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EDITORIAL

# Sex- and Gender-specific Diabetes Guidelines: Not Just Gallantry

Suhas Gopal Erande*

Once bitten, twice shy—are we?

When scientific studies and randomized controlled trials (RCTs) did not include women, and observations of men were extrapolated to women, the thalidomide tragedy happened in 1953. The drug Contergan (Grunenthal Pharma), sold as an antiemetic, sedative, and sleeping pill, resulted in nearly 10,000 deformed births.[1]

Pharmacology had already noted fatal cardiac arrhythmia with cisapride (excess QT prolongation in women) and also zolpidem causing prolonged sedation and even vehicular accidents in women (excess store and slower release of zolpidem from adipose tissue).

The United States Food and Drug Administration (USFDA) suggested inclusion of women in RCTs as late as the 1990s, and now even animal experiments need to incorporate female studies.

Since sex and gender can result in different epidemiological, pathophysiological, clinical, investigative, and even drug response differences in diabetes, clinical practice guidelines (CPGs) are one pertinent way to approach diabetes in women specifically to reduce cardiovascular morbidity and mortality and improve quality of life (QoL). Categorical standard-of-care–driven systems can be expected to reduce complications.

Even with advanced therapy and the latest interventions, major adverse cardiovascular events (MACE) in diabetic women remains suboptimal compared to men. We need a change in stance![2]

## World Health Organization Definition of Sex and Gender

Sex refers to different biological and physiological characteristics of men and women (reproductive organs, hormones, and chromosomes).

Gender refers to socially constructed features (roles, norms, relationships of and between men and women, etc.). Sex and gender interact, forming a Gordian node, and it is difficult to separate them. For simplicity, we define sex not by karyotyping everyone but by simple clinical methods. We avoid interchangeable use of sex and gender.

## Is Diabetes in Women Different?

It is noteworthy that diabetes affects women across their lifespan, and it is very distinctive compared to men.[3] Readers can refer here for detailed deliberations.[4]

Not only that diabetes affects women differently, but women respond differently to the antidiabetic drugs as well. Metformin gives more gastrointestinal (GI) side effects in women but better glycemic control than in men. Similarly, newer sodium-glucose cotransporter 2 (SGLT2) inhibitors [more genitourinary (GU) mycotic infections] and glucagon-like peptide-1 (GLP1) agonists give more GI side effects in women than in men; however, these drugs are more beneficial for women (especially more weight reduction). Differences in body surface area, in fat mass and volume of drug distribution, and different estimated glomerular filtration rate (eGFR) may be important here. So women may need different dosing of drugs.

## Are Other Societies Adopting Gender Specific Guidelines?

This initiative has been taken by the cardiology societies and academicians for a very long period of time. The American College of Cardiology (ACC) focuses on heart failure (HF)/HF in women in the cardiology magazine (February 2, 2024), delving deep into differences in HF (women vs men), and mentions that women are more likely to be obese and have a higher risk of HF, especially heart failure with preserved ejection fraction (HFpEF), nonischemic variety, compared to men. It further mentions that diabetic women are at even higher risk of HF and have adverse left ventricle (LV) remodelling [increased LV thickness and left ventricular mass index (LVMI)]. Further, smoking is a bigger risk factor in women (double the risk compared to men). The ACC/American Heart Association (AHA) atherosclerotic cardiovascular disease (ASCVD) risk calculator and the eGFR calculators incorporate sex as a variable in their formula.

Once again, ACC distinguishes hypertension and women interface.[5] This pertains to different epidemiology, pathophysiology, differences in screening and diagnosis, and different responses to drug treatment. It has been observed that lifestyle modification is more helpful in hypertensive women.

It seems that cardiologists, though not officially publishing sex/gender-aligned CPGs, are at least intensively focusing on women from a cardiovascular disease (CVD) point of view.[6–9] Cardiology World has ascertained that the historic Framingham risk scale underestimates CV risk in women. Even the latest SCORE2 method underestimates CVD risk in middle-aged women.

National Lipid Association (NLA) has been discussing lipid guidelines for women for ~9 years.

## What Are Clinical Practice Guidelines?

Institute of Medicine (IOM) defines CPGs as statements that include recommendations intended to optimize patient care. They are informed by systematic review of evidence and assessment of harms and benefits of alternative care options. CPGs help collect the best evidence to help clinical decision making and to avoid discrepancy in practices while maintaining cost and quality. CPGs are systematically developed, but they may vary widely in quality. Increasing scientific literature and publications may confuse physicians while managing patients. Critically appraised and synthesized scientific evidence remains very important. Canadian academicians have taken a lead in sex- and gender-differentiated guidelines, though in bits and pieces. For example, the Canadian Diabetic Association (CDA) recommends aspirin for reducing nonfatal myocardial infarction (MI) in men but not in women (without a history of CVD). The same CDA notes that type 1 diabetes mellitus (T1DM) in adolescent girls be regularly screened for eating disorders and be offered more support for weight management and body image issues.

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## Is the Gender Bias Decreasing?

It is interesting to note the proportion of women included in various diabetes and cardiology RCTs over the last 75 years.[10] Framingham (2,873 W, 2,336 M), DCCT (615 W, total 1,441), EMPAREG (7,020 W, 28.5%), DECLARE-TIMI (17,610 W, 37.4%), LEADER (9,340 W, 35.7%), REWIND (9,901 W, 46.3%), SUSTAIN-6 (3,297 W, 36.8%), SOUL (9,650 W, 28.9%)

Though it has been illustriously noted that HF is a bigger problem in women (especially diabetic women), the inclusion of women in the latest HF trials has not been optimal. For example, PARADIGM-HF (22% women), DAPA-HF (23%), EMPEROR-Reduced (24%), GALACTIC-HF (21.3%), and VICTORIA (23.9%). Greater benefit of ARNI in women (PARAGON-HF trial) and the newer agent Omecamtiv Mecarbil needs more studies to help diabetic HF women. In fact, PARAGON-HF is one of the very few recent studies that included a sizeable number of women (51.6% in ARNI arm and 51.8% in valsartan arm, where ~43% of patients were diabetic).[11] Women with HFpEF reaped better rewards than men in this study. CPGs have large RCTs as their backbone, so more women in RCTs can better balance the CPGs from sex- and gender-point-of-view.

