, 48.3% females were diagnosed with stage II, and 51.7% had stage I breast cancer. In a modified radical mastectomy, a single preoperative steroid dose reduced mean drainage volume more than control. (P=0.048)**.**

Conclusion: Our findings showed that that the preventive steroid injections prescription in women following modified radical mastectomy were more effective in lowering mean drainage volume for female participants with stage I and II breast cancer when compared to normal saline.

Key words: Steroid injections; Mastectomy; drainage volume

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INTRODUCTION

One of the most prevalent cancers in women is breast cancer, also known as CA breast (CAB), which is thought to kill one out of every four women. The data on CAB in Pakistan is imprecise since fewer instances are reported, but a thorough analysis of the statistics indicates that CAB accounts for 34.6% of female cancers. CAB accounts for 23% of all malignancies in postmenopausal women.[1] In Pakistan, the prevalence of CAB is increasing. Modified radical mastectomy (MRM), one of the available treatment options, is performed with the goal of curing the condition. More than 35% of patients had morbidity following surgery, including increased seroma development and wound drainage.[2] Following MRM, a number of conditions are recommended to lessen drainage and the likelihood of seroma development. Postoperative drainage in MRM can be decreased by using pressure dressings, flap fixation methods, OK-432, preoperative steroid injections, and ultrasonic scalpels.[3-6] Steroids may reduce the development of seromas and decrease inflammation in the injured region. In certain procedures, the steroids have been given intermittently to reduce localized wound leakage. A randomized controlled experiment was carried out by Khan, M. A. (2017, to examine the impact of a single steroid injection dosage on postoperative drainage following MRM. The findings indicated that the steroid group had less drainage than the control group, with the steroid group having 755.4 ± 65 ml and the control group having 928.3 ± 102.5 ml (p value <0.005).[7] Increased seroma production and wound drainage are invariably linked to morbidity, including infections, delayed healing, and hospital discharge. Chemotherapy or radiation therapy may be delayed as a result of the healing delay. There is just one research in Pakistan.[2] Regarding this particular subject, there is little

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national and international information available. The combination of surgery, radiation, hormonal therapy, and chemotherapy has been the primary treatment strategy for breast cancer in recent years. However, surgery is essential. Among all surgical techniques for locally advanced breast cancer, modified radical mastectomy (MRM) with axillary lymph node clearing (ALND) is frequently used. Following MRM, surgeons face a number of postoperative surgical site problems, with seroma production being one of the most common, occurring at an incidence rate of 3-85%.[4] Fluid accumulation in the axilla and post-mastectomy skin flap after breast cancer surgery is known as seroma formation in the dead space. It often begins on the seventh postoperative day, peaks on the eighth, and gradually decreases until the sixteenth day, when it largely goes away on its own[5]. It is also possible to think of or hypothesize that after extensive tissue dissection, lymphatic leakage builds up in the dead space, and that inflammatory responses during the acute phase of wound healing during postsurgical procedures promote the development of seroma.[6] Following tissue damage, pro-inflammatory cytokines including interleukin (IL)-1b, IL-6, and tumor necrosis factor (TNF) alpha are produced, along with anti-inflammatory cytokines like IL-10. Later on, an imbalance of them causes infectious problems. Seroma fluid is gathered in the dead space after thorough tissue dissection and axillary clearing. Over the course of the next several days, this fluid's composition changes. Because of the disintegration of blood arteries and lymphatics, it first looks like clots of blood with clear lymph. It turns into an exudate a few days later as a result of inflammatory changes. The accompanying morbidity, including flap necrosis, wound dehiscence, infection, longer hospitalization, increased expense, and many physician visits, may cause adjuvant cancer therapy to be delayed, even though it was not classified as a life-threatening disease. [7] Nowadays, a variety of methods are used to decrease dead space and lessen seroma development. These include the use of sutures, suction drains, bandages for compression, ultrasonic scalpels for dissection, sclerotherapy, topically applied tranexamic acid, and fibrin glue for fixing flaps. [8-14] Methylprednisolone succinate was administered intravenously (IV) prior to surgery in a randomized pilot trial to monitor seroma development. Following MRM, there was a decrease in the amount of seroma generation as well as the number of seroma aspirations and drainage volume after surgery.[15]

Therefore the current study was carried out to find out the Effect of Preoperative Steroid Injection on Wound Drainage after Modified Radical Mastectomy.

METHODOLOGY

The current Quasi-experimental study was carried out at the department of surgery Ibn e siena hospital and research institute Multan and Bakhtawar Ameen Medical and Dental College Multan for a period of six months from January, 2023 -June, 2024 after taking permission from the ethical board of the institute (Ref no: 027/ERC/024, date: 26/01/2024) . Female patients between the ages of 30 and 60 who were scheduled for MRM are included in the inclusion criteria. A total of 62 females with breast cancer and were planned for modified radical mastectomy were included. The age of the study population was from 30 to 60 years. Individuals with long-term medical comorbidities and those who were already taking steroids, those who had previously received radiation, and pregnant or nursing mothers were not excluded . After each patient was admitted, formal informed consent was obtained. A thorough history, a clinical examination, and pertinent investigations were used to evaluate the patient. The pre-anesthesia workup and assessment were completed. The patients were assigned computer-generated numbers to form two equal groups, A and B. An hour before to surgery, group A received a 120 mg a day (3 ml) injection of depomedrol, while group B received 3 ml of regular saline. The same consultant surgeon conducted MRM on both groups using the same dissection technique, which is steel scalpel dissection. Two suction drains, one at the breast site and one at the axillary area, were positioned at the end of the treatment. Every patient received the same routine preoperative and postoperative treatment. After the drain was taken out, the volume of the drain was measured using operational criteria. A custom created proforma that is attached as Annexure A contains all of the data. Data was analyzed by SPSS 14. The mean and standard deviation was used to express the quantitative variables of age, BMI, illness duration, and drainage volume. The stage of illnesses (qualitative variable) was reported as frequency and percentage. The independent sampling t test was used to compare the drainage volumes of the two groups. Age, BMI, disease duration, and disease stage were among the factors that were stratified and then further examined using the independent sample t test. A P value of less than 0.05 was deemed significant.

RESULTS

Over all 62 females participated in this study whose mean body mass index was 26.9±3.38 kg/m2, and symptom mean duration was 1.6±0.62 years. The drainage volume in A group was 573±116.63 ml, whereas in B group was 1020 ± 159.9 ml. 48.3% were diagnosed with stage II breast cancer, and 51.7% had stage I. When the mean drainage volume (in milliliters) of the two groups was compared, it was found that in individuals having a modified radical mastectomy, a single preoperative steroid dose reduced mean drainage volume more than control. This variance was noteworthy (t-test value 4.078 and P value was 0.048). Table 1. There was no impact of these effect modifiers on the mean drainage volume for age, Body mass index, period of symptoms, and illness stage using independent t-test as shown table (2-5).

Table 1. Comparison of the Mean Drainage Volumes of the Two Groups by Independent T-Test

Groups	Frequency	Mean± standard deviation	T test	
A	31	573±116.63	F	Significance
B	31	1020±159.9	4.078	0.048

Table 2. Age's Impact on Mean Drainage Volume.

Age groups	Frequency	Mean± standard deviation	T test	
Early Middle Age	25	879.5±221.3	F	Significance
Late Middle Age	37	823.6±226	0.001	0.978

Table 3: Effect of body mass index on Drainage Volume

Category of BMI	Frequency	Mean± standard deviation	T test	
normal BMI (20-25 Kg/m 2)	22	841.7±221.9	F	Significance
Abnormal BMI (>25 Kg/m2)	41	848±227.9	0.001	0.978

Table 4: Results of Disease Duration Using Mean Drainage Volume

Disease duration	Frequency	Mean± standard deviation	T test	
Short duration less than one years	25	824±239.6	F	Significance
Long duration more than one year	37	860.5±215.1	0.001	0.978

Table 5: on Mean Drainage Volume the effect of Breast Cancer Stage

Disease stage	Frequency	STD and mean	T test	
Stage 1	32	815.9±235.9	F	Significance
Stage 2	30	878±209.7	0.041	0.840

DISCUSSION

More than 1 out of 10 new cancer diagnoses in women are for breast cancer, making it the most prevalent disease diagnosed in this population.[1] According to the International Agency for Research on Cancer (IARC), 6.3 million women have survived breast cancer in the past five years, whereas 1.7 million new instances of the disease were recorded in 2012.[7 In] 2018, the number of fatalities from breast cancer grew to 14%, while the incidence of the disease climbed to more than 20%. [8]. Furthermore, compared to its neighbors, Pakistan has a roughly 2.5-fold greater incidence of breast cancer [9]. Contrary to what is seen in the West, one intriguing element about Pakistan is the participation of younger women in CAB. Surgery is a crucial step in the multimodal management of CAB, which is aided by hormone treatment, chemotherapy, and radiation therapy. Modified radical mastectomy (MRM) with axillary clearance is thought to be the most often used surgical technique.[8] Numerous intraoperative and postoperative issues can arise from AB surgery, making it a complicated procedure.

With a frequency of 35–80%, seroma development is the most prevalent of these problems.[10–14] Preventing seroma development is crucial because it leads to longer hospital stays, drawn-out outpatient follow-ups, and delays in later adjuvant treatments, all of which worsen patient suffering.[15] It is very controversial if steroids can stop seroma production. The current study found that the mean drainage amount in the normal saline group were 1020 ml, but the mean draining volume of women who underwent the modified radical mastectomy procedure and received an injection of steroids an hour before was 672 ml.This difference between the groups was statistically significant (value of P equal to 0.048). The drainage volume significantly lower among people with stage 1 breast cancer, those with a normal BMI (20–25 kg/m2), those in the age group 46–60 years and those with a short illness duration (<1 year). Nevertheless, these results were not statistically significant (p>0.05).

There has been a lot of data in recent years that suggests seroma is not only a simple deposit of serous fluid but rather an exudative discharge that results from acute inflammation following surgical trauma. [16]. This idea is supported by the seroma fluid's cytokines and proteinases and their inhibitors.[17] According to evaluations, immunomodulatory substances are useful in halting the development of seroma [18]. One such drug was 5-fluorouracil in a rat model, and sapylin was utilized in a human model. Therefore, steroids are also effective anti-inflammatory medicines that can be used to manage seroma. Glucocorticoids are commonly given as

local intramuscular injections or intraarticular injections to treat a variety of inflammatory disorders, including rheumatic fever, as well as allergy problems. The effectiveness of steroids was also assessed in a variety of surgical procedures, including neck and scalp surgery, cosmetic surgery, heart surgery, and colon resection. In an RCT, Taghizadeh and colleagues.[19] evaluated the impact of steroids on seroma recurrence following breast reconstruction utilizing the latissimus dorsi. Following the first aspiration of the seroma, the authors administered a single dose of triamcinolone to one group while normal saline to the other group, and they monitored for recurrence.[19] and observed findings that were comparable to those of the current investigation, namely that patients who got steroid injections had lower mean drainage volumes than those who got normal saline. The number of punctures, total volume of fluid drained, and time it took for a seroma to form were all statistically significantly reduced when Axelsson et al. [9] matched the effects of injecting local steroids in the mastectomy cavity with normal saline at the time of drain removal. Furthermore, Qvamme et al.[12] carried out a randomized controlled research wherein participants having mastectomy received a single steroid injection in one group and normal saline in another.. They also reported a noteworthy decrease in the drainage volume in the steroid group as compared to normal saline. Khan et al. (2017) found that in the steroid group the mean drainage was 749.4±64 via. 928.3±102.5 ml, correspondingly, substantially lower than that of the control group.[2] These results are consistent with a recent study that shown that when administered prophylactically to patients having modified radical mastectomy, steroids are superior to normal saline in terms of decreased drainage volume.

Using a similar method on a rat model, Turel et al.[15] injected methylprednisolone into the area beneath the skin flaps following mastectomy and axillary lymph node removal. Although administering steroids was successful in avoiding seroma development and decreasing drainage volume, the author disclosed that due to the significant risk of wound infection, it should not be done frequently. Similar to what Turel et al.[15] found, our investigation showed a decrease in drainage volume within the steroid group. In a controlled experimental study, Okholm et al. assessed whether a single intravenous dosage of glucocorticoids administered half and one hours before to surgical procedure was helpful in avoiding seroma development following axillary dissection and mastectomy.[20] There was a small drop in the drainage volume, total seroma volume, and number of seroma punctures during the first 2 postoperative days. The authors came to the conclusion that there was no discernible decrease in drainage volume following steroid administration. The findings of Okholm and colleagues differs with the findings of our study, which showed that patients who received preventive steroids saw a considerable decrease in drainage volume.[25] According to the current study, individuals having a modified radical mastectomy benefit from preventive steroid injections. However, as steroids can raise the risk of infection, the danger of wound infection must be considered while handling such instances. In order to limit drainage volume and lower the incidence of seroma development, steroids must be administered in conjunction with a sufficient prophylactic antibiotic cover. Seroma development is still a significant and inevitable issue after mastectomy for breast cancer surgery, despite all the advancements in surgical technique.[21] Seroma formation has been linked to higher patient morbidity. Because of the connected drains, it has also been linked to restrictions in the ipsilateral side hand's range of motion and general mobility. [22] Cytokine release is a hallmark of the systemic inflammatory response that surgery causes. Serous fluid rises as a result of enhanced fibrinolytic activity in the days that follow. Thus, the etiology of seroma is thought to involve a build-up of immunoglobulin (IG), inflammatory cells, and elevated IL-6 during the exudative phase of the inflammatory response. [23-24] Inhibiting the inflammatory response with steroids may reduce seroma development and perhaps enhance the patient's quality of life after mastectomy. By blocking the function of cytokines, they may be employed to stop the inflammatory process. As IL-6 levels in seroma fluid decreased, it was shown that local injection of 80 mg of triamcinolone significantly decreased the development of seroma after abdominal surgery. Clinically, a decrease in seroma accumulation was correlated with the suppression of inflammatory markers. [25] Similarly, the use of triamcinolone injections during breast reconstruction surgery showed that 55% of patients did not develop seromas. Conversely, among those given 0.9% normal saline, 95% had seroma development. [26] One hour before to surgery, women receiving MRM were given a preoperative single dose of 8 mg IV dexamethasone in another controlled clinical study. Improved pulmonary functions, a decrease in the need for analgesics and antiemetic medications, and a low frequency of postoperative nausea, vomiting, and pain were all seen. Additionally, only one patient in the control group had seroma development, whereas none in the intervention group. [27] A research on the decrease of auricular seroma after blunt trauma damage was also carried out. Triamcinolone acetate was injected intralesionally after the seroma was first aspirated. The recurrence of seroma was decreased by this one minimally invasive technique. [28] Similarly, a research that employed an injection of 120 mg depo-medrol prior to MRM revealed that the intervention group saw a 6% decrease in seroma incidence, whereas the control group experienced an 18% decrease.[29] The present research has various limitations since it did not track the equipment used for dissection, the patient-controlled analgesia administered, or the size and volume of the tumor dissection. In addition, the sample size was little. To confirm and corroborate the present findings, more study should take all these aspects into account.

CONCLUSION

Our findings concluded that that the preventive steroid injections prescription in women following modified radical mastectomy were more effective in lowering mean drainage volume for female participants with stage I and II breast cancer when compared to normal saline.

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Authors Contribution:
Asma Aziz: Primary researcher, conception, acquisition, analyzing the data and writing manuscript
Muhammad Waqas Arshad: Primary researcher, conception, acquisition, analyzing the data and writing manuscript
Muhammad Shahzeb Asghar: Primary researcher, conception, acquisition, analyzing the data and writing manuscript

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Original Article **Open Access**

Role of Tranexamic Acid in Prevention of Seroma Formation after Ventral Herioplasty

Faiz ur Rehman, Aamir Ali Khan, Muhammad Kashif, Zia Ullah, Muhammad Ali, Muhammad Ibrahim Shuja

Abstract:

Objective: The aim of this study was to explore the role of tranexamic acid in prevention of seroma formation after ventral herioplasty.

Study Design and Setting: The present cross-sectional study was carried out at the department of general surgery Bacha Khan Medical Complex / Gajju Khan Medical College – SWABI from January 2025 to June 2025 after taking permission from the research team of the hospital.

Methodology: In our study, Non-probability consecutive sampling approach was used for sample collection. A total of 100 individuals diagnosed with ventral hernia repair were included. All individuals were treated with the standard-only mesh. A vacuum drain was used to measure the seroma's volume. One gram of intravenous tranexamic acid was administered following skin closure, and 500 mg of oral tranexamic acid was administered for 12 hours on the 5th post-operative day. On daily basis the drain output was recorded. When the output was less than 30 milliliters per day, the drain was removed. SPSS version 24 was used for analysis of data.

Results: A total of 100 individuals participated in this study out of which 70(70%) were females and 30 (30%) were males. The mean age of the study participants was 81.05±41.75 years. In 84 individuals (84%) the seroma resolved within five days after surgery, but in 16 individuals (16%) it took longer than five day.

Conclusion: The current study concluded that Tranexamic acid significantly lowers the development of for seromas following surgery ventral hernia repair.

Key Words: ventral hernia repair, seromas, tranexamic acid

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INTRODUCTION

The bulging of all or part of the contents of the abdominal cavity due to a weakening in the abdominal wall is known as an abdominal hernia. [1–3] A non-inguinal, non-hiatal defect in the abdominal wall's fascia is known as ventral hernia. Approximately 350,000 ventral hernia procedures are performed each year. General surgeons frequently operate to fix these abnormalities in the abdominal wall. Surgery is usually advised for those with symptomatic hernias, acceptable surgical risk, or those who are more likely to experience hernia-related complications. Someone may have an impact on a person's quality of life, result in hospital stays, or even cause death in certain situations. The most common surgery done globally is hernia repair is 10–14%.[4] There are two primary types of ventral hernia that are acquired and congenital. Although the great majority of hernias seen and treated by general surgeons are acquired, some people have ventral hernias from birth and live with them for extended periods of time before having them surgically fixed. Acquired ventral hernias are frequently caused by trauma, recurrent stress on the abdominal wall's naturally weak spots, and prior surgery that resulted in an incisional hernia.[5] Pain, swelling, or fullness at the location of the hernia are the typical symptoms of an abdominal wall hernia, and however these might vary depending on

the posture or Valsalva manoeuvre. The expansion may be erythematous or result in an asymmetry in some situations where a hernia has been choked or confined. Although a history and physical examination are usually sufficient to diagnose an abdominal hernia, excessive obesity, a significant risk factor, may restrict the examination. Because hernias can alter with activity or simply standing, it is crucial that the patient be evaluated in a variety of postures throughout the examination.[6] Patients who have significant procedures, such as mesh repair for abdominal hernias, are more likely to develop seroma. There is a greater chance of seroma development and related problems the larger the mesh repair area. In addition, age, the quantity of tissue removed, prior operations, heparin or oral anticoagulant usage, and a history of seroma are other risk factors. [6] 5.6% to 42% of instances of mesh-assisted abdominal hernia surgeries result in postoperative seroma.[7] The accumulation of fluid that happens following surgery is known as a seroma. There is debate over the aetiology of seroma development. It is thought to be the gathering of lymphatic fluid, inflammatory exudates, serum, and liquid fat behind a skin flap.[8]

Many parameters, such as the extent of dissection and the technique used to raise the skin flap—electrocautery, knife, or scissors—influence the quantity and duration of seroma production. Because the plasmin system has fibrinolytic action in the lymphatic and serum systems, it also aids in fluid collection. Fibrin complexes also have a role in lymph and blood leaking from the arteries.[9] There are several methods for managing and preventing seroma.[10] After surgery, suction drains are utilized to track the quantity of seroma. [11, 12] Larger seromas are treated with needle aspiration, but most serom as go away on their own. Antibiotics are frequently needed for infected seromas, and occasionally surgery is required. Tranexamic acid can be used to stop the production of seromas.[13] This artificial antifibrinolytic drug is derived from the amino acid lysine. Despite the appropriate use of bleeding control techniques, surgical bleeding may occur when fibrinolysis surpasses coagulation. The purpose of tranexamic acid is to prevent fibrinolysis. It stops plasminogen from being activated to plasmin. It can be given intravenously or orally.[14] The present study was carried out to find the role of tranexamic acid in prevention of seroma formation after ventral herioplasty.

METHODOLOGY

The present cross-sectional study was carried out at the department of general surgery Bacha Khan Medical Complex / Gajju Khan Medical College – SWABI from January 2025 to June 2025 after taking permission from the research team of the hospital (Ref No: 016/BKMC/2024, date:December/18/2024). Non-probability consecutive sampling approach was used for sample collection. A total of 100 individuals of both genders and different age group (ranged 21-61 years) diagnosed with ventral hernia repair were included while individuals who had bleeding disorders, strangled hernias cirrhosis and uncontrolled diabetes mellitus excluded. Anticoagulant medication had to be discontinued five days before to surgery by the participants. Clinical history and laboratory results were documented. Using pelvic and abdominal ultrasonography, the defect's size and content were assessed. All individuals were treated with the standard-only mesh. A vacuum drain was used to measure the seroma's volume. One gram of intravenous tranexamic acid was administered following skin closure, and 500 mg of oral tranexamic acid was administered for 12 hours on the 5th post-operative day. On daily basis the drain output was recorded. When the output was less than 30 milliliters per day, the drain was removed. SPSS version 24 was used for analysis of data. Descriptive statistics were used to show numerical and categorical data and were presented in frequencies and percentages.The results were categorized based on age and gender and presented in tables. To determine statistical significance the Chisquare test was employed. P-values less than.05 were regarded as statistically significant.

RESULTS

A total of 100 individuals participated in this study out of which 70(70%) were females and 30 (30%) were males. The mean age of the study participants was 81.05±41.75 years. Out of the total participants 12(12%) 21-32 years old, 26 (26%) were between the ages of 33 and 41, and 38 (38%) were between the ages of 42 and 61 years. Participants were categorized based on these factors in order to ascertain the effect of age and gender on seroma development as presented in table 1. In 84 individuals (84%) the seroma resolved within five days after surgery, but in 16 individuals (16%) it took longer than five day as presented in table 2.

DISCUSSION

"Inguinal" means groin. An inguinal hernia is a protrusion in the groin. The bulge is a bag of fat, peritoneum, and bowel that has slipped through a weak region in the abdominal muscles and into the groin. A hernia can be pushed back or reduced automatically when lying down. Hernias can make it unpleasant to bend and lift weights. You may find it difficult to accomplish daily chores.

Surgical repair is the sole cure.[8] Inguinal hernia is a prevalent

Table 1. Factors affecting the development of seromas

Factors	Stratification	Patients no	Mean ±SD	P value
Gender	Male	30	84±24.24	0.728
	Female	70	104±47.85	
Age in years	21-41	38	80.04±40.64	0.188
	42-61	38	108.76±50.83	

Table 2. The relationship between post-operative days and seroma reduction

Post-operative days	Patients number	percentage	Mean ±SD
Above 5 days	84	84%	84±24.24
Less than 5 days	16	16%	130±43.87

surgical condition, among abdominal wall hernias. The frequency is high among adult males. Inguinal hernias, which develop when a portion of the intestine or fatty tissue pushes through a weak spot in the groin or scrotum, are the most frequent type of hernia in men. This is because of the structure of the inguinal canal, a groin channel that accounts for around 75% of all hernias and is more prone to weakening in men. The prevalence of inguinal hernias is unknown. Approximately 500,000 instances of inguinal hernia are reported to medical experts each year. Worldwide surveys indicate that untreated inguinal hernias affect 5-7% of males. However, approximately the same percentage of males have surgical repair.[9] Inguinal hernia instances in the US result in more work days missed than any other chronic intestinal ailment. Every year, around 400,000 people limit their activities severely.[10] Patients with untreated inguinal hernias may experience problems such as intestinal blockage and strangulation. The risk of problems is greater in older guys. Inguinal hernias are common and serious medical problems. Limited information is known on the risk factors for inguinal hernia. Three case-control studies linked inadequate education and manual job to an increased incidence of inguinal hernia. Rural origin was identified as a risk factor for females. Symptoms of prostatic hypertrophy were reported among men having hernias in another study. Strenuous exertion was also found a risk factor [11] A hernia is an illness when the tissues of the abdominal region protrude from a weak area on the abdomen. It is mostly caused by the intestine or omentum bulging due to an abdominal wall abnormality. Hernias often require surgery to be corrected, and they may develop between the hips and the chest.[12] There is a significant chance of seroma production after major surgical procedures like hernia repair. Risk factors include age, anticoagulant usage, the location of the dissected tissue, and previous history of surgery & seroma development. Seroma development is caused by a number of unavoidable events, such as overuse of cautery, dissection in the plane under Scarpa's fascia, and use of sclerosants, among others. If this seroma becomes infected and cannot be drained, it might result in wound infection and dehisces. [13] Serum is the fluid that is collected, while seroma is the term used after surgery. It occur as a result of blood vessel and lymphatic injury leaking. These are frequently evacuated via suction drains. These drains can also be used to monitor the fluid collected in the closed cavity.[14] Following abdominal hernia repair, seroma develops in 5.6%–42% of patients.[15] Below the skin, there is swelling, and the fluid has a clear or yellow appearance. The fluid may turn purulent or blood-stained when infected.[16] A smaller volume of fluid can be handled conservatively, but a greater volume necessitates either needle aspiration or open drainage.[17] When mesh is used for hernia repair, fluid builds up. The larger the area mended with mesh, the higher the chance of seroma production. It is possible to prevent seroma production by using tranexamic acid.[18] Because of its anti-fibrinolytic properties, it stops and manages excessive bleeding in the early phases of recovery. Transexamic acid (TXA) is used in hernia repair surgery to reduce bleeding and fluid collection, hence preventing the formation of a seroma, a common postoperative complication. It acts as an anti-fibrinolytic agent. In the setting of hernia repair, particularly with mesh installation (hernioplasty), surgical tissue injury can cause bleeding from tiny blood vessels & damaged lymphatics, leading in the buildup of serous fluid. Reduces bleeding and stabilizes clots. Post-operative bleeding is reduced by 34% when tranexamic acid inhibits the activation of plasminogen to plasmin.[14] The number and duration of seroma production after surgery are determined by factors such as tissue dissection extent and surgical procedures. Over time, several treatments have been implemented to address seroma development and its associated problems. Tranexamic acid has been shown to reduce seroma development when administered systemically. It also promotes wound healing. This study demonstrated that tranexamic acid effectively reduces seroma development. Although prosthesis-related infections are uncommon, they remain a significant issue. This occurs in around 5% of restorations and causes delays in recovery. Major risk factors include pre-existing skin infections or ulcers, excessive obesity, and clogged or perforated bowels. Seroma is a frustrating complication for both surgeons and patients. Anxiety, pain, repeated follow-up visits, higher expenditures, and feeling poorly can all contribute to morbidity. Seroma promotes bacteria growth, which can lead to wound dehiscence and septicemia. [19] The present study was carried out to find the Role of tranexamic acid in prevention of seroma formation after ventral herioplasty. A total of 100 individuals participated in this study out of which 70% were females and 30% were male .our study findings are similar to the study conducted by Zubair, et all[20] in which females were predominant. Our study results are also parallel to the study of Ahmed, in which female were 75% and male were 25%.[24] But the findings of our study are contrasted with Gulzar et al [5] in which the male were female were 45 % and male were 65%. We provided one gram of tranexamic acid to one hundred individuals who had been diagnosed with the repair of a ventral hernia. Participants were categorized based on these factors in order to ascertain the effect of age and gender on seroma development as presented in table 1. In 84 individuals (84%) the seroma resolved within five days after surgery, but in 16 individuals (16%) it took longer than five day. A similar study was conducted by Tarar et al. on 110 individuals with ventral hernia repair.[21] They reported that 81% seroma resolved within five days after surgery which and the results of their study are comparable to the present study. Hernia affects the abdominal wall. Non-lingual and non-hiatal abnormalities in the abdominal wall fascia are known as ventral abdominal hernias. Ten to fifteen percent of all surgical procedures carried out worldwide involve the standard surgical procedure known as hernia repair.[16]

Following a laparotomy, muscle-splitting incision, or laparoscopy, the likelihood of having a hernia is 10%, 5%, and 1%, respectively. After hernia repair, seromas are frequently seen, especially when there is extensive tissue disturbance and a broad area involved. It is a collection of serum, lymphatic fluid, liquefied fat, and inflammatory exudates; its etiology is unknown. The length of time and quantity of seroma are affected by a number of variables, such as the depth of dissection and the technique used to raise the skin flap (such as electrocautery or a knife). If left untreated, seromas become infected.[22] additionally, it raises the chance of infection. It is a great place for bacteria to grow and can lead to deadly side effects such wound dehiscence and septicemia. Seroma was a frequent post-hernia repair consequence in this study. Age and gender had no effect on seroma formation, according to other research assessing the risk factor for seroma formation. Seromas are common after hernia repair, particularly for large hernias with significant tissue disruption. The exact cause of seroma development is unclear, however it is thought to be the accumulation of liquefied fat, serum, inflammatory exudates, and lymphatic fluid beneath the skin flap.

Seroma formation varies and is regulated by factors such as dissection extent and method of raising the skin flap (electrocautery or knife). Untreated seromas can become contagious. Tranexamic acid improves wound healing by successfully reducing postoperative serous fluid and seroma development.[2] Utako Okamoto made the discovery of tranexamic acid (TXA) in 1962. It is a well-known medication used for treating or preventing heavy menstruation, serious trauma, postpartum hemorrhage, surgery, tooth extraction, and nasal bleeding. The WHO's list of essential medications now includes it as well. In high-income, middle-income, and low-income nations, TXA is a cheap therapy that is thought to be very cost-effective. It can be injected into a vein or taken orally. Every 6 to 8 hours, a gradual intravenous injection of 1 g (1 ampoule of 10 ml or 2 ampoules of 5 ml) of tranexamic acid is recommended. This is comparable to 15 mg/kg body weight. It is a safe medication for those with chronic liver illness since individuals with hepatic impairment do not need to modify their dosage. Tranexamic acid has a proven effect in reducing bleeding during orthopedic procedures, according to many researches. Consequently, fewer transfusions are required after surgery. In these situations, the TXA has been injected intra-articularly, utilized to irrigate the surgical site, or both. Transexamic acid reduced seroma, serous fluid, and post-operative soreness in 81% of patients, according to a research.[23] The results of our study demonstrated that it successfully lowers seroma formation. Post-operative drainage is decreased when 1g of tranexamic acid is taken on daily basis .[23] The results of our study showed that the mean duration of seroma in the majority of patients was ten days. Our study's strength is that tranexamic acid seems to be an independent factor in seroma reduction. Similar type of study was conducted recentrly to evaluate the seroma reduction and Role of tranexamic acid in ventral hernia repair. The research comprised a total of 80 patients. Of the patients, 25% were men and 75% were women. The patients' ages ranged from 20 to 60 years. Average age was 45 years. In 81% of individuals, seroma resolved after 5 days, but in 19%, it took longer.[24] which support our study findings. Attempts to lower systemic levels of the medication via topical treatment at the surgical site constitute another strategy to address safety concerns with TXA. In this context, the Journal of Bone & Joint Surgery reported the findings of a clinical trial comparing the use of topical TXA against intravenous administration in patients having primary total knee arthroplasty.[25] Research indicates that following hernia surgery, seroma development is reduced. In a randomized double-blind trial, Poeran et al. [26]demonstrated that peri-operative and post-operative administration of tranexamic acid 1gm three times daily significantly reduced the mean post-operative seroma drainage volume in 160 women undergoing lumpectomy or mastectomy with axillary clearance when compared to patients receiving a placebo (283 versus 432 ml, $P < 0.001$). Tranexamic acid therapy also reduced the prevalence of postoperative seroma development (27 versus 37%, $P = 0.2$). After mesh hernioplasty, tranexamic acid decreases the development of post-operative seromas in individuals with ventral hernia repair. Additionally, it shortens the duration of drain removal following surgery. We conclude that administering tranexamic acid in split doses lowers the patient's total costs and morbidity and facilitates an early return to normal life. One of the most frequent issues that general surgeons handle worldwide is ventral hernias. There are several methods for repairing ventral hernias described in the literature, but the most common one at the moment is hernioplasty, which may be performed either openly or laparoscopically. Prolene mesh is the most often utilized form of mesh in hernioplasty because it reduces the likelihood of recurrence. But in the present study we used the standard-only mesh. Further large scale studies are needed to evaluate the potential role of tranexamic acid in prevention of seroma formation after ventral herioplasty.

There are several limitations of our study. Its study design is cross-sectional; a retrospective study design will allow results to be compared with those of the control group.

CONCLUSION

The current study concluded that Tranexamic acid significantly lowers the development of seromas following surgery for ventral hernia repair.

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Source of Funding: Nil

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Authors Contribution:
Faiz ur Rahman: Primary researcher, conception, acquisition, analyzing the data and writing manuscript
Aamir Ali Khan: Primary researcher, conception, acquisition, analyzing the data and writing manuscript
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Original Article **Open Access**

Comparative Study between the Effects of Dexmedetomidine and Lidocaine Infusion on Intraoperative Hemodynamic and Requirement of Nalbuphine for Postoperative Analgesia in Upper Limb Orthopaedic Surgeries

Komal Mumtaz, Liaqat Ali, Saima Zia, Ramisa Afzal, Soman Nadim Iqbal, Malaika Nasir

Abstract

Objectives: To compare the intraoperative and postoperative hemodynamics and requirement of nalbuphine for postoperative analgesia in upper limb orthopedic surgeries between dexmedetomidine and lidocaine.

Study Design: Comparative analytical study

Place and duration of study: Department of Anesthesia, Fauji Foundation Hospital, Rawalpindi, Pakistan from 17th Oct 22 to 15th July 23.

Methodology: Patients undergoing upper limb orthopedic surgeries in our tertiary care setup. Ninety patients undergoing upper limb orthopaedic surgeries were divided into two equal groups of forty-five patients each. Group A received Dexmedetomidine infusion, while Group B received Lidocaine infusion. Data collection involved gathering information related to upper limb orthopaedic procedures, including both intraoperative and postoperative parameters.