## Conclusion: Will Gender Specific Clinical Practice Guidelines Help?

Looking at various epidemiological, pathophysiological, clinical, and pharmacological differences in diabetic men and women, gender-aligned CPGs definitely will be a good help and navigator to improve patient outcomes and better QoL for diabetic women. The academicians and researchers would note that inclusion of women even in problem areas like diabetes and HF and dyslipidemia has not been adequate over the last 75 years. With newer diabetes drugs like GLP-1 analogs offering more benefits in women, or calcium channel blockers (CCBs) proving better for women (hypertension), or cardiac resynchronization therapy (CRT) more rewarding in women (HF) compared to implantable cardioverter-defibrillator (ICD), we have some better offerings for diabetic women. McKinsey Health Institute January 2024 Insight Report (World Economic Forum) urges closing the gap between women's lifespan (longer than men) and their longer healthspan (shorter than men) to improve lives and economies by 1 trillion United States Dollar (USD) by 2040. Organizations like the National Institutes of Health, USA, Canadian Institutes of Health Research, and European Commission in Europe are increasingly rewarding (financially) excellence in integrated sex- and gender-research in biomedical sciences.

Time to form sex- and gender-aligned diabetes and medical guidelines is now!

## Orcid

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ORIGINAL ARTICLE

# Gastric Emptying Patterns in Type 2 Diabetes Mellitus Patients with Symptoms of Gastroparesis and the Impact of Levosulpiride on These Patterns

Ravi Kant[1*], Kavya NP[2], Rashi Mittal[3], Vinay Tulsian[4], Vandana Dhingra[5]

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## Abstract

**Background:** Diabetes mellitus (DM) is a global health concern with rising prevalence, particularly in India, where undiagnosed cases are significant. A common yet often overlooked complication, diabetic gastroparesis impairs gastric motility and significantly reduces quality of life. Current treatments focus on symptom management, but the relationship between gastric motility patterns and therapeutic outcomes remains underexplored. This study evaluates the efficacy of levosulpiride in managing diabetic gastroparesis and its impact on gastric scintigraphy patterns.

**Methods:** This analytical observational study included 27 adult patients with type 2 DM (T2DM) and gastroparesis, conducted at a tertiary care hospital in North India from April 2021 to 2022. Patients received 25 mg levosulpiride thrice daily for 4 weeks. Gastroparesis symptoms were assessed using the Gastroparesis Cardinal Symptom Index (GCSI). Gastric motility was evaluated *via* gastric scintigraphy before and after treatment. Changes in GCSI scores and scintigraphy patterns were analyzed using paired *t*-tests and the Stuart–Maxwell test.

**Results:** Participants (mean age 56.41 ± 9.48 years) showed significant improvement in GCSI scores (11.48 ± 3.02 to 6.04 ± 2.08, $p < 0.001$). Gastric scintigraphy revealed significant changes, with 66.7% of patients demonstrating normalized motility patterns posttreatment ($\chi^2 = 14.000$, $p = 0.016$). While delayed gastric emptying persisted in some cases, levosulpiride alleviated key symptoms like nausea, vomiting, and early satiety.

**Conclusion:** Levosulpiride significantly alleviated symptoms of diabetic gastroparesis, as evidenced by reduced GCSI scores and improvements in gastric scintigraphy patterns. Despite minimal changes in delayed gastric emptying, the drug's effect on motility dysfunction highlights its therapeutic potential. This study underscores the importance of focusing on motility patterns in symptom management, suggesting levosulpiride as a promising option for targeted treatment of diabetic gastroparesis.


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## Introduction

Diabetes mellitus (DM) is a significant global health challenge, affecting over half a billion individuals worldwide. Projections indicate that the prevalence of DM, currently estimated at 10.5% among adults aged 20–79 years, may rise to 12.2% by 2045.[1,2] This increasing prevalence, driven by factors such as population growth, aging, urbanization, and lifestyle changes, has positioned DM as a leading cause of morbidity and mortality globally. In India alone, the number of individuals with diabetes is projected to increase from 77 million in 2019 to nearly 134 million by 2045, with over 50% of cases remaining undiagnosed.[3]

Diabetes-related neuropathy is a common complication that affects multiple organ systems, including the cardiovascular, nervous, gastrointestinal (GI), and genitourinary systems.[4] Chronic diabetes can disrupt GI tract functioning and motility, leading to GI autonomic neuropathy, a significant but often overlooked complication. This condition can affect any part of the GI tract, from the esophagus to the large intestine.[5]

Gastroparesis, a multifactorial disorder, is characterized by delayed gastric emptying in the absence of mechanical obstruction.[6] It affects up to 29% of patients with diabetes and is more prevalent in individuals with long-standing diabetes or poor glycemic control. Other causes of gastroparesis include idiopathic origins (36%), surgical complications like vagal nerve injury (13%), hypothyroidism, postviral syndromes, and pharmacological agents (e.g., narcotics, anticholinergics, GLP-1 analogs).[7] The pathophysiology of diabetic gastroparesis involves autonomic nervous system dysfunction, oxidative stress, and the loss of interstitial cells of Cajal, which disrupts coordinated gastric motility.[8–10]