Results: Ninety patients undergoing upper limb surgeries were randomized into two groups (Dexmedetomidine: Group A, Lidocaine: Group B). Group A experienced statistically significant reductions in intraoperative mean arterial pressure (MAP) by 20% ($p<0.05$) and heart rate (HR) by 15% ($p<0.01$) compared to Group B at all time points (10-120 minutes). Postoperative pain scores were significantly higher in Group B (mean difference: 1.5 points, $p<0.001$) across all time points (2-24 hours). Group A also exhibited significantly higher sedation scores (mean difference: 2 points, $p<0.001$) and required significantly less postoperative analgesia (one dose vs. multiple doses, $p<0.001$) than Group B.

Conclusion*:* The findings affirm dexmedetomidine infusion's advantages in achieving optimal outcomes: improved hemodynamics, reduced pain, and lowered postoperative analgesic demands, reinforcing its role in effective pain management.

Keywords: Dexmedetomidine, Heart rate, Lidocaine, Mean Arterial Pressure, Numeric rating scale,

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INTRODUCTION

Surgical procedures, vital for treating diverse medical issues, often lead to postoperative pain and related complications like nausea, vomiting, blood clots, and cognitive impairment. The management of postoperative analgesia and intraoperative analgesics is an essential concern in surgical procedures and anaesthetic agents play a crucial role in this. In recent years, practicing anesthesiologists utilized various non-opioid analgesic adjuncts such as dexmedetomidine and lidocaine in the perioperative periods to curtail the use of opioids as a part of enhanced recovery after surgery protocol and to minimize opioid-related adverse events. [1] These two commonly used agents include dexmedetomidine and lidocaine that have exhibited promising results in improving hemodynamic parameters and alleviating requirement for postoperative pain. There is limited data available for upper limb surgeries that directly compares the effectiveness of these agents in this particular context.[2]

Dexmedetomidine is an alpha-2 adrenergic agonist and is wellknown for its sedative and analgesic properties. Its capacity to attenuate the stress response during surgery

procedures and maintain hemodynamic stability makes it a valuable solution. [3] Dexmedetomidine has also been found to reduce the opioid requirement in the postoperative period, potentially mitigating opioid-related side effects.[4] It can also be used for procedural sedation such as during colonoscopy.[5] It can be used as an adjunct with other sedatives like benzodiazepines, opioids, and propofol to enhance sedation and help maintain hemodynamic stability by decreasing the requirement of other sedatives.[6,7] Intravenous dexmedetomidine shows the linear pharmacokinetics with a rapid distribution half-life of approximately 6 minutes in healthy volunteers and a longer and more variable distribution half-life in ICU patients. Dexmedetomidine is also used for procedural sedation in children.[8]

It can be used for sedation required for awake fibreoptic nasal intubation in patients with a difficult airway.[9] On the other hand, lidocaine, which is a well-known local anaesthetic and antiarrhythmic, is increasingly being used as for systemic analgesia and anti-inflammatory effects.[10]This is one approach which is also known as opioid-free anaesthesia (OFA), which avoids narcotics by combining drugs like dexmedetomidine, ketamine, and lidocaine with conventional anaesthetics. These agents help reduce the noxious stimulation and improve efficacy while capitalizing on the analgesic potential of dexmedetomidine and ketamine. [11]

One of the key challenges in postoperative care is the management of pain at times done through opioid analgesics like Nalbuphine. [12] Opioids are very effective but they come with a plethora of adverse effects such as nausea, vomiting, and potential dependency. However the risk of dependency is not high in limited postoperative administration.[13] The consequences of opioid use extend beyond initial pain relief, they are well-known to cause neuroadaptation and provoking 'opioid-induced hyperalgesia,' which undermines its capacity for sustained analgesia.[14] Maintaining the postoperative hemodynamics stability is another important concern, as variability in blood pressure and heart rate may persist due to unresolved pain, residual anaesthetic effects, or autonomic stress responses.[15]

Despite these potential benefits, there remains a significant gap in comparative research assessing dexmedetomidine and lidocaine particularly in the context of upper limb orthopaedic procedures. These surgeries pose distinct challenges due to tourniquet use, prolonged operative times, and varying degrees of nociceptive stimulation. Additionally, investigating their impact on postoperative opioid consumption, particularly nalbuphine ,a commonly used analgesic in many perioperative settings, can provide important insights into optimizing pain management strategies while minimizing opioid exposure.

This study's aim is to seek a comprehensive comparison of the efficacy of dexmedetomidine and lidocaine infusion during a variety of orthopaedic surgeries. By evaluating the following parameters: hemodynamic, nalbuphine requirements, and postoperative analgesia, the aim is to uncover insights that can further refine perioperative protocols and overall improve patient outcomes. The aim is to establish a foundation for more tailored and effective pain management strategies by delving into the potential synergies between these adjuvant techniques and conventional anaesthesia.

METHODOLOGY:

A comparative analytical study was conducted at Fauji Foundation Hospital, Rawalpindi from 7th Oct 2022 to 15th July 2023. The ethical review board of Fauji Foundation Hospital granted ethical approval (reference number 556/RC/FFH/RWP dated 17th October 2022) for this project and informed consent was obtained from all participants. Proper measures were used to ensure patient confidentiality and compliance with associated ethical guidelines. Sample size was estimated by WHO Calculator using formula ($n= 2ó^2[z_{1-á} + z_{1-â}]^2 /[\mu_{1-} \mu_2]^2$) after thorough study of literature with 95% confidence interval.Reported heart rate with dexmedetomidine(73) and lidocaine infusion (83)Variance 235.469, so estimated sample size was 45 per group. The sample included patients presenting for upper limb orthpaedic surgeries in a 10 month period, this included 90 patients with them being divided into two groups.

Included patients receiving dexmedetomidine 1mcg/kg over 10min and lidocaine infusion 0.3 to 0.5 mg/kg/hr after the induction of anesthesia till the end of upper limb surgeries in our setup. Those patients with ASA 3-4, pregnant females, patients who are allergic to dexmedetomidine and lidocaine infusion, and patients with any cardiac, renal, neurological, respiratory or hepatic dysfunction were excluded from the study. Patients were equally divided into two groups A and B, with one receiving dexmedetomidine and the other lidocaine infusion.

Receiving Loading dose: Dexmedetomidine infusion 1mcg/kg over 10min. Maintenance dose Dexmedetomidine infusion 0.3 to 0.5 ug/kg/hr after induction of anaesthesia (Group A). Receiving Lidocaine infusion 0.3 to 0.5 mg/kg/hr after induction of anaesthesia(Group B)

Data collection included both intraoperative and postoperative parameters relevant to upper limb orthopaedic procedures. Intraoperative parameters included the mean heart rate and mean arterial pressure, recordings of which were made at intervals prior to surgery, 10 mins, 15 mins, 30 mins, 60 mins, 90 mins and 120 mins after induction throughout the procedure. Postoperative factors included the numerical rating pain scale (NRS) for pain assessment, opioid dose requirements, and the Ramsey sedation score.

Statistical analyses were carried out using appropriate methods usingusing statistical package for social sciences (SPSS) version 22. The quantitative data was expressed in mean and standard deviation (SD) and qualitative data was expressed by using Frequency and percentages.Discrete

variables such as NRS scores, and opioid dose requirements, were analysed using the Mann-Whitney U test with a significance level of< 0.05.Because data was not normally distributed.

RESULTS

Ninety patients undergoing upper limb orthopaedic surgeries was meticulously assigned to two distinct groups, each consisting of forty-five individuals. Comparison between group A and group B according to demographic data has been shown (Table I). In our research, a greater proportion of the cases pertained to males. 34 (75.6%) in group A, and 31(68.9%) in group. The normality of data was assessed through the Shapiro Wilk test and it was not normally distributed, because of which the Mann-Whitney U test(Non-Parametric Test) was applied. Notably, the dynamic interplay between the two groups showcased intriguing trends. In Group A, which received Dexmedetomidine infusion, a notable reduction in both intraoperative mean arterial pressure (MAP) and heart rate (HR) was observed. This contrasted distinctly with Group B, where such a reduction was not as

Table 3: Comparison between group A and group B according to Ramsay Sedation Score

Ramsay Sedation Scores	Group A (n=45) Median(IQR)	Group B (n=45) Median(IQR)	P value
After surgery	34.34	56.66	<0.00
After 2hrs	36.16	54.84	<0.00
After 4hrs	38.66	52.34	<0.011
After 6hrs	50.94	40.06	<0.040
After 9hrs	51.00	40.00	<0.042
After 12hrs	49.40	41.60	<0.151
After 24hrs	39.03	51.97	<0.016

Table-4 Comparison between group A and group B according to post-operative analgesic requirement

Doses	Study Groups		p-value
	Group A (n=45)	Group B (n=45)	
1st dose	25 (55.56%)	4 (8.89%)	**0.00<0.05**
2nd dose	6 (13.33%)	19 (42.22%)	
3rd dose	14 (31.11%)	22 (48.89%)	

Figure-1: Comparison between group A and group B according to Intra operative parameter to be assessed numeric rating scale

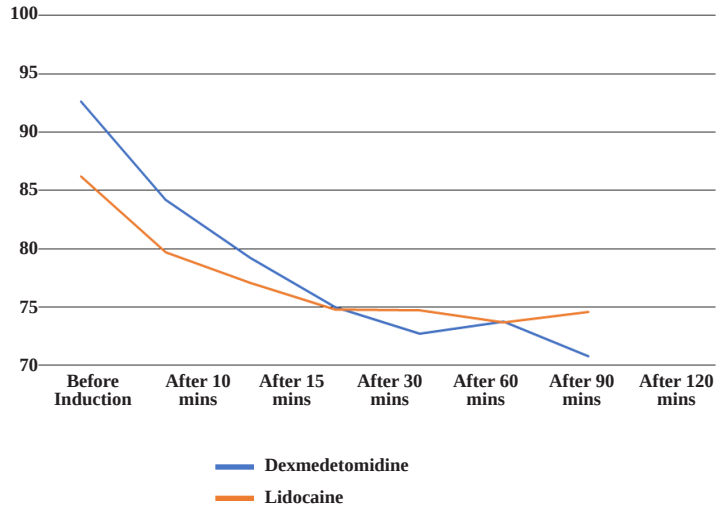

Table-1: Demographic Characteristics of both groups (n=90)

PARAMETERS	GROUP A (n=45)	GROUP B (n=45)
Gender		
Male	34 (75.6%)	31 (68.9%)
Female	11 (24.4%)	14 (31.1%)
Age		
Median(IQR)	42.00(34.50)	37.00(21.00)
Range	15-73	16-70
ASA		
ASA 1	28 (62.2%)	31 (68.9%)
ASA 2	17 (37.8%)	14 (31.1%)

Table-2: Distribution of various parameters in group A and group B

Parameter	GROUP A		GROUP B	
	Shaipiro-wilk Test	Distribution*	Shaipiro-wilk Test	Distribution*
After surgery	0.00	Skewed	0.00	Skewed
After 2hrs	0.00	Skewed	0.00	Skewed
After 4hrs	0.00	Skewed	0.00	Skewed
After 6hrs	0.00	Skewed	0.00	Skewed
After 9hrs	0.03	Skewed	0.00	Skewed
After 12hrs	0.029	Skewed	0.009	Skewed
After 24hrs	0.00	Skewed	0.006	Skewed

Value generated according to Shapiro-wilk Test. Data normal if p-value >0.05

pronounced. Furthermore, a key dimension of patient experience, post-operative pain intensity, was explored using the numeric rating scale. The results unveiled a statistically significant trend – patients in Group B reported higher mean post-operative pain values compared to those in Group A. This distinction persisted immediately after surgery and extended to subsequent time intervals of 2, 4, 6, 9, 12, and 24 hours. Expanding the scope of assessment, the Ramsay Sedation Score was employed to gauge patient sedation levels. Impressively, Group A showcased consistently higher sedation scores across various time points post-surgery – at intervals of 2, 4, 6, 9, 12, and 24 hours – in comparison to Group B. This finding emphasizes the efficacy of Dexmedetomidine in inducing and sustaining higher levels of sedation in the postoperative period. (table 4) The investigation also delved into the realm of post-operative analgesic requirements, a cornerstone of postoperative care. Strikingly, Group A exhibited a notably reduced demand for postoperative analgesia, necessitating only one dose, in stark contrast to Group B, which required multiple doses to achieve adequate pain relief. This stark divergence substantiates the effectiveness of Dexmedetomidine in minimizing the need for postoperative pain management. (Table 5)

DISCUSSION

Dexmedetomidine stands out as a remarkably precise and potent activator targeting central alpha-2 adrenergic receptors. When introduced via neuraxial pathways, dexmedetomidine influences both somatic and visceral pain sensations effectively. Additionally, it displays the ability to alleviate postoperative pain and extend the duration of pain relief. Intravenous lidocaine infusion, on the other hand, hampers nerve transmission at injury sites and boasts substantial anti-inflammatory attributes by curbing cytokine release. This, in turn, minimizes cytokine-triggered cell damage through ATP-gated potassium channels, stemming fromneutrophil suppression. [15,16] In our study, patients receiving intraoperative dexmedetomidine infusion exhibit considerable drops in mean arterial blood pressure and heart rate, along with reduced numeric rating scale scores post-surgery, leading to decreased postoperative analgesic needs, unlike their counterparts on lidocaine infusion.

In a study conducted in CMH Malir, the mean Ramsay Sedation Scale was found to be significantly higher in group-1 compared to group-2, indicating a deeper level of sedation in the dexmedetomidine group during septoplasty under monitored anesthesia care. Additionally, a significantly lower number of patients in dexmedetomidine group required analgesia compared to group 2, suggesting better pain control with dexmedetomidine. Thesefindings support the conclusion that dexmedetomidine is superior to group 2 (midazolam) for providing both sedation and analgesia during septoplasty, highlighting its potential as a preferred option for anesthesia management in this context. [17]

The study at Liaquat National Hospital found that Group D had significantly lower heart rates and mean arterial pressures compared to Group P, indicating superior hemodynamic stability. This highlights the clinical relevance of Group D's treatment for maintaining cardiovascular stability. Also, the study at Sindh Institute of Urology & Transplantation Karachi, highlighted dexmedetomidine's role in improving anesthesia by enhancing safety, comfort, and reducing anesthesia requirements during laryngoscopy-induced hemodynamic changes.[12]

Our study echoes Vishwadeep Singh's research on laparoscopic surgery patients, affirming that dexmedetomidine usage leads to sustained lower heart rate and mean arterial pressure during procedures compared to controls. Dexmedetomidine significantly prolongs early functional recovery discharge, with consistently lower pain levels indicated by visual analogue scale scores, underscoring its superior pain management efficacy versus lignocaine in the control group.[18]Confirming our findings, there exists a strong and statistically significant decrease in heart rate (HR) due to dexmedetomidine, a contrast that differed from the effects of lidocaine (L) in laparoscopic gynaecologic surgery. Importantly, the largest increase in average HR values within the lidocaine group remained below 20% of the starting value. Moreover, this change did not result in a significant rise in the average mean arterial pressure (MAP). These differences could be attributed to variations in the surgical procedures employed in their study. [19]

Similarly, another study revealed marked reductions in heart rate (HR) and mean arterial pressure (MAP) during laryngoscopy and intubation, notably more significant in the dexmedetomidine group compared to lignocaine, highlighting its pronounced impact on hemodynamics.[20]

Corroborating our own findings, a Randomized Clinical Trial conducted among individuals afflicted with failed back surgery syndrome unveiled noteworthy results on the Visual Analog Scale (VAS). This outcome showcased a considerable divergence in pain levels between the cohort administered with dexmedetomidine and the control group during the post-test period. Consequently, we are firmly positioned to affirm that the application of dexmedetomidine injections distinctly facilitated a significant alleviation of pain within the experimental group.[21]

In contrast to our own research, Ebru Tarýkçý Kýlýç and Gaye Aydýn's study found that using Dexmedetomidine during spinal anesthesia did not prolong postoperative effects or reduce the need for pain relief. They also discovered notable insights regarding the Ramsay Sedation Score, revealing a significant and distinct divergence in sedation levels based on the timing of dexmedetomidine administration during spinal anesthesia. This underlines the significant influence of dexmedetomidine on sedation, suggesting that its timing during the procedure can significantly impact

patient sedation experiences. These insights enhance our understanding of how dexmedetomidine can modulate sedation levels during medical procedures.[22]

In a study examining the efficacy of multimodal and conventional approaches for mitigating postoperative pain among oral cancer patients, a noteworthy finding came to light concerning the need for postoperative analgesia. Specifically, the time at which the initial need for analgesia arose was markedly extended (with a p-value of 0.001) in Group C, which received dexmedetomidine, in comparison to both Group B and Group A. This finding suggests that patients in Group C experienced a delayed requirement for pain-relieving measures, indicating a potentially enhanced pain management effect associated with the administration of dexamethasone.[23]

The utilization of epidural dexmedetomidine infusion holds potential for abdominal cancer-related surgeries, possibly leading to a broader impact on clinical approaches. The gentle calming influence of dexmedetomidine might contribute to a reduction in postoperative restlessness, extended period before the initial analgesic administration, and diminished pain severity during the initial 48 hours following surgery, all without adverse effects on hemodynamic stability.[24]Choosing opioid-free anesthesia helps alleviate postoperative pain and minimize analgesic consumption, reducing typical opioid-related complications such as postoperative nausea and vomiting (PONV), with potential benefits extending into long-term outcomes.[25]Our study presents significant findings regarding the potential benefits of dexmedetomidine and lidocaine infusion in upper limb surgeries, but it is essential to acknowledge its limitations as well. The sample size determined at 90 patients undergoing upper limb procedures may introduce some limitations in the extent of our results to broader patient populations. While we did provide some demographic information; a more detailed exploration considering variables like medical history and surgical background could offer a deeper understanding of how these factors influence treatment responses in the population. An exciting avenue for development would be to investigate the combined use of dexmedetomidine and lidocaine, this approach could lead to better understanding of distinct impacts and potential synergies. More than that while our focus centred around upper limb surgeries other procedures involving general anaesthetics could be used in comparison to upgrade guidelines.

Limitations: This study was conducted in a single tertiary care hospital, that may limit the generalizability of the findings to the other institutions with different population of patients, surgical protocols, or anaesthesia practices. Also, it has relatively small sample size, as the inclusion of only 90 patients may not reflects the full variability of responses, particularly among the subgroups with the different surgical complexities. The exclusion of ASA III-IV patients, pregnant females, and the patients with significant organ dysfunction would not apply to high-risk or medically complex patients. This study assessed postoperative pain and analgesic requirements up to 24 hours only. The longer postoperative duration could provide more authentic and valuable information related to rebound pain, late analgesic needs or delayed adverse effects. The only individual drugs were compared. The synergistic impacts of combining dexmedetomidine and lidocaine, which is a relevant emerging trend in opioid-sparing anaesthesia, were not explored. The lack of blinding also considered one of the limitations, as the study design does not specify blinding of anaesthetists or outcome assessors. Knowledge of the administered drug may introduce observer bias, particularly in subjective measures such as pain scores and sedation levels. Sedation scores were evaluated but the other known side effects such as hypotension, PONV, bradycardia, neurotoxicity or lidocaine toxicity were not officially analyzed.

CONCLUSION

This study evaluated dexmedetomidine and lidocaine infusion efficacy as opioid alternatives for post-upper limb surgery pain control, emphasizing dexmedetomidine's benefits like improved hemodynamics, reduced pain, and lower analgesic needs.The findings align with existing evidence, endorsing dexmedetomidine for optimized pain management and highlight the potential for synergistic effects with lidocaine, encouraging further research in opioid-sparing approaches to contribute to the evolving medical landscape aiming to combat the opioid crisis and enhance pain management guidelines.

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Authors Contribution:
Komal Mumtaz: Contribution to study design, acquisition of data, has given final approval of the version to be published
Liaqat Ali: Substantial contribution to analysis and interpretation of data, has given final approval of the version to be published
Saima Zia: Substantial contribution to analysis an interpretation of data, has given final approval of the version to be published
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Original Article **Open Access**

Frequency of Treatment Patterns of Kidney Protective Therapies among Patients with Chronic Kidney Disease at Tertiary Care Hospital, Karachi.

Sana Moin, Sonia Yaqub

ABSTRACT

Objective: To determine the frequency and treatment patterns of kidney-protective therapies, including ACE inhibitors, ARBs, and SGLT2 inhibitors, among patients with chronic kidney disease (CKD) at a tertiary care hospital in Karachi.

Study Design and Setting: This cross-sectional study was conducted in the Department of Nephrology, Aga Khan University Hospital, Karachi, from 12TH May 2025 to 10th October 2025.

Methodology: A non-probability consecutive sampling was used to recruit 133 clinically confirmed CKD patients aged 40-80 years. Demographic information, clinical features, lifestyle, and kidney-protective drugs were documented using a structured proforma. Anthropometric measurements were made following standard procedures and the status of smoking and physical activity was determined by interviewing the patients. Prescriptions and comorbidities were proven by medical records. The data were analyzed using SPSS version 22 descriptive statistics and chi-square/Fisher exact test, $p<0.05$ was significant.

Results: Of the 133 patients, 68.4% were aged 61–80 years, and 51.1% were female. ACE inhibitors were prescribed to 39.8% of patients, ARBs to 15%, and SGLT2 inhibitors to 34.6%. The use of ACE inhibitors was significantly higher among patients with diabetic nephropathy and those with a shorter duration of disease. SGLT2 inhibitor prescriptions were more common in younger and urban populations and among diabetic patients, suggesting awareness of newer therapeutic options.

Conclusion: Patients with CKD were undertreated with key kidney-protective therapies, particularly ARBs and SGLT2 inhibitors. Younger, diabetic, and urban patients were more likely to receive evidence-based treatments, indicating gaps in guideline adherence and inequitable access.

Keywords: Angiotensin-Converting Enzyme Inhibitors; Angiotensin Receptor

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INTRODUCTION

Chronic kidney disease (CKD) is a condition characterized by renal structural or functional abnormality for at least 3 months with implications affecting the glomerular filtration rate (GFR) which can potentially lead to progressive decline in kidney function. It is a serious public health problem worldwide because of its growing prevalence, relationship with diverse comorbidities and high risk to progress to end-stage kidney diseases. CKD causes not only high morbidity and mortality, but also carries a substantial economic burden on the health systems worldwide.[1]

In the last few decades, CKD has increasingly been acknowledged as an alarming public health problem especially in developing countries. The burden is expected to rise dramatically in Asia where more than 60% of the global population resides, primarily due to increasing prevalence of diabetes, hypertension and an aging demographic.[2] In light of the anticipated rise in prevalence of CKD in Asian countries, there is an urgent call for measures to prevent and treat this disease in order to reduce long-term complications.[3]

CKD treatment is multi-factorial and involves both drug- and non-drug-based strategies. Following the diagnosis, the main objectives are to slow disease progression and reduce complications and cardiovascular morbidity and mortality.[4] Lifestyle changes, dietary changes and optimal control of risk factors like hypertension and diabetes are crucial toward attaining these goals. Pharmacotherapy continues to be an important piece in the care of CKD, and therapeutic categories have shown some efficacy in slowing disease progression. Renin–angiotensin system inhibitors (RASIs), such as an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), are the mainstay of treatment in most patients with CKD.5 These

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agents exert effects by lowering intraglomerular pressure and proteinuria, which result in the preservation of renal function and cardiovascular risk reduction.[6] The Reno protective role of these drugs has been repeatedly demonstrated in clinical trials, such as the "classic" trials showing a substantial decrease in progression to kidney disease and mortality rates among patients receiving RAS blockade.

Despite these established advantages, underuse of RAS blockade still represents a common problem in clinical practice.[8] Observational data demonstrate that a significant proportion of diabetic patients with CKD are not initiated or do not have an up-titration during the earliest stages of the disease.? These differences may reflect differences in physician knowledge, economic constraints, patient compliance and regional variation in treatment patterns. Identifying such treatment gaps is important for increasing the adherence to evidence-based quality standards, ultimately leading to improved patient outcomes.

During the last years, SGLT2 inhibitors have represented a revolutionary advancement in the treatment of CKD. Originally used as hypoglycemic agents, these drugs have shown major Reno protection and cardio protection regardless of glucose levels. Findings from both large-scale randomized trials and real-world studies have shown that SGLT2 inhibitors decrease the risk of CKD progression, hospitalization, and death in patients with or without diabetes.[6] Their effects are more than glycemic and include lowering intraglomerular pressure, bettering tubuloglomerular feedback, as well as decreasing inflammation and oxidative stress.8

Nonetheless, the utilization of SGLT2 inhibitors in clinical practice is limited worldwide when compared with classical Reno protective agents.[2] Real-world prescribing patterns studies show that the number of CKD patients prescribed SGLT2 inhibitors is low, and prescription rates for ACEIs/ARBs are higher. [2] This phenomenon represents a combination of clinical inertia and the friction that new therapies face when they are introduced into practice. Regular monitoring of treatment use patterns can enable the identification of facilitators and barriers to implementation and optimization of newer guidelines for CKD care.4

Drug utilization studies are the key contributors which help in identifying prescribing, dispensing and use of drugs in clinical practice.[1°] Analyzing adherence can evaluate how planning in treatment decision based on guidance is and be able to become a good referring point for intervention.[11] These studies also reflect the level of rational drug use, polypharmacy and compliance with the WHO prescribing indicators—an important aspect in treating CKD patients who are frequently prescribed multiple medications and more likely to experience adverse drug reactions.[12] Prescription pattern analysis assists in ascertaining current trends in practice and identifies potential areas for clinician- or system-level focused intervention.[1°]

In addition, evaluating drug prescribing patterns in various populations and health care facilities is important to assess the pragmatic effects of guidelines.[11] They went on to say: "For a better plan of health management, there is a need to design strategies toward improving the therapeutic results and decreasing variability in CKD care; and therefore, determination of prevalence of use and predictors for prescription is important. Through analyzing the prevalence and pattern of kidney-protective therapies, investigators can find gaps in treatment deployment and compare whether any interventions of novel treatments have been well employed.

In summary, chronic kidney disease continues to be an emerging public health crisis and a multimodal approach including lifestyle and pharmacological approaches is required for management.[1,12] Pharmacologic "fine-tuning" including use of submaximal ACEI, ARB and SGLT2 inhibitors may represent a promising option for enhancing renal and cardiovascular outcomes. Evaluating treatment patterns is not only a reflection of the realities of clinical practice, but also provides useful information for updating.[12] guidelines, rational use of drugs and ultimately the quality of care offered to CKD patients. In line with its objectives, the present study focuses exclusively on lifestyle-related factors and pharmacological treatment patterns among patients with CKD, and does not evaluate other non-pharmacological or multidisciplinary management strategies.

METHODOLOGY

It was a descriptive cross-sectional study, which was carried out in the Department of Nephrology, Aga Khan University hospital (AKUH), Karachi over a period of six months (April 2025 -September 2025), following a six-month exemption granted by the ethical review committee at Aga Khan University (ERC # 2025-10772-34517 dated May 11th, 2025). The aim was to evaluate the prescribing rates of kidney-protective medications, especially reninangiotensin system inhibitors (RASIs) and sodium-glucose co-transporter-2 (SGLT2) inhibitors, among patients with CKD.

A sample of 133 patients with CKD was recruited through non-probability consecutive sampling technique, i.e. all the eligible patients who came forward in the process were recruited to get to the required sample size. The sample size was calculated by the WHO sample size calculator basing on a previous reported 53.4% rate of Losartan usage by CKD patients with a margin of error of 8% and power of 95%. This gave the minimum required sample size of 133 participants to be used in establishing sufficient precision in estimating the patterns of treatment utilization. Inclusion criteria were set to ensure a sample with homogeneity, male and female patients aged 40 to 80 years with clinically established CKD by a nephrologist or with laboratory data

were included. The exclusion criteria included people with concomitant conditions that may affect the therapeutic plan or results including malignancy, those on hemodialysis, intravenous drug abuse, pregnant, asthma, recent myocardial infarction (MI), congestive cardiac failure (CCF), chronic liver disease (CLD), chronic obstructive pulmonary disease (COPD) and cerebrovascular accident. Patients who did not want to make an informed consent were also excluded.

Each qualified participant was informed about the aim and objectives of the study before enrolment. Written informed consent was taken after an assurance of confidentiality and voluntary participation. All the ethical standards were observed in full following the Declaration of Helsinki. A structured and pretested proforma specifically designed to address the study was used to collect data, comprised of sociodemographic characteristics, clinical profile and treatment history. Demographic variables (age, sex and place of residence) were noted and clinical variables (duration of CKD, disease stage and comorbid diabetes mellitus and hypertension). Data on antihypertensive/antidiabetic treatment, classes of Reno-protective medications was recorded.

The anthropometric measurements were done through the standard procedures. The weight was measured to the nearest 0.1 kg with the participants being loosely dressed and with bare feet weighing them with a calibrated digital weighing scale. The measurement of height was taken to the closest 0.1 cm using a wall-mounted stadiometer in the Frankfort plane to the upright stance of the participant. Body mass index (BMI) was determined as the weight divides by the height in terms of meters squared (kg/m^2) and the participants were classified as underweight, normal, overweight or obese based on traditional parameters. The data on the lifestyle was collected via interviews with the participants. The question on physical activity was on the basis of whether the patients had any form of regular physical activity (yes/no), and in the event of yes, whether the activity was light, moderate or vigorous, depending on their own self-concept, which then allowed the categorization on the basis of routine practice. The smoking status was measured by asking the respondents whether they were present smokers, former smokers or had not smoked at all and smoking status was operationalized as current smoking (any cigarette use during the last 30 days), former smokers(previously smokes but no more during the last 30 days) or never smokes. Medical records were also cross checked with all responses where there was a comparison. The comorbidities such as hypertension (BP 140/90mmHg or taking antihypertensive medication) and diabetes mellitus (fasting plasma glucose 126mg/dl or taking antidiabetic medication) were classified using operational definitions. Medical prescriptions were used to affirm the use of kidney-protective medications (ACE inhibitors, ARBs and SGLT2 inhibitors).

All the data collected were inputted and were analyzed by use of SPSS (Statistical Package for the Social Sciences) software version 22. Univariate analysis was done to describe data. The quantitative variables like age, BMI and the duration of the disease were displayed as mean SD when data had a normal distribution or median with interquartile range (IQR) when data were non-normal. Frequencies and percentages were used to report categorical variables such as sex, comorbidities and medication use. The post-stratification analyses were conducted to test associations between patient factors and treatment utilization. Categorical variables were compared using chi-square or fisher exact tests and the p-value of less than 0.05 was taken to be significant in all tests.

RESULTS

A total of 133 patients with chronic kidney disease (CKD) were enrolled. The mean age was 66.2 ± 8.4 years, and the majority (68.4%) were between 61 and 80 years old. Gender distribution was almost equal, with 48.9% males and 51.1% females. Most participants (88%) resided in urban areas, while 12% were from rural regions. More than two-thirds (70.7%) had CKD for over 2.5 years, reflecting a chronic disease burden (Table 1).

Regarding comorbidities, 24.8% had type II diabetes mellitus and 45.9% had hypertension. Lifestyle-related factors showed that 36.8% were smokers, and 45.1% engaged in regular physical activity. Socioeconomic data revealed that 45.9% reported a monthly household income =50,000 PKR, while 60.2% were unemployed. Educational attainment varied, with 9.8% illiterate, 39.8% with primary education, 26.3% with secondary, and 24.1% with higher education (Table 2).

Table 3 presents the relationship between patient characteristics and the prescription of kidney-protective therapies, including ACE inhibitors, ARBs, and SGLT2 inhibitors. Younger patients (40–60 years) showed a higher likelihood of receiving SGLT2 inhibitors, with a statistically significant association (p=0.01), whereas age was not significantly associated with ACE inhibitor or ARB use. Urban residents were more frequently prescribed SGLT2 inhibitors compared to rural residents (38.5% vs. 6.2%, p=0.01), and a similar but non-significant trend was observed for ACE inhibitor use. Patients with a shorter CKD duration (=2.5 years) were more often prescribed ACE inhibitors (p=0.03), although CKD duration did not show an association with ARB or SGLT2 inhibitor use.

Diabetic patients were significantly more likely to receive ACE inhibitors (p=0.04) and SGLT2 inhibitors

(p=0.05), reflecting their established role in this population. Education level showed a significant association only with ARB use (p=0.01), with higher utilization among illiterate participants. In contrast, smoking status, physical activity, and hypertension did not demonstrate statistically significant associations with any of the treatment categories.

DISCUSSION

Prescription pattern and utilization of kidney-protective agents among CKD patients: A study at tertiary care hospital in Karachi. Angiotensin converting enzyme (ACE) inhibitors were prescribed in less than half and angiotensin receptor blockers (ARBs) in only few patients, while nearly one-third of participants received SGLT2 inhibitors. These findings indicate a wide discrepancy between evidence-based guidelines and the actual clinical practice, despite the Reno protective and cardio protective effects of these therapeutic drugs are well documented.

The low usage of ACE inhibitors and SGLT2 inhibitors in this population mirrors that seen in studies from other middle-income countries. The same trends had been observed in South Asian and Latin American countries that all have an uneven access to RASIs and SGLT2 inhibitors (13). In Colombia, SGLT2 inhibitors were least commonly used in places apart from the largest cities and differences across socio-economic status particularly impacted prescribing. Our findings are consistent with these observations, as urban patients were also more likely to be prescribed SGLT2 inhibitors compared rural ones. Availability of care, affordability and lack of familiarity with new drug classes are important barriers to CKD management in LMICs Management of CKD in developing countries has been characterized by unavailability, high cost for treatment and tremulous experience of newer drug types.