Patients with diabetic gastroparesis may experience symptoms such as nausea, vomiting, retching, stomach fullness, early satiety, bloating, visible abdominal enlargement, and loss of appetite. These symptoms significantly impair quality of life and complicate diabetes management by causing erratic blood glucose levels.[11] The Gastroparesis Cardinal Symptom Index (GCSI) is a validated tool used to quantify these symptoms, grouping them into three categories and scoring each from 0 (absent) to 5 (very severe) based on patient perception.[12]

Managing diabetic gastroparesis remains challenging, focusing primarily on symptom relief, maintaining nutritional status, and improving gastric motility. Prokinetic agents like metoclopramide and domperidone are widely used; however, their long-term use is limited by adverse effects. Levosulpiride, a benzamide derivative with antidopaminergic and prokinetic properties, has shown promise in alleviating gastroparesis symptoms with a relatively favorable safety profile.[13]

Gastric emptying is commonly assessed using gastric emptying scintigraphy (GES), which tracks the passage of a radiolabeled meal through the stomach and quantifies delayed emptying if >10% of the meal remains after 4 hours. Delayed gastric emptying is observed in 32–47% of patients with type 2 diabetes. While techniques like ultrasonography and MRI are available, their use is primarily limited to research settings due to operator dependency.[14]

Despite its significant impact, there is limited research on the correlation between scintigraphic patterns and symptomatic improvement following treatment in diabetic gastroparesis. Understanding this relationship is essential for tailoring therapeutic interventions and optimizing outcomes in these patients.

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This study aims to evaluate the efficacy of levosulpiride in alleviating symptoms of diabetic gastroparesis and its impact on gastric motility patterns as observed through gastric scintigraphy. By examining changes in both clinical and imaging parameters, the study seeks to provide a comprehensive understanding of the role of levosulpiride in managing diabetic gastroparesis, contributing to evidence-based treatment approaches for this challenging condition.

## Methods

### Study Design

This analytical observational study was conducted at the All India Institute of Medical Sciences (AIIMS), Rishikesh, a tertiary public healthcare center, from April 2021 to 2022. The study aimed to evaluate the efficacy of levosulpiride in improving symptoms and altering gastric motility patterns in patients with diabetic gastroparesis.

### Study Population

The study included adult patients diagnosed with type 2 diabetes mellitus (T2DM) presenting with symptoms of gastroparesis. Eligible participants were recruited from both inpatient and outpatient services of the Department of Internal Medicine.

### Inclusion Criteria

- Adults aged ≥18 years.
- Diagnosed T2DM according to the American Diabetes Association (ADA) criteria.
- Presence of at least two gastroparesis symptoms, such as nausea, vomiting, retching, early satiety, bloating, or abdominal fullness.

### Exclusion Criteria

- Gastroparesis secondary to drug-induced causes (e.g., opioids, anticholinergics, GLP-1 analogues).
- History of gastric surgery or vagotomy.
- Thyroid disorders or neurological conditions such as Parkinsonism.
- Chronic smoking (>30 pack-years) or alcohol consumption (>5 years).
- Pregnant or lactating individuals.
- Recent viral infections associated with gastroparesis.

### Sample Size and Recruitment

This time-bound study enrolled 27 participants over 1 year. Eligible patients were selected consecutively from the study population after screening against inclusion and exclusion criteria.

### Study Procedure

*Baseline Evaluation*

Participants underwent a detailed clinical assessment, including a medical history, physical examination, and laboratory investigations. The severity of gastroparesis symptoms was measured using the GCSI, a validated tool for quantifying symptom burden. Glycemic parameters (fasting blood sugar, postprandial blood sugar, and HbA1c) and anthropometric data (BMI) were also recorded.

*Gastric Emptying Scintigraphy*

All participants underwent baseline gastric scintigraphy using a standardized low-fat meal labeled with technetium-99m sulfur colloid. The procedure adhered to standard protocols:

- Preparation: Participants fasted for at least 6 hours before the test, with medications permitted only with minimal water. Smoking was prohibited during the study.
- Procedure:
  - The labeled meal was ingested within 10 minutes.
  - Static and dynamic images were captured at 0, 30, 60, 120, 180, and 240 minutes using a dual-headed gamma camera.
  - Regions of interest (ROI) were manually defined, and radioactivity counts were analyzed.
  - Gastric emptying was quantified, with >10% retention at 4 hours defined as delayed gastric emptying.

### Intervention

Participants were prescribed levosulpiride (25 mg three times daily) for 4 weeks. Compliance was ensured through pill counts and weekly telephonic follow-ups. In addition to medication, patients received:

- Dietary counseling: Participants were provided a personalized low-fat, low-fiber diet plan developed by a dietitian, tailored to their cultural and food preferences.
- Glycemic optimization: Blood glucose levels were managed through individualized regimens of insulin or oral hypoglycemic agents.

### Follow-up

At the end of the 4-week treatment period, participants were reassessed for symptom severity using the GCSI and underwent repeat gastric scintigraphy. Changes in gastric emptying times and scintigraphy patterns were documented.

### Outcome Measures

- Change in GCSI scores before and after treatment.
- Analysis of specific gastric scintigraphy patterns (e.g., abnormal distribution, reduced fundic compliance) before and after treatment.

### Statistical Analysis

Data analysis was performed using SPSS version 23. Statistical methods included:

*Descriptive Statistics*

Mean, median, and standard deviation for continuous variables; frequencies and percentages for categorical variables.

*Comparative Analysis*

- Paired *t*-tests or Wilcoxon signed-rank tests for pre- and posttreatment comparisons of continuous data.
- Chi-square or Fisher's exact tests for categorical data.

*Significance Threshold*

A $p$-value $< 0.05$ was considered statistically significant.