Our findings are in agreement with those of Indian studies as well, which have reported high prevalence of antihypertensive drug usage especially among CKD patients but very low use of ACE inhibitors and ARBs. In India, common prescription patterns were reported for diuretics and calcium channel blockers, ACE inhibitors and ARBs use remained low especially in advanced CKD stages. These trends were also observed in cross-sectional surveys of prescribing practices among tertiary care hospitals, with practitioners being less likely to recommend ACE inhibitors or ARBs out of fear for hyperkalemia or an exacerbation in renal function. These tendencies may also account for the underuse seen among our

Table 1. Demographic Characteristics of Patients with Chronic Kidney Disease (n = 133)

Variable	Categories	n (%) / Mean ± SD
Age (years)		66.2 ± 8.4
	40–60	42 (31.6)
	61–80	91 (68.4)
Gender	Male	65 (48.9)
	Female	68 (51.1)
Residence	Urban	117 (88.0)
	Rural	16 (12.0)
Duration of CKD	=2.5 years	39 (29.3)
	>2.5 years	94 (70.7)

Table 2. Comorbidities, Lifestyle, and Socioeconomic Profile

Variable	Categories	N (%)
Comorbidities	Type II Diabetes Mellitus	33 (24.8)
	Hypertension	61 (45.9)
Lifestyle Factors	Smoker	49 (36.8)
	Physically Active	60 (45.1)
Socioeconomic Indicators	Family income =50,000 PKR	61 (45.9)
	Unemployed	80 (60.2)
Education Level	Illiterate	13 (9.8)
	Primary	53 (39.8)
	Secondary	35 (26.3)
	Higher	32 (24.1)

Figure 1. Distribution of Kidney-Protective Therapy Prescriptions among CKD Patients

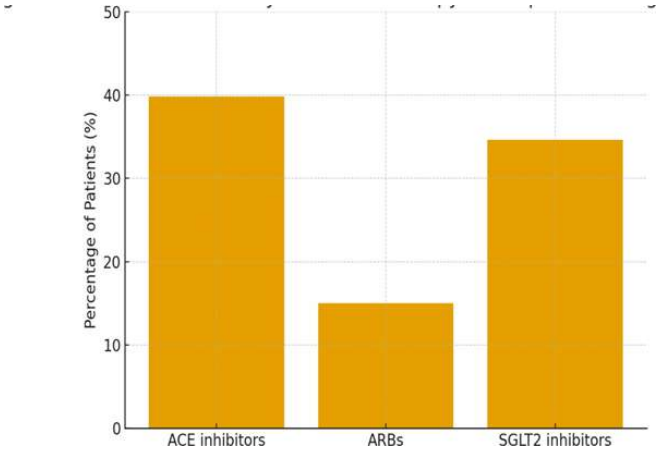

Table 3. Distribution of Kidney-Protective Therapies and Significant Associations

Variable	ACE Inhibitor Use (%)	ARB Use (%)	SGLT2 Inhibitor Use (%)	p-value (ACE / ARB / SGLT2)
Age (40–60 vs. 61–80 years)	50.0 vs. 35.2	13.0 vs. 16.5	50.0 vs. 27.5	0.10 / 0.60 / 0.01
Residence (Urban vs. Rural)	42.7 vs. 18.8	14.5 vs. 18.8	38.5 vs. 6.2	0.06 / 0.70 / 0.01
Duration of CKD (=2.5 vs. >2.5 years)	53.8 vs. 34.0	12.8 vs. 15.9	33.3 vs. 35.1	0.03 / 0.68 / 0.84
Diabetes Status (Yes vs. No)	54.5 vs. 35.0	18.2 vs. 14.0	48.5 vs. 30.0	0.04 / 0.60 / 0.05
Education Level (Illiterate vs. others)	41.0	30.8	32.0	0.30 / 0.01 / 0.28
Smoking Status (Yes vs. No)	40.8 vs. 39.3	16.3 vs. 14.1	36.7 vs. 33.3	0.85 / 0.79 / 0.72
Physical Activity (Active vs. Inactive)	41.7 vs. 38.0	18.3 vs. 12.7	36.7 vs. 32.4	0.68 / 0.40 / 0.62
Hypertension (Yes vs. No)	41.0 vs. 38.0	16.4 vs. 13.4	36.1 vs. 32.4	0.74 / 0.64 / 0.65

study population, where patients with advanced disease or numerous comorbidities are particularly prevalent.

In the present study, diabetics and those with less advanced CKD were more likely to be prescribed ACE inhibitors. This is congruent with prior research demonstrating higher probability of RASI use in patients with diabetes or albuminuria.[13] In the current analyses, patients with diabetes appeared more likely to receive guideline-directed therapy: thus comorbidity profiles exert important effects on prescribing practices. These findings were consistent with the results of previous studies, which reported that renoprotective drugs were more frequently used among milder disease stage patients and less likely used in advanced to ESRD stages due to concerns for further decline of renal function and hyperkalemia.[14]

The apparently low rate of prescription of ARBs in this group is interesting, and may be representative of local prescribing patterns, financial considerations or a preference to keep ARBs as second line drugs for patients who are intolerant to ACE inhibitors. These results are consistent with those of studies in South Asia and Africa that also report this preference.[15 1 6] In Kenyan study, the prevalence and treatment control of hypertension among CKD patients was poor, there were substantial disparities in patient access to guideline-based medications driven mainly by cost-related and supply related factors. [17] These findings cumulatively emphasize that cost, availability and clinical conservatism still drive practice rather than evidence based guidelines in various LMIC's.

In the present analysis, younger patients and those living in urban areas were also significantly more likely to be dispensed SGLT2 inhibitors. This is consistent with international trends where newer agents are usually introduced in urban tertiary referral centers, which have better healthcare resources and access to specialists. The 653-fold ratio of diabetes to SGLT2 inhibitor exposure in our cohort underlines again the redundancy these antihyperglycemic agents are considered for therapy rather than renoprotective agents. While the glucose-lowering benefit of these drugs is well established, new evidence indicates that SGLT2i offer significant renal and CV protection in a broad range of patients with kidney disease, even those without diabetes.[18?1?]

Recent meta-analyses have shown a significant reduction in risk for progression of CKD, hospitalization due to heart failure, and all-cause mortality with use of SGLT2 inhibitors among diabetic as well as non-diabetic CKD populations.[18] These have resulted in substantial changes to clinical practice guidelines, most notably by the 2023 UK Kidney Association guideline where SGLT2 inhibitors have moved into pole position as first line therapy for adults with CKD regardless of diabetic status.[1?] Moreover, meta-analysis data have shown that in combination with RASIs, SGLT2 inhibitors are able to provide additional renal benefits as well as anti-inflammatory and glomerular hyper filtration protection.[2°] This changing paradigm, which Emerging evidence suggests that SGLT-2 inhibitionation should not be restricted to glycemic control but rather viewed as an important renoprotective therapeutic strategy within the CKD management algorithm.

The renal effect of SGLT-2 inhibitors is not only due to the glucose control mechanism. They decrease intraglomerular pressure mechanistically, ameliorate dysfunctional tubuloglomerular feedback, and inhibit cytokine pro-inflammatory-mediated pathways.[21] Other than their beneficial renal effects, they are presumably safe and have a potential renal protective effect even in patients with chronic dialysis therapy as the follow-up studies especially among peritoneal dialysis populations were reported recently.[22] Such data continue to support the case for wider availability of SGLT2 inhibitors as well as greater physician experience across a range of CKD phenotypes.

Although our research involved the correlation of the outcome with the place of residence of the patients (urban versus rural), some of the studies with which we compared our results analyzed outcomes obtained in hospitals situated in an urban environment. This is a contextual incompatibility, since the location of hospitals is not always indicative of the residential features or exposure history of the patient population. Interpretations should therefore be made with respect to the fact that urban based hospitals could be serving urban based as well as rural citizens and this is likely to water down the real residential effects. In order to enhance the contextual relevance we analyzed local evidence and the literature already in Pakistan has revealed significant differences in presentation patterns and health-seeking behavior between urban and rural population, which justify the need to assess the differences in residence based disparities in our context.[4]

While these benefits are powerful, our study results underscore an ongoing challenge in closing the evidence- to-practice gap. The documented underuse of ACE inhibitors, ARBs and SGLT2 inhibitors points to barriers at clinician and system levels. Barriers at clinician-level may stem from lack of knowledge regarding updated guidelines, and inexperience with new agents, as well perception of potential side-effects. At the system level, costs, restricted drug availability, lack of standardized treatment pathways and absence of electronic prescribing reminders all contribute to this inequity. To fill this space, comprehensive interventions are necessary. Continuing medical education programmes, incorporation of evidence-based prescribing guidelines into electronic health record systems and national procurement or subsidy policies all have the potential to maximize access to, and adherence with optimal therapeutic regimens.

In summary, the use of ACE and ARB therapy among patients with CKD in this tertiary care cohort was much lower than anticipated, suggesting a significant evidence-practice discordance. Sociodemographic and clinical characteristics determined the uptake of therapy, being more likely to be prescribed in younger, diabetic and urban individuals. Tackling the obstacles to deliver GP-based access and prescription in line with guidelines is still essential to enhance renal and cardiovascular outcomes among patients with CKD.

There are several limitations in the study, which must be considered. It was performed in a single tertiary care hospital and it can be difficult to generalize these findings to other health care settings. It is also worth noting that the study did not assess drug adherence,

and contraindications in the reason given by rheumatologists for non-prescription, which may influence the differential patterns observed here. Nevertheless, the results provide an important snapshot of practice at the time and identify key areas for improvement in CKD care.

CONCLUSION

In this study, we observed that patients with CKD in a tertiary care hospital of Karachi were undertreated for kidney protective therapies. We found that younger patients, as well as those with diabetes and in urban areas, were more likely to be prescribed with ACE inhibitors and SGLT2 inhibitors compared to ARB use which remained notably low. These patterns indicate areas of shortfall in guideline adherence and inequities in access, highlighting the importance of targeted interventions to improve prescribing practices, and for broader dissemination of effective treatments.

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Authors Contribution:
Sana Moin: Study conception, design, data collection, statistical analysis, and manuscript drafting.
Sonia Yaqub: Critical review of the manuscript, supervision, and final approval for submission.

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Original Article **Open Access**

Surgical Intervention for Arterial Thoracic Outlet Syndrome: A Retrospective Observational Study on Post-operative Outcomes and Quality of Life; Single Center Experience from Karachi Pakistan

Muhammad Muqeem, Waryam Panhwar, Fahad Tariq Berlas, Fahad Memon, Misbah Nizamani, Asif Ali Khuwaja

Abstract:

Objective: Thoracic outlet syndrome results from compression of the brachial plexus and/or subclavian vessels. Arterial thoracic outlet syndrome carries the most severe consequences. To assess the surgical outcomes and its impact on quality of life in patients with aTOS undergoing surgical treatment.

Study Design and Setting: A retrospective study was conducted on patients undergoing surgical decompression with/without arterial reconstruction at the Department of Vascular & Endovascular Surgery SMBBIT, Karachi from July 2019 to December 2023.

Methodology: Limb salvage, complication rates and QoL using DASH score were assessed retrospectively. P-value of less than 0.05 was considered significant

Results: A total of 22 patients underwent surgery for aTOS over the past five years. The cohort was predominantly male (59.1%) with a mean age of 32.05 ± 14.3 years. All patients presented with Acute or acute on chronic limb ischemia, the most common symptoms being pain (90.9%), numbness (45.5%) and blackish discoloration (27.3%). Imaging showed post-stenotic aneurysm as the most prevalent arterial pathology (54.5%). All patients had a cervical rib, and the supraclavicular approach was used exclusively for surgery with infraclavicular incision for axillary artery control and distal anastomosis where needed. Arterial reconstruction was performed in 90.5% of patients. Postoperative complications occurred in 27.3% of patients. No in-hospital or 30-day mortality was observed. Limb salvage was achieved in 95.5% of patients. Follow-up data showed a progressive improvement in post operative DASH scores (p= <0.001).

Conclusion: Surgical decompression of aTOS with/without arterial reconstruction is associated with high limb salvage rates and QoL improvement.

Keywords: ATOS, cervical rib, DASH score

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INTRODUCTION:

Thoracic outlet syndrome (TOS) is a well-recognized clinical condition caused by compression of the brachial plexus and/or the subclavian vessels within the thoracic outlet. The syndrome is categorized into neurogenic, venous, and arterial subtypes based on the structure involved. The neurogenic form constitutes over 90% of all TOS cases, making it the most prevalent, whereas the venous subtype accounts for approximately 3–5%, and the arterial form comprises less than 1%.[1,2] Arterial thoracic outlet syndrome (aTOS) is specifically defined by a demonstrable abnormality in the subclavian artery secondary to chronic extrinsic compression, most commonly by an anomalous first rib, cervical rib, or fibrous band located at the base of the scalene triangle.[3]

Although aTOS is the rarest subtype of TOS, it carries the most severe clinical implications. Patients frequently presents with upper limb ischemia, distal thromboembolism, digital gangrene, or, in advanced cases, potential limb loss.[4] The etiologies of aTOS may be broadly classified as bony or non-bony. Bony causes include congenital anomalies such

as cervical ribs or anomalous first ribs, as well as acquired pathologies such as clavicular fractures or hypertrophic fracture callus. Non-bony causes involve hypertrophy of scalene muscles, post-surgical or post-radiation fibrosis, or intrinsic arterial lesions such as aneurysmal dilation or thrombosis.[5]

Epidemiological data indicate that aTOS is more commonly observed in younger individuals, particularly those presenting within the first two decades of life.[6] The clinical presentation varies depending on the chronicity and severity of arterial compromise. Symptoms may range from acute ischemia, pain, paresthesia, and upper limb weakness to limb discoloration or cold intolerance. In long-standing or severe cases, rest pain, ischemic ulcerations, or tissue necrosis may develop.[7]

A range of imaging modalities is available for the diagnosis and etiological assessment of aTOS. These include plain chest radiography, digital plethysmography, pulse volume recordings, segmental pressure measurements, duplex ultrasonography, computed tomography angiography (CTA), and conventional catheter-based angiography. Among these, a plain chest radiograph is typically the initial investigation of choice due to its accessibility and ability to detect bony abnormalities such as cervical ribs, anomalous first ribs, and clavicular trauma or callus formation.[8] Definitive vascular imaging with duplex ultrasonography or CTA is frequently required for operative planning and assessment of arterial damage.

The management of aTOS is not standardized and largely depends on the underlying etiology, extent of arterial pathology, and patient presentation. The principal objective of surgical intervention is to relieve extrinsic compression of the neurovascular bundle and restore distal perfusion. This is commonly achieved through resection of the first rib, excision of fibrous bands, division of the anterior and middle scalene muscles, and neurolysis of the brachial plexus. In many cases, vascular reconstruction such as arterial bypass or end-to-end anastomosis is warranted when aneurysmal degeneration or post-stenotic dilation is present. Multiple surgical approaches have been described, including transaxillary, supraclavicular, infraclavicular, posterior, combined transaxillary–supraclavicular, combined supraclavicular–infraclavicular (paraclavicular), and minimally invasive techniques such as endoscopic- or video-assisted thoracoscopic surgery, with or without robotic assistance. Each technique offers distinct advantages and limitations; however, evidence suggests that when complete decompression of the compressive lesion is achieved, outcomes are comparable across approaches.[9] Although postoperative complications such as nerve injury, pneumothorax, or vascular thrombosis have been reported, overall mortality in aTOS remains exceedingly low.[10]

The objective of this study is to evaluate surgical outcomes and their impact on quality of life in patients with arterial thoracic outlet syndrome managed operatively at the Department of Vascular and Endovascular Surgery (DVES), Shaheed Mohtarma Benazir Bhutto Institute of Trauma (SMBBIT), Karachi. Current literature from developing countries, particularly within South Asia, is limited, despite notable differences in patient demographics, disease chronicity at presentation, and healthcare delivery systems compared to high-income regions. This study aims to address this gap by contributing locally relevant data on clinical presentation, surgical management, and postoperative functional recovery in patients with aTOS.

METHODOLOGY:

This retrospective observational study was conducted to evaluate the clinical and functional outcomes of patients undergoing surgical management for arterial thoracic outlet syndrome (aTOS) at the Department of Vascular and Endovascular Surgery (DVES), Shaheed Mohtarma Benazir Bhutto Institute of Trauma (SMBBIT), Karachi, Pakistan. All patients of any age or gender who underwent surgical intervention for arterial TOS between July 2019 and December 2023 and met the inclusion criteria were included using a consecutive sampling technique. Patients were excluded if they had other established causes of upper limb ischemia such as athero-embolic disease, had undergone prior surgical procedures for similar symptoms in other departments, or presented with a non-salvageable limb. The primary objective of the study was to assess postoperative limb salvage, graft patency, and complications following surgical management of aTOS, while the secondary objective was to evaluate postoperative quality of life using the Disabilities of the Arm, Shoulder, and Hand (DASH) score.

Data were collected using a pre-designed pro forma. Eligible patients admitted during the study period were identified, ensuring a minimum follow-up duration of 12 months. Relevant data were extracted from admission records, radiological imaging, operative notes, and outpatient follow-up documentation. Study variables included demographic characteristics, clinical presentation, comorbidities, imaging findings, surgical details, perioperative and postoperative outcomes, and functional outcomes assessed by the DASH score at 3, 6, and 12 months postoperatively. To address missing data, patients were contacted through follow-up calls or clinic visits, and additional information was obtained after informed consent.

Statistical analysis was performed using IBM SPSS Statistics version 24. Continuous variables were expressed as means and standard deviations, while categorical variables were summarized as frequencies and percentages. Data normality was assessed using the Shapiro–Wilk test. Comparisons for normally distributed continuous variables were conducted using independent sample t-tests or ANOVA as appropriate. Categorical variables were analyzed using the Chi-square

test, with Fisher's exact test applied when Chi-square assumptions were not met. For non-parametric data, the Mann–Whitney U test was used. A p-value of less than 0.05 was considered statistically significant. Ethical approval for the study was obtained from the Institutional Ethical Review Committee (IRB-000160/SMBBIT/Approval/2025).

Operational definitions:

• Quality of Life:

Quality of Life is defined as the patient's self-reported physical, psychological, and social well-being following surgical intervention for arterial TOS as assessed by change in DASH (Disability of the Arm, Shoulder, and Hand) score after surgery.[11]

• Limb salvage:

Limb salvage in this study refers to preservation of the affected limb without requiring amputation, following surgical intervention for arterial Thoracic Outlet Syndrome.

• Scher Classification:

The Scher classification was used to categorize the severity and type of aTOS based on clinical presentation and radiologic findings. This classification helped guide the choice of surgical intervention and was used in outcome analysis.

Stage 0: Asymptomatic subclavian artery compression

Stage 1: Subclavian artery stenosis with minor post-stenotic dilation but no intimal injury

Stage 2: Subclavian artery aneurysm with mural thrombus and intimal damage

Stage 3: Arterial thrombosis or distal embolization leading to occlusion [12]

RESULTS:

A total of 22 patients underwent surgery for arterial TOS at our center over the specified period of which 59.1% (n=13) were male. The mean age was 32.05 +/- 14.3 years. Most of the patients (90.9%, n=20) had no comorbid conditions. Only one patient had hypertension, and another had both diabetes mellitus and hypertension, while two patients were smokers. (Table no.1). Among the 22 patients who underwent surgery for aTOS, the most frequently reported symptom was hand and arm pain, present in 90.9% (n=20) of cases. Numbness was the second most common symptom, occurring in 45.5% (n=10) of patients. Blackish discoloration of fingers was observed in 27.3% (n=6), followed by burning sensation in 13.6% (n=3), restricted movements in 9.1% (n=2), and claudication in 4.5% (n=1). Notably one of our patients had an episode of ipsilateral cerebral ischemic event 2 weeks before presentation. Many patients experienced more than one symptom (Figure no.1). Most patients experienced symptoms for a short period before seeking medical care. The median duration of symptoms was 3 months, with IQR of 1 to 6 months. All patients were right-hand dominant (100%, n=22). Symptoms were present on the right side in 77.3% (n=17) of patients and on the left side in 22.7% (n=5). Most patients (90.9%, n=20) had not undergone any prior interventions, while 9.1% (n=2) had underwent embolectomy for acute ischemia before thoracic outlet decompression surgery. Imaging studies were performed on all patients in the cohort. Chest X-ray (CXR) and CT scan were each conducted as per departmental policy (Table no.1).

The most prevalent arterial injury observed was post stenotic aneurysmal dilation, occurring in 54.5% (n=12) of patients, followed by thrombosis in 27.3% (n=6). Only extrinsic compression without identifiable arterial damage was present in 18.2% of patients (n=4). According to the Scher classification, the majority of patients were classified as stage 3 (47.6%, n=10), followed by stage 2 (42.9%, n=9) and stage 1 (9.5%, n=2).

All patients had a bony abnormality in the form of a cervical rib (100%, n=22), with no other bony anomalies identified. The supraclavicular approach was utilized exclusively in all cases along with infra clavicular incision, for axillary artery control and distal anastomosis when required.

Arterial reconstruction was performed in 90.5% of patients (n=19), while 9.5% (n=2) did not require reconstruction. Among the patients who underwent reconstruction, the most common procedure was interposition graft placement, performed in 85.7% of cases (n=18). Distal bypass was done in 4.7% (n=1). Concomitant distal embolectomy was performed in 36.8% of cases. Autologous Vein Grafts were used in 70% (n=14) of cases while prothesis was used in 30% (n=6) of cases. In two patients, pleura was opened intra-operatively, which was repaired, without need for chest tube placement.

The mean length of hospital stay was 7.73 ± 4.06 day. No In-hospital or 30-day mortality was observed in all patients (Table no.2). Postoperative complications were observed in 27.3% of patients (n=6), while the remaining 68.2% (n=15) had an uncomplicated recovery. Among those who experienced complications, the most common issues included hematoma formation (n=2), surgical site infection (n=2), graft thrombosis (n=1) and lymphatic leak (n=1) (Table no.3). Out of the 22 patients included in the study, 21 (95.5%) achieved limb salvage, while 1 patient (4.5%) required a below-elbow amputation due to graft thrombosis.

Reintervention was required in 4 patients (18.2%). These included one case of drainage of collection, two cases of hematoma evacuation, and one suture ligation of lymphatic leak. Data on functional outcomes could be achieved only for 12 out of 22 patients. The mean DASH score demonstrated a consistent decline over time, indicating significant

Table 1: Demographics and Operative Details

Variable	N	%
Gender		
Male	13	59.1
Female	9	40.9
Co-morbid		
HTN	1	4.5
DM and HTN	1	4.5
None	20	90.9
Smokers	2	9.1
Laterality		
Right	17	77.3
Left	5	22.7
Dominant Hand		
Right	22	100
Left	0	0
Imaging Modality		
CXR	22	100
CT scan	22	100
Arterial Pathology on imaging		
Thrombosis	6	27.3
Aneurysm	12	54.5
Extrinsic compression only	4	18.2
Scher Classification		
Stage 0	0	
Stage 1	2	9.5
Stage 2	9	42.9
Stage 3	10	47.6
Surgical decompression	22	100
Type of Arterial reconstruction		
Interposition Graft	18	85.7
Distal Bypass	1	4.7
No reconstruction	2	9.5
Graft		
Vein	14	70
Prosthesis	6	30

Table 2: Postoperative Length of Stay and Functional Outcomes as assessed by DASH score

Length of stay (in days)	Mean (SD) 7.73 (± 4.06)	Median 6.5	IQR 4.75-11.25
DASH score			
Pre-op	64.78± 9.39	64	57-73
3-months	33.33 ± 3.60	34	30-37
6-months	32.25 ± 3.95	32	29-36
12-months	31.58 ± 4.21	37	28-36

Figure 1: Presenting Symptoms

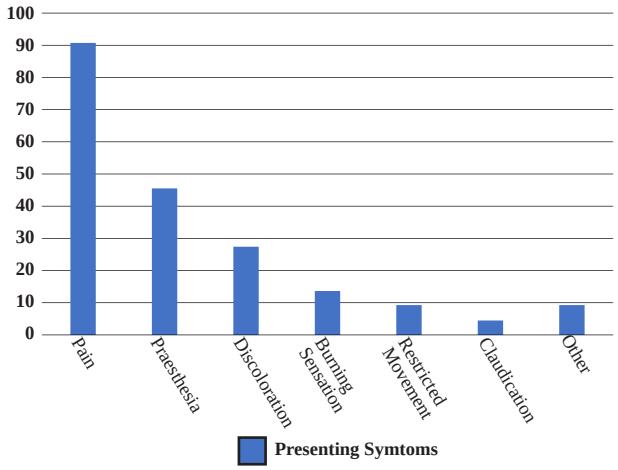
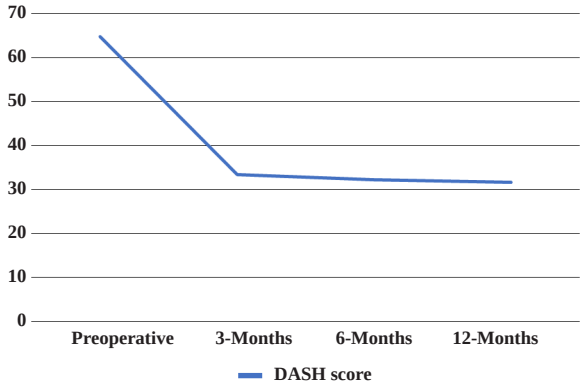


Table.3: Post-operative complications.

Post-operative Complications	**N**	**%**
Hematoma formation	2	9.1%
Infection	2	9.1%
Lymphatic leak	1	4.5%
Graft thrombosis	1	4.5%
None	16	72.7%

Figure 2: Mean DASH scores at preoperative, 3-month, 6-month, and 12-month follow-up



improvement in upper limb function following surgery. The mean preoperative DASH score was 64.78 ± 9.39, which decreased to 33.33 ± 3.60 at 3 months, 32.25 ± 3.95 in 6 months, and 31.58 ± 4.20 in 12 months. The median scores followed a similar trend, decreased steadily from 64.6 preoperatively to 30.5 in 12 months, indicating a sustained improvement in upper limb function over time. (Table no.2).

We evaluated the preoperative DASH scores and compared it with DASH scores at 3-, 6-, and 12-months follow-up using repeated measures ANOVA. The analysis revealed a statistically significant effect of time on DASH scores ($p < 0.001$) with a large effect size. The estimated marginal means showed a significant linear trend and indicated rapid early improvement in the first 3 months followed by a plateau. These findings suggest that the most functional recovery occurred within the first 3 months postoperatively, with gradual but less pronounced improvements up to 12 months (Figure no 2).

There was no notable interaction between improvement in DASH score and Scher classification (p = 0.320), indicating that the rate of improvement over time was consistent across Scher groups. No statistically significant correlation was found between operative time and the change in DASH score (p = 0.901). Additionally, there was no significant relationship between the type of arterial reconstruction and the degree of functional improvement, as assessed by the change in DASH score (p = 0.801).

DISCUSSION:

In this retrospective cohort study, we analyzed 22 patients who underwent surgical treatment for arterial thoracic outlet syndrome (TOS) over a five-year period. This study demonstrated a slight male predominance (59.1%), which contrasts with existing literature that generally reports a higher prevalence among females.[13] The majority (77.3%) presented with symptoms on the right side. Pain was the most common presenting complaint (90.9%), followed by numbness and discoloration suggesting either acute or acute on chronic limb ischemia. One of our patients had an episode of an ipsilateral Cerebral ischemic event 2 weeks prior to presentation. Notably, posterior circulation stroke has been reported as one of the potential sequelae of arterial TOS, where retrograde embolization of clot secondary to subclavian artery injury can lead to permanent neurological deficit.[14,15]

In this study only two patients (9.1%) had undergone prior embolectomy, having presented to the emergency department with acute or subacute thromboembolic events. This approach is consistent with current practices and recommendations for the initial management of arterial TOS.[16]

The aneurysmal degeneration of the subclavian artery was the predominant vascular abnormality, followed by thrombosis. All patients had cervical ribs, and the supraclavicular (SC) approach was used exclusively in our surgical management. Although no approach has found to be superior to others as far as literature is concerned, supraclavicular approach was used for various reasons. SC exposure provides optimal vascular control and offers superior access to the anatomical structures within the scalene triangle.[17] Concomitant infraclavicular incision was used where reconstruction was required as arterial damage usually extends behind the clavicle which needs to be resected out till normal artery below the clavicle.

Arterial reconstruction was performed in most patients, with autologous vein grafts being more commonly used than prosthetic grafts. Concomitant neurolysis was performed in all the cases, due to significant overlap between arterial and neurogenic TOS in many patients.[18] Additionally, distal embolectomies were carried out during the same surgery in 36.8% of patients, reflecting the extensive nature of the disease.

Functional recovery in our cohort was evaluated using the Disabilities of the Arm, Shoulder and Hand (DASH) score. The progressive improvement in DASH scores observed in this study highlights the significant functional recovery achieved following surgical intervention. The median DASH score declined from 64.6 preoperatively to 34.0 in 3 months, with continued improvement in 6 months (31.5) and 12 months (30.5). This trend was statistically significant, as demonstrated by repeated measures ANOVA, suggesting that surgery leads to substantial and sustained improvement in upper limb function. Notably, the most marked improvement occurred within the first 3 months postoperatively, followed by a gradual plateau, a pattern that aligns with the natural course of neuromuscular recovery. These findings are consistent with prior studies that have reported early postoperative gains in function, particularly in cases involving thoracic outlet decompression or nerve release procedures. The narrowing of interquartile ranges and decreasing standard deviation over time further support the consistency of functional recovery among patients. Collectively, this reinforces the role of surgical treatment in improving quality of life and reducing disability in patients with arterial TOS.[15,19]

Kaczynski et al.[19] demonstrated that surgical intervention leads to significant improvement in functional outcomes, as reflected by the DASH score, across all subtypes of thoracic outlet syndrome. However, the improvement was most pronounced in patients with arterial TOS. Davidoviæ et al. [20] found complete resolution of symptoms in the studied patients upon follow-up, indication good functional outcome following surgical decompression in patient with TOS.

The postoperative complication rate in our cohort is within the range reported in other surgical series.[18] Graft thrombosis, hematoma formation, and wound infections were the most frequently encountered complications, reflecting the known risks associated with vascular reconstruction and decompression in this patient population. Due to the young

age of most patients, comorbidities were uncommon which otherwise could have negatively influenced the outcomes and complication. The majority of patients showed good functional recovery over time, as evidenced by declining DASH scores at 3, 6, and 12 months. The high limb salvage rate observed in our study highlights the effectiveness of timely surgical decompression and revascularization in preventing irreversible ischemic damage in patients with arterial TOS. One of our patients presented late, with a gangrenous hand at the time of admission. Although arterial reconstruction had been performed, the patient ultimately required a below-elbow amputation. This finding is consistent with the literature, which highlights that delayed presentation, particularly with gangrenous digits or extremities, often necessitates amputation despite technically successful reconstruction.[21]

This study contributes valuable regional data to the limited body of global literature on arterial thoracic outlet syndrome, addressing a significant gap in evidence from lower-middle-income healthcare settings. A distinctive strength of this research is its evaluation of postoperative functional recovery using the validated Disabilities of the Arm, Shoulder, and Hand (DASH) score, which provides an objective and internationally recognized measure of functional outcomes. Despite the inherent resource constraints of the study setting, the surgical outcomes were notably favorable, demonstrating high rates of limb salvage, a low incidence of postoperative complications, and complete absence of perioperative mortality.

This study is limited by its retrospective design, small sample size, and single-center setting, which may restrict the generalizability of the findings. Follow-up was incomplete, with DASH scores available for only 12 patients, thereby introducing the potential for selection and reporting bias. Additionally, the absence of a control group prevents direct comparison with nonoperative or alternative surgical strategies. The lack of long-term follow-up further limits the ability to assess the durability of surgical outcomes and the possibility of late complications or functional decline.

CONCLUSION:

This study offers valuable insights into the management of arterial thoracic outlet syndrome (aTOS), a rare and underreported condition, particularly from South Asia. Our findings emphasize the importance of early diagnosis and referral for surgical management in patients with arterial TOS. Given the rarity of this condition, multicenter prospective studies with larger sample sizes and standardized outcome assessments are needed to validate our results and explore long-term functional outcomes.

Conflicts of Interest: Nil

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Fahad Tariq Berlas: Conception and Supervision
Fahad Memon: Conception, analysis and Supervision
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Asif Ali Khuwaja: Analysis and manuscript writing

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Original Article **Open Access**

Functional Outcome of Limb Operated with Ilizarov Ring Fixation Method in Patients Presenting with Tibial Aseptic Non-Unions Fractures at Tertiary Care Hospital, Karachi

Muhammad Haris, Saeed Ahmed Shaikh, Syed Ghulam Mujtaba Shah, Muhammad Fahad Javed, Subhan Jakhrani, Madiha Muzammil

Abstract

Objectives: This study looked at how patients with tibial non-union fractures recovered after treatment with the Ilizarov ring fixation method at a tertiary care hospital in Karachi, Pakistan. It also aimed to find factors that affect recovery, such as age, health conditions, lifestyle, and vitamin levels.

Study Design and Setting: This was a descriptive cross-sectional study done at the Orthopedics Department of Jinnah Postgraduate Medical Centre (JPMC), Karachi. It was carried out over six months and included 137 patients with tibial non-union fractures treated by the Ilizarov method.

Methodology: Patients between 20 and 80 years with post-traumatic tibial non-unions were included. Information on age, gender, health conditions, and lab results was collected. Data were analyzed with different statistical tests. Recovery was rated as poor, fair, good, or excellent.

Results: The average age of patients was 41.5 years. Smoking ($p = 0.013$), diabetes ($p = 0.014$), and vitamin D deficiency ($p = 0.002$) were strongly linked to poor recovery. Age and physical activity before surgery also affected recovery ($p = 0.001$). Diabetes and smoking were found to be independent predictors of poor outcomes. Patients with fractures in the middle part of the tibia (diaphyseal) had worse results ($p = 0.020$).

Conclusion: The study showed that smoking, diabetes, and vitamin D deficiency make recovery harder for tibial non-union patients treated with the Ilizarov method. Managing these risk factors can improve healing. More research, with larger studies and long-term follow-up, is needed to confirm these results.

Keywords: Tibial non-union, Ilizarov fixation, functional outcomes, smoking, diabetes, vitamin D deficiency

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INTRODUCTION:

Tibial non-union fractures are a big health problem worldwide.[1] In Pakistan, they are especially common because trauma and fractures are leading causes of illness. A tibial non-union happens when the leg bone (tibia) does not heal after an injury.[2] This often leads to long-term pain and disability.

These fractures are common in rural areas, where people do not have quick access to hospitals or advanced treatment.[3] Poor nutrition, late treatment, and weak healthcare systems make the problem worse.

Normally, bones heal with time. But in non-unions, the healing process fails. Reasons include infections, poor blood supply, or unstable fractures.[4] The tibia is a weight-bearing bone, so it is at higher risk. Smoking, poor diet, and illnesses like diabetes also slow healing. Patients with non-unions often suffer from pain, deformity, and difficulty walking.[5] Severe cases may need surgery, bone grafts, or external fixation devices.[6]

One treatment is the Ilizarov ring fixation. It helps bones heal and can correct deformities.[7] While many studies show success, results are not always the same. Most research comes from developed countries, where healthcare is better.[8] In countries like Pakistan, outcomes may differ due to limited resources, cultural differences,

and patient conditions.

In Asia, the Ilizarov method is becoming more popular. An Indian study showed good results, but one from Bangladesh found more problems, such as infections and device failures. This shows that outcomes depend on healthcare quality and patient background.[9]

Worldwide, external fixation is well studied, but little is known about how well it works in Pakistan. Global studies often ignore differences in patient access to care, follow-up treatment, and nutrition.[10] Because of this, their results may not apply directly to Pakistan. Local research is needed to understand how well the Ilizarov method works here.

This study looks at patients with tibial non-unions treated with the Ilizarov method at a tertiary care hospital in Karachi. The goal is to check how well patients recover and to identify the factors that affect outcomes. These factors may include age, health conditions, complications, and aftercare.

We believe that while the Ilizarov method is effective, the results in Pakistan may differ. Issues like limited healthcare access, poor nutrition, and weak post-surgery care may influence recovery.

The primary objective of the study is to evaluate the functional outcomes of tibial non-union patients treated with the Ilizarov method in Karachi. The secondary objectives of the study are to show how patient background, health problems, and surgical complications affect recovery.

This study aims to fill the gap in research from Pakistan. By focusing on local patients, it can provide useful insights to improve treatment and care in low-resource settings.

METHODOLOGY:

A descriptive cross-sectional study was conducted at the Department of Orthopedics, Jinnah Postgraduate Medical Centre (JPMC), Karachi. The duration of the study was six months from 10th April 2025 to 10th September 2025, after approval of the synopsis form by the College of Physicians and Surgeons Pakistan (CPSP). The study aimed to evaluate the functional outcomes of tibial non-union fractures treated with the Ilizarov ring fixation method. The sample size was estimated to be 137 patients, calculated using the WHO sample size calculator. A confidence level of 95% and a margin of error of 8% were applied, with a reported prevalence of good functional outcome in 35.56% in previous studies.[11]

Non-probability consecutive sampling was used for participant selection. All patients aged 20 to 80 years who presented with post-traumatic aseptic non-union of tibial fractures were included in the study. Both male and female patients were eligible. The exclusion criteria included non-consenting individuals, patients with a history of seropositive or seronegative arthritis, malnourished patients, those with a history of osteoporosis, osteomalacia, or malignancy, pregnant women (confirmed by dating scan), and patients with chronic conditions such as congestive heart failure, myocardial infarction, chronic liver disease, chronic obstructive pulmonary disease (COPD), or stroke.

In this study, patients with tibial aseptic non-union fractures were included if they had been experiencing the condition for more than three months. The tibial fractures were classified according to the Kulkarni classification, which is used to categorize the severity of non-union fractures. This classification system has four types. Type I fractures are those where the bone fragments are in apposition, meaning they are aligned, and there may be mild infection, with or without an implant. Type II fractures also have fragments in apposition, but they are accompanied by severe infection, with either a large or small wound. Type III fractures are more severe, and they are divided into subtypes. Type IIIa involves severe infection with a gap, deformity, or shortening of the bone. Type IIIb represents a defect with loss of full circumference of the bone, while Type IIIc involves a defect that affects more than one-third of the bone's cortex or is associated with an infected non-union and deformity.

For this study, the Karlstrom and Olerud system was used to check how well patients recovered after surgery. This system gives points to patients based on how they are able to move, how much pain they feel, and how well they function six weeks after surgery. The recovery was divided into five groups. A score of 33 points meant excellent recovery. Scores between 30 and 32 were counted as good recovery. A score of 27 to 29 was satisfactory, while 24 to 26 was moderate. A score between 21 and 23 meant poor recovery.

The tibial fractures were also grouped using Kulkarni's classification. By combining this system with the Karlstrom and Olerud criteria, the study was able to clearly measure both the severity of the fracture and the level of recovery. This helped in understanding how the type of fracture was linked to the patient's outcome after treatment with the Ilizarov method.

Data was collected through hospital records and clinical assessments. Sociodemographic variables, including age and gender were recorded. Clinical variables included history of comorbidities, smoking status, and details about the fracture (e.g., type and duration of non-union). The laboratory investigations included measurements of hemoglobin levels, white blood cell count, and vitamin D levels, with standard cutoff values defined by the hospital's clinical guidelines. For hemoglobin levels, a value of <12 g/dL was considered low. For white blood cell count, a threshold of =10,000/mm³ was used to indicate infection risk. Vitamin D deficiency was defined as a level <20 ng/mL.

The normality of continuous variables, including age, hemoglobin, and white blood cell count, was assessed using the Shapiro-Wilk test along with visual inspection of histograms and Q-Q plots. The variables that were normally distributed were presented as means ± standard deviation (SD), while non-normally distributed variables, such as duration of non-union, were reported as medians with interquartile range (IQR). Parametric tests, such as the independent t-test, were applied to normally distributed data, whereas non-parametric tests, such as the Mann–Whitney U test, were used for data not following normal distribution.

Ethical approval was obtained from the Institutional Review Board (IRB) of JPMC. Informed consent was obtained from all participants. The confidentiality and anonymity of the participants were maintained throughout the study. The study adhered to the ethical

principles outlined in the Declaration of Helsinki.

The data was analyzed using SPSS version 26 (IBM Corp., Armonk, NY). Simple statistics like averages, percentages, and frequencies were used to describe the results. The chi-square test compared group data, such as gender and smoking status. For numbers like age or duration of non-union, the independent t-test or Mann-Whitney U test was used, depending on the data type. Correlation tests checked how different factors were related. A p-value less than 0.05 was considered significant.

Percentages and frequencies were used for group data like gender, smoking, and health conditions. Averages and standard deviations (SD) were shown for data with a normal pattern, such as age and hemoglobin levels. For data not following a normal pattern, like the duration of non-union, the median and interquartile range (IQR) were used.

The study examined how patients with tibial non-unions recovered after treatment with the Ilizarov method. It also explored social, medical, and biochemical factors that could affect healing. The goal was to identify which factors helped improve recovery in Pakistani patients.

RESULTS:

A total of 137 patients took part in this study. There were 85 men (62%) and 52 women (38%). The average age was 41.5 years, with a standard deviation of 10.2. Most patients (68%) were between 20 and 40 years old. About 24% were between 41 and 60 years, and 8% were older than 60 years.

The study also found that the use of the Ilizarov method was associated with a significant reduction in limb length discrepancy, with 80% of patients reporting a discrepancy of less than 2 cm post-surgery. However, 10% of patients reported limb length discrepancies greater than 4 cm, which were statistically associated with prolonged non-union duration ($\div^2 = 4.62$, $p = 0.032$).

The study revealed several significant findings regarding the functional outcomes of tibial non-unions treated with the Ilizarov ring fixation method. The analysis demonstrated that the mean duration of non-union was 9.3 ± 3.5 months, which correlated significantly with functional outcomes. A longer duration of non-union was strongly associated with poorer functional recovery, as reflected by the negative correlation between duration of non-union and functional outcomes (Spearman's rho = -0.57, $p = 0.001$). This result aligns with previous studies indicating that prolonged non-union is a key factor in determining the final functional outcome of tibial fractures.

Diabetes and smoking were found to be strong predictors of poor recovery. Patients with diabetes ($p = 0.014$) and smokers ($p = 0.042$) had a harder time healing, as both conditions slowed bone repair. This agrees with earlier studies showing that diabetes can delay fracture healing and recovery. Another important finding was that 58% of patients had low vitamin D levels. Those with vitamin D deficiency had longer non-union times and poorer recovery outcomes ($p = 0.002$).

The type and location of the fracture also mattered. Patients with fractures in the middle of the tibia (diaphyseal fractures) recovered worse compared to those with fractures near the ends of the bone ($p = 0.027$). This is likely because the middle part of the bone carries more weight and faces more complications. Patients who were more active before surgery recovered better, suggesting that good physical fitness helps with healing ($p = 0.001$).

Further analysis confirmed that diabetes and smoking greatly reduced the chances of good recovery. Stopping smoking and better control of diabetes could improve outcomes. Low vitamin D was also a strong predictor of poor healing, which shows the importance of good nutrition and supplements in recovery.

Most patients (80%) had limb length differences of less than 2 cm, which is generally acceptable. However, 10% had differences of more than 4 cm. These larger differences were linked to longer non-union times, suggesting that early treatment may help prevent major length problems.

This study gives helpful information about what affects recovery in patients with tibial non-union treated by the Ilizarov method in Pakistan. It shows that controlling changeable risks—like smoking, diabetes, and low vitamin D—can lead to better healing.

Table I shows how different factors, such as age, gender, fracture type, smoking, and other health problems, were distributed among the patients. The chi-square and Fisher's exact tests were used to compare these groups and see how they related to non-union fractures. The Table 2 provides the distribution of tibial fractures based on the Kulkarni classification system. Fractures are categorized by type and the corresponding distribution in the sample. This categorization helps in understanding the severity of non-unions and their relation to functional outcomes in the study. The Table 3 summarizes the functional outcomes based on the Karlstrom and Olerud criteria. The scores range from excellent to poor, and the distribution of outcomes in the sample is shown. Statistical analysis was performed using chi-square tests to compare the proportions of patients in each functional outcome category. The Table IV presents the results of a logistic regression model analyzing the predictors of functional outcomes in tibial non-union fractures treated with Ilizarov fixation. Variables like smoking, diabetes, and vitamin D deficiency were included in the model. The adjusted odds ratios (OR) and 95% confidence intervals (CI) indicate the strength of association for each predictor. The Table V shows correlation coefficients and subgroup analyses based on functional outcomes. Pearson and Spearman correlation coefficients were used to assess relationships between continuous variables such as age, duration of non-union, and functional outcomes. Subgroup analyses were performed to compare patients based on preoperative physical activity levels.

These tables clearly show the factors that affect recovery in tibial non-unions treated with the Ilizarov method. The statistical tests make the results trustworthy. They show that smoking, diabetes, vitamin D deficiency, and fracture type are linked to healing and recovery. The study gives helpful information that can guide doctors in treating patients in Pakistan.

DISCUSSION

This study examined how patients with tibial non-unions recovered after Ilizarov ring fixation. It found that long-lasting non-unions, smoking, and diabetes were linked to poor recovery.[12] Low vitamin D levels were also common and connected to slower healing and worse results. Age, smoking, and physical activity before surgery also affected how well patients recovered.[13]

The results match with other studies done in Pakistan and South Asia. Earlier research has also shown that diabetes slows down bone healing, and smoking increases the risk of delayed recovery.[14] What stands out in this study is the very high number of patients with vitamin D deficiency (58%). This may be due to diet, less sun exposure, and lack of regular supplements.

Regional studies also show similar results.[15] Diabetes is linked with poor healing after surgery, while vitamin D deficiency has shown mixed results in different groups.[16] Research from India showed that the Ilizarov method works, but other factors like health conditions and physical activity affect outcomes too.

International studies from the US and Europe also confirm that smoking and diabetes make bone healing harder. Smoking reduces blood supply to the bone, which delays healing. This was seen in our study too.[17] Other studies from the UK showed that patients who were more active before surgery had better recovery, just like in our findings.

The high number of patients with low vitamin D is worrying. Vitamin D is important for calcium absorption and bone strength.[18]

Table 1. Demographic Statistics of the Sample Population (n=137)

Variable	n (%)
Age group at the time of surgery	
< 20 years	4 (2.9%)
20–40 years	93 (67.9%)
41–60 years	30 (21.9%)
> 60 years	10 (7.3%)
Gender	
Male	85 (61.9%)
Female	52 (38.0%)
Duration of non-union before surgery	
< 6 months	42 (30.7%)
6–12 months	53 (38.7%)
> 12 months	42 (30.7%)
Previous treatments for tibial non-union	
None	27 (19.7%)
Cast immobilization	58 (42.3%)
External fixation	36 (26.3%)
Surgical debridement	16 (11.7%)
Smoking status	
Yes	33 (24.1%)
No	104 (75.9%)
History of diabetes	
Yes	25 (18.2%)
No	112 (81.8%)
History of hypertension	
Yes	23 (16.8%)
No	114 (83.2%)

**Chi-square test (Fisher's exact where necessary)*

Table 2. Tibial Non-Union Classification of the Sample Population (n=137)

Non-Union Type	n (%)
Type I (Fragments in apposition)	48 (35.0%)
Type II (Severe infection)	42 (30.7%)
Type III (Severe infection, gap or deformity)	47 (34.3%)
Type IIIa (Gap or deformity)	26 (19.0%)
Type IIIb (Defect with full circumference loss)	14 (10.2%)
Type IIIc (Defect >1/3 cortex)	7 (5.1%)

Table 3. Functional Outcome Scores of the Sample Population (n=137)

Functional Outcome	n (%)
Excellent (33 points)	16 (11.7%)
Good (30-32 points)	34 (24.8%)
Satisfactory (27-29 points)	40 (29.2%)
Moderate (24-26 points)	25 (18.2%)
Poor (21-23 points)	22 (16.1%)

**Chi-square test (Fisher's exact where necessary).*

Table 4. Logistic Regression Model for Predictors of Functional Outcome (n=137)

Variable	Adjusted OR (95% CI)	p-value
Smoking status (Yes)	2.3 (1.1–4.9)	0.027
Diabetes (Yes)	2.5 (1.2–5.3)	0.015
Vitamin D deficiency (Yes)	2.1 (1.0–4.3)	0.031
Age (years)	1.03 (0.99–1.06)	0.27
Preoperative physical activity	1.8 (1.2–2.9)	0.005

**Adjusted Odds Ratios (OR) using logistic regression, adjusted for age, smoking, and diabetes*

Table 5. Correlation and Subgroup Analyses of the Sample Population (n=137)

Variable	Test Statistic	p-value
Duration of non-union and functional outcome	Spearman's rho = -0.57	0.001
Preoperative physical activity and functional outcome	H = 14.85	0.001
Age and functional outcome	Pearson's r = -0.12	0.17

**Spearman correlation for continuous vs continuous variables, ANOVA for continuous vs categorical data*

Without it, bones take longer to heal, or may not heal properly at all. Improving vitamin D levels through diet or supplements could help patients recover better.[19]

This study has strengths. It included a clear group of patients, a proven treatment method, and a good sample size of 137 patients, which makes the results stronger.[20,21]

Future research should include more hospitals and larger groups of patients.[22] Long-term studies are also needed to check how patients recover over years, not just months. Research should also test if vitamin D supplements can improve healing in patients who are deficient.

Limitations of Study: The study was done in one hospital only, so results may not apply to all parts of Pakistan. Patients in rural areas or smaller hospitals may have different challenges. Another limit is that not all factors, like nutrition and income, were measured. These could also affect recovery. The study only looked at patients at one point in time, so long-term outcomes were not assessed.

Disclosure: The authors have no conflicts of interest to declare.

CONCLUSION

This study showed that smoking, diabetes, long-lasting non-unions, and vitamin D deficiency are key reasons for poor recovery in tibial non-union patients treated with the Ilizarov method in Pakistan. These results highlight the importance of early treatment, quitting smoking, managing diabetes, and improving nutrition, especially vitamin D intake.

The findings add to global research on the Ilizarov method, but they are especially important for Pakistan. Access to healthcare and follow-up care is not equal everywhere, so local factors must be considered. More research across different regions is needed to confirm these results.

By focusing on risk factors that can be changed like smoking and vitamin D deficiency better outcomes can be achieved. This is very important in Pakistan, where resources are limited. Improving these factors may help patients heal faster and live with fewer complications.

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Authors Contribution:
Muhammad Haris: Introduction + Discussion, data collection+ conclusion
Saeed Ahmed Shaikh: Review article + dissuasion
Syed Ghulam Mujtaba Shah: Data Collection + review article
Muhammad Fahad Javed: Data Collection + review article
Subhan Jakhrani: Data Collection + data analysis
Madiha Muzammil: Review article and dissociation

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Original Article **Open Access**

Assessment of Complications of Transurethral Resection of Prostate (TURP) Using Clavien Dindo Classification

Bashir Ahmed, Arif Ali, Ayesha Khan, Naresh Kumar Valecha, Abdul Mujeeb, Shahid Hussain

Abstract

Objective: To evaluate the magnitude of complications that manifest in patients undergoing Transurethral Resection of the Prostate (TURP), the Clavien-Dindo Classification System (ranging from Grades I to V) shall be employed.

Methodology: This cross-sectional investigation was performed within the Department of Urology at the Jinnah Postgraduate Medical Center (JPMC) located in Karachi. The selection criteria included male patients aged between 40 and 65 years presenting with benign prostatic hyperplasia and who were deemed eligible for Transurethral Resection of the Prostate. Postoperatively, patients were treated and followed closely for any TURP related complications by classifying them according to the Clavien-Dindo Classification System (Grade I–V). The data were analyzed using SPSS software, version 26, with 5% level of significance.

Results: In 87 male patients, the mean age was 59.32 ± 6.44 years. Complications occurred in 33.33% of cases. Grade I complications were most frequent (48.3%), followed by Grade II (24.1%) and Grade III (13.8%), with Grade IV and V each at 3.4%. No significant association was found with age, prostate volume, or operative time (P >0.05).

Conclusion: The investigation elucidates that Transurethral Resection of the Prostate (TURP) continues to be a procedure characterized by a generally favorable safety profile and efficacy, albeit accompanied by the potential for complications. The implementation of the Clavien-Dindo classification system facilitated a methodical evaluation of postoperative morbidity. These results underscore the imperative for diligent perioperative management and the adoption of standardized protocols for complication assessment to enhance patient care and surgical results within the domain of clinical urology.

Keywords: Prostatic hyperplasia, Transurethral resection of prostate, Postoperative complications, Clavien-Dindo classification

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INTRODUCTION

Benign Prostatic Enlargement (BPE) is one of the most prevalent urological disorders in older men it was estimated that in 2019 there were 79 million cases in the world in both genders aged at least 60 years old[1]. The prevalence of histopathological Benign Prostatic Enlargement rises from approximately 20% in men aged 41-50 years, to 50% in men aged 51-60 years and up-to 90% in men older than 80 years. The enlargement of the prostate gland leads to an obstruction of urinary flow from the bladder, which is clinically manifested through a constellation of lower urinary tract symptoms (LUTS) that include difficulty initiating urination, straining, intermittent urinary flow, and the sensation of incomplete bladder evacuation[2]. If not addressed therapeutically, this condition may result in a multitude of complications, such as urinary retention, urinary tract infections, the development of bladder calculi, acute renal injury, as well as alterations in bladder contractility and compliance, including trabeculation and the formation of diverticula[3]. Alpha-adrenergic antagonists and 5-alpha-reductase inhibitors represent the primary pharmacological agents employed in the medical management of uncomplicated benign prostatic enlargement, whereas surgical intervention is advised when benign prostatic

enlargement is accompanied by the aforementioned complications[4].

Although latest techniques like laser enucleation and prostate artery embolization have showed considerable efficacy is terms of improvement in lower urinary tract symptoms, Transurethral resection of prostate (TURP) still remains the most commonly performed surgical procedure for BPE worldwide[5]. It is a minimally invasive procedure and involves endoscopic removal of obstructing prostate using resectoscope[6]. It can be performed using mono-polar or bipolar electro-resection and is associated with significantly reduced complications compared to traditionally performed open surgical procedures like trans-vesical prostatectomy[7]. Though generally considered a safe procedure, it may also be associated with significant complications like urethral or capsular injury, severe bleeding and TURP syndrome[8]. Early post-operative complications of Transurethral resection of prostate include secondary hematuria, infective complications and failure to void following catheter removal while long term complications of TURP include urinary incontinence, urethral stricture, bladder neck contracture, impotence or recurrence of BPE[9]. Different studies have attempted to determine the incidence of intra-operative and early post-operative complications of mono-polar Transurethral resection of prostate.

Mbaeri et al, studied frequency of complications in patients undergoing monopolar Transurethral resection of prostate using Clavien Dindo Classification system and reported that complications were observed in 24.74% patients. Out of these, 55.2% patients had Grade II complications, 20.7% patients had Grade I complications, 20.1% patients had Grade IIIa complications while Grade IV b complications were seen in 3.45% patients[10].

Dubey et al, reported that complications were seen in 19.9% patients undergoing bipolar Transurethral resection of prostate. Out of these, 52.4% patients had Grade I complications, 23.8% had Grade II complications, 9.5% had Grade III a complication and 4.8% patients had Grade III b complications. Grade IV a and IV b complications were seen in 4.8% patients[11].

Complications like TURP syndrome and urosepsis are significant life-threatening complications of Transurethral resection of prostate and are associated with adverse patient outcomes. The rationale of this study will be to determine the frequency of common complications of monopolar Transurethral resection of prostate in a local hospital setting, in terms of Clavien Dindo Classification system. No study has been conducted in our hospital with this objective and this study will also aim to fill this gap. Findings of this study will help urologists in assessing the burden of different complications of mono-polar transurethral resection of prostate which will also lead to improvements in preoperative patient counselling and education.

METHODOLOGY

This descriptive cross-sectional research was carried from 20-06-2025 till 20-10-2025 in the department of urology, Jinnah postgraduate medical center (JPMC), Karachi, following ethical approval. Institutional Review Board (IRB) approval was obtained from Jinnah Postgraduate Medical Centre under reference NO.F.2-81/2025-GENL/341/JPMC.

Sample size of 87 participants was obtained by the W.H.O calculator, based on prevalence of Grade I complications at (20.69%)[9,] an allowable margin of error of 8.7%, and a confidence level of 95%. An informed consent was taken from all the participants. Male patients aged 40–65 years diagnosed with benign prostatic hyperplasia (BPH) and scheduled for TURP were selected through non-probability consecutive sampling. Inclusion criteria were based on prostate enlargement confirmed by ultrasonography (40–100 cc), IPSS scores between 8–35, and persistent symptoms despite medical therapy. Additional eligibility included recurrent urinary tract infections (=2 episodes within six months or =3 episodes in one year), recurrent hematuria, or upper urinary tract obstruction with raised serum creatinine. Patients with an ASA score >2, prior prostate surgery, urological malignancy, neurogenic bladder, PSA =4 ng/mL, or cognitive impairment were excluded

All patients underwent TURP under spinal anesthesia, performed by experienced urologists using monopolar resectoscopes. The Barnes technique involved resection starting from the median lobe and proceeding circularly to the lateral lobes using a clock-face reference (typically from 5 or 7 o'clock), aiming for complete removal from bladder neck to verumontanum Hemostasis was achieved using a roller ball or coagulation loop. Resected chips were evacuated using an ellik evacuator followed by placement of a 22-24 FR three-way Foley catheter for continuous irrigation.

Postoperative complications were assessed by follow-up within one month after the procedure and were graded using the Clavien-Dindo classification system, defined as follows:

• **Grade I**: Any deviation from the normal postoperative course without need for pharmacological treatment or surgical, endoscopic, or radiologic interventions.

• **Grade II**: Complications requiring pharmacological treatment with drugs other than such allowed for Grade I (e.g., antibiotics, transfusions).

• **Grade III**: Complications requiring surgical, endoscopic, or radiological intervention

IIIa: Intervention not under general anesthesia.

IIIb: Intervention under general anesthesia.

• **Grade IV**: Life-threatening complications requiring intensive care management.

IVa: Single-organ dysfunction.

IVb: Multi-organ dysfunction.

- **Grade V:** Death of the patient due to complications

The analysis of data was carried out with SPSS 26.0. Demographic and clinical variables used descriptive statistics (mean, standard deviation, frequency and percentage). The Chi-square test was used to determine association of the grade of complications with demographic and clinical variables, with p = 0.05 taken as the level of significance.

RESULTS :

In our study comprising 87 subjects undergoing prostatectomy, the mean age was calculated to be 59.32 years (±6.44), with a noteworthy majority (87.4%) exceeding the age of 50 years. The average recorded prostate volume was 97.77 ml (±14.61), and 67.8% of the participants exhibited prostate volumes surpassing 90 ml, thereby suggesting a heightened occurrence of larger prostate dimensions within the studied population. The mean duration of surgical procedures was 69.06 minutes (±9.69), with 83.9% of the operations lasting beyond 60 minutes. The average duration of postoperative hospitalization was 2.2±0.1 days, and 1.79% of the subjects remained hospitalized for a period exceeding 2 days (TABLE I).

As shown in Table II, postoperative complications among the 29 patients who underwent transurethral resection of the prostate (TURP) were graded according to the Clavien-Dindo classification system. The majority of complications were of low severity, with Grade I events accounting for 48.3% of cases. The most common complication was hematuria requiring washout and irrigation, occurring in 37.9% of patients, all classified as Grade I. Other Grade I events included stress urinary incontinence and failed trial without a catheter, each reported in 6.9% of patients. Grade II complications, requiring pharmacological treatment were observed in 24.1% of cases, including epididymorchitis (17.2%) and primary hemorrhage requiring transfusion (6.9%). Grade III complications, necessitating surgical or endoscopic intervention, were reported in 13.8% of patients, primarily due to hematuria requiring operative intervention and failed catheter trials necessitating re-resection of residual tissue. Severe complications were infrequent but notable: one patient (3.4%) developed TURP syndrome, categorized as Grade IV, and one patient (3.4%) experienced mortality due to hemorrhage, classified as Grade V. These findings underscore that while TURP is generally associated with manageable postoperative morbidity, vigilance is warranted for potentially severe or life-threatening complications.

In the comparison of Clavien-Dindo complication grades with age group, prostate volume, and operative time, no statistically significant associations were observed. Among patients aged 40–50 years, Grade I complications were most frequent (57.1%), followed by Grade II (28.6%) and Grade III (14.3%), with no cases of Grade IV or V. In those aged over 50 years, Grade I complications were also most common (50.0%), followed by Grade II (22.7%), Grade III (13.6%), Grade IV (4.5%), and Grade V (9.1%) (p=0.897). Regarding prostate volume, patients with =90 ml prostates most frequently experienced Grade I complications (45.5%), followed by Grade II (27.3%), Grade III (18.2%), and Grade V (9.1%), whereas those with >90 ml prostates had Grade I complications in 55.6%, Grade II in 22.2%, Grade III in 11.1%, Grade IV in 5.6%, and Grade V in 5.6% (p=0.880). For operative time, cases lasting =60 minutes showed Grade I complications in 42.9%, Grade II in 14.3%, Grade III in 28.6%, and Grade IV in 14.3%, with no Grade V events, whereas cases >60 minutes had Grade I complications in 54.5%, Grade II in 27.3%, Grade III in 9.1%, and Grade V in 9.1%, with no Grade IV events (p=0.218) (TABLE III).

DISCUSSION

The objective of the current study was to assess the incidence and severity of complications associated with TURP, grading them by the Clavien-Dindo Classification System (Grade I–V). Our results indicated a 33.33% complication rate. Among these, Grade I and Grade III complications were 20.7% each while Grade II complications were the highest (55.1%). 6 Other complications included grade IV (3.4% of patients) and grade V (3.4% of patients). These results modestly illustrate the morbidity of TURP in tertiary care and largely conform to regional and international reports.

In a study by Mbaeri et al.[10], complications encountered in 24.74% of the cases. Among them, Grade II complications occurred most frequently (55.2%), followed by Grade I (20.7%), Grade IIIa (20.1%), and Grade IVb (3.45%). Another study done by Dubey et al complications[11] were distributed as grade I: 52.4%, grade II : 23.8%, grade IIIa: 9.5%, gradeIIIb: 4.8%, grade Iva: 4.8%, and grade IVb: 4.8%. These figures are consistent with our results. Also Nadjimitdinov and co-workers[12] concluded that the complications following TURP were recorded in 19.4% of the patients: 50% were Grade I,20.8% Grade II, 16.7% Grade IIIb, and 12.5% were Grade IVb. The overall complication rate of their series may have been lower, yet the relative distribution of higher-grade complications, particularly that of Grade IVb, was significantly higher than in our series.

Table 1: Characteristics of Study Participants (N=87)

Variable	**n (%)**
Age (Mean ± SD) = 59.32 ± 6.44 years	
40 - 50 years	11 (12.6)
>50 years	76 (87.4)
Prostate Volume (Mean ± SD) = 97.77 ± 14.61 ml	
=90 ml	28 (32.2)
>90 ml	59 (67.8)
Operative Time (Mean ± SD) = 69.06 ± 9.69 minutes	
=60 minutes	14 (16.1)
>60 minutes	73 (83.9)

Table 2: Clavien-Dindo Grading of Complications in Patients with Transurethral Resection of the Prostate (N=29)

Complications	Clavien-Dindo Grading				
	Grade I	Grade II	Grade III	Grade VI	Grade V
Hematuria requiring washout and irrigation	11 (37.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failed trial without a catheter	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stress urinary incontinence	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epididymorchitis	0 (0.0)	5 (17.2)	0 (0.0)	0 (0.0)	0 (0.0)
Primary hemorrhage requiring transfusion	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	1 (3.4)
Hematuria requiring operative intervention	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)
Failed trial without catheter requiring resection of residual apical tissue	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)
TURP syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)
Hemorrhage resulting in Mortality	0 (0.0)	0 (0.0)	(0)	0 (0.0)	1 (3.4)

Table III: Comparison of Clavien-Dindo Complication Grades with Age Group, Prostate Volume, and Operative Time

Clavien-Dindo Grading	Age Group		P-Value
	40 - 50 years	>50 years	
Grade I	4 (57.1%)	11 (50.0%)	0.897
Grade II	2 (28.6%)	5 (22.7%)	
Grade III	1 (14.3%)	3 (13.6%)	
Grade IV	0 (0.0%)	1 (4.5%)	
Grade V	0 (0.0%)	2 (9.1%)	
Clavien-Dindo Grading	**Prostate Volume**		**P-Value**
	<90 ml	**>90 ml**	
Grade I	5 (45.5%)	10 (55.6%)	0.880
Grade II	3 (27.3%)	4 (22.2%)	
Grade III	2 (18.2%)	2 (11.1%)	
Grade IV	0 (3.6%)	1 (5.6%)	
Grade V	1 (9.1%)	1 (5.6%)	
Clavien-Dindo Grading	**Operative Time**		**P-Value**
	<60 minutes	**>60 minutes**	
Grade I	3 (42.9%)	12 (54.5%)	0.218
Grade II	1 (14.3%)	6 (27.3%)	
Grade III	2 (28.6%)	2 (9.1%)	
Grade IV	1 (14.3%)	0 (0.0%)	
Grade V	0 (0.0%)	2 (9.1%)	

Chaudhary et al.[13], who described an overall complication rate of 6.17%: Grade I complications were 3.70%, grade II were 1.85%, and grade IV were 0.62%. The marked discrepancy in complication rates compared to our results could possibly be explained by the variations in study type, the patient population, surgical experience, and follow-up period. Similarly, underreporting of less severe complications or inconsistencies in the assessment of Clavien-Dindo grades could explain these differences.

In contrast, Agrawal et al.[14] there is an increased complication rate of 34.4%, surpassing that in the present series. The explanation for this is likely to be related to shifting patient characteristics over the decade (with a rise in elderly and co-morbid patients who are at risk of developing postoperative complications). Sagen et al. reported the results of their biochemical analyses of these samples[15] also support this heterogeneity as their series demonstrated a broader spectrum of complications may be found in routine clinical practice when the Clavien-Dindo grading is formalized.

Pan et al.[16] also showed the practical application of the Clavien-Dindo classification in comparison of complication between various endoscopic treatments for benign prostatic hyperplasia. Their prognostic analysis highlighted the need for standardized classification to enable significance comparisons, particularly when assessing surgical outcomes between institutions.

Further, the research by Islam et al.[17] noted predictors of morbidity using a modified Clavien system and emphasized the importance of meticulous perioperative care to decrease complications. Shukla et al. [18] reported on inter-observer agreement in the grading of TURP complications, emphasizing the role of subjective bias that might impact on the fidelity of findings between centers. The study by Gravas et al.[19] demonstrated that monopolar and bipolar TURP have similar morbidity when graded equally. Rassweiler et al. identified urethral stricture and bladder neck sclerosis as relevant late complications following TURP, indicating that postoperative evaluation remains important in long-term patient management.[20]

Our observations confirm that postoperative complications following TURP are frequent, although they are mainly in the grade I range. The Clavien–Dindo grading was effective for categorization of the severity of complications and comparison of data with different studies. These findings highlight the importance of preoperative evaluation, standardized surgical techniques, and close postoperative care to mitigate complications and optimize patient management in TURP interventions.

The main limitation was cross-sectional design that observations were confined to hospital stay and complications were not taken into account after discharge. A limitation

might be the relatively small number of patients (n=87) that may not have offered enough strength for subgroup analyzes. Additionally, the Clavien-Dindo Classification System is a widely used system for stratifying complications, although some clinical events might be assessed subjectively, potentially affecting the inter-observer agreement

The study had several strengths despite these limitations. It used a well- defined inclusion and exclusion criteria, which minimized the risk of confounding factors due to preexisting urologic or systemic diseases. A validated complexity grading system led to the possibility of a more meaningful comparison with other international series. Moreover, all operations were carried out by professional urologists in accordance with the standardized institutional practice patterns, which greatly increased the reliability of the results. Further research should be conducted using a prospective, multicenter design in a larger number of cases with longer follow-up time for possible late postoperative complications. The addition of patient-reported outcome measures and quality-of-life studies after TURP would also provide a more complete picture of surgical success and patient satisfaction.

CONCLUSION

The investigation elucidates that Transurethral Resection of the Prostate (TURP) continues to be a procedure characterized by a generally favorable safety profile and efficacy, albeit accompanied by the potential for complications. The implementation of the Clavien-Dindo classification system facilitated a methodical evaluation of postoperative morbidity. These results underscore the imperative for diligent perioperative management and the adoption of standardized protocols for complication assessment to enhance patient care and surgical results within the domain of clinical urology.

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Authors Contribution:
Bashir Ahmed: Data collection, Analysis and interpretation, Manuscript Drafting, Conceived original idea
Arif Ali: Supervision of study, critical revision of the manuscript, input on study design
Ayesha Khan: Supervision of study, critical revision of the manuscript, input on study design
Naresh Kumar Valecha: input on study design, data interpretation, critical revision of manuscript
Abdul Mujeeb: Provided clinical oversight, reviewed and revised the manuscript for accuracy
Shahid Hussain: Contributed to data collection and assisted in the critical revision of the manuscript

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Original Article **Open Access**

Comparative Study between Prophylactic Ilioinguinal Neurectomy and Nerve Preservation in Lichtenstein Tension-Free Meshplasty for Inguinal Hernia Repair

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Abstract:

Objective: To compare prophylactic ilioinguinal neurectomy with nerve preservation in lichtenstein tension-free meshplasty for inguinal hernia repair

Study Design and Setting: The present comparative study was carried out at the surgical department in Mayo Hospital Lahore for a period of 6 months after approval of synopsis.