### Ethical Considerations

This study was conducted as a part of a thesis on the topic "Efficacy of Levosulpiride in Type 2 Diabetes Mellitus with Gastric Autonomic Neuropathy Based on Gastric Scintigraphy Patterns: An Analytical Observational Study," which was approved by the Institutional Ethics Committee of AIIMS Rishikesh, an institute of national importance (IEC no. AIIMS/IEC/21/368; approval date: August 13, 2021). Written informed consent was obtained from all participants. Data confidentiality was strictly maintained, and no identifiable patient information was disclosed during publication or presentations.

## Results

A total of 27 patients with T2DM and symptoms of gastroparesis were recruited over a period of 1 year. About 13 (48.1%) of the 27 patients were male, while 14 (51.9%) were female. The mean age (years) was 56.41 ± 9.48. The mean duration of diabetes (years) was 11.78 ± 6.20. Other baseline demographics and clinical details are summarized in Table 1. The baseline gastric scintigraphy patterns have been depicted in Figure 1.

### The Changes Observed in Gastric Scintigraphy Patterns with Treatment

Following treatment, notable changes were observed in gastric scintigraphy patterns. A total of seven patients (25.9%) transitioned from the abnormal distribution of gastric contents category to the no specific pattern category. Similarly, three patients (11.1%) moved from reduced fundic compliance to no specific pattern, and two patients (7.4%) shifted from antral dysmotility to no specific pattern. Additionally, one patient (3.7%) each transitioned from gastric hurrying and gastroesophageal reflux to the no specific pattern category. These changes in gastric scintigraphy patterns were statistically significant, as confirmed by the Stuart–Maxwell test ($\chi^2 = 14.000$, $p = 0.016$) (Table 2).

### The Changes Observed in GCSI Score with Treatment

The average GCSI score significantly decreased from 11.48 ± 3.02 before treatment to 6.04 ± 2.08 after treatment. This reduction was statistically significant, as shown by the paired *t*-test ($t = 14.2$, $p < 0.001$) (Table 3).

**Table 1:** Baseline characteristics of patients

| *Characteristic* | *Mean* |
|---|---|
| Age (years) | 56.41 ± 9.48 |
| BMI (kg/m$^2$) | 27.13 ± 2.28 |
| Duration of diabetes (years) | 11.78 ± 6.20 |
| HbA1c (%) | 9.69 ± 1.76 |
| Fasting blood sugar (FBS, mg/dL) | 195.30 ± 29.32 |
| Postprandial blood sugar (PPBS, mg/dL) | 329.37 ± 54.55 |
| GCSI total score (pretreatment) | 11.48 ± 3.02 |
| Gastric scintigraphy patterns | |
| Abnormal distribution | 12 (44.4%) |
| Reduced fundic compliance | 6 (22.2%) |
| Antral dysmotility | 2 (7.4%) |
| Gastric hurrying | 2 (7.4%) |
| Gastroesophageal reflux | 1 (3.7%) |
| No specific pattern | 4 (14.8%) |
| Gastric emptying at 4 hours (%) | 88.63 ± 11.03 |

## Discussion

Diabetic gastroparesis is a common complication in individuals with long-standing DM and presents a barrier to glycemic control. In its severe stages, it can lead to complications such as fluctuations in blood glucose levels, predisposing patients to hypoglycemia and diabetic ketoacidosis. Other complications include malnutrition, electrolyte imbalances, esophagitis, and bezoar formation, all of which contribute to a lower quality of life.[15] Moreover, survival rates are significantly poorer in patients with diabetic gastroparesis compared to those with idiopathic gastroparesis.[16] Antidopaminergic drugs like levosulpiride may offer relief in diabetic gastroparesis by counteracting the inhibitory effects of hyperglycemia on gastric motility, as dopamine receptor stimulation is implicated in this dysfunction. In a study by Mansi et al., levosulpiride was

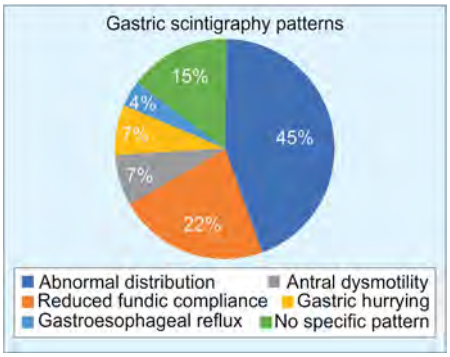


**Fig. 1:** Baseline scintigraphy pattern observed in the 27 patients

**Table 2:** Gastric scintigraphy patterns (pre- and posttreatment)

| *Scintigraphy pattern* | *Pretreatment n (%)* | *Posttreatment n (%)* | *Change (%)* |
|---|---|---|---|
| Abnormal gastric content distribution | 12 (44.4) | 5 (18.5) | –58.3 |
| Reduced fundic compliance | 6 (22.2) | 3 (11.1) | –50 |
| Antral dysmotility | 2 (7.4) | 0 (0) | –100 |
| Gastric hurrying | 2 (7.4) | 0 (0) | –100 |
| Gastroesophageal reflux | 1 (3.7) | 0 (0) | –100 |
| No specific pattern | 4 (14.8) | 19 (70.4) | +375 |

**Table 3:** GCSI symptom scores (pre- and posttreatment)

| *Symptom* | *Pretreatment mean (SD)* | *Posttreatment mean (SD)* | *p-value* |
|---|---|---|---|
| Nausea | 1.67 (0.88) | 1.00 (0.55) | <0.001 |
| Retching | 0.78 (0.75) | 0.37 (0.56) | 0.001 |
| Vomiting | 0.19 (0.40) | 0.00 (0.00) | 0.036 |
| Stomach fullness | 1.85 (0.95) | 0.96 (0.59) | <0.001 |
| Early satiety | 0.85 (0.60) | 0.56 (0.58) | 0.006 |
| Fullness after eating | 1.81 (0.68) | 1.07 (0.62) | <0.001 |
| Loss of appetite | 0.44 (0.51) | 0.41 (0.57) | 0.766 |
| Bloating | 3.04 (0.85) | 1.44 (0.64) | <0.001 |
| Belly visibly large | 0.85 (0.77) | 0.22 (0.42) | <0.001 |

shown to improve upper GI symptoms and reduce gastric emptying time in diabetic gastroparesis, though gastric emptying was assessed using ultrasonography.[17]

Patterns observed in gastric scintigraphy in patients with functional dyspepsia, such as reduced fundic compliance, abnormal gastric content distribution, gastric hurrying, antral dysmotility, and gastroesophageal reflux, have been well documented.[18] Our study aimed to explore changes in the gastric scintigraphy patterns in diabetic gastroparesis patients before and after treatment with a prokinetic agent, levosulpiride.

This study is, to the best of our knowledge, the first to assess the effects of levosulpiride on gastric scintigraphy patterns in diabetic gastroparesis. A total of 27 participants were included, comprising 13 (48.1%) males and 14 (51.9%) females. The study by Jung et al. on diabetic gastroparesis epidemiology, conducted in Olmsted County, Minnesota, found that women had a significantly higher age-adjusted prevalence of gastroparesis compared to men.[19] However, in our study, there was no significant gender difference. Studies by Stanghellini et al. have also shown that female sex is associated with delayed gastric emptying, regardless of the presence of underlying organic diseases.[20] The mean age of our participants was 56.41 ± 9.48 years, which aligns with findings by Ye et al., who observed that patients with diabetic gastroparesis tend to be older at the time of diagnosis and more likely to be obese or overweight.[21]

Levosulpiride demonstrated a statistically significant improvement in the total GCSI score and in most individual symptoms, except for loss of appetite. Levosulpiride, a substituted benzamide, selectively acts on dopamine D2 receptors and is used in the treatment of dyspepsia and as an atypical antipsychotic and antidepressant. It works by blocking D2 receptors in the presynaptic dopaminergic pathways, improving gastric motility.[17,22] Although no significant improvement in delayed gastric emptying was observed in our study, levosulpiride still led to symptomatic improvement, a result consistent with findings from Mearin et al. The study indicated that various prokinetic agents, including levosulpiride, do not show a clear correlation between symptomatic relief and gastric emptying times. However, levosulpiride, in particular, has been shown to effectively alleviate symptoms like nausea, vomiting, and early satiety, likely due to its action on the chemoreceptor trigger zone, a benefit not shared by cisapride.[23]

Gastric motility relies on coordinated contractions that move food from the fundus to the antrum. Dysfunction in this process, assessable *via* gastric scintigraphy, can present as abnormal gastric content distribution, which was the predominant pattern in our study (44.4%). Although most patients had symptomatic improvement, 18.5% of patients retained this pattern posttreatment. Abnormal distribution often manifested as reduced fundic uptake and early pylorus visibility, reflecting impaired motor function of the distal stomach. Prior studies, such as the study by Urbain et al., highlighted similar patterns, emphasizing the role of antral dysfunction in nonexpulsive contractions and the potential for therapies targeting antral motor activity.[24]

Reduced fundic compliance was the second most common pattern (22.2%), with 50% resolution posttreatment. This aligns with existing literature linking decreased fundic compliance to early satiety and weight loss, observed in approximately 40% of functional dyspepsia cases.[25] Antral dysmotility and gastric hurrying were less frequent (7.4%), with the latter persisting in half of the affected patients. Dysregulated antral activity, crucial for food breakdown and transit, has been associated with postprandial nausea.[26] Gastroesophageal reflux was rare (3.7%) but resolved with levosulpiride therapy. Additionally, 14.8% of patients had no specific motility pattern but showed symptomatic improvement.

At the end of 4 weeks, 66.7% of patients demonstrated no abnormal scintigraphy patterns, with significant improvement in GCSI scores (Stuart–Maxwell test: $\chi^2 = 14.000$, $p = 0.016$). While levosulpiride's prokinetic effects did not directly improve delayed gastric emptying, its influence on abnormal patterns suggests broader therapeutic potential. Importantly, symptomatic improvement in gastroparesis often occurs independently of changes in gastric emptying, emphasizing the value of pattern recognition in scintigraphy.

The results of this study provide new insights into the complex nature of diabetic gastroparesis, particularly in relation to gastric scintigraphy patterns and the therapeutic effects of levosulpiride. Despite the absence of significant improvement in gastric emptying times, the prokinetic effects of levosulpiride led to significant symptomatic relief, particularly in symptoms like nausea, early satiety, and vomiting. These results suggest that levosulpiride may help address specific motility dysfunctions that underlie the symptoms of diabetic gastroparesis, even in the absence of noticeable changes in gastric emptying. This underscores the importance of focusing not only on gastric emptying times but also on patterns of motility dysfunctions when assessing and treating diabetic gastroparesis. Our study contributes to a growing body of evidence indicating that symptomatic relief in diabetic gastroparesis can be achieved through targeted therapies that correct these abnormal patterns, even if they do not directly improve gastric emptying time. Future research should focus on larger sample sizes and long-term follow-up studies to explore the role of levosulpiride in managing motility patterns and to evaluate its potential as a cornerstone of treatment for diabetic gastroparesis.