Methodology: Non-probability consecutive sampling technique was used. The sample size was 60 and was determined by using the WHO calculated. Patients were divided randomly into 2 groups by using lottery method. In group A, patients underwent surgery and prophylactic ilioinguinal neurectomy was performed. In group B, patients had done surgery via conventional method with nerve preservation. Operative time and intra-operative blood loss were noted. Patients were followed-up in OPD for 1, 3 and 6 months and evaluated for outcomes. Data was entered and analyzed in SPSS -26.

Results: The mean age of the study participants in PINE group was 42.2 ±4.39 and INPE was 41.8±7.45 years. 10% of the participants in Ilioinguinal Nerve Preservation had pain at rest between the three and six months following surgery but no individuals experienced pain in the PINE. The incidence of pain from any kind of hernia in either group did not differ significantly.

Conclusion: The current study concluded that one serious and incapacitating side effect after inguinal hernia repair was chronic groin pain. The frequency and severity of pain were greater in ilioinguinal nerve preservation group than prophylactic ilioinguinal neurectomy group.

Key words: Inguinal hernias, neurectomy, ilioinguinal nerve preservation

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INTRODUCTION

A hernia is the abnormal protrusion of a viscus or part of a viscus through a defect or weakened area in the wall of the cavity that normally contains it. The most prevalent kind is an external abdominal hernia, with the inguinal, femoral, and umbilical types making about 75% of occurrences. The main consequence following open inguinal hernia repair has recently shifted from recurrence to persistent groin discomfort due to increased focus on patient outcomes. Inguinal hernias, which have an incidence rate of 18% to 24%, have become one of the most common disorders in the world. Amazingly, inguinal hernias have been discovered to occur more frequently in men than in women. [1, 2] The extensive literature on the topic has documented a variety of hernia repair approaches over time. Mesh Lichtenstein, a more recent approach, is currently the gold standard. In the Lichtenstein tension-free repair, which is a standard open surgical procedure for inguinal hernias, a polypropylene mesh is placed to strengthen the weakened abdominal wall. Because the mesh spans the hernia defect and eliminates the need to pull and stitch tissue together, this technique is known as "tension-free" and lowers discomfort and the risk of recurrence. The procedure entails separating the hernia

sac, covering the defect with the mesh, and fastening it to the internal oblique muscle and inguinal ligament. [3, 4] A significant problem that develops following open inguinal hernia surgery is post-operative groin discomfort, which has been documented to occur between 18% and 63% of the time. It is possible for this uncomfortable condition to seriously hinder and interfere with one's normal daily activities.[5]Five Additional factors that have been suggested as possible predictors of chronic post-operative pain and hypo/hyperaesthesis include damage to the inguinal nerves, entrapment of the ilioinguinal nerve during suturing, the occurrence of fibrosis in the mesh placement area and surrounding area, mesh implantation, partial division, and neuroma formation.[6] One strategy to lower the chance of experiencing chronic postoperative pain has been suggested: elective ilioinguinal nerve division. Initially, it was suggested that safeguarding ilioinguinal nerve could decrease the possibility of chronic discomfort after surgery.[7]According to a study, the elective ilioinguinal nerve division group experienced mean post-operative discomfort of 0.6±0.7, whereas the nerve preservation group experienced 1.5±0.7. [8] In another research, the elective ilioinguinal nerve division group experienced mean post-operative pain of 0.5±2, whereas the nerve preservation group experienced mean post-operative pain of 2.6±2.[9] In another research, the elective ilioinnguinal nerve division group experienced mean post-operative pain of 0.98±0.25, whereas the nerve preservation group experienced mean post-operative discomfort of 1.72±0.61.The risk of discomfort is lower with preventive ilioinguinal neurectomy than with traditional nerve preservation techniques, according to the literature. However, nerve preservation is used routinely, and this is the main reason for pain after surgery .[10]

METHODOLOGY

This was comparative study, carried out at the surgical department in Mayo Hospital Lahore during a period of 6 months after approval of synopsis. The approval of the study was taken from the ethical committee of the research (ref No:657/RC/KEMU, Date: 28/08/2024) Non-probability consecutive sampling technique was used. The sample size was determined by using the WHO calculator by taking 95% confidence level, 80% power of study and mean pain score (effectiveness) i.e. 0.7±0.7 with ilioinguinal neurectomy and 1.5±0.7 with nerve preservation.[8] The total sample size determined was 60. Male patients of age 18-50 years diagnosed with inguinal hernia undergoing Lichtenstein's tension-free meshplasty inguinal hernia repair were enrolled in this study. Individuals with irreducible or strangulated hernia and those with infections at the surgery site (on clinical examination) were excluded. After taking approval from hospital's ethical committee, 60 patients fulfilling the selection criteria were enrolled in the study from surgical wards. Informed consent were taken. Basic information of each patient (name, age, BMI, marital status, number of children, duration of hernia, size of hernia, lateral side, type of hernia (direct or indirect), diabetes (BSR> 200 mg/dl), hypertension (BP=140/90 mmHg), anemia (hb<11 g/dl), occupation, life style, ASA status were noted. Patients were divided randomly into 2 groups by using lottery method. In group A, patients underwent surgery and prophylactic ilioinguinal neurectomy was performed. In group B, patients had done surgery via conventional method with nerve preservation. Operative time and intraoperative blood loss were noted. All procedures were performed by single surgical team under spinal anesthesia with assistance of researcher. After 48 hours, each patient was moved to a post-surgical unit and discharged. For one, three, and six months, patients were monitored in the outpatient department. Patients were evaluated in the following ways: at rest, following a typical everyday activity, during walking, following a ten-stair climb, and following a strenuous exercise (such doing exercises, jogging, mild weightlifting, etc.). Pan score was recorded. If score was 0, then effectiveness was noted (as per operational definition)."All the data were collected in proforma in a specialized designed profoma. SPSS-26 was used for data entry and analysis. Quantitative factors, such as age, hernia size, and duration, are shown as mean and ±SD. Frequencies and percentages were used to display qualitative characteristics such as lateral side and the kind of hernia (direct or indirect). The chi-square test was employed to assess differences in efficacy between the two groups, and a P value of less than 0.05 was considered significant statistically. Age, BMI, hernia duration, hernia size, marital status, number of children, lateral side, hernia type (direct or indirect), diabetes, hypertension, anemia, employment, lifestyle, ASA status, operating time, and intraoperative blood loss were all taken into consideration when stratifying the data. After stratification, the chi-square test was applied within each stratum to evaluate the efficacy between the two groups. A P value of less than 0.05 was considered as significant statistically."

RESULTS

A total of 60 male patients (aged 18-50 years) receiving hernioplasty for an inguinal hernia were enrolled. Participants of the study were divided equally in to group A and group B with same number of individuals. Group A underwent a prophylactic ilioinguinal neurectomy (PINE) and group B underwent ilioinguinal nerve preservation(INPE) during hernia repair. The mean age of the study participants PINE group was 42.2 ±4.39 and INPE was 41.8±7.45 years. In terms of the kind of anesthesia, the side of the hernia, and baseline pain assessments during different activities, both groups were comparable. Most participants in both groups were aged 29–38 years (43.3% vs. 46.6%). The age distribution was not significant (p value =0.82) as presented in table 1. 40% of patients in PINE group had a hematoma, compared to 53.3 in INPE Group. Urinary retention was

Table 1. Demographic features of the study participants

Features		PINE(Group A)	INPE (Group B)	Value of P
Age (years) Mean ±SD		42.2 ±4.39	41.8±7.45	0.42
Age (Years)	18 or below	2(6.6%)	4(13.3%)	0.83
	19-28	5(16.6%)	6(20%)	
	29-38	13(43.3%)	14(46.6%)	
	39-48	7(23.3%)	6(20%)	
	49-50	3(10%)	2(6.6%)	
Pain While Cycling/ Heavy Activities: No Pain: Mild Pain		20:10	22:8	0.68
Pain While Straining: No pain: Mild Pain		18:10	22:8	0.72
Pain at Rest: No pain: Mild Pain		17:13	24:	0.63
Hernia Side: Right: Left		17:13	19:11	0.26
Type of Anesthesia: Spinal: General		16:14	18:12	0.062

Table 2. Early complications in both groups

Complications	PINE (Group A)	INPE (Group B)	Value of P
Wound infection	2(6.6%)	5(16.6%)	0.38
Urinary retention	4(13.3%)	2(6.6%)	0.52
Haematoma	12(40%)	16(53.3%)	0.72

Table 3.types of Inguinal Hernia

Inguinal Hernia	PINE(Group A)	INPE (Group B)
Right indirect	14(46.6%)	16(53.3%)
Left direct	8(26.6%)	6(20%)
Right direct	6(20%)	4(13.3%)
Left Indirect	2(6.6%)	2(6.6%)
Total	30	30

Table 4 Pain in both groups during various activities

Pain	PINE	INPE	P value (Fischer's Exact Test)
One month	2(6.6%)	4(13.3%)	1
Three months	zero	3(10%)	0.2
Six month	Zero	3(10%)	0.2
Pain in both groups during moderate activities			
Pain	PINE	INPE	P value
One month	5(16.6%)	8(26.6%)	0.50
Three months	1(3.3%)	3(10%)	0.2
Six month	Zero	2(6.6%)	0.02
Pain in both groups during vigorous activities			
Pain	PINE	INPE	P value
One month	15(50%)	20(66.6%)	0.50
Three months	4(13.3%)	13(43.3%)	0.005
Six month	2(6.6%)	8(26.6%)	0.05
Postoperative Hyperesthesia in two study groups			
Postoperative Hyperesthesia	PINE	INPE	P value
One	8(26.6%)	12(40%)	0.3
Three months	3(10%)	5(16.6%)	0.5
Six months	1(3.3%)	3(10%)	0.5

noted in 6.6% of PINE group participants and 13.3% of INPE group individuals. The difference between the two groups was not statistically significant as shown in table 2. In the PINE group, the frequency of right indirect hernia was 46.6%, whereas in the INPE group, it was 53.3%. Left indirect hernias were the least common, accounting for 6.6% of cases in both groups as presented in table 3.

10% of the participants in Ilioinguinal Nerve Preservation had pain at rest between the three and six months following surgery but no individuals experienced pain in the PINE. Majority of the participants 13(43.3%) in INPE group had seen to have pain after three months during vigorous activities as compared to PINE group (13.3%).this difference was statistically significant (p value 0.005). Ten percent of participants in INPE group and 3.3% of participants the PINE group experienced hyperaesthesia six months after surgery as presented in table 4. The incidence of pain from any kind of hernia in either group did not differ significantly.(table 5). The restriction of physical activities had a significant impact on group A patients (6.6%) and group B patients (10%).Likewise, 10% of the individuals in group B and 6.6% of patients in group A reported limited social activities as shown in table 6.

DISCUSSION

Globally, inguinal hernias are among the most prevalent conditions affecting men [11]. Pain that lasts longer than three months is referred to as inguinal postoperative chronic pain (PCP), often called inguinodynia or groin pain .[12] It is one

Table 5. Post-operative pain related to hernia type (vas score)

Hernia type	Pain	PINE One month	INPE	PINE 3rd month	INPE	PINE 6th month	INPE
Direct	Yes	2	1	2	2	0	2
	No	10	7	2	8	10	7
Indirect incomplete	Yes	6	7	2	5	3	5
	No	4	6	8	8	7	8
Indirect complete	Yes	7	8	3	4	2	3
	No	1	1	3	3	8	5
Total		30	30	30	30	30	30

Table.6 Quality of life- Physical Functioning in both groups

Activities	PINE n= 30	INPE n= 30	P value (Fischer's Exact Test)
No	27(90%)	25(83.3%)	0.01
Mild	1(3.3%)	1(3.3%)	0.4
Severe	2(6.6%)	4(13.3%)	0.6
Table.11 Quality of life- social health in both groups			
Activities	PINE	INPE	
No	26(86.6%)	24(80%)	0.3
Mild	2(6.6%)	3(10)	0.5
Severe	2(6.6%)	3(10%)	0.5

of the most frequent side effects following inguinal hernia surgery [13]. Regardless of the surgical methods employed, the incidence rate of PCP varies from 0% to 63% [13]. This wide variation is caused by disparate definitions of inguinal postoperative pain, study endpoints, and pain assessment methodology. Oral analgesics, local anesthesia, physical therapy, or additional procedures may be necessary to treat inguinal postoperative chronic pain, which can be caused by inflammation, fibrotic responses, neuroma development, or entrapment or stretching of nerves.[13] The extensive literature on the topic has documented a variety of hernia repair approaches over time. Mesh Lichtenstein, a more recent approach, is currently the gold standard. In the Lichtenstein tension-free repair, which is a standard open surgical procedure for inguinal hernias, a polypropylene mesh is placed to strengthen the weakened abdominal wall. Because the mesh spans the hernia defect and eliminates the need to pull and stitch tissue together, this technique is known as "tension-free" and lowers discomfort and the risk of recurrence. The procedure entails separating the hernia sac, covering the defect with the mesh, and fastening it to the internal oblique muscle and inguinal ligament.[3-4] The mesh was fixed inferiorly with polypropylene sutures to the pubic tubercle, lacunar ligament, and inguinal ligament outside the internal ring. The upper edge is attached to the internal oblique muscle or aponeurosis using a few interrupted sutures. After cutting the mesh along its side and bringing the two tails around to encircle the cord at the inside ring, a single polypropylene suture is employed to secure the mesh to the inguinal ligament. As a result, another internal ring and shutter mechanism is created.[5] Chronic inguinal neuralgia is defined by the International Association for the Study of Pain as "pain that lasts three months or longer." It has been demonstrated that 1.8% of patients experience post-operative discomfort for more than five years, and up to 7.5% of patients may experience greater pain than they had before to the procedure.[22] Treatment is frequently tough and demanding. One of the most frequent surgeries performed in any hospital is an inguinal hernia. One of the most prevalent issues these people have is chronic inguinal pain. Inguinal hernia repairs are not the only surgical procedure that uses the idea of regular neurectomy. The intercosto brachial and larger auricular nerves are sacrificed during routine neurectomy, which is frequently carried out during axillary & neck dissections. Routine excision of the ilioinguinal nerve has been proposed to prevent the long-term complication of post-herniorrhaphy neuralgia, potentially reducing the occurrence of persistent postoperative groin pain. In our study, a total of 60 male patients (aged 18-50 years) receiving hernioplasty for an inguinal hernia were enrolled. Participants in the study were divided equally in to group A and group B with same number of individuals. During hernia repair, Prophylactic ilioinguinal neurectomy was done for Group A participants while group B participants underwent ilioinguinal nerve preservation. The mean age of the study participants PINE group was 42.2 ±4.39 and INPE was 41.8±7.45 years. A similar study was conducted by Sharma in India in which same differences in age were

reported.[14] Our study results were also comparable to Christou et al.[1] In terms of the kind of anesthesia, the side of the hernia, and baseline pain assessments during different activities, both groups were comparable**.** Majority of the study participants were in the age group 29-38 years in both groups (43.3% versus 46.6%) . The age distribution was not significant (p value =0.82). These findings are similar with the study conducted by Uppada [15]. 40% of patients in PINE group had a hematoma, compared to 53.3 in INPE Group. In the present study urinary retention was noted in 6.6% of PINE group participants and 13.3% of INPE group individuals. The difference between the two groups was not statistically significant. Our study findings are similar to the previous research.[16] In our study most of the participants 43.3% in INPE group had seen to have pain after three months as compared to PINE group (13.3%).this difference was statistically significant (p value 0.005). Ten percent of participants in INPE group and 3.3% of participants the PINE group experienced hyperaesthesia six months after surgery. Similar to our study double blinded, randomized trial was conducted on 120 patients who were having open anterior mesh surgery for an inguinal hernia. Out of the 120 individuals, 60 were given nerve preservation and 60 were given neurectomy. Pain was observed in 21% of the nerve-preserved group and 7% of the neurectomy group."The findings showed that following elective intestinal hernia repair, the neurectomy reduced post-operative pain which support our results.[17] Another retrospective study was carried out on 90 individuals who had done Lichtenstein inguinal hernia repair. The study found that the frequency of neuralgia was significantly lower in the neurectomy group compared to the nerve preservation group (3% vs. 26%, $P < 0.001$). The neurectomy group did not have a significantly greater prevalence of paresthesia after 1 year.[18] According to these results, neurectomy does not always result in a statistically important long-term increase in paresthesia when compared to nerve preservation, even if it is linked to a decreased prevalence of chronic pain (neuralgia).The findings of the current study were consistent with those of the previously mentioned studies. Numerous studies and meta-analyses indicate that the ilioinguinal nerve neurectomy (division) group frequently has less severe and frequent postoperative pain than the nerve preservation group. The outcome runs counter to the user's argument. Regarding preoperative pain, it has been noted that the two groups measured similarly. Pain during regular activities was experienced by 6.6% of patients in study group A at one month, and by six months, it had disappeared. In contrast, 13.3% of patients in group B experienced pain at one month, and 10% of patients continued to experience it after six months. The findings aligned with a prior investigation.[19]In this study at three and six months of follow-up, there were notable differences between the two groups in the occurrence of pain following vigorous activity. These results aligned with those of other similar research.[19]There was no discernible variation in hyperaesthesia between the two groups in the present study. These findings were consistent with previous study.[20] Significant difference was not observed between the two study groups based on' health-associated quality of life. The results of the earlier study served to support this.[21] After comparing the findings of the current study with the previous studies it was explored that chroic groin pain is a major problem after the treatment of hernia. The nerve preservation study group had noticeably increased pain frequency and severity. This suggests that preventive neurectomy may be a suitable way to avoid persistent groin pain after Lichtenstein inguinal hernia surgery, and it may be a perfect addition to the routine hernia repair treatments.

CONCLUSION

The current study concluded that one serious and incapacitating side effect after inguinal hernia repair was chronic groin pain. The frequency and severity of pain were greater in ilioinguinal nerve preservation group than prophylactic ilioinguinal neurectomy group. Therefore, prophylactic neurectomy may be a suitable alternative to traditional hernia repair treatments and a suitable means of preventing persistent groin pain after Lichtenstein inguinal hernia surgery.

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Muhammad Talha Khan: Primary researcher, conception, acquisition, analyzing the data and writing manuscript
Noor-Ul-Ain Mujahid: Drafting, editing and reviewing the manuscript
Hamza Mustafa: Interpretation of data
Balakh Sher Zaman: Review and expert guidance
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Original Article **Open Access**

Constellation of Neurological Signs in Patients with Diabetes Mellitus of more than 5 Years

Zakia Kanwal, Abdul Khalid Awan, Syeda Aiman Naqvi, Shaista Imtiaz, Zainab Shahab, Tayyaba Haroon

Abstract

Objective: To identify the prevalence and related characteristics of peripheral neuropathy among diabetes mellitus patients with over five years of duration.

Study Design and Setting: A cross-sectional study at the Abbas Institute of Medical Sciences in Muzaffarabad, Azad Jammu and Kashmir.

Methodology: Non-probability consecutive sampling was used to select 266 patients with a diagnosis of either type 1 or type 2 diabetes mellitus of a duration of greater than five years. Patients with a history of vitamin B12 deficiency, cerebrovascular accident, or motor neuron disease were excluded. Sociodemographic data, clinical history, smoking, family history of diabetes, and comorbidities data were obtained. The data analysis was conducted using SPSS version 22. Post-stratification Chi-square test was used, and p= 0.05 was regarded as significant.

Results: The mean age of participants was 52.6 ± 10.8 years, with a mean diabetes duration of 9.4 ± 3.2 years and a mean HbA1c of 8.6 ± 1.4%. Peripheral neuropathy was detected in 53.4% of patients. Significant associations were observed with age =50 years ($p = 0.012$), rural residence ($p = 0.042$), illiteracy ($p = 0.021$), smoking ($p = 0.011$), hypertension ($p = 0.034$), diabetes duration =10 years ($p < 0.001$), and HbA1c =8% ($p < 0.001$). Gender and family history were not significantly associated.

Conclusion: Long-term diabetes patients are very susceptible to peripheral neuropathy. Its burden should be mitigated by implementing early screening and managing all risk factors, particularly those that are modifiable, i.e., glycaemic control, hypertension, and smoking.

Keywords: Diabetes Mellitus, Diabetic Neuropathies, Glycated Hemoglobin

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INTRODUCTION

Diabetes mellitus (DM) is a non-contagious metabolic disease that is hyperglycemic and is associated with a defect in insulin secretion, insulin activity, or both.[1] It is among the most urgent health issues worldwide, as the prevalence is steadily increasing, and the associated systemic complications are very numerous.[2] In Pakistan, diabetes has become a major burden causing serious morbidity, diminished quality of life, and elevated healthcare expenditure because of lifestyle changes, urbanization, and genetic susceptibility, according to the recent statistics which show that the number of adult affected individuals is estimated to be almost 33 million and this figure is projected to grow to 643 million by 2030 and 783 million by 2045.[2] South Asia, in particular, Pakistan, is experiencing a rapid surge in diabetes-related morbidity due to lifestyle changes, urbanization, and genetic predisposition.[3] Beyond its metabolic derangements, the insidious complications of diabetes, especially those involving the nervous system, pose significant morbidity, reduce quality of life, and increase healthcare costs.

Diabetes's neurological manifestations cover a wide variety of clinical signs and symptoms.[4] These may arise from a

direct metabolic impact due to chronic hyperglycemia, the development of microvascular complications, or through an immunologic mechanism. The most well-known complication is diabetic peripheral neuropathy (DPN), which affects upwards of 50% of patients with chronic diabetes.[5] DPN can present as distal symmetrical sensorimotor neuropathy with accompanying features of numbness, tingling, burning, and in severe cases, neuropathic pain and/or ulcerations of the skin. Nonetheless, the neurological manifestations of diabetes extend well beyond the peripheral nervous system. Neurological involvement can also include autonomic neuropathy, cranial nerve palsies, radiculoplexopathies, and even central nervous system (CNS) involvement with clinical signs ranging from postural hypotension and gastroparesis to visual deficits, seizures, or cognitive decline.[6]

The pathophysiological processes related to these neurological manifestations are not singular but multifactorial. The long-term hyperglycemia results in the flux through the polyol pathway, build-up of advanced glycation end products (AGEs), oxidative stress, and the activation of protein kinase C, which result in microvascular injury, demyelination, and axonal degeneration of the peripheral and autonomic nerves.[3] Ischemic injury to neural tissues is further worsened by dysfunction of vascular endothelial cells. Key processes, including impaired insulin signaling in the brain, can be a contributive factor to the development of cognitive impairment and increased risk of developing dementia in diabetic patients. Noteworthy, patient duration of diabetes continues to remain a significant predictor of neuropathological complications, with patients over five years of disease showing a sharp upward trend in incidence and severity of neuropathy.

Epidemiological reports note that close to two-thirds of individuals diagnosed with type 2 diabetes develop one or another form of neuropathy within their first 10 years of diagnosis, and many adults are already experiencing deficits of a subclinical nature even sooner. In type 1 diabetes, neuropathy risk increases substantially after 5–10 years of duration of illness.[8] This risk is predominantly observed, except for acute neuropathy, among individuals with suboptimal glycemic control, especially when hemoglobin A1C levels are <10%–12%.[8] All of these complications add substantial morbidities: diabetic foot ulcerations and amputations, urinary and fecal incontinence, erectile dysfunction, cardiovascular autonomic neuropathy resulting in sudden cardiac death, and impaired cognitive and motor function that disrupts activities of daily living. All of these individual patient impacts result not only in human suffering but also instigate significant economic upstream burden. Studies from the United States and Europe approximate nearly 25% of healthcare costs supporting diabetes are for neuropathic complications, and likely higher in low- and middle-income countries where prevention is hindered [9, 10]

Though neurological manifestations are common and can impact diabetic patients significantly, they often remain under-recognized or not fully evaluated. Clinical attention has typically been placed on glycemic targets and macrovascular end points like myocardial infarction and stroke, while subtle or progressive neurological changes may not be observed until the late stages of the disease. Furthermore, the constellation of signs is highly variable, ranging from quietly observed absent sensory loss to obvious motor deficits, autonomic dysfunction, and cognitive decline. This reinforces the importance of characterizing and documenting full clinical presentation in longer-standing cases of diabetes, especially when 5 years or longer.

The combination of signs representing neurological involvement (e.g., loss of sensation, autonomic dysfunction, etc.) in patients with diabetes represents a major but under-appreciated burden of disease. To address this burden of disease, increased understanding of the frequency, distribution, and characteristics of neurological manifestations should lead to earlier diagnoses, which can improve patient care and quality of life. The purpose of the study herein was to determine the frequency of peripheral neuropathy incidence in diabetic patients over a period of 5 years or more.

METHODOLOGY

This cross-sectional study was conducted in the Department of Medicine at Abbas Institute of Medical Sciences (AIMS), Muzaffarabad, Azad Jammu and Kashmir. The total duration of the study was six months from 1st January 2025 to 30th June 2025, following the approval of the study by the ethical committee certificate (ECC) of AIMS, Approval No: MED/AIMS/24176, Dated: 28th November 2024.

The sample size was calculated using the WHO population proportion sample size calculator, with an assumed prevalence of 51% for peripheral neuropathy in patients with diabetes mellitus, a margin of error of 6%, and a 95% confidence interval.[11] Based on these parameters, a total of 266 patients with diabetes mellitus were recruited. A non-probability consecutive sampling technique was used to enroll participants.

Patients were eligible for inclusion if they had a diagnosis of diabetes mellitus, either type 1 or type 2, for a duration exceeding five years. The age range was set between 14 and 70 years, as patients below the age of 14 were managed in the pediatric department, and the median life expectancy in the region was estimated to be between 60 and 70 years. Exclusion criteria included patients with a known history of vitamin B12 deficiency, confirmed either clinically or by laboratory evidence of serum B12 levels below 220 mg/dl. Similarly, patients with a documented history of cerebrovascular accident or motor neuron disease, ascertained clinically and by history, were excluded from the study.

Diabetes mellitus was defined as the presence of classical symptoms, including increased thirst beyond routine, polyuria exceeding 3 liters per day (measured at home by a urine

collection pot), or excessive hunger compared to normal, with fasting plasma glucose (FPG) >126 mg/dl. Fasting was defined as no caloric intake for at least eight hours. In addition, patients who were already diagnosed cases of diabetes for more than five years were also included.

Peripheral neuropathy was deemed positive when diabetic individuals noted bilateral leg and or foot symptoms, including pain, numbness, or restlessness. A formal neurological examination was conducted to confirm and characterize neuropathy. Clinical findings included a formal evaluation of pinprick sensation, light touch, temperature, vibration, proprioception, and monofilament testing, in addition to examining knee and ankle reflexes. Each of the aforementioned modalities was first assessed at the forehead, to ensure patient understanding of the examination, and then subsequently examined in order from distal (big toe) to proximal (knee) regions. Pinprick sensation was assessed with a disposable toothpick, which was discarded after each use. Light touch sensation was assessed with cotton wool lightly applied to the skin. Temperature was assessed with a cold metallic object placed on the skin surface.

A 128 Hz tuning fork that was placed over a bony prominence, namely the medial aspect of the first metatarsophalangeal joint, was used to test vibration sense. The monofilament test was determined by applying a 10-gram monofilament to the plantar part of the foot in standard locations. Proprioception was assessed by placing the joint between the feet (interphalangeal) of the big toe in an upright or downward position with the eyes of the patient closed, and requesting that he should determine the direction of movement. Deep tendon reflexes were evaluated in the knee (quadriceps tendon) and ankle (Achilles tendon) with a common rubber reflex hammer, and reinforcing measures were taken in case of necessity to obtain the reflexes.

The research was initiated on the basis of the institutional ethical review committee. All the participants were recruited with informed written consent. The patients who came to the Medicine Department with the problem of diabetes mellitus, as per the operational definition, were approached sequentially. On a structured pro forma, data were gathered on demographic variables, which included age, sex, place of residence (urban or rural), and education level (illiterate, primary, intermediate, or graduate and above). Clinical information, such as the length of diabetes, the history of diabetes in the family, smoking habits, and comorbid conditions, hypertension, etc., was also noted.

Each participant had blood samples (venous) collected under aseptic conditions and forwarded to the institutional laboratory to assess the level of glycated hemoglobin (HbA1c). The clinical examination was then conducted to determine the presence of the neurological manifestations with specific attention to the peripheral neuropathy. Peripheral neuropathy diagnosis was developed on the clinical level, according to the symptoms of the patient and the observed neurological alterations when examining the patient. All the information was recorded on a pro forma that was approved and designed.

This study did not include randomization or a control group because it was designed as a cross-sectional observational study aimed at assessing the prevalence and associated factors of peripheral neuropathy at a single point in time. As the objective was to measure existing neurological outcomes among patients already diagnosed with diabetes mellitus of more than five years' duration, random allocation or comparison with a separate control population was neither feasible nor required for this type of epidemiological design.

The use of SPSS version 22 was used to manage and analyze the data and provide statistical analysis. The age, period of diabetes, and HbA1c levels were the quantitative variables that were represented in terms of means and standard deviations. The qualitative variables, such as gender, residence, educational status, family history of diabetes, smoking, hypertension, and peripheral neuropathy, were given in the form of frequencies and percentages. Stratification with respect to age, gender, place of residence, educational status, and duration of diabetes, HbA1c levels, family history, and smoking status was done to take care of the possible effect modifiers. After stratification, the chi-square test was used to test the relationship between categorical variables. A p-value of =0.05 was statistically significant.

RESULTS

The study involved 266 diabetes mellitus. The average age of the participants was 52.6±10.8 years. The study population was composed of males (55.6%) and females (44.4%). Most of the patients (61.7%) were found in the urban areas as compared to 38.3% in rural environments. As far as the education level is concerned, 32.3% of the patients were illiterate, 27.1% completed primary education, and 20.3% had at least graduated or higher. The majority of the subjects (66.2%) had a positive family history of diabetes mellitus. The prevalence of smoking was 33.1% and that of non-smokers was 66.9% with 53.4% of the study population being hypertensive. The average HbA1c level and the mean diabetes duration measured 8.6 ± 1.4 and 9.4 ± 3.2, respectively. (Table 1) Peripheral neuropathy was identified in 53.4% of the study population, accounting for 142 out of 266 patients. The remaining 124 patients (46.6%) did not exhibit clinical evidence of neuropathy. (Figure 1) There was a significant association between age group and peripheral neuropathy, with 62% of patients aged =50 years affected compared to 40.7% in those <50 years (p = 0.012). Residence was also significantly associated, as neuropathy was more common in patients living in rural areas (60.8%) than those living in urban areas (48.8%) (p = 0.042). Educational status showed that illiterate patients had a greater prevalence of neuropathy (67.4%) than those who had

primary education or higher (46.7%) (p = 0.021). Smoking was significantly associated, as 63.6% of smokers had neuropathy compared to 48.3% of non-smokers (p = 0.011). Similarly, hypertension was linked to neuropathy, affecting 59.2% of hypertensive patients compared to 46.8% of non-hypertensive patients (p = 0.034). Duration of diabetes showed a strong relationship, with 66.7% of patients having diabetes for =10 years developing neuropathy versus 43.4% with <10 years duration (p < 0.001). HbA1c was also highly significant, as 61.4% of patients with HbA1c =8% had neuropathy compared to 37.8% with HbA1c <8% (p < 0.001). In contrast, no statistically significant associations were found with gender (p = 0.723) or family history of diabetes (p = 0.192). (Table 2)

DISCUSSION

In this cross-sectional cohort of 266 patients with diabetes for >5 years, peripheral neuropathy was present in 53.4% of participants. This prevalence is within the broad range reported in recent literature, but towards the higher end of estimates from multinational and regional studies. A 2023 meta-analysis of studies performed in Pakistan reported a pooled prevalence of diabetic peripheral neuropathy (DPN) of 43.2% (95% CI 32.9–53.7%), with important heterogeneity between provinces and a particularly high pooled prevalence in Khyber Pakhtunkhwa (˜55%). The pooled estimate and the regional variation reported in that meta-analysis help explain why our estimate (53.4%) is comparable to some Pakistani subgroups and higher than many single-site reports.[12]

Multinational observational data from the INTERPRET-DD

Table 1. Baseline Characteristics of Patients (n = 266)

Variable	Categories	Mean ± SD / n (%)
Age (years)		52.6 ± 10.8
Gender	**Male**	148 (55.6)
	Female	118 (44.4)
Place of Residence	**Urban**	164 (61.7)
	Rural	102 (38.3)
Educational Status	**Illiterate**	86 (32.3)
	Primary	72 (27.1)
	Intermediate	54 (20.3)
	Graduate or above	54 (20.3)
Family History of DM	**Yes**	176 (66.2)
	No	90 (33.8)
Smoking	**Yes**	88 (33.1)
	No	178 (66.9)
Hypertension	**Yes**	142 (53.4)
	No	124 (46.6)
Duration of Diabetes (years)		9.4 ± 3.2
HbA1c		8.6 ± 1.4

Figure 1: A pie chart showing the frequency of peripheral neuropathy among study participants

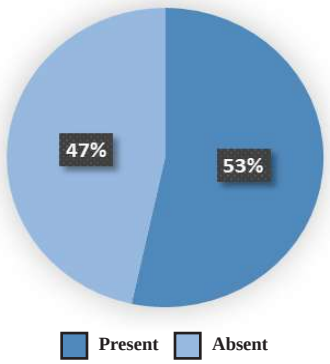

Table 2. Association of Peripheral Neuropathy with Various Factors (n = 266)

Variable	Categories	Neuropathy		p-value
		Present	Absent	
Age Group (years)	<50	44 (40.7)	64 (59.3)	0.012*
	=50	98 (62.0)	60 (38.0)	
Gender	Male	80 (54.1)	68 (45.9)	0.723
	Female	62 (52.5)	56 (47.5)	
Residence	Urban	80 (48.8)	84 (51.2)	0.042*
	Rural	62 (60.8)	40 (39.2)	
Education	Illiterate	58 (67.4)	28 (32.6)	0.021*
	Primary/Above	84 (46.7)	96 (53.3)	
Family History of DM	Yes	100 (56.8)	76 (43.2)	0.192
	No	42 (46.7)	48 (53.3)	
Smoking	Yes	56 (63.6)	32 (36.4)	0.011*
	No	86 (48.3)	92 (51.7)	
Hypertension	Yes	84 (59.2)	58 (40.8)	0.034*
	No	58 (46.8)	66 (53.2)	
Duration of DM (years)	<10 years (n=152)	66 (43.4)	86 (56.6)	<0.001*
	=10 years (n=114)	76 (66.7)	38 (33.3)	
HbA1c	<8% (n=90)	34 (37.8)	56 (62.2)	<0.001*
	=8% (n=176)	108 (61.4)	68 (38.6)	

consortium (data from 14 countries; n = 2,733) and other large cohorts have repeatedly shown that advancing age and longer diabetes duration are among the strongest and most consistent risk factors for DPN. In our study, the prevalence increased markedly in those =50 years (62.0% vs 40.7% in <50; p = 0.012) and with diabetes duration =10 years (66.7% vs 43.4%; p < 0.001). These patterns mirror findings from INTERPRET-DD and other large cohorts in which age and duration of diabetes are independent predictors of neuropathy, reflecting the cumulative metabolic and microvascular injury that accrues with time.[13, 14]

Glycaemic control emerged as a strong correlate in our sample: neuropathy affected 61.4% of patients with HbA1c =8% versus 37.8% with HbA1c <8% (p < 0.001). This relationship between sustained hyperglycemia and neuropathy is consistent with longitudinal and case-control evidence. For example, a claims-based case–control study reported that higher multi-year mean HbA1c was significantly associated with DPN, and other large clinical cohorts (including long-term follow-up studies of intensive vs standard glycaemic control) have demonstrated that better long-term glucose control reduces the risk and progression of neuropathy. These data collectively support the biological plausibility that chronic hyperglycemia mediates axonal and microvascular injury in peripheral nerves.[14, 15]

Recent work has also emphasized not only the mean HbA1c but the pattern of glycaemia: glycaemic variability has been linked to the severity of painful DPN and to neuropathy outcomes. A 2024 study found associations between HbA1c variability and neuropathy severity, suggesting that both chronic hyperglycemia and fluctuations in glucose contribute to neural injury, an observation that supports the idea that interventions should target both average control and stability of glycemia. Our finding that poor glycaemic control (HbA1c =8%) was associated with higher neuropathy prevalence aligns well with these newer lines of evidence.[16]

Lifestyle and cardiovascular risk factors matched previous studies of prediabetes and neuropathy. Smoking was also correlated with a greater rate of neuropathy in our cohort (63.6% for smokers vs. 48.3% for non-smokers; p = 0.011). Previous mechanistic and epidemiologic data have identified smoking as a modifiable risk factor for microvascular complications, including DPN, through the potential mechanisms of endothelial dysfunction, oxidative stress, and reduced perfusion to the nerves. Though the strength of associations varies across studies, the direction is consistent, supporting smoking cessation as a plausible preventive strategy [17, 18]

Hypertension likewise showed a significant relationship with neuropathy in our sample (59.2% with HTN vs 46.8% without; p = 0.034). Several recent analyses and reviews have highlighted hypertension as a contributor to nerve ischemia and an independent correlate of DPN; some authors have even described hypertension as a "missed" modifiable risk factor for DPN. Our results reinforce the importance of comprehensive cardiovascular risk management in diabetes to lower neuropathy risk.[19, 20]

Geographic and socioeconomic determinants surfaced in our data: neuropathy prevalence was higher in rural patients (60.8%) compared with urban patients (48.8%; p = 0.042), and patients classified as illiterate had higher neuropathy rates (67.4% vs 46.7% in those with primary education or higher; p = 0.021). These observations echo regional meta-analytic results showing province-level differences in Pakistan and multiple facility-based studies in low- and middle-income countries where rural residence, lower education, and limited access to preventive care contribute to delayed diagnosis and worse metabolic control. For instance, facility studies from Ethiopia (2024) and multiple single-site studies across South Asia document higher neuropathy prevalence where health-system access and education are limited—consistent with our findings that social determinants influence neuropathy burden [12, 21]

Methodological differences offer an important lens when comparing prevalence estimates. Studies that use questionnaire screens alone (e.g., MNSI questionnaire) or rely on self-reported symptoms often report lower or higher prevalence than studies using structured clinical examination with monofilament, vibration, pinprick, and reflex testing; some recent facility-based reports have shown prevalence ranges from about 16% to >60% depending on case definition and tools used. For example, a 2024 Indian study reported lower prevalence when using some screening instruments but higher rates when structured clinical assessment and nerve conduction tests were applied. These methodological differences likely account for part of the heterogeneity between our 53.4% estimate and other published values.[21]

Comparing with specific recent studies: a 2024 facility-based study in Ethiopia reported substantial DPN prevalence and identified age, duration, poor glycemic control, and comorbid hypertension as associated factors, findings that mirror ours. A 2020 multi-country INTERPRET-DD analysis and the DCCT/EDIC long-term evidence both emphasize the protective effect of sustained glycaemic control; Nozawa et al. (2022) demonstrated the link between higher average HbA1c and neuropathy in claims data; and multiple 2022–2024 site studies from South Asia and Africa report associations with smoking, HTN, duration, and socioeconomic indicators, again concordant with our results [13, 21]

This study provides several important clinical insights. The finding that more than half of patients with diabetes of over five years' duration had peripheral neuropathy highlights the urgent need for systematic neuropathy screening in clinical practice. As neuropathy commonly progresses insidiously and may be asymptomatic for some time,

assessment and screening with simple, inexpensive bedside instruments should become a standard part of diabetes clinical care. This is especially true for diabetes patients who have had the disease for a longer time or have had poor glycaemic control. All of the substantial associations highlighted in this report with modifiable risk factors (glycaemic control, hypertension, tobacco abuse, etc.) underscore the importance of a comprehensive and multifactorial approach to diabetes treatment. Clinicians should not only focus on the optimization of blood glucose but also aggressively manage cardiovascular risk factors, such as treating hypertension and providing structured smoking cessation counseling. These therapies, if applied early, are thought to delay or even prevent the development of neuropathy.

The greater incidence of neuropathy seen in rural and less educated individuals points to a serious public health issue: inequality in diabetes education, screening, and management. This indicates that community-level approaches are warranted, including mobile health, local language campaigns, and primary care provider training on simple identification of neuropathy. Educational approaches tailored to patients with limited literacy may also improve self-care behaviors and lower the risks of complications.

The second implications from a research standpoint indicate that neuropathy screening should be endorsed at all levels of the healthcare system and incorporated into diabetes management guidelines in Pakistan, specifically in resource-poor contexts like AJK. Health policymakers may consider incorporating monofilament testing as the standard of care in diabetic clinics, and ensuring affordable HbA1c testing is available to help track glycaemic control. Lastly, for researchers, the findings highlight areas to discuss further implications, including the need for longitudinal studies to understand the progression of symptoms and trials evaluating multifactorial interventions aimed at lowering the incidence of neuropathy, as well as studies incorporating electrophysiological or histopathological confirmation to characterize neuropathy more accurately.

Although this research is important, it has limitations that should be considered. First, the study was limited to a single tertiary care center, which may limit the broader applicability of the findings to the larger diabetic population even within Azad Jammu and Kashmir. Patients who present to a tertiary hospital are often likely to have more severe disease or complications than those at primary or secondary healthcare levels; thus, this potentially leads to an overestimate of the prevalence of peripheral neuropathy. Second, the study was cross-sectional in nature, limiting our ability to determine causal relationships. Though correlations were noted between age, duration of diabetes, glycaemic control, hypertension, smoking, and neuropathy, we did not know the temporality or directionality of these predictors. Longitudinal studies will be needed to better delineate the cause-and-effect nature of diabetes, glycaemic control, hypertension, and neuropathy.

The third reason was that peripheral neuropathy was assessed through clinical examination with bedside modalities of monofilament testing, vibration perception, temperature sensation, proprioception, and reflex testing. These modalities are commonly used and are relatively inexpensive; however, they are not as sensitive as more advanced diagnostic testing, such as nerve conduction studies or quantitative sensory testing, and small-fiber neuropathy may have been under-detected. In addition, clinical diagnosis can vary between examiners even after trying to standardize the assessment process. The fourth reason was additional biochemical factors that can also contribute to neuropathy, including serum lipid profiles and renal function, as well as micronutrient levels (besides B12 exclusion), which were not examined in detail. This limits our ability to control for important contributors to neuropathic risk. Finally, nonprobability consecutive sampling was used in the study, which may have introduced selection bias. Although this type of sampling is feasible, it limits representativeness and may have skewed the findings if particular risk subgroups were over- or underrepresented.

CONCLUSION

Among patients with diabetes mellitus for more than five years, peripheral neuropathy was the most common complication affecting over half of the cohort. The associations observed with longer diabetes duration, poor glycaemic control, smoking, hypertension, and sociodemographic factors such as living in rural areas and possessing low educational status illustrate the many factors that played a role in this debilitating condition. Our data have shown that neuropathy is not simply the expected outcome of diabetes, but rather is a largely preventable complication when the appropriate actions are implemented regarding the unreasonable risk factors of diabetes, and generally, diabetes itself. By identifying neuropathy early through systematic clinical screening along with comprehensive management of glycaemia and cardiovascular risks, there could be a significant reduction in the burden of neuropathy as a complication of diabetes. At the same time, it is important to stress the need for systematic public health initiatives aimed at vulnerable groups to fill the gaps in awareness and access to care for peripheral neuropathy as a complication of diabetes. Overall, our study highlights the need to bridge the gap of putting simple and timely bedside measures and holistic management of type 2 diabetes into practice with the fundamental objective of maintaining quality of life and preventing long-term disability for individuals living with diabetes.

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Authors Contribution:
Zakia Kanwal: Intro, Literature review, deta collection, data analysis
Abdul Khalid Awan: Literature review, data collection, results
Syeda Aiman Naqvi: Literature review, data collection, data analysis
Shaista Imtiaz: Review the article, results and data analysis
Zainab Shahab: Literature review, data collection
Tayyaba Haroon: Data collection, Data analysis

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Original Article **Open Access**

Incidence of Early-Onset Neonatal Sepsis in Neonates with Meconium-Stained Liquor

Hajra Begum, Saadia Karim, Nadeem Sadiq, Rida Ali, Nadia Iqbal, Inshal Jawed

Abstract

Objective: The incidence of clinically suspected and culture-proven early-onset sepsis in newborns born through meconium-stained liquor compared to clear liquor controls.

Study Design and Setting: A comparative cross-sectional study was conducted at the Department of Pediatric Medicine and Neonatal Unit, PNS Shifa Hospital, Karachi, Pakistan, from 15 April 2025 to 15 Oct 2025.

Methods: A comparative cross-sectional study was conducted at the PNS Shifa Hospital. The study enrolled consecutive liveborn neonates delivered during the study period, with 42 MSL and 65 clear-liquor controls. Ineffective antibiotic treatment and clinical findings of sepsis were included. Other outcomes included admission rate to the neonatal intensive care unit, occurrence of meconium aspiration syndrome, and mortality. For statistical analyses, Fisher's exact test and Mann-Whitney U test were employed.

Results: MSL neonates displayed a higher incidence of suspected sepsis compared to controls (57.1% vs. 13.8% p<0.01). The MSL group had considerably larger rates of culture-proven sepsis (21.4% vs 3.1%, p<0.01). The MSL group had a much higher rate of having meconium in the lungs with both of those results above. There was no difference in mortality rates (4.8% versus 1.5%; p=0.56).

Conclusion: Neonates with meconium-stained liquor are at higher risk of early-onset neonatal sepsis. Thus, increased clinical suspicion and intervention are indicated in such cases.

Keywords: Meconium-stained liquor; early-onset neonatal sepsis; meconium aspiration syndrome; neonatal outcomes; intra-amniotic infection

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INTRODUCTION

Meconium-stained amniotic fluid is one of the most common clinical entities in obstetrical practice, taking place in 10-15% of deliveries. It is increasing in post-dated deliveries.[1,2] Although meconium was traditionally thought to indicate fetal maturity or response to lack of oxygen, studies show otherwise. It could reflect complex disease processes that may be caused by infectious or inflammatory processes.[3-5] When meconium gets into the amniotic fluid, it can cause several complications in infants. They can have trouble breathing through aspiration. Also, it can cause systemic inflammatory responses. These situations look very similar to neonatal sepsis.[3,4]

Sepsis of newborns, as defined as an infection of the blood (which can be a type of meningitis), is said to be early onset if it occurs within the first 72 hours of life. The disease continues to be a major cause of morbidity/mortality throughout the world. Approximately 1 to 2 in every 1000 live births suffer from early-onset sepsis in developed countries, while this number is considerably higher in resource-limited settings.[5,6] There are various exposures of the infant to the bacterial flora of the maternal lower genital tract, which is not pathogenic for the mother and her fetus.

Due to vertical transmission, early-onset deficiency occurs.[6,7] Neonatal sepsis is now recognized as having clinical signs that can be subtle and nonspecific. These often mimic those seen in other neonatal conditions such as respiratory distress, metabolic problems, and transient physiological adaptations to life outside the womb.[6-9]

The possibility of an intersection between meconium-stained liquor and early-onset sepsis deserves scrutiny for several reasons. Meconium has pro-inflammatory properties and can cause a systemic inflammatory response that mimics infectious processes, thus making it difficult to differentiate a sterile inflammatory process from a bacterial infection.[4,10] Second, the presence of meconium may indicate an underlying chorioamnionitis or intrauterine infection, which greatly increases the risk of sepsis.[1,4] To begin with, respiratory distress, fever, and other clinical signs of premature newborns born through meconium-stained liquor are commonly considered clinical markers of neonatal sepsis. In fact, this leads to confusion, misdiagnosis, and the use of antibiotics, as reported in references.[9,11,12]. The uncertain diagnosis will have major implications for antimicrobial resistance activities. Rose highlighted that inappropriate exposure to antibiotics poses a risk in itself because it selects for resistant organisms and disrupts the developing neonate microbiome.

Despite this intersection's clinical relevance, literature scans exhibit significant inconsistencies and gaps regarding the actual risk and sepsis occurrence in such neonates. Some studies have shown that meconium-stained liquor is associated with bad neonatal outcomes like respiratory problems and NICU admission. Culture-proven bacterial sepsis is less well described.[2,3] In addition, much of the relevant data is obtained from studies that mixed term and preterm neonates, used various definitions of sepsis, or lacked adequate controls. As a result, interpretation of data and findings may be limited.[3] Recent studies have shed some light on the clarification that, although meconium passage at term may be a concerning indicator of intrauterine infection, the same may be less clear for term babies, who comprise the majority of meconium-exposed subjects.[1]

Neonates born in meconium-stained liquor are differentially managed by institutions. Some monitor a baby who appears well normally. Others perform a systemic sepsis evaluation (e.g., blood cultures, start of empirical antibiotics).[5,6] The disparities in practice reflect how vague we really are about who is at risk and how likely it is that bacteria will infect them. Establishing reliable estimates for the number of newborns exposed to meconium who develop sepsis would help facilitate evidence-based assessment and management. This helps solve problems that are caused by too much treatment when the sepsis isn't found or they don't get treatment, and too much treatment that gives them antibiotics they do not need and that separates mother and baby.[7,9]

Pathophysiological perspectives suggest that meconium exposure may increase sepsis risk via a number of mechanisms. Fetal stress-response to intrauterine infection or inflammation is indicated by the passage of meconium. It serves more as a marker indicating infection or inflammation than as a risk factor for sepsis itself.[1,4] Meconium components can directly or indirectly impair immune function or epithelial integrity. Meconium present in the airways may also alter local immune responses and the capacity to clear bacteria, promoting pneumonia and secondary bacteremia.[13,14] To gauge the effectiveness of this type of rebuttal, we will need to conduct a carefully designed epidemiological study with relevant comparison groups and a comprehensive outcome assessment of our results.

The complex pathophysiology of meconium-stained amniotic fluid and intra-amniotic inflammation, along with the possibility of infection, has been emphasized in several recent comprehensive reviews.[4] Thus, it is currently well understood that meconium aspiration syndrome is an inflammatory injury to the lung rather than merely a mechanical obstruction both locally and systemically.[13-15] The distinction between neonatal inflammation due to meconium aspiration and bacterial disease may be hard to make. The differential diagnosis during the critical early hours of life is essential for effective therapy.[9,11,12]

For this purpose, we carried out a comparative cross-sectional study to objectively measure suspected and culture-positive early-onset sepsis in newborns born through meconium-stained liquor versus contemporaneously born through clear liquor. To address important literature gaps, we utilized recent clinical trial sepsis definitions, a thorough culture collection methodology, and a universal capture of maternal and neonatal covariates. We hypothesized that meconium exposure would cause an increase in suspected and culture-proven sepsis rates, accounting for delivery method and fetal compromise during labor. Additionally, we aimed to improve other neonatal outcomes, such as meconium aspiration syndrome, admission to intensive care, and mortality, to better assess the clinical burden of meconium-stained liquor and enhance our results.

METHODOLOGY

This was a comparative cross-sectional study. It was conducted at the labor ward and neonatal unit of PNS Shifa Hospital, Karachi, Pakistan. It is a tertiary care hospital that provides comprehensive obstetric and neonatal services. The study spanned six months, from April 15, 2025, to October 15, 2025.

All neonates who met the selection criteria and were born during the study period were recruited using a consecutive nonprobability sampling technique. The study groups comprised:

(i) Meconium-stained liquor (MSL) neonates.

(ii) Contemporaneous clear-liquor controls.

Informed consent was obtained from parents or guardians. All newborns, irrespective of any gestational age, were eligible for inclusion. We excluded records with major congenital anomalies, outborn transfers prior to the first assessment, and incomplete primary outcome data. No a priori sample size was set; the final sample reflected all eligible births during the study period (MSL n=42; controls n=65; total N=107).

The initial birth hospitalization infection outcomes were summarized as suspected sepsis (initiation of antibiotics after clinical or laboratory evaluation) and culture-proven sepsis (growth of a pathogenic organism from a sterile (blood or cerebrospinal) site, as per hospital microbiology reporting) . Other information of interest was admission to the NICU, meconium aspiration syndrome, and in-hospital death .

A standardized data collection procedure was followed. The intrapartum and maternal variables included mode of delivery and NR-CTG. Meconium exposure was graded as MSL Grade 1, 2, or 3, according to a standard visual assessment . Neonatal variables collected included gestational age (weeks), birthweight (grams), sex, Apgar scores at 1 and 5 minutes, and the need for resuscitation in the delivery room, according to the standard neonatal resuscitation protocol. Data were collected from delivery logs and neonatal records using a standard pro forma created to enhance uniformity.

When needed, blood cultures and additional laboratory tests are performed in a standardized, aseptic manner. Processed by the hospital laboratory in a routine manner. Recorded microbiology reports. Contaminant identification was conducted according to established laboratory standards and included in each report .

As the study used a time-bound consecutive inclusion design, an a priori sample size was not calculated. The study size is the total number of eligible cases within the study period. Medians and interquartile ranges (IQRs) describe continuous variables; frequencies and percentages describe categorical variables. Fisher's exact test (two-sided) was used to compare group differences for categorical outcomes: suspected sepsis, culture-proven sepsis, NICU admission, mortality, non-reassuring CTG, and cesarean delivery. To test continuous and ordinal variables, such as Apgar scores, gestational age, and birth weight, the Mann-Whitney U test was used. For this study, $p<0.05$ was significant. All inferential statistics were done using the IBM SPSS version 25.

The research was approved by the PNS Shifa Hospital Ethical Review Committee (ERC Number: ERC/2025/PAEDS/, dated 10 April 2025). The study was conducted in accordance with the Declaration of Helsinki and institutional guidelines for human research. The parents or guardians of all neonates involved in the study gave consent. Patient confidentiality was maintained by the use of code and restricted access to laboratory reports and clinical data. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations for observational studies were used to report.

RESULTS

MSL neonates had higher rates of suspected sepsis, with 24/42 (57.1%) treated with antibiotics versus 9/65 (13.8%) controls (Fisher's exact test, $p<0.01$), and higher rates of

Table 1. Maternal and Intrapartum Characteristics

Characteristic	MSL (n=42)	Controls (n=65)	p-value
Cesarean delivery, n (%)	23 (54.8)	21 (32.3)	0.02
Non-reassuring CTG/FHR, n (%)	19 (45.2)	12 (18.5)	<0.01
MSL Grading			
Grade 1, n (%)	8 (19.0)	-	-
Grade 2, n (%)	9 (21.4)	-	-
Grade 3, n (%)	25 (59.5)	-	-

MSL = meconium-stained liquor; CTG = cardiotocography; FHR = fetal heart rate Fisher's exact test used for categorical comparisons

Table 2. Primary and Secondary Neonatal Outcomes

Outcome	MSL (n=42)	Controls (n=65)	p-value
Primary Outcomes			
Suspected sepsis, n (%)	24 (57.1)	9 (13.8)	<0.01
Culture-proven sepsis, n (%)	9 (21.4)	2 (3.1)	<0.01
Secondary Outcomes			
NICU admission, n (%)	15 (35.7)	7 (10.8)	<0.01
Meconium aspiration syndrome, n (%)	9 (21.4)	0 (0.0)	<0.01
In-hospital mortality, n (%)	2 (4.8)	1 (1.5)	0.56

Table 3. Distribution of Meconium Grading and Delivery Characteristics

Parameter	n (%)
Meconium Grading (MSL group, n=42)	
Grade 1 (thin, light)	8 (19.0)
Grade 2 (moderate)	9 (21.4)
Grade 3 (thick, heavy)	25 (59.5)
Mode of Delivery	
Cesarean - MSL group	23/42 (54.8)
Cesarean - Control group	21/65 (32.3)
Vaginal - MSL group	19/42 (45.2)
Vaginal - Control group	44/65 (67.7)

culture-proven sepsis, with 9/42 (21.4%) in MSL versus 2/65 (3.1%) in controls (Fisher's exact test, $p<0.01$). The MSL group also had higher morbidity, with NICU admission in 15/42 (35.7%) versus 7/65 (10.8%) controls (Fisher's exact test, $p<0.01$). Meconium aspiration syndrome was only present in the MSL group, 9/42 (21.4%) versus 0/65 (0%) controls (Fisher's exact test, $p<0.01$). And in-hospital death occurred in 2/42 (4.8%) in MSL versus 1/65 (1.5%) controls, which was not significant (Fisher's exact test, $p=0.56$). These findings are summarized in Table 2.

Neonatal characteristics (in the period immediately after birth) at baseline were comparable among groups, although some differences were significant. In the MSL category, the median gestational age was 39.4 weeks (interquartile range 37.2-40.6 weeks) in the paper. Whereas, 38.6 weeks (IQR 37.8-40.2 weeks) in controls indicated that MSL is a later incident. Weight distribution was similar in MSL neonates and controls, with median birthweight being 3020 grams (IQR 2580-3460 grams) and 3150 grams (IQR 2870-3420 grams), respectively. Of the 42 MSL neonates, 24 (57.1%) were male. Of the 65 control neonates, 38 (58.5%) were male. Thus, sex distribution was similar.

None of the groups showed a significant difference in Apgar scores. In the MSL group, the median Apgar score at 1 minute was 6 (IQR 5-9), compared with 7 (IQR 6-9) in controls. 5-minute medians were 8 (IQR 7-10) and 9 (IQR 7-10), respectively. This suggests a more depressed initial transition in meconium-exposed neonates, but both groups achieved reassuring scores ultimately. The features and clinical characteristics have been detailed in Table 4.

DISCUSSION

This comparative cross-sectional study indicated that in comparison to infants born through clear liquor, infants who were born through meconium-stained liquor had a much higher incidence of suspected early onset neonatal sepsis as well as culture-proven early onset neonatal sepsis. According to the findings, more than 20% of newborns exposed to meconium developed a confirmed bacterial infection, compared with only 3% of the controls who were not exposed. The rate of infection was sevenfold. The observed effects are consistent with accumulating evidence that meconium passage is linked to infectious and inflammatory events rather than merely reflecting fetal maturity .

The link between meconium-stained liquor and early-onset sepsis likely involves complex mechanisms. Comprehensive recent reviews show that meconium-stained amniotic fluid is linked to intra-amniotic inflammation, likely a fetal response to intrauterine infection or inflammatory stimuli . The finding of substantially higher rates of non-reassuring fetal heart rates in the MSL group suggests that fetal compromise, due to infections or other inflammatory processes, may be a probable interpretation. The components of Meconium are naturally pro-inflammatory and can initiate systemic inflammatory cascades that may both reflect the infection process and enhance damage caused by these mechanisms . Our observation of a high rate of suspected sepsis (57.1%) may be due to the difficulty clinicians have in distinguishing sterile inflammation from meconium-induced inflammation. However, the high prevalence of culture-positive cases suggests that bacterial infection is a true and common complication, not just a diagnostic dilemma.

Neonatal sepsis is now understood to be a complex condition that is difficult to risk-stratify and diagnose early . Recent international consensus statements and reviews have emphasized that clinical signs of sepsis in neonates may be subtle and non-specific and will very much overlap with those of other neonatal syndromes like respiratory distress and metabolic derangements . When meconium is involved, the differential diagnosis becomes even more difficult. This is because meconium aspiration syndrome can also result in respiratory distress, temperature instability, and cardiovascular compromise; features that can often overlap with sepsis . The pathogenic organisms that are responsible for early-onset sepsis in meconium-exposed neonates are probably similar to those found in conventional early-onset sepsis, although the design of our study disallowed this analysis . Recent research on bacterial etiology and risk prediction models for neonatal sepsis shows that pathogen-specific risk factors play an integral role in its prevention .

The significantly higher incidence of meconium aspiration syndrome (21.4%) noted in our study group defined with meconium-stained liquor is in line with the definition of meconium aspiration syndrome and is not unexpected. However, it does highlight multiple other clinical implications of meconium exposure . Recent book reviews show that meconium aspiration syndrome is not just a blockage caused by particles sucked in. It is actually a lung injury that causes inflammation. Moreover, it also indirectly affects other systems . Clinical presentation of meconium aspiration syndrome and early-onset sepsis has a lot of overlapping features; both might present with respiratory distress, cardiovascular compromise, and features of sickness . The resemblance in appearance makes it harder to make decisions at the bedside. In turn, this increases the use of antibiotics

that we recorded. Systematic reviews and meta-analyses have been published that study the delivery room management of meconium-exposed infants. Available evidence indicates that routine endotracheal intubation for tracheal suctioning for non-vigorous neonates does not improve outcomes and may be associated with increased risks. As such, the resuscitation guidelines are changing .

The NICU admission rates for meconium-exposed neonates were much higher (35.7% vs 10.8%). This suggests increased clinical severity and monitoring needs in this group. The interpretation of these admissions probably encompasses clinical respiratory support requirements as well as sepsis evaluation and therapy . Using a clinically and health economically centered approach, this three-fold increase in intensive care utilization comes at a huge price. The latest management initiatives for newborns with meconium aspiration and co-existing concerns increasingly recommend tailored respiratory support strategies and relevant advanced ventilation options when conventional support fails . Recent agreement contributing to the oxygen therapy of critically ill newborns with hypoxemic respiratory failure makes the cardiac and pulmonary physical examination a priority and precise repair efforts .

Although the mortality rate was numerically higher in the MSL group than in the MSL group (4.8% vs. 1.5%), this difference did not reach statistical significance. This is likely due to the relatively small sample size as well as the fact that term and near-term neonates generally have a good prognosis even when complications do occur . Modern neonatal intensive care capabilities have significantly decreased mortality from meconium aspiration syndrome and early-onset sepsis, but morbidity is still high . The mortality outcomes we observed are consistent with what would be expected in tertiary neonatal units caring for these conditions. Outcomes that we did not measure but may contribute to burdens not captured in acute hospital mortality include longer-term neurodevelopmental and respiratory outcomes.

The demographic characteristics of our group should be considered when interpreting these results. The MSL group's median gestational age was 39.4 weeks, confirming that meconium passage occurs mainly at or near term, consistent with physiological expectations for intestinal motility and sphincter control maturation . The comparability of birthweights and sex distributions across groups suggests that our comparison is valid and that differences in outcomes are due to meconium exposure rather than fundamental differences in neonates. The slightly lower Apgar scores observed in MSL newborns, although not markedly different, suggest a potentially compromised initial transition, possibly attributed to intrapartum stress or early aspiration events .

The expected association between operative delivery and meconium passage explains the much higher cesarean delivery rate in the MSL group (54.8% vs 32.3%). The latter probably also reflects the obstetric practice of expediting delivery in cases of fetal compromise. Likewise, the increased occurrence of non-reassuring cardiotocography in cases of MSL suggests that fetal meconium passage often takes place against the background of an abnormal fetal condition, either as the cause or effect of meconium passage. Intrapartum factors could confound the association with sepsis. Alternatively, there could be components of a causal pathway in which intrauterine infection causes fetal compromise and meconium passage.

Our results have several clinical implications for meconium-exposed neonates. The high rates of culture-proven sepsis (21.4%) give a strong rationale for a systematic sepsis work-up (including blood culture) in neonates born through thick meconium-stained liquor, especially when associated with other risk factors . Modern guidelines for the treatment of early-onset sepsis use a risk-based approach that incorporates maternal and neonatal factors . According to our data, meconium-stained liquor should be regarded as an important risk factor for increased alertness. Whether all meconium-exposed neonates should receive empirical antibiotics pending culture results is debatable since routine initiation of antibiotics to the 57.1% who were suspected of sepsis will, of course, come with considerable overtreatment given that "only" 21.4% were infected . Future work is warranted on refining predictions as to which meconium-exposed newborns, if any, actually have true infection.

Several limitations warrant acknowledgment. Detailed subgroup analyses by meconium grade or gestational age were not possible due to the small sample size. Although consecutive non-probability sampling was a practical choice, it may have introduced a selection bias. The design of the observational study limits the ability to establish a cause-and-effect relationship due to unmeasured confounders, such as maternal antibiotics, the length of labor, and indications for delivery. The absence of detailed information about aetiological bacteria on treatment regimens and duration limits the understanding of these infectious complications .Outcome definitions, although clinically meaningful, had their own limitations. Sepsis is suspected when antibiotics are administered. This reflects clinical judgement and institutional practice patterns as much as the true probability of infection, which may overestimate the likelihood of true infection . Culture-proven sepsis is more specific but suffers from imperfect sensitivity of blood cultures, particularly when small-volume samples are taken and when potential antibiotic pretreatment may inhibit bacterial growth . Molecular or biomarker-based diagnostics were not assessed, which might have provided additional diagnostic resolution . In addition, our short-term follow-up window prevented us from assessing longer-term developmental and respiratory conditions that may impose substantial morbidity burdens beyond in-hospital outcomes alone.

Our research has several important strengths despite the limitations. The presence of a contemporaneous control group of clear liquor-born infants provides important context for the interpretation of the MSL results. It also strengthens causal inference beyond that which could be achieved with case series alone. The findings become more reliable with systematic data collection using a standard pro forma and the use of objective microbiological endpoints (culture results) rather than mere clinical impressions. The approach used consecutive patient enrollment to enhance generalizability to similar tertiary care settings. Ultimately, compliance with STROBE reporting standards and the use of robust statistical techniques strengthen the credibility and reproducibility of our analyses.

Future studies should focus on several critical areas. More widespread, multicenter studies will be useful in determining whether meconium grade, the interval from membrane rupture to delivery, and maternal risk factors can assist in further risk stratification.. Comprehensive microbiological characterization to define bacterial etiology in meconium-exposed neonates . Research on inflammatory markers, molecular diagnostics, and immune signatures can likely provide more effective tools for differentiating meconium-induced sterile inflammation from true bacterial infections, which is beneficial for antibiotic stewardship Long-term follow-up studies to assess neurodevelopmental outcomes, chronic respiratory morbidity, and quality of life are important for fully characterizing the burden of meconium-related complications . Finally, intervention studies to evaluate modified delivery room practices, early antibiotic strategies, and specific respiratory management approaches will help define optimal care paradigms for this high-risk population. The large burden of morbidity attributed to meconium-stained liquor (MSL) that we document demonstrates the need for quality antenatal-intrapartum care to prevent fetal compromise and achieve good outcomes when meconium passage does occur. In light of this, it would be especially important to reduce post-term pregnancies and improve intrapartum fetal monitoring, neonatal resuscitation, and intensive care expertise. In settings with limited resources, where meconium aspiration syndrome and early-onset sepsis have high mortality, the collaborative targeting of meconium aspiration syndrome may be beneficial in these settings.

Meconium in the liquor increases the risk of sepsis. In fact, 21.4% of neonates in this population showed culture-proven infection. This is significantly different from the 3.1% rate in controls. Examining the meconium exposure has become essential as there were high sepsis, meconium aspiration syndrome, and NICU admissions (57.1%, 21.4%, and 35.7%, respectively). It is important to distinguish meconium-induced sterile inflammation from early-onset sepsis. The use of antibiotics is more effective when true infection is differentiated from a sterile inflammatory response.

CONCLUSION

In our study, meconium-stained liquor (MSL) neonates were at a significantly higher risk of developing early-onset neonatal sepsis as compared to clear-liquor controls, which fulfilled the study's main objective. The rate of culture-confirmed sepsis was 7 times higher among meconium-exposed neonates. According to our study, meconium passage was not a sign of maturity, but rather a marker for an underlying infection or inflammation.

Meconium-stained liquor is indicative of a potential sepsis risk. Neonates having thick meconium and other risk factors should be systematically evaluated, including blood culture. Management must strike a balance between the need for antimicrobial coverage and the avoidance of overuse. Future studies should lead to the development of validated tools and biomarkers that can distinguish between sterile inflammation and bacterial infection, allowing antibiotics to be used only when necessary.

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Hajra Begum: Substantial contributions to conception and design or acquisition of data analysis and interpretation of data, Drafting the article or revising it critically for important intellectual content, final approval of the version to be published
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Original Article **Open Access**

Accuracy of Knee MRI Findings in Detecting Soft Tissue Injury, Taking Arthroscopy as the Gold Standard

Zeeshan Haider, Abbas Ali, Shehryar Khan, Luqman Khan, Ubaid Ullah, Waqas Ahmad

Abstract

Objective: To assess the diagnostic validity of Magnetic Resonance Imaging (MRI) in detecting soft tissue knee injuries using arthroscopy as the gold standard.