### Limitations

- Small sample size: The study included only 27 participants, which limits the generalizability of the findings. Larger studies are needed to validate the results and ensure their applicability to a broader population.
- Short duration of follow-up: The 4-week follow-up period may not have been sufficient to observe long-term effects of levosulpiride on symptom relief and gastric motility patterns.
- Single-center design: Conducted at a single tertiary care center, the study may not capture variations in patient characteristics and healthcare practices across different settings.
- Limited assessment of long-term safety: The study did not evaluate the long-term safety profile of levosulpiride, particularly concerning adverse effects associated with prolonged use.

## Conclusion

Diabetic gastroparesis is a debilitating complication of long-standing diabetes, significantly impairing quality of life and complicating glycemic control. This study demonstrated that levosulpiride, a prokinetic agent, effectively alleviated gastroparesis symptoms such as nausea, vomiting, and early satiety, as reflected in significantly reduced GCSI scores. Despite limited changes in delayed gastric emptying, improvements in gastric scintigraphy patterns, including reductions in abnormal content distribution and fundic compliance issues, highlight levosulpiride's potential in addressing underlying motility dysfunctions.

By focusing on symptom relief and motility abnormalities rather than solely on gastric emptying times, this study offers a nuanced approach to managing diabetic gastroparesis. These findings emphasize the importance of pattern recognition in gastric scintigraphy to optimize therapeutic strategies. Future research with larger sample sizes and longer

follow-up is needed to validate these results and further explore the role of levosulpiride in managing diabetic gastroparesis. This study contributes to the growing body of evidence supporting targeted treatment approaches for this complex condition.

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ORIGINAL ARTICLE

# Impact of a Focused Thesis Writing Workshop on Knowledge and Confidence of Medical Postgraduate Students: A Cross-sectional Study

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## Abstract

**Background:** The National Medical Commission (NMC) of India requires medical postgraduate students to conduct research in the form of a thesis or dissertation. However, students often face challenges throughout the process, including topic selection, protocol approval, data collection, and thesis writing. This study aimed to assess the effectiveness of a 1-day focused thesis writing workshop in improving the knowledge and confidence of medical postgraduate students.

**Methods:** A cross-sectional mixed-methods study was conducted involving 68 postgraduate students from various medical disciplines who participated in a thesis writing workshop. Participants were administered pre- and post-test questionnaires to assess their knowledge of key thesis writing components, including literature review, results, discussion, and conclusion. The workshop included interactive sessions on each of these topics. Descriptive and inferential statistics were used to analyze the results, and qualitative feedback was gathered to assess participant satisfaction and perceived improvements in confidence.

**Results:** The pre- and post-test scores showed a significant improvement in knowledge, particularly in the areas of literature review, results, and discussion ($p < 0.05$). However, the improvement in knowledge regarding thesis conclusions was not statistically significant. Feedback from participants indicated high satisfaction with the workshop, with 85% reporting increased confidence in their thesis writing skills. The majority of students (78%) found the workshop relevant and helpful in enhancing their understanding of thesis writing.

**Conclusion:** A focused, 1-day workshop significantly improved the knowledge and confidence of medical postgraduate students in thesis writing. This suggests that such workshops can be an effective intervention to support postgraduate students in completing their research. The study advocates for the integration of similar workshops into postgraduate curricula. Further research with larger, multicenter studies is needed to evaluate the long-term impact and feasibility of institutionalizing such programs.


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## Introduction

The National Medical Commission (NMC) of India mandates conducting research work in the form of a thesis or dissertation as an essential part of a medical postgraduation degree course.[1] However, medical students doing postgraduation encounter lot of challenges in various stages of their thesis work, starting from choosing a research topic, finalizing their protocol, getting ethics approval, conducting the research work, collecting data appropriately, constructing the master chart, analysis and presentation of results, as well as writing the discussion and conclusion.[2,3] Thesis phobia in medical postgraduate students is mainly due to lack of knowledge about conducting research properly as well as in writing the thesis.[4]

Previous studies have shown that multiple factors can affect thesis quality, including student-related factors such as knowledge, sincerity, commitment, socioeconomic conditions, communication skills, and time management; institutional conditions, such as cooperation, guidance, budget, infrastructure, and facilities; and supervisor-related factors such as knowledge, interest, and approachability.[5,6] Lack of adequate time due to a vast curriculum of postgraduate subjects (59.5%), lack of a structured research curriculum (25%), and inadequate facilities (25.8%) were stated as major obstacles to pursuing research by postgraduate students in a study from Maharashtra, India.[7]

Many of the medical colleges currently run an orientation program for the recently joined postgraduate students to orient them about how to write their thesis protocol. However, in the majority of medical colleges, no systematic training is provided to the postgraduate student thereafter, and the student is solely dependent upon his or her thesis guide's experience, expertise, approachability, and availability of adequate time to help them in this endeavor. As per Ghadirian et al., thesis quality is highly dependent on the supervision received by the postgraduate students.[6,8] A study from South Africa, done among 34 postgraduate students who engaged in research, revealed that communication breakdown, poor feedback, nonavailability of some supervisors, and lack of ethical consideration were some of the major factors that contributed to the negative experiences of the students who participated in research.[9] In a study by Changiz et al., it was observed that the majority of tutors did not devote sufficient time for reviewing and correcting the thesis. Over 40% of the faculty members considered financial problems, administrative difficulties for proposal approval, and lack of technical support, such as statistical consultations, the main obstacles in the way of the research process, while the majority believed that students' lack of time, delay, and contradictory decisions by different levels of supervising committees were the barriers to research.[10]

Medical students need guidance and hand-holding at various levels to make thesis writing easier for them and to ensure a better and meaningful contribution to the medical scientific literature.[11] Some of the steps that can be taken for easing the stress due to thesis include regular organization of thesis writing workshops for medical students, training of young or new faculty in various aspects of thesis writing, giving more weight to research methodology during undergraduation, providing grants for carrying out research projects, and providing free access to various research articles. Motivating the students and showing appreciation by giving awards for the few best theses in the institution, with preference given to challenging or new

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research topics, has also been shown to boost their aptitude for research.[12]

However, there is a paucity of studies that evaluate the impact and utility of thesis writing workshops conducted for medical postgraduate students. In this study, we attempted to determine the effect of a 1-day training workshop on thesis writing for medical postgraduate students and to assess improvement in their knowledge and confidence about various aspects of thesis writing, following this focused thesis writing workshop.

## Methodology

This cross-sectional, mixed-methods study was planned to assess the improvement in knowledge and confidence of postgraduate students following a focused 1-day thesis writing workshop for them. The study was initiated after obtaining approval from the Institutional Ethics Committee, and the participants were enrolled after obtaining informed consent from them. All the medical students pursuing postgraduation in any specialty, who had already submitted their thesis protocol, obtained clearance from the Institutional Ethics Committee, and started their thesis work were invited to participate in this study. Postgraduate trainees who had already submitted their final thesis work to the university were excluded from this study. All the heads of the departments, as well as the postgraduate education coordinator from each of the clinical and paraclinical departments of our institute were approached, and a request was made to encourage participation of as many postgraduate students as possible for this workshop. The program schedule and flyers were disseminated among all postgraduate students through the Dean's office. Participation of postgraduates in this workshop was voluntary. The interested postgraduate residents had to fill a registration-cum-pretest form, in the form of a Google form that was circulated among the residents of all the departments. It included some questions pertaining to the demographic details of the study subjects along with 15 questions testing their thesis-writing-related knowledge, encompassing various aspects of review of literature, results, discussion, and conclusion. The first 4 of the 15 questions were pertained to the knowledge about review of literature, question numbers 5–9 assessed the knowledge about results, 10 and 11 about the conclusion, and 12–15 about the discussion. The posttest consisted of the same set of knowledge-based questions along with additional questions for capturing the feedback of the postgraduate residents about this focused workshop. It included questions that required the participants to rate their satisfaction with the thesis writing workshop on a 5-point Likert scale (1 = highly unsatisfied to 5 = highly satisfied) and the change in the confidence of study participants after attending the workshop as compared to before attending the workshop (1 = decreased a lot to 5 = increased a lot), and two open-ended questions. Both the questionnaires were reviewed by two expert faculty, and a pilot run was done on two postgraduate students who were not included in the study before actually administering the questionnaire to everyone.

The workshop module was designed by a team of faculty, with one of the team members already trained in the advanced course in Medical Education. Two external experts, who were faculty of medical education units of two reputed government medical colleges of Delhi, were also involved in the planning and execution of this workshop. These external experts supervised the conduct of this workshop and provided additional valuable inputs as well. The sessions for this workshop covered details about writing a review of literature, presentation of results, including the use of tables and figures, and writing a discussion and conclusion.

Data were analyzed using SPSS 20.0. Descriptive analysis was done, and the results were presented in the form of medians with interquartile ranges and proportions. The Wilcoxon signed-rank test was used to compare the quantitative data. The *p*-values < 0.05 were considered significant. The qualitative data were recorded through the use of some open-ended questions, administered along with the posttest, and analyzed using rapid content analysis. Grounded theory was used to generate relevant themes. The themes with some select quotations have been presented.

## Results

The pretest-cum-registration form for the thesis writing workshop was filled by 105 participants. The workshop was attended by 80 participants, of whom 68 participants filled the posttest form and were included in the final analysis. Out of the 68 study participants, 43 (63.2%) were females and 25 (36.8%) were males. The maximum number of participants was from the pediatrics department (27.9%), followed by anesthesiology department (16.2%). The department-wise breakup of study participants is shown in Figure 1.

The mean pretest score of the 68 study participants was 7.68 ± 3.35, with a median and IQR of 7 and 5, respectively, while the mean post-test score was 10.49 ± 4.15, with a median and IQR of 13 and 7, respectively. Wilcoxon signed-rank test revealed a significant improvement in the posttest scores as compared to the pretest, with a *p*-value of <0.05. The observations found on the component-wise analysis of the pretest and post-test questions before and after conducting the thesis writing workshop are shown in Table 1.

Significant improvement was observed in all aspects of thesis writing except the conclusion. Figure 2 also highlights the changes in mean knowledge score (percentage) in the domains of review of literature, results, discussion, and conclusion before and after the thesis writing workshop. It shows that the pretest score about knowledge related to writing a conclusion was good (74.3 ± 35.1%), and although the post-test score showed some improvement (80.8 ±

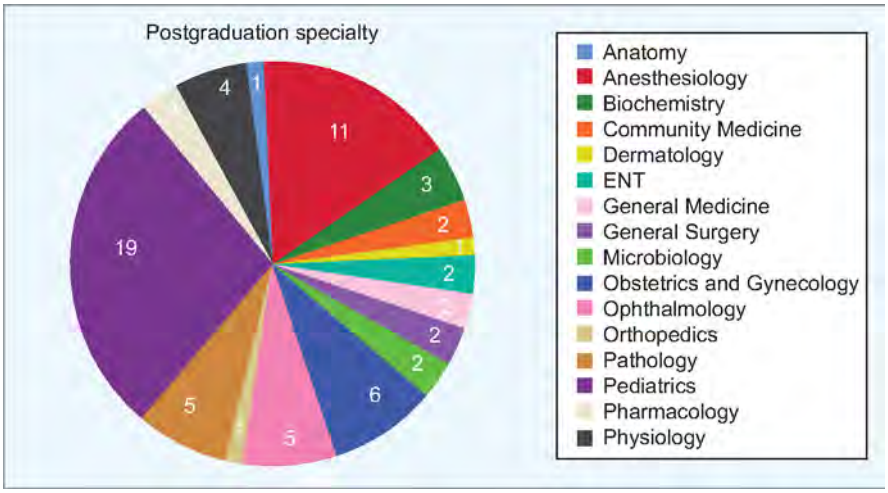


**Fig. 1:** Distribution of study participants based on specialty

32.4%), this difference was not found to be statistically significant.

The feedback obtained from the students suggested that the majority of the study participants felt that the thesis writing workshop was relevant (78% participants), and helped in increasing their knowledge (68% participants). About 85% of students rated their confidence about the thesis writing workshop as 4 or 5 on a Likert scale of 1–5, while 90% of students rated their overall satisfaction with the thesis writing workshop as 4 or 5. Qualitative analysis of two of the open-ended questions asked in the post-test, that is, "What did you like most about the workshop?" and "Suggestions on how to improve the workshop," was done. Two of the investigators independently analyzed the feedback received from each of the participants and identified the various themes, as shown in Table 2. Some of the noteworthy responses received from the participants were: "Thesis writing is no longer a headache!" and "The workshop was very insightful and well organized!"

## Discussion

The present study aimed to determine the effect of a 1-day focused training workshop on thesis writing for medical postgraduates and to assess their improvement in knowledge and confidence following the same. We also obtained feedback from the study participants to improve future workshops. This focused thesis writing workshop for postgraduate residents led to significant improvement in the overall knowledge about thesis writing. Further analysis revealed significant improvement in the knowledge about writing a review of the literature, results, and discussion. However, statistically significant improvement was not seen in the knowledge score related to the conclusion. This was possibly because the pretest score percentage for knowledge related to conclusion was already quite high, so even though an improvement in knowledge about conclusion was seen in the posttest, it was not of statistical significance. The result of our study is similar to the significant improvement observed by Singh et al., while comparing the pretest (5.86 ± 1.75) and posttest scores (11.82 ± 2.47), following a workshop on biomedical research for 1st-year medical undergraduate students.[13]

Lack of a structured training program fails to ensure the production of high-quality research work from the medical postgraduate students. A cross-sectional study by Ibrahim et al. revealed that knowledge about research was generally low among medical students and interns. This further underscores the need for structured training of medical undergraduate as well as postgraduate students in research methodology and research paper or thesis writing. In their study, participants who received research training had significantly higher knowledge scores compared to others ($p < 0.001$).[14]

The impact of proper, focused training sessions about thesis writing for postgraduate residents goes beyond medical students and promotes better medical research, and can translate into improvement in evidence-based patient care and self-capacity and confidence building for the residents themselves. While there are some structured faculty development programs mandated by NMC, there is a dearth of any such structured intervention for training of postgraduate students in various aspects of thesis writing. Even though obtaining passing marks in the basic course in biomedical research has been recently made compulsory for the medical postgraduates by the NMC, this course is in the form of a noninteractive, online, distance-learning program that covers broad concepts of medical research but is not focused enough to help medical postgraduates in conducting and writing their postgraduation thesis confidently. There has been a felt need among the medical postgraduates for guidance about various aspects related to their postgraduate thesis.

A prospective study from South India provided intensive support to 27 postgraduate students throughout their six-semester course, which included orientation for guides, research methodology workshop for students, and presubmission external review in the first semester, mid-2nd-year review in the fourth semester, and presubmission (final dissertation) and selection for award and workshop for paper submission in the fifth semester. Out of the 27 dissertations included in that study, 19 papers (70.4%) were published within a span of 1 year, and 8 were in various stages of publication. They concluded that with sustained guidance and support from the institution, students perform very well, leading to improved publication status.[11]

The feedback received from the study participants revealed that most of the students

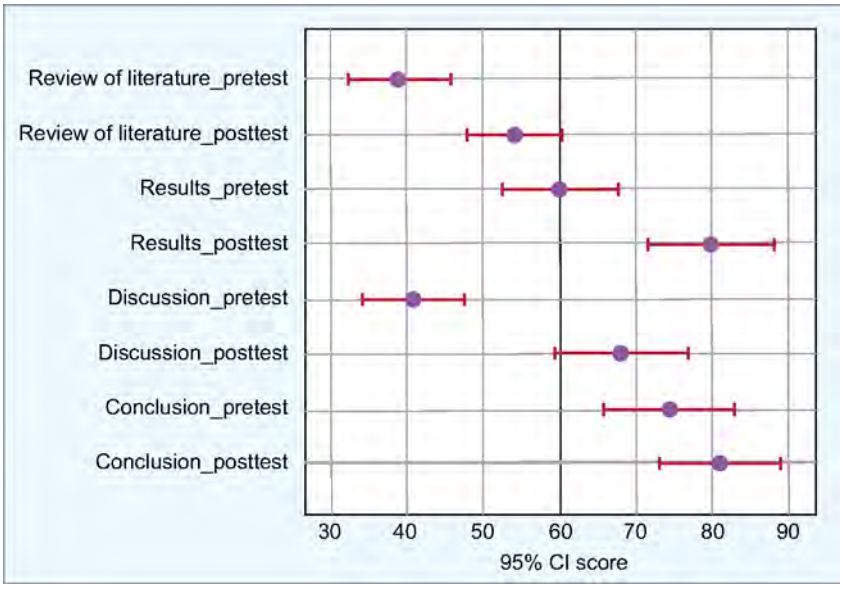


**Fig. 2:** Improvement in mean knowledge score (percentage) in the domains of review of literature, results, discussion, and conclusion before and after the thesis writing workshop

**Table 1:** Pre- and post-test scores reflecting the knowledge about various aspects of thesis writing

| | *Pretest score Median% (IQR)* | *Posttest