Study Design and Setting: A cross-sectional validation study was conducted at Khyber Teaching Hospital, Peshawar.

Methodology: A total of 192 patients with clinical suspicion of soft tissue knee injury were enrolled using non-probability consecutive sampling for six months from 1st January 2025 to 30th June 2025. Inclusion criteria involved patients aged 18–60 years presenting with knee pain (VAS >4) and a popping sound, with normal X-ray findings. MRI scans were interpreted for the presence of soft tissue tears based on hyperintense signals on T2-weighted images and fiber discontinuity. All patients subsequently underwent arthroscopic evaluation. The diagnostic accuracy of MRI was determined using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's Kappa for agreement.

Results: MRI showed high sensitivity for the medial meniscus (91.8%), anterior cruciate ligament (88.6%), and posterior cruciate ligament (83.3%), while the lateral meniscus had moderate sensitivity (68.2%). Specificity ranged from 74.3% (medial meniscus) to 86.7% (lateral meniscus). Agreement between MRI and arthroscopy was substantial for medial meniscus injuries ($\hat{e} = 0.81$) and moderate for anterior cruciate ligament, posterior cruciate ligament, and lateral meniscus.

Conclusion: MRI has high diagnostic utility and a substantial agreement with arthroscopy, specifically for anterior cruciate ligament and medial meniscus injuries. Given its non-invasive nature and strong predictive validity, MRI should be considered an effective first-line diagnostic tool when evaluating soft tissue knee injuries.

Keywords: Anterior Cruciate Ligament Injuries, Arthroscopy, Diagnostic Imaging, Knee Injuries,

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INTRODUCTION

Knee injuries are among the most common injuries, accounting for approximately 40% of all sports injuries.[1] Soft tissue injuries to the menisci and cruciate ligaments are most common. There are almost 200,000 anterior cruciate ligament (ACL) Injuries annually in the United States alone. The meniscal tears occur at a rate of 60-70 per 100,000 persons per year, usually requiring surgical intervention.[2] Accurate diagnosis of the injuries is necessary for the timely management and prevention of long-lasting complications, including chronic instability, degeneration, and osteoarthritis.[3] Imaging is a key tool in this clinical challenge, with MRI and arthroscopy being the two most common imaging used for knee injuries.[4]

Knee injuries are one of the most common areas of musculoskeletal pathology in orthopedic practice, resulting from direct trauma, sports, and degenerative changes in the knee joint.[5] Quick and accurate identification of internal knee derangements leads to appropriate therapeutic measures and better outcomes. In addition to various imaging techniques available for the knee, magnetic resonance imaging (MRI) has evolved as the preferred imaging tool whcih non-invasively evaluate most of the soft tissue structures of the knee, including the menisci, cruciate

ligaments, articular cartilage, and surrounding soft tissues.[6]

MRI offers outstanding contrast resolution and multiplanar imaging as compared to other imaging techniques, which makes it particularly helpful for detecting subtle abnormalities. There has been a significant acceptance of MRI in clinical practice as it is completely non-invasive and does not use ionizing radiation, which is especially important for visualizing soft tissues in detail.[7] Despite these advantages, there is still a debate on the reliability and diagnostic accuracy of MRI findings in comparison to arthroscopy, which is considered the gold standard for visualizing and diagnosing intra-articular knee pathologies.

Arthroscopy is a minimally invasive surgical technique that enables direct visualization of the of the knee. This can provide high diagnostic accuracy and the possibility of immediate treatment.[8] Arthroscopy carries inherent surgical risks, including infection, hemarthrosis, and postoperative stiffness, and its invasive nature and associated costs limit its suitability as a routine diagnostic procedure unless a therapeutic intervention is planned.[9]

Numerous studies have compared MRI findings with arthroscopic results, yielding variable outcomes. One such study demonstrated high sensitivity and specificity of MRI in detecting meniscal tears and ligamentous injuries.[10] Other studies have reported variability in diagnostic accuracy depending on factors such as image quality, MRI protocols, the expertise of the interpreting radiologist, and the type of injury. A meta-analysis by Wang et al. (2023) demonstrated pooled sensitivity and specificity of 93% and 88%, respectively, for MRI in detecting ACL tears, while for meniscal injuries the sensitivity was 88% and specificity 94%.[11] Consequently, false-positive and false-negative results do occur, as in clinical assessment, and MRI findings should therefore be interpreted with caution rather than relied upon in isolation.

In addition, the timing of MRI following injury influences diagnostic accuracy. Acute injuries are often associated with joint effusion and edema, which can obscure soft-tissue visualization, while chronic changes may mimic degenerative tears and lead to misinterpretation.[12] Moreover, partial tears and subtle lesions may not be detected on MRI but can be clearly identified during arthroscopy. These limitations necessitate careful clinical correlation and often justify arthroscopic confirmation, particularly in symptomatic patients with inconclusive or equivocal MRI findings.

Recent advances in MRI technology, including higher field strength imaging (3-T), 3D isotropic sequences, and improved coil designs, have shown promising improvements in image quality and diagnostic performance. However, access to these technologies remains limited, particularly in resource-constrained settings, restricting their widespread application. Therefore, evaluating the validity of conventional MRI in routine clinical practice by comparing its diagnostic yield with arthroscopy remains clinically relevant. Assessing the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI provides important insight into its diagnostic accuracy and aids clinicians in informed decision-making regarding management and treatment strategies. Furthermore, this study aimed to determine whether MRI can function as a standalone diagnostic modality or whether arthroscopy remains an essential component of the diagnostic algorithm for internal derangements of the knee. Using arthroscopy as the gold standard, the present study sought to establish the diagnostic accuracy of MRI in detecting soft-tissue injuries of the knee.

METHODOLOGY

This study was a cross-sectional validation study conducted in the Department of Orthopedics at Khyber Teaching Hospital, Peshawar. The total study duration was six months from 1st January 2025 to 30th June 2025. Ethical approval for this study was obtained from the Institutional Research and Ethical Review Board (IREB) of Khyber Medical College, Peshawar. The study was reviewed and approved under approval number 1052/DME/KMC, dated: 13th-12-2024.

The sample size was calculated using Buderer's formula based on the following parameters: an anticipated prevalence of medial meniscus tear of 36.0%, expected MRI sensitivity of 76.5%, specificity of 90.1%, a margin of error of 10%, and a confidence level of 95%.[13] The required sample size was calculated to be 192 participants.

A non-probability consecutive sampling technique was employed for participant selection. Patients aged 18 to 60 years of either gender, presenting with symptoms suggestive of soft tissue knee injury, were included in the study. Exclusion criteria included patients with a prior history of any intervention on the same knee, those with contraindications to MRI or arthroscopy, dislocated knee joints, or associated femoral condyle or tibial plateau fractures.

After obtaining informed consent, eligible patients were recruited from the outpatient department. Each patient's baseline demographic data, age, gender, BMI, duration of complaints, side of involvement (right/left), residence (urban/rural), educational background, profession, and socioeconomic status were recorded on a structured proforma. The radiology department used a 1.5 Tesla scanner to perform MRIs. Imaging was done using a 3 mm slice thickness in the axial, coronal, and sagittal planes. Proton density (PD), T1, T2, STIR (Short Tau Inversion Recovery), and PD with fat suppression were among the sequences. Soft tissue knee injury was defined as the presence of pain rated above 4 on the Visual Analogue Scale (VAS), accompanied by a popping sound in the knee joint, with a normal radiograph. Among the soft tissue structures evaluated were the medial meniscus (MM), lateral meniscus (LM), posterior cruciate ligament (PCL), and anterior cruciate ligament (ACL).

MRI findings for tears were characterized by discontinuity in the ACL, PCL, MM, or LM fibers and increased signal intensity on T2-weighted images. One senior radiologist with at least five years of post-fellowship expertise evaluated all MRIs.

Following MRI, all participants underwent diagnostic arthroscopy under spinal or general anesthesia. A consultant orthopedic surgeon with specialized training in knee arthroscopy performed arthroscopy. Any disruption in the continuity of the ACL, PCL, medial meniscus (MM), or lateral meniscus (LM) fibers directly visualized through arthroscopy during a comprehensive intraoperative examination of the knee joint was considered a positive finding for a tear. Arthroscopic findings were regarded as the gold standard against which MRI results were compared.

Using arthroscopy as the reference standard, the primary objective was to determine the diagnostic accuracy of MRI in detecting soft-tissue injuries of the knee. Diagnostic performance was assessed using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity was defined as the ability of MRI to correctly identify patients with arthroscopically confirmed soft-tissue injuries, while specificity represented its ability to identify patients without such injuries correctly. The PPV was calculated as the proportion of MRI-positive cases that were confirmed as true injuries on arthroscopy, whereas the NPV represented the proportion of MRI-negative cases that were verified as injury-free on arthroscopy. Overall diagnostic accuracy was calculated by dividing the sum of true-positive and true-negative results by the total number of cases.

SPSS (Version 25) was used to analyze the data. The normality of continuous variables such as age, body mass index (BMI), and symptom duration was evaluated using the Shapiro-Wilk test. Frequencies and percentages were used to summarize qualitative data, whereas means ± standard deviations were used to convey quantitative variables that were normally distributed. Two-by-two contingency tables were constructed to compare the diagnostic performance of MRI with arthroscopy, which was considered the gold standard. Standard formulas were applied to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy from these tables. The degree of agreement between MRI and arthroscopy results for injuries to the medial meniscus (MM), lateral meniscus (LM), posterior cruciate ligament (PCL), and anterior cruciate ligament (ACL) was also evaluated using Cohen's Kappa statistic. P-values = 0.05 were regarded as significant.

RESULTS

The study included 192 patients with suspected soft tissue knee injuries. The average age of participants was 37.8 ± 10.4 years. The mean BMI of the study population was 26.3 ± 4.1 kg/m². The average duration of symptoms before presentation was 18.6 ± 9.7 days, with most patients reporting symptoms lasting between 8 to 30 days. The right knee was more commonly involved than the left. Educationally, a considerable proportion of patients had completed intermediate or higher education, while others had education up to matric or no formal schooling. In terms of occupation, the population included a mix of unemployed individuals or housewives, laborers, skilled workers, and students. Most participants belonged to the middle socioeconomic class, followed by low and high-income groups. (Table 1)

The diagnostic performance of MRI in detecting soft tissue injuries of the knee was assessed using arthroscopy as the gold standard. Sensitivity, specificity, and overall accuracy were calculated for each structure examined. Among the evaluated structures, the medial meniscus showed the highest diagnostic performance in terms of sensitivity and accuracy. Both the anterior and posterior cruciate ligaments also demonstrated high sensitivity and acceptable levels of specificity. The lateral meniscus showed relatively lower sensitivity but maintained a high specificity. (Table 2)

Further evaluation of diagnostic metrics, including positive predictive value (PPV) and negative predictive value (NPV), revealed that MRI consistently demonstrated good predictive capabilities across all structures, particularly for the anterior cruciate ligament and medial meniscus. Despite some variation, the values for the posterior cruciate ligament and lateral meniscus also remained within clinically acceptable ranges. (Table 3)

The agreement between MRI and arthroscopy in diagnosing soft tissue knee injuries was evaluated using Cohen's Kappa statistic. The analysis revealed substantial to almost perfect agreement across all evaluated structures. The highest level of agreement was observed for the medial meniscus, followed by strong concordance for the anterior cruciate ligament, lateral meniscus, and posterior cruciate ligament. All comparisons demonstrated statistically significant agreement. (Table 4)

DISCUSSION

In the current validation investigation, which compared MRI and arthroscopy for the detection of knee soft-tissue injuries such as ACL, PCL, medial meniscus (MM), and lateral meniscus (LM), we found strong performance in cruciate ligaments and LM (ê ? 0.53–0.70) and significant agreement for MM (ê ? 0.81). These findings align closely with recent evidence in the literature. A study conducted by Dawkins et al. (2022) reported pooled sensitivity/specificity values of approximately 94%/79% for medial meniscal tears and 81%/87% for lateral meniscus, while ACL injuries achieved 92% sensitivity and nearly 99% specificity. Our sensitivity (91.8%) for MM and specificity (86.7%) for LM are consistent with those pooled estimates, supporting that MRI remains highly accurate for meniscal pathology in modern protocols.[10]

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (n = 192)

Variable	n (%)/ Mean ± SD
Age (years)	37.8 ± 10.4
18–30	58 (30.2%)
31–45	81 (42.2%)
46–60	53 (27.6%)
Gender	
Male	124 (64.6%)
Female	68 (35.4%)
BMI (kg/m²)	26.3 ± 4.1
< 18.5 (Underweight)	12 (6.3%)
18.5–24.9 (Normal)	71 (37.0%)
25.0–29.9 (Overweight)	66 (34.4%)
= 30 (Obese)	43 (22.4%)
Duration of Symptoms (days)	18.6 ± 9.7
= 7 days	49 (25.5%)
8–30 days	96 (50.0%)
> 30 days	47 (24.5%)
Side of Involvement	
Right	109 (56.8%)
Left	83 (43.2%)
Residence	
Urban	112 (58.3%)
Rural	80 (41.7%)
Educational Background	
No formal education	39 (20.3%)
Primary to Matric	72 (37.5%)
Intermediate or above	81 (42.2%)
Profession	
Unemployed/Housewife	61 (31.8%)
Laborer	37 (19.3%)
Office/Skilled worker	48 (25.0%)
Student	46 (24.0%)
Socioeconomic Status	
Low	73 (38.0%)
Middle	95 (49.5%)
High	24 (12.5%)

Table 2: Relationship between MRI and Arthroscopy in the Diagnosis of Soft Tissue Knee Injuries (n = 192)

Structure	Sensitivity (%)	Specificity (%)	Accuracy (%)
MM	91.8	74.3	85.4
LM	68.2	86.7	79.2
ACL	88.6	80.2	84.4
PCL	83.3	78.6	81.8

Abbreviations:
MM stands for medial meniscus, LM for lateral meniscus, PCL for posterior cruciate ligament, and ACL for anterior cruciate ligament.
Kappa Meaning:

Table 4: Agreement Between Arthroscopy and MRI in Diagnosing Soft Tissue Knee Injuries (n = 192)

Structure	Kappa Value	Level of Agreement	p-value
ACL	0.72	Substantial	(p = 2.22×10?²³)
PCL	0.66	Substantial	(p = 3.68×10?²°)
MM	0.81	Almost Perfect	(p = 3.54×10?²?)
LM	0.70	Substantial	(p = 2.05×10?²²)

Abbreviations:
MM stands for medial meniscus, LM for lateral meniscus, PCL for posterior cruciate ligament, and ACL for anterior cruciate ligament.
Kappa Meaning:
Moderate agreement is between 0.41 and 0.60; substantial agreement is between 0.61 and 0.80.
0.80 indicates nearly complete agreement.
Cohen's Kappa statistic was used to evaluate agreement, and the Z-test based on the standard error of Kappa was used to compute p-values.
The agreement is considered statistically significant if the p-value is less than 0.05

Table 3: Detailed Diagnostic Accuracy of MRI Compared to Arthroscopy (n = 192 knees)

Structure	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
ACL	88.6	80.2	84.4	85.5	83.8
PCL	83.3	78.6	81.8	80.1	82.5
MM	91.8	74.3	85.4	86.2	83.9
LM	68.2	86.7	79.2	78.4	80.1

Abbreviations:
MM stands for medial meniscus, LM for lateral meniscus, PCL for posterior cruciate ligament, and ACL for anterior cruciate ligament.
Kappa Meaning:

A single-center prospective study from Pakistan in 2021–22 (Jinnah Hospital Lahore) reported considerably lower specificity as low as 45% for MM and around 65% for LM, despite decent sensitivity.[14] The discrepancy appears attributable to differences in MRI field strength, reporting standards, and patient population. In contrast, our values suggest superior diagnostic fidelity, reflecting optimized MRI protocols and experienced radiological interpretation. Another study focusing on combined injuries in BMC Musculoskeletal Disorders 2021 found MRI to perform well for detecting cruciate ligament injuries, but markedly less reliable for meniscus tears in the setting of multi-ligament injury, especially for peripheral posterior horn tears.[15] Similarly, our slightly lower sensitivity for LM (68%) aligns with known limitations in detecting subtle or posterior horn tears, particularly when ACL or PCL is involved.

A 2024 observational cohort by Bin Abd Razak et al. in Annals of Translational Medicine showed nearly perfect MRI reliability for ACL and strong performance for PCL, but moderate sensitivity (76–77%) and accuracy (up to ~92%) for meniscal tears. That study highlighted decreased PPV for LM and MM tears limited to the posterior horn.[13] Our results parallel these patterns, suggesting our MRI protocol effectively captures moderate-to-severe lesions but may underperform in subtle presentations. A study by Vo et al 2024 reported moderate agreement for meniscal tears when accompanied by ACL injuries, attributing discrepancies to postoperative effusion and injury-induced signal alterations on MRI. Our substantial ê for MM and moderate ê for LM also reflect that imaging in the context of acute injuries remains challenging, particularly for LM.[16]

Across the literature, false negatives tend to occur in peripheral longitudinal or root tears involving the posterior horn, positions often obscured by anatomical artifacts and edema, leading to variable detection rates even with high-field MRI.[17] This may underlie our comparatively lower LM sensitivity and modest PPVs for certain structures. A recent systematic review by Botnari et al. (2024) utilizing deep learning approaches demonstrated improved diagnostic consistency, with weighted ê values surpassing 0.80 for ACL classification and comparable accuracy for meniscal tears, suggesting potential future enhancement through AI assistance.[18] While our current study did not employ machine learning, it underscores that conventional MRI remains highly reliable under experienced interpretation. Finally, a prospective single-center study by Shantanu et al. (2021) documented MRI diagnostic accuracy of 88% for ACL and up to 100% for PCL injuries.[19] This closely mirrors our results (ACL 88.6%, PCL 83.3%), reinforcing that MRI, particularly high-field systems, performs well for cruciate ligaments.

Our findings, demonstrating substantial agreement between MRI and arthroscopy for the medial meniscus (MM; ê ? 0.81) and moderate agreement for ACL, PCL, and lateral meniscus (LM), are in line with contemporary literature. A prospective cohort of 150 knees using 1.5T MRI found ACL sensitivity significantly higher than cartilage injuries ($p = 0.0083$), reinforcing the robust performance of MRI for cruciate ligaments and menisci in routine clinical settings.[20] Similarly, a prospective study of 50 knee trauma patients reported perfect sensitivity for ACL and PCL and moderate sensitivity for LM (90.1%), while specificity for MM was modest (69.7%).[21] These results reflect the common challenge in imaging subtle meniscal tears and support our observation of lower LM sensitivity.

A retrospective review at Kenyatta National Hospital reported MRI sensitivity of 100% for ACL and PCL tears, with specificity of 96.6% and 98.5% respectively. However, sensitivity for PCL was low (50%), and the lowest accuracy was seen for MM (80.5%).[22] This variability mirrors our context, where MM specificity (74.3%) and LM sensitivity (68.2%) are lower than for cruciate ligaments, likely reflecting tear location and imaging complexity.

A systematic logistic regression analysis of over 5,600 MRI-arthroscopy correlations revealed that false negatives for MM were more common in younger, higher-BMI patients and partial tears ($p < 0.001$).[23] Similarly, LM false negatives were significantly associated with partial tears and female sex ($p < 0.05$). These findings help explain our lower LM sensitivity and emphasize the need for careful interpretation in specific patient subgroups.

In a machine learning–assisted imaging study, DL algorithms achieved an AUC of 0.96 for MM and 0.99 for ACL detection, while physician sensitivity improved from 83% to 91% with AI assistance.[24] Though our study did not utilize AI, this underlines the potential to enhance MRI performance further. Lastly, a recent observational study reported MRI accuracy of 94% for ACL and PCL injuries, and 96% for MM detection, confirming MRI as a highly reliable imaging tool.[25] Our results, ACL accuracy 84.4%, PCL 81.8%, and MM 85.4%, closely align, albeit showing slightly lower performance, possibly due to tear complexity or reader variability.

In summary, our findings are consistent with the latest evidence demonstrating that modern MRI protocols yield high sensitivity, specificity, and substantial agreement with arthroscopy for key knee structures, especially ACL and MM. Lower sensitivity for LM highlights persistent limitations in imaging posterior horn tears. MRI should continue to be considered a highly valid non-invasive modality for diagnosing knee soft-tissue injuries, with the caveat that arthroscopy remains indispensable in equivocal or complex cases.

The findings of this study reinforce the role of MRI as a highly effective, non-invasive diagnostic tool for evaluating soft tissue knee injuries, particularly in identifying tears of the ACL, PCL, and menisci. Its high sensitivity and substantial

agreement with arthroscopic findings support its use as a reliable first-line investigation in patients presenting with knee trauma. Incorporating MRI into diagnostic algorithms may reduce the need for unnecessary diagnostic arthroscopies, lower procedural risks, and guide precise preoperative planning. This is particularly valuable in resource-limited settings where surgical facilities may not be readily accessible.

Despite its strengths, the study has several limitations. Being conducted at a single tertiary care center may limit the generalizability of the findings to other populations or healthcare settings. MRI interpretations were performed by a single radiologist, which could restrict inter-observer reliability assessment and introduce potential observer bias. Additionally, the inherent limitations of conventional MRI sequences may have hindered the detection of subtle or complex tears, particularly in the posterior horn of the lateral meniscus. Future multicenter studies employing standardized imaging protocols and blinded, multi-observer evaluations are recommended to strengthen the validity and applicability of the results.

CONCLUSION

MRI demonstrates excellent diagnostic performance and strong concordance with arthroscopy in the evaluation of knee soft-tissue injuries, particularly those involving the ACL and medial meniscus. Its high accuracy, noninvasive nature, and wide availability make it an essential diagnostic modality in orthopedic practice. Although arthroscopy remains the gold standard, MRI serves as a highly valuable and patient-friendly alternative that can facilitate timely diagnosis, reduce unnecessary invasive procedures, and optimize treatment strategies, thereby improving overall patient outcomes in musculoskeletal care.

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Authors Contribution:
Zeeshan Haider: Introduction + Discussion, data collection+ conclusion
Abbas Ali: Review article + dissuasion
Shehryar Khan: Data Collection + review article
Luqman Khan: Data Collection + review article
Ubaid Ullah: Data Collection + data analysis
Waqas Ahmad: Review article and dissociation

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Student Corner - Original Article **Open Access**

A Study on the Association between Internet Addiction and Its Impact on Cognitive Absorption in Young Adults

Areeshah Tariq, Sara Ansari, Shahira Zainab, Hafsa Akbar, Fatima Abid

Abstract:

Objectives: In today's digital era, Internet has become a basic necessity. With the prevalence of internet addiction of 11.3% among young adults, it is alarming to note the ramifications that comes with it. One of many, is the neurological abnormalities that may result in onset of cognitive deficits from young age. This study was conducted to see the association between Internet Addiction Disorders and the related neurocognitive deficits between young adults aged 18-26.

Study design and setting: This study was conducted by filling out 154 questionnaires, using random sampling techniques, from university students of Karachi, Pakistan.

Methodology: Data analysis was performed by IBM SPSS statistics v27. Mean and standard deviation were calculated for quantitative variables. Frequency and percentages were reported for qualitative variables. Chi-square/fisher exact test was applied to check association between qualitative variables. Our findings indicate that 98.4% participants use the Internet every day with a mean screen time of 5.42±2.47 hours. Six-item Cognitive Impairment Test (6CIT) and internet addiction test(IAT20) were used to assess cognitive impairment and internet addiction, respectively.

Results: The mean cognitive impairment and internet addiction test scores were 4.75±3.78 and 43.19±17.92, respectively, with 32.5% subjects exhibiting substantial cognitive impairment. Moreover, our research noted significant correlation of internet addiction with aggression, slowness with everyday tasks and headache.

Conclusion: Our study highlighted the grave reality of today's generation where excessive use of the Internet is turning Young Adults into addicts and causing neural abnormalities which results in behavioral changes, memory deficits, lack of concentration and poor reasoning.

Keywords: Cognitive Dysfunction, Internet Addiction Disorder, Media Exposure, Neurocognitive Disorders, Young Adult

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INTRODUCTION

Delirium and dementia are closely related conditions that frequently cause cognitive deterioration in the elderly. Delirium is an abrupt confusion characterized by altered awareness, concentration problems, and cognitive deterioration. Whereas, dementia is characterized by a steady and progressive decline in previously learned cognitive abilities. Reportedly, it is estimated that about 50 million people are suffering from dementia worldwide and it is predicted to increase up to 3-folds by 2050.[1] In a previous study, it was predicted that Alzheimer's Disease and Related Dementia (ADRD) will significantly rise up to 4-6 folds by 2060 than that observed in 2014.[2] In a recent study, a positive significant correlation (p=0.394; p=0.004) was found between cognition in students and internet usage.[3] A strong relation was observed between the internet addiction and the right precentral gyrus as well as right superior parietal lobule.[4] Internet Addiction Disorder (IAD) refers to a variety of internet-related behavioral addictions. In people with Internet Gaming Disorder (IGD) and Internet Anxiety Disorder, EEG analysis can identify certain neurological abnormalities that are similar to those observed in drug addiction disorders.[5] "Internet addiction" refers to harmful internet-related activities that repeatedly changes the neural architecture and networking of the brain in charge of inhibitory processes and spontaneous behavior. People who have higher propensities to become internet addicts act as a transitional state between healthy and unhealthy

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states, eventually leading to a behavioral addictive illness.[4] The global proliferation of smartphones has led to a notable rise in internet accessibility. Globally, the count of Internet users has increased to 3.9 billion, with developing nations experiencing a significant rise in Internet usage from 7.7%to 43.4%, from 2005 to 2018. Additionally, over the last 20 years, there has been marked prevalence of internet addiction among children and teenagers,[6] where the prevalence in youth was found to be 11.3% in Pakistan.[7] Although internet addiction disorder has both genders under its grip, and majority being the youth, a huge portion of Internet Gaming Disorder is of young males.[5]

In this digital age, there is an increasing rate of phone usage seen in university students. An estimation of about to 2.32 billion people globally own Internet accessible smartphones. Problematic Smartphone Use (PSU) is defined as excessive dependency and inability to control its usage despite experiencing its negative impacts in life.[8] A study focusing on child's brain development also concluded that regular usage of screen time during developmental stages of a child will lead to increased neurodegeneration in later stages of life, possibly resulting in memory loss and early onset dementia.[9] Another study on children and adolescents revealed that children with increased Screen Media Activity (SMA), have increased rate of cortical thinning in their visual system.[10]

Emerging research indicates that excessive internet use is linked to structural changes in the brain's gray and white matter, which is compatible with the cognitive reserve theory of dementia. It suggests that a lack of cognitive stimulation, often characterized by simplistic online activities, may deplete neural resources, increasing the likelihood of cognitive decline and dementia. By engaging in more mentally demanding activities, individuals can build cognitive reserve, reduce risk of dementia and promote brain health.[2] Furthermore, mild cognitive impairment can be a precursor to dementia.[11] In addition, excessive screen time due to internet usage has been shown to be directly associated with anxiety, low mood, decreased cognition, and impaired social development, leading to dementia and delirium.[12] Engaging in regular physical activity and spiritual practices can enhance cognitive function and promote overall brain health. Additionally, various brain stimulation techniques, such as meditation, mindfulness, and cognitive training programs, certain pharmaceutical interventions, like neuroplasticity-enhancing drugs and cognitive enhancers, can also boost brain function and improve memory, attention, and processing speed.[13]

The impacts of unrestrained screen time resemble the manifestation of Mild Cognitive Impairment (MCI) which is observed in adults at onset of dementia. These can include lack of concentration, orientation difficulties and anterograde amnesia.[2] In the current digital age, the pervasive exposure of the younger generation to excessive screen time significantly raises the likelihood of developing internet addiction disorder. This addiction, coupled with an increasing rate of dementia and delirium symptoms in young adults, underscores the pressing need to address mental health concerns regarding neurocognitive functions. The study aims to shed light on detrimental impact of excessive screen time on mental health especially on neurocognitive functions of young adults. Additionally, it aims to raise awareness regarding the escalating rates of dementia and delirium among young adults, stemming from internet addiction.

The objectives of this study are to investigate the relationship between Neurocognitive Disorders (Dementia and Delirium) and internet addiction disorders in young adults aged between 18-26 years old. Operational definitions included in this research are: Delirium: is characterized by sudden onset of awareness and attention issues which deviates from usual cognitive state. At least one other cognitive problem is needed for diagnoses such as: disorientation, memory loss, impaired spatial perception or fluctuating mental status throughout the day.[3] Dementia: entails a progressive deterioration in cognitive function in multiple domains which includes: awareness of surroundings, memory, acquisition of new knowledge, linguistics skills, judgment and decision making.[14] internet addiction disorder: refers to an umbrella term for many addictive behaviors including internet gaming disorder and excessive social networking via smartphones which particularly affects adults and leads to psychosocial problems.[3]

METHODOLOGY

This is a case control study conducted to see the correlation between dementia and delirium with internet addiction disorders among the young adults as simplistic online activities deplete neural resources hence, affecting cognitive decline and dementia. This research was approved by independent local review body of JSMU- institutional review board (IRB No.: JSMU/IRB/2024/920) and was conducted from 30th September, 2024 to 19th March, 2025. In this study, random sampling technique was used, where young adults aged 18-26 were recruited from universities and colleges of Karachi, Pakistan.

To calculate sample size we have used OpenEpi app.[12] While adding data in it we have used prevalence percentage of IAD which was 11.3% , measured in a research conducted on Pakistani population.[7]

Hence according to OpenEpi app our study sample size would be 154 taking 95% confidence level.

The study includes a total sample size of 154 participants, comprised of 77 individuals identified as internet addicts and 77 individual classified as non-internet addict

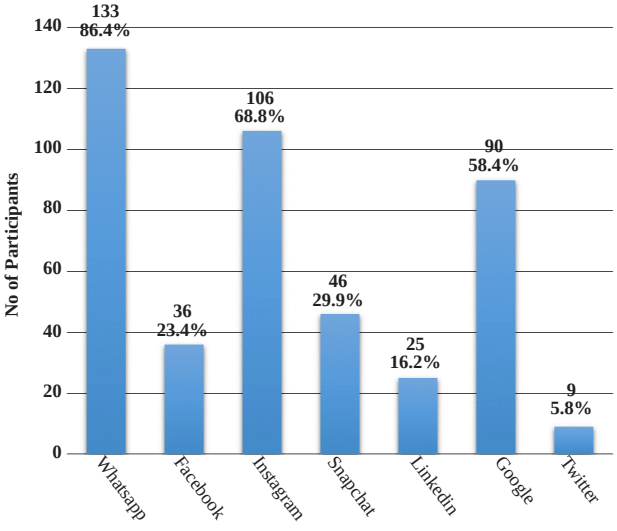
The data was selectively collected from Young Adults aged 18-26 years' old who were active and frequent internet users, spending atleast 4 hours per day online, (excluding work or

Table-1: Demographic profile of study participants (n=154)

	n (%)
Gender	
Male	23(14.9)
Female	131(85.1)
Age(years); mean ± std. dev	21.20±1.92
Age Group	
18-20 years	52(33.8)
21-23 years	91(59.1)
24-26 years	11(7.1)
Education Level	
Intermediate	12(7.8)
Graduate or above	142(92.2)
Socio-economic class	
Upper class	13(8.4)
Middle class	141(91.6)
Employment Status	
Unemployed	18(11.7)
Employed full-time	4(2.6)
Employed part-time	9(5.8)
Student	123(79.9)
Monthly Income	
No income	127(82.5)
=30,000 PKR	17(11)
>30,000 PKR	10(6.5)

Table-3: Responses on six-item cognitive impairment test

Description	n (%)
1-What year is it?	
Correct	140(90.9)
Incorrect	14(9.1)
2-What month is it?	
Correct	133(86.4)
Incorrect	21(13.6)
3-About what time is it (within one hour)?	
Correct	140(90.9)
Incorrect	14(9.1)
4-Count backwards from 20-1	
Correct	146(94.8)
1 error	5(3.2)
More than one error	3(1.9)
5-Say the months of the year in reverse	
Correct	83(53.9)
1 error	41(26.6)
More than one error	30(19.5)
6-Repeat the address phrase asked in Q38	
Correct	60(39)
1 error	45(29.2)
2 errors	24(15.6)
3 errors	19(12.3)
4 errors	6(3.9)



school-related activities), for entertainment, social media, online gaming, or other leisure activities.[8] This specific demographic is targeted to investigate the effects of internet addiction on young adults, a crucial age range for cognitive, social, and emotional development. By focusing on frequent and active internet users within this age range, we aim to gain a deeper understanding of the potential risks and consequences associated with excessive internet use. The Exclusion Criteria consists of participants aged less than 18 and greater than 26years old and Non-internet users.

After getting approval from the IRB questionnaire was distributed among participants via Google form and Paper sheets by the principal investigators and co-principal investigators. In the following research, Internet Usage was determined by Internet Addiction Test (IAT). It is a reliable and validated test made by Young for assessing internet addiction. Its validity has shown strong internal consistency (á = 0.90–0.93) and good test-retest reliability (r = 0.85) values.[15,6] It was previously validated in a Pakistani setting showing Cronbach alpha of .88, indicating excellent reliability.[7] Dementia in young adults will be assessed through Six- Item Cognitive Impairment Test (6-CIT). This test has 0.90 sensitivity and 1.00 specificity.[16]

Furthermore, SPSS version 27 will be used to analyze the data. The mean plus standard deviation will be computed for continuous variables. For categorical variables like gender, duration, and related characteristics, frequency and percentages will be computed. Any differences between the continuous variables, such as age, will be examined using the t-test. Any differences between the category variables will be examined using the chi square (÷2) test. If the P-

Table-2: Impact of screen time and internet usage on cognitive and behavioral health

	n (%)
Internet usage	
Daily	146(94.8)
Weekly	2(1.3)
Monthly	6(3.9)
Daily screen time(hours); mean ± std. dev	5.42±2.47
Excessive Screen Time	44(28.6)
Hyperactive state symptoms ever encountered after excessive screen time	
Agitation	43(27.9)
Delusion	22(14.3)
Aggression	47(30.5)
Hallucinations	7(4.5)
Hypoactive state symptoms ever encountered after excessive screen time	
Lethargy	63(40.9)
Slowness with everyday task	79(51.3)
Excessive sleeping	55(35.7)
Inattention	51(33.1)
Degree of headache	
Extremely	13(8.4)
Slightly	56(36.4)
Normal	28(18.2)
Not Really	57(37)
How much screen time affect sleep	
Extremely	17(11)
Slightly	30(19.5)
Moderately	40(26)
Neutral	23(14.9)
A little	44(28.6)
Cognitive Impairment Test score; mean ± std. dev	4.75±3.78
Cognitive impairment	
Significant (>8)	50(32.5)
Normal (=7)	104(67.5)
Internet Addiction Test Score; mean ± std. dev	43.19±17.92
Internet addiction level	
Normal (=30)	39(25.3)
Mild (31-49)	63(40.9)
Moderate (50-79)	46(29.9)
Severe (=80)	6(3.9)

value is less than 0.05, it will be deemed statistically significant for comparison analysis.

Ethical considerations such as every participant was asked for their informed consent. During the interview, the person didn't experience any discomfort. The study's goals and objectives were explained to them. Additionally, they were made aware that participants are free to withdraw from the study at any point while it is underway and their privacy of their answers and personal data will be maintained.

RESULTS

Data analysis was performed by IBM SPSS statistics v27. Mean and standard deviation were calculated for quantitative variables. Frequency and percentages were reported for qualitative variables. Chi-square/fisher exact test was applied

Table-4: Responses on internet addiction test

	n (%)						Mean ± std. dev
	0	1	2	3	4	5	
How often do you find that you stay online longer than you intended?	5(3.2)	17(11)	29(18.8)	25(16.2)	50(32.5)	28(18.2)	3.18±1.39
How often do you neglect household chores to spend more time online?	11(7.1)	36(23.4)	34(22.1)	33(21.4)	30(19.5)	10(6.5)	2.42±1.38
How often do you prefer the excitement of the Internet to intimacy with your partner?	114(74)	11(7.1)	8(5.2)	8(5.2)	10(6.5)	3(1.9)	0.68±1.34
How often do you form new relationships with fellow online users?	47(30.5)	67(43.5)	10(6.5)	9(5.8)	15(9.7)	6(3.9)	1.32±1.41
How often do others in your life complain to you about the amount of time you spend online?	21(13.6)	51(33.1)	27(17.5)	23(14.9)	20(13)	12(7.8)	2.03±1.5
How often do your grades or school work suffer because of the amount of time you spend online?	18(11.7)	53(34.4)	25(16.2)	25(16.2)	17(11)	16(10.4)	2.11±1.53
How often do you check your email before something else that you need to do?	29(18.8)	44(28.6)	26(16.9)	26(16.9)	19(12.3)	10(6.5)	1.94±1.51
How often does your job performance or productivity suffer because of the Internet?	26(16.9)	31(20.1)	36(23.4)	27(17.5)	18(11.7)	16(10.4)	2.18±1.56
How often do you become defensive or secretive when anyone asks you what you do online?	40(26)	55(35.7)	18(11.7)	22(14.3)	9(5.8)	10(6.5)	1.57±1.48
How often do you block out disturbing thoughts about your life with soothing thoughts of the Internet?	13(8.4)	28(18.2)	29(18.8)	32(20.8)	25(16.2)	27(17.5)	2.7±1.57
How often do you find yourself anticipating when you will go online again?	16(10.4)	37(24)	30(19.5)	31(20.1)	26(16.9)	14(9.1)	2.36±1.49
How often do you fear that life without the Internet would be boring, empty, and joyless?	19(12.3)	28(18.2)	27(17.5)	37(24)	20(13)	23(14.9)	2.51±1.58
How often do you snap, yell, or act annoyed if someone bothers you while you are online?	25(16.2)	48(31.2)	17(11)	30(19.5)	24(15.6)	10(6.5)	2.06±1.54
How often do you lose sleep due to being online?	18(11.7)	42(27.3)	17(11)	35(22.7)	27(17.5)	15(9.7)	2.36±1.55
How often do you feel preoccupied with the Internet when off-line, or fantasize about being online?	24(15.6)	45(29.2)	24(15.6)	27(17.5)	24(15.6)	10(6.5)	2.07±1.51
How often do you find yourself saying "just a few more minutes" when online?	8(5.2)	22(14.3)	21(13.6)	29(18.8)	35(22.7)	39(25.3)	3.15±1.55
How often do you try to cut down the amount of time you spend online and fail?	16(10.4)	26(16.9)	28(18.2)	31(20.1)	36(23.4)	17(11)	2.62±1.53
How often do you try to hide how long you've been online?	29(18.8)	54(35.1)	17(11)	21(13.6)	20(13)	13(8.4)	1.92±1.59
How often do you choose to spend more time online over going out with others?	33(21.4)	48(31.2)	24(15.6)	19(12.3)	17(11)	13(8.4)	1.85±1.57
How often do you feel depressed, moody, or nervous when you are off-line, which goes away once you are back online?	21(13.6)	53(34.4)	23(14.9)	23(14.9)	21(13.6)	13(8.4)	2.05±1.53

Table-5: Association of internet addiction with demographic, screen time, cognitive and behavioral health

	Internet addiction n (%)		p-value
	Yes	No	
Gender			
Male	16(13.9)	7(17.9)	0.541
Female	99(86.1)	32(82.1)	
Age Group			
18-20 years	36(31.3)	16(41)	0.256
21-23 years	72(62.6)	19(48.7)	
24-26 years	7(6.1)	4(10.3)	
Education Level			
Intermediate	6(5.2)	6(15.4)	0.076
Graduate or above	109(94.8)	33(84.6)	
Socio-economic class			
Upper Class	10(8.7)	3(7.7)	1.000
Middle Class	105(91.3)	36(92.3)	
Employment Status			
Unemployed	11(9.6)	7(17.9)	0.533
Employed full-time	3(2.6)	1(2.6)	
Employed part-time	7(6.1)	2(5.1)	
Student	94(81.7)	29(74.4)	
Monthly Income			
No income	90(78.3)	37(94.9)	0.056
=30,000 PKR	16(13.9)	1(2.6)	
>30,000 PKR	9(7.8)	1(2.6)	
Excessive Screen Time			
Yes	36(31.3)	8(20.5)	0.197
No	79(68.7)	31(79.5)	
Hyperactive state symptoms ever encountered after excessive screen time			
Agitation	35(30.4)	8(20.5)	0.233
Delusion	16(13.9)	6(15.4)	0.820
Aggression	42(36.5)	5(12.8)	0.005*
Hallucinations	6(5.2)	1(2.6)	0.680
Hypoactive state symptoms ever encountered after excessive screen time			
Lethargy	52(45.2)	11(28.2)	0.062
Slowness with everyday task	67(58.3)	12(30.8)	0.003*
Excessive sleeping	44(38.3)	11(28.2)	0.257
Inattention	43(37.4)	8(20.5)	0.053
Degree of headache			
Extremely	10(8.7)	3(7.7)	0.003*
Slightly	47(40.9)	9(23.1)	
Normal	25(21.7)	3(7.7)	
Not Really	33(28.7)	24(61.5)	
How much screen time affect sleep			
Extremely	13(11.3)	4(10.3)	0.174
Slightly	25(21.7)	5(12.8)	
Moderately	33(28.7)	7(17.9)	
Neutral	17(14.8)	6(15.4)	
A little	27(23.5)	17(43.6)	
Cognitive impairment			
Significant (>8)	43(37.4)	7(17.9)	0.025*
Normal (=7)	72(62.6)	32(82.1)	

Chi-square/fisher exact test was applied. p-value=0.05 were considered as significant.

*Significant at 0.05 levels

Table-6: Odds for internet addictive participants

PART-I

	Un-Adjusted		Adjusted	
	p-value	**Odds (95% CI)**	**p-value**	**Odds (95% CI)**
Gender				
Male	0.542	0.739(0.279-1.956)		
Female		1.000		
Age Group				
18-20 years	0.718	1.286(0.329-5.021)		
21-23 years	0.254	2.165(0.574-8.175)		
24-26 years		1.000		
Education Level				
Intermediate	0.050*	0.303(0.091-1.002)	0.096	0.302(0.074-1.238)
Graduate or above		1.000		1.000
Socio-economic class				
Upper Class	0.846	1.143(0.298-4.385)		
Middle Class		1.000		
Employment Status				
Unemployed	0.170	0.485(0.172-1.365)		
Employed full-time	0.947	0.926(0.093-9.242)		
Employed part-time	0.926	1.080(0.212-5.487)		
Student		1.000		
Monthly Income				
No income	0.222	0.270(0.033-2.210)		
=30,000 PKR	0.696	1.778(0.099-31.976)		
>30,000 PKR		1.000		
Excessive screen time				
Yes	0.201	1.766(0.739-4.221)		
No		1.000		
Agitation ever encountered after excessive screen time				
Yes	0.236	1.695(0.708-4.058)		
No		1.000		
Delusion ever encountered after excessive screen time				
Yes	0.821	0.889(0.321-2.459)		
No		1.000		
Aggression ever encountered after excessive screen time				
Yes	0.008*	3.912(1.421-10.770)	0.013*	2.921(1.287-6.630)
No		1.000		1.000
Hallucinations ever encountered after excessive screen time				
Yes	0.501	2.092(0.244-17.939)		
No		1.000		
Lethargy ever encountered after excessive screen time				
Yes	0.065	2.101(0.955-4.621)		
No		1.000		

to check association between qualitative variables. Odds were calculated using binary logistics regression. Odds were adjusted for variables found significant on uni-variate binary logistics regression. P-value =0.05 were considered as significant.

Total 154 young adults were included in the current study with a mean age of 21.20±1.92 years. The male to female ratio was 1:5.7, with the majority (59.1%) of participants aged 21 to 23 years. There were 92.2% of participants with a graduation or higher education level, 8.4% from the upper and 91.6% from the middle class of society. The majority (82.5%) of participants have no income. Detailed

PART-I

	Un-Adjusted		Adjusted	
	p-value	Odds (95% CI)	p-value	Odds (95% CI)
Slowness with everyday task ever encountered after excessive screen time				
Yes	0.004*	3.141(1.448-6.813)	0.010*	2.921(1.287-6.630)
No		1.000		1.000
Excessive sleeping ever encountered after excessive screen time				
Yes	0.260	1.577(0.714-3.484)		
No		1.000		
Inattention ever encountered after excessive screen time				
Yes	0.057	2.314(0.975-5.492)		
No		1.000		
Degree of headache				
Extremely	0.213	2.424(0.602-9.764)		
Slightly	0.003*	3.798(1.566-9.212)		
Normal	0.007*	6.061(1.639-22.415)		
Not Really		1.000		
How much screen time affect sleep				
Extremely	0.271	2.046(0.572-7.319)		
Slightly	0.048*	3.148(1.011-9.803)		
Moderately	0.036*	2.968(1.074-8.203)		
Neutral	0.307	1.784(0.587-5.419)		
A little		1.000		
Cognitive impairment				
Significant (>8)	0.029*	2.730(1.109-6.721)	0.015*	3.292(1.264-8.573)
Normal (=7)		1.000		1.000

Binary logistic regression was applied.
p-value=0.05 were considered as significant.
*Significant at 0.05 levels.

demographic profiles of study participants are presented in Table-1.

Among 154 participants, 94.8% used the internet every day, with an average screen time of 5.42±2.47 hours. There were 28.6% of participants, found to have excessive screen use (more than 6hoursperday).

Table 2 shows that 27.9% of participants had agitation, 14.3% had delusion, 30.5% had aggression, 4.5% had hallucinations, 40.9% had lethargy, 51.3% had slowness with everyday tasks, 35.7% had excessive sleeping, and 33.1% had inattention symptoms as a result of excessive screen time.

WhatsApp was determined to be the most frequently used application, with 86.4% of participants indicating regular usage. Instagram is the second most popular platform, used by 68.8% of participants. Google is also frequently utilized, with 58.4% of interviewees reporting frequent use. In contrast, 23.4% of participants utilize Facebook, as showninFigure1. The Six-item Cognitive Impairment Test (6CIT) and Internet Addiction Test(IAT20) were used to assess cognitive impairment and internet addiction, respectively. Tables 3 and 4 give the responses to both instruments. The mean cognitive impairment and internet addiction test scores were 4.75±3.78 and 43.19±17.92, respectively, with 32.5% of subjects exhibiting substantial cognitive impairment. Table 1 shows that 40.9% of participants had mild, 29.9% had moderate, and 3.9% had severe internet addiction.

We found a significant association of internet addiction with aggression(p=0.005), Slowness with everyday tasks(p=0.003), Degree of headache(p=0.003) and Cognitive impairment(p=0.025). Detailed results of association are presented in Table-5. Males were shown to be less likely to develop internet addiction than females (OR=0.739, p=0.542). People aged 18–20 years (OR=1.286, p=0.718) and 21–23 years (OR=2.165, p=0.254) are more likely to develop internet addiction than people aged 24-26 years. Participants with excessive screen time were also more likely to be addicted to the internet than those who did not (OR=1.766, p=0.201). Participants with cognitive impairment were more likely to be addicted to the in ternet than those without (OR=2.730, p=0.029). Table 6 shows detailed results for unadjusted and adjusted odds, where aggression was associated with higher odds of internet addiction (AOR= 2.92, 95% CI: 1.29-6.63).

DISCUSSION

This study aimed to assess the prevalence of internet addiction among young adults and its association with cognitive and behavioral impairments. From the past few years, the internet has conquered our lifestyles, dominating the way of communication, education and in various recreational activities. Despite its various advantages, excessive internet usage has led to its addiction in young adults. Internet addiction disorder consisting of social networking and internet gaming disorder, primarily using smart phones has shown increased rates of psychosocial issues in adults.[3]

In our study, participants with excessive screen time were probably addicted to the internet than those who did not (OR=1.766, p=0.201). Among 154 participants, 98.4% use the internet everyday with an average of 5.42±2.47 hours per day. The findings also indicate a high prevalence of daily internet usage among young adults, with a significant proportion of participants exhibiting symptoms of internet addiction. Notably, 40.9% of participants had mild level, 29.9% had moderate level, and 3.9% had severe level of internet addiction. A similar study also noted 16.8% prevalence of internet addiction.[17] These findings align with prior studies suggesting that internet addiction is becoming a more serious public health issue, particularly among young populations with frequent internet engagement. Similar findings were reported in previous studies too. A study done by Kandasamy et al. reported 6% of students being Internet addicts and 20% had the possibility of being addicted.[18] Moreover, a study conducted by Bhatia et al. also reported 24% moderate level internet addiction and 6% has severe level of internet addiction.[19] In a recent study, this problematic usage was divided into 3 categories namely, addictive consumption patterns, antisocial consumption patterns and adverse use patterns, which leads to deteriorating academic, social and professional functioning. Widespread usage has led to development of a new term: Nomophobia, which is characterized as compulsivity and prolonged smartphone use accompanied with anxiety when smartphones are inaccessible.[20]

A key finding of this study is the significant association of internet addiction and behavioral symptoms, including aggression (p=0.005), slowness in everyday tasks (p=0.003), and degree of headache (p=0.003). These results support existing literature that links excessive screen time and internet addiction to increased irritability, cognitive fatigue, and attention deficits. In a recent study, the greatest mean correlation was noted between internet addiction and aggression (r+=0.391), succeeded by depression, psychological health and self-esteem. It was also noted that problematic internet usage can lead to increased suicidal ideation and it is strongest in adolescents who show greater aggression levels.[21] Another study showed significant correlation between internet addiction and total aggression, where Internet Addicts showed significant association with its subtypes: physical aggression, hostility and indirect aggression. It was concluded that some internet activities like gaming, scrolling through videos etc. decreases the guilt for aggressive behaviors and decreases personal responsibility for such violent activities by providing extreme sensory and novel stimuli. Consequently, Internet overuse would reduce self-awareness, guilt and shame which contributes to aggressive behaviors.[22]

Slowness in everyday tasks and lethargic attitude stems from sedentary lifestyle. It was stated that over 2 hours of daily screen time was negatively related with misbalanced body composition, fitness and self-esteem. It is also reported that individuals with excessive screen time are less active physically and consume greater amounts of snacks which ultimately leads to obesity.[23,24] In another study, 40% of students preferred the internet over physical activities. Furthermore, this study also elaborated the various health concerns arising due to excessive Internet usage, among which headache accounted for about 24%. [19]

The mean cognitive impairment and internet addiction test scores were 4.75±3.78 and 43.19±17.92, respectively, with 32.5% of subjects exhibiting substantial cognitive impairment. Cognitive impairment was also significantly correlates with internet addiction (p=0.025), with individuals exhibiting cognitive deficits were seemingly Internet Addicts (OR=2.730, p=0.029). This finding is particularly concerning as it suggests a bidirectional relationship, where excessive internet use may contribute to cognitive decline while cognitive deficits may increase susceptibility to compulsive internet behaviors. According to a previous study, Internet Usage and cognition in students had significant association (ñ = 0.394; p = 0.004). Hence, it was deduced that internet addiction leads to abnormalities in the brain's white matter integrity in areas concerned with executive functioning, cognition, and making decisions. It was also reported that Internet Addicts were found to have decreased levels of dopamine transporters.[3] In another study, it was deduced that internet addiction has significant association with cognitive defects in inhibiting attention, motor activities, working memory due to dysfunction in the striatal region.[25] A recent study showed that internet addiction has led to abnormal changes in both white and gray matter of the brain, resulting in neurocognitive disorders from early ages, coupled with their spontaneous abnormal activity results in mediocre task performance. In our study, 14.3% reported about experiencing delusions and 4.5% reported to hallucinate. According to a study, Alzheimer's Disease and Related Dementias (ADRDs) include manifestations like retrograde, anterograde amnesia, delusions and hallucinations which help in progression of these disorders. ADRDs are gradual, progressive brain disorders which result in inattention, disorientation, poor concentration, affecting memory, reasoning and decision making abilities.[2]

The study also highlights gender and age-related differences

in internet addiction. Although males had a lower likelihood of developing internet addiction than females (OR=0.739, p=0.542), the association was not statistically significant. This contrasts with some previous studies that report higher internet addiction rates among males.[26] However, the sample in this study was predominantly female (85.1%), which may have influenced the observed gender differences. Young adults (18–23 years) showed greater levels of internet addiction than those aged 24–26 years, though the association was not statistically significant. This trend aligns with previous research indicating that younger individuals, particularly university students, are more susceptible to problematic internet use due to academic, social, and recreational online activities. A study in China included that 28.4% of the total online age group was the 10-29 years age group, among which college students made up to 21%.[27] Similarly, a recent study also concluded that younger population is more prone to become Internet Addicts than older as they spend more time online playing games, chatting with colleges and social media browsing. It was also observed that young adults choose to be online for hours to overcome loneliness and emotional distress which results in obsessive thoughts and compulsive behavior.[28] However, participants with excessive screen time reported a range of cognitive and behavioral disturbances as well, such as lethargy (40.9%), excessive sleeping (35.7%), and inattention (33.1%). These findings reinforce the negative implications of prolonged internet use, particularly its impact on mental well-being and daily functioning. It is due to overstimulation of the brain which results in fatigueness and excessive compensation sleeping leading to poor sleep quality. A previous study deduced that sleep disturbances due to excessive screen time is due to exposure of blue-green light which reduces melatonin levels hence, induce alertness and correlates with decreased physical activity thereby leading to poor sleep quality and abnormal circadian rhythm.[9]

The study has a number of limitations. First, its casual inference is limited by its case control design; while correlations are evident, it is unclear whether internet addiction leads to cognitive impairment or if pre-existing cognitive deficits predispose individuals to excessive internet use. Second, self-reported measures were used to assess internet addiction and cognitive impairment, which may introduce response biases. Third, the study sample was not gender-balanced, limiting generalizability across different demographic groups. Lastly, 6CIT is primarily validated for older adults. Its use in younger populations has limited validation, so results should be interpreted with caution.

Given the case-control design, casual inferences cannot be made. Observed associations may be influenced by potential confounders such as sleep quality, anxiety and socioeconomic stress, which could affect both exposure and outcome. In spite of these limitations, the study provides enlightening perspectives into the prevalence and impact of internet addiction among young adults. Future research should explore relationships between internet addiction and cognitive health longitudinally, incorporating objective measures of screen time and neurocognitive assessments. Given the significant associations found, targeted intervening steps such as digital detox programs, behavioral therapies, and educational campaigns may be valuable in mitigating the adverse effects of internet addiction.

CONCLUSION

Long lasting screen exposure due to internet addiction created a negative impact on the young minds. Due to excessive screen gazing adolescents and young adults are at risk of cognitive impairment, emotional and behavioral disturbances even lacking attention with learning and memory disruption. Our study exposes the dark side of internet addiction which shows that it increases agitation, irritation, lethargy and sleep disturbances. Even 32% of the participants are facing cognitive decline. Our research warns us to become serious about screen time and internet addiction and awakens us toward the urgent need of less or responsible screen and internet usage.

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Authors Contribution:
Areeshah Tariq: lead the research, design work, data collection, wrote discussion and prepared manuscript
Sara Ansari: helped in synopsisand descussion writing, data collection and interpretation of data
Shahira Zainab: helped in synopsis, data collection and conclusion
Hafsa Akbar: helped in synopsis and data collection
Fatima Abid: supervised the research and analysis

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Case Report **Open Access**

Anaesthesia management of a Patient with Hypertrophic Obstructive Cardiomyopathy Undergoing c2-c5 Decompression in Cervical Myelopathy

Sayed Makarram Ahmed Bukhari, Atif Nazir

Abstract

Hypertrophic obstructive cardiomyopathy (HOCM) presents unique challenges in perioperative management due to its dynamic left ventricular outflow tract obstruction, diastolic dysfunction, and susceptibility to arrhythmias. This report highlights the anesthetic considerations in an 80-year-old female with HOCM and cervical spondylotic myelopathy undergoing C2-C5 decompressive surgery. The patient, an ASA-III with poorly controlled hypertension, experienced acute hemodynamic instability post-induction, necessitating emergent optimization. Re-attempted surgery under transesophageal echocardiography guidance, invasive hemodynamic monitoring, and tailored anesthetic techniques ensured uneventful completion. This case underscores the critical role of echocardiographic assessment, precise fluid management, and pharmacological strategies in minimizing perioperative risks in HOCM patients. The report aims to contribute to the limited literature on HOCM anesthetic management and to guide clinicians facing similar complexities.

Key words: Cervical Spondylotic Myelopathy, Hypertrophic Obstructive cardiomyopathy (HOCM), Perioperative care

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INTRODUCTION:

Hypertrophic obstructive cardiomyopathy (HOCM) is a rare disorder characterized by hypertrophy of the left or right ventricle, which may be symmetric or asymmetric and classified as either obstructive or non-obstructive.[1,2] The most common form, subaortic HOCM, involves asymmetric hypertrophy of the interventricular septum, leading to dynamic obstruction of the left ventricular outflow tract (LVOT).[3] The extent and location of hypertrophy vary significantly, influencing the clinical presentation. This autosomal disorder exhibits a male-to-female predominance of 2:1.3, with an annual mortality rate of approximately 3–4% under medical management.[4] Treatment approaches include medical therapy, electrophysiological interventions, percutaneous transluminal septal myocardial ablation, and surgical options.[5] Anesthetic management in HOCM poses unique challenges, particularly in undiagnosed cases. We present the case of a previously undiagnosed HOCM patient undergoing C2-C5 decompressive cervical spine surgery and describe the perioperative anesthetic management in this context.

Case Report

An 80-year-old female with cervical spondylotic myelopathy was scheduled for decompressive surgery (laminectomy, C2-C5) under general anesthesia at Bahria International Hospital, Bahria Town Phase 8, Rawalpindi. The patient was classified as ASA-III, with a history of uncontrolled hypertension despite a quadruple antihypertensive regimen comprising hydralazine 100 mg, irbesartan 300 mg, hydrochlorothiazide 12.5 mg, and lercanidipine 10 mg. She was New York Heart Association (NYHA) Class II and Canadian Cardiovascular Society (CCS) Class I, with no significant limitations on ordinary physical activity. Preoperative echocardiography revealed concentric left ventricular hypertrophy (LVH), a left ventricular end-diastolic dimension (LVEDD) of 46 mm, and an interventricular septal thickness of 12 mm, with a normal ejection fraction (EF) of 60%. No overt left ventricular outflow tract (LVOT) obstruction was reported at rest.

Induction of anesthesia with propofol, nalbuphine, and cis-atracurium resulted in profound hypotension, refractory to multiple boluses of epinephrine (2.5 µg). Peak airway pressures were elevated (28–29 cmH2O), and pink frothy sputum was observed, indicating acute pulmonary edema. Bedside echocardiography confirmed severe obstructive cardiomyopathy with systolic anterior motion (SAM) of the mitral valve, moderate mitral regurgitation, and a small left ventricular cavity, consistent with dynamic LVOT obstruction.(Fig 1) The surgery was aborted, and the patient was stabilized with beta-blocker therapy (bisoprolol 2.5 mg BID) and fluid optimization.

On the subsequent day, surgery was reattempted with a revised anesthetic plan to address hemodynamic challenges. Preoperative anxiolysis with midazolam was administered to reduce anxiety and facilitate smooth induction. Invasive

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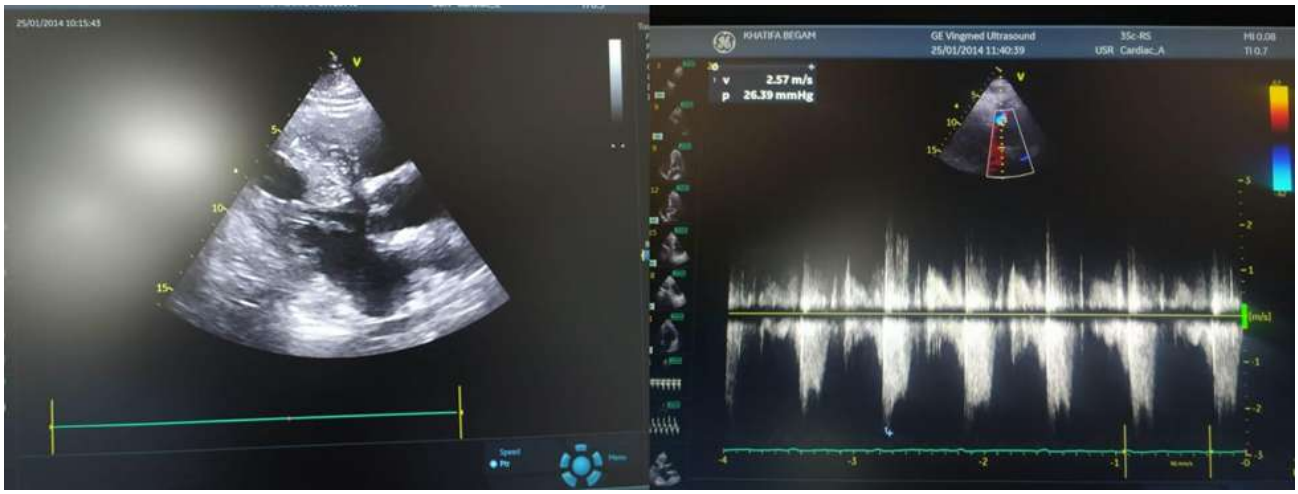
Figure 1. Echocardiogram showing increased IVS thickness, SAM & LV outflow acceleration



monitoring included transesophageal echocardiography (TEE) to assess real-time ventricular function and loading conditions, along with placement of an arterial line in the left brachial artery and a 7.0Fr central venous catheter in the right femoral vein. Anesthesia was induced with low-dose propofol and fentanyl to blunt the sympathetic response to laryngoscopy, while cis-atracurium was used for neuromuscular blockade due to its minimal cardiovascular effects.Maintenance was achieved with sevoflurane (0.5 MAC), nitrous oxide (0.5 MAC), and dexmedetomidine (0.3µg/kg/hr) to ensure hemodynamic stability.Dynamic LVOT obstruction was monitored throughout the procedure using TEE, which guided adjustments in preload and afterload. Phenylephrine was used to maintain systemic vascular resistance (SVR), while care was taken to avoid hypovolemia or agents that could increase contractility. Glyceryl trinitrate was used sparingly to manage blood pressure without exacerbating obstruction. The surgical procedure proceeded uneventfully, and the patient was extubated in a deep plane and transitioned to an i-gel airway to minimize postoperative stress.

DISCUSSION

Hypertrophic obstructive cardiomyopathy (HOCM) is characterized by asymmetric septal hypertrophy and dynamic left ventricular outflow tract (LVOT) obstruction, often exacerbated by specific physiological triggers. These include reduced preload, increased contractility, and decreased afterload, all of which contribute to a worsening intraventricular gradient. The perioperative period poses significant risks for these patients due to the interplay of hemodynamic fluctuations, anesthetic agents, and surgical stress.

The pathophysiology of HOCM is marked by diastolic dysfunction, as impaired ventricular relaxation reduces cardiac compliance. Additionally, systolic anterior motion (SAM) of the mitral valve leaflet can further exacerbate LVOT obstruction and mitral regurgitation. These features complicate the perioperative management, as seen in this case, where the patient developed acute pulmonary edema and refractory hypotension following anesthesia induction. SAM, unmasked post-induction, highlighted the importance of understanding latent versus overt LVOT obstruction, especially in previously undiagnosed cases.[6,7]

In managing such patients, the primary anesthetic objectives are to maintain sinus rhythm, optimize preload, sustain afterload, and avoid increases in myocardial contractility. Beta-blockers, like bisoprolol administered in this case, are fundamental for reducing heart rate and mitigating the severity of LVOT obstruction. Volume optimization through judicious fluid administration is crucial to maintain ventricular filling and prevent hypovolemia.

The intraoperative use of transesophageal echocardiography (TEE) was instrumental in this case. It enabled dynamic monitoring of SAM, LVOT obstruction severity, and ventricular filling conditions, allowing timely adjustments in fluid and pharmacologic therapy. TEE is considered the gold standard for intraoperative assessment in HOCM and is particularly valuable in guiding management decisions.

The anesthetic strategy employed included the use of agents with minimal negative inotropic effects, such as sevoflurane, nitrous oxide, and dexmedetomidine, alongside careful titration of phenylephrine to maintain systemic vascular resistance (SVR).[8] These agents were chosen to avoid exacerbating LVOT obstruction while ensuring hemodynamic stability. Opioids and sedatives were administered to suppress catecholamine surges, reducing sympathetic outflow and associated risks of tachycardia.

Furthermore, rapid administration of induction agents and vasodilators must be avoided in HOCM due to their propensity to precipitate hemodynamic collapse. Instead, slow, controlled administration of induction agents, as performed in this case, mitigates such risks.[9]

This case underscores the importance of preoperative optimization, the utility of advanced intraoperative monitoring, and a multidisciplinary approach in managing HOCM patients undergoing non-cardiac surgery.[10] By tailoring anesthetic and pharmacologic strategies, clinicians can minimize perioperative complications and achieve favorable outcomes even in complex cases.

CONCLUSION

Hypertrophic obstructive cardiomyopathy presents significant anesthetic challenges due to its complex hemodynamic profile and dynamic LVOT obstruction. This case highlights the pivotal role of preoperative optimization, intraoperative echocardiographic guidance, and tailored anesthetic techniques in ensuring favorable surgical outcomes. Advanced monitoring with TEE and the judicious use of beta-blockers, vasopressors, and volatile anesthetics contributed to the safe and successful management of this patient. This report adds to the limited literature on HOCM management in non-cardiac surgical settings and provides a framework for perioperative care in similar high-risk cases.

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Authors Contribution:
Sayed Makarram Ahmed Bukhari: Substantial contribution to design of study, acquisition of data, Initial manuscript drafting
Atif Nazir: vSubstantial contribution to design of study, acquisition of data, Critical Review and final version of the manuscript

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Letter to Editor **Open Access**

Revolutionizing healthcare; Overcoming Obstacles and Advancing the Electronic Health Record System in Pakistan

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Electronic health record (EHR) is defined as an electronic patient record that is housed in a system created especially to assist health care staff with the availability of full and accurate patient data, clinical history, investigations, alerts and reminders and connections to repositories of medical knowledge.[1] EHR systems have demonstrated improvements in the delivery of high-quality healthcare in a number of areas, such as clinical decision support tools that assist clinicians in making decisions about patient care, computerized physician order entry that boosts the effectiveness of order administration for patient care, and health information registries that allow patient data to be shared between various healthcare facilities leading to safe, timely and economical care.[2] Any EHR system's implementation in a low-middle-income-country is still understudied and difficult because of staff inexperience and a lack of resources. Health care system in Pakistan is comprised of primary, secondary and tertiary health centers.[3] The majority of people live in rural areas, so the primary or secondary health unit is their only option to visit for various illnesses considering the fact that tertiary health care facilities are only found in a few major cities.[3,4] Lack of electronic health records is a major domestic issue within the current healthcare system. As a result, patients are not registered at primary or even secondary health unit, proper referrals cannot be made, and when a patient visits a tertiary care facility, he is not able to present any documentation of his previous medical history, medications usage, surgical procedures, co-morbidities, etc. The development of databases pertaining to diseases or treatments is also impeded by the absence of registries. Progress on implementing EHR systems in Pakistani hospitals has been slow due to challenges such as budget constraints, lack of necessary infrastructure, resistance from staff members accustomed to manual documentation methods and concerns about data privacy regulation compliance.[5] To overcome these obstacles, a multifaceted approach must be taken involving collaboration among government agencies, private sector organizations, academic institutions and healthcare professionals. This includes investment in modern IT infrastructure with secure networking capabilities, training programs designed specifically for physicians, nurses, pharmacists, lab technicians etc., raising awareness campaigns highlighting the benefits of electronic record keeping, developing localized versions of popular international software platforms tailored according to our unique requirements and introducing policies aimed at protecting patient confidentiality rights.[3,5] Ultimately, legislators and stakeholders should ensure the strict application of rules and recommendations.

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Figures should be professionally drawn and photographed. Photographic prints 127 × 173 mm (5 × 7 inches). Photomicro-graphs should have internal scale markers. Symbols, arrows, or letters used in photomicro graphs should contrast with the background. If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

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Measurements of length, height, weight, and volume should be reported in metric units. Temperatures in degrees Celsius, Blood pressure in millimeters of mercury and all hematologic and clinical chemistry measurements in the metric system in terms of the International System of Units (SI).

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5	Short Communication / Commentary / Opinions/ Perspective	-	-	1200-2000	15-20	2-3
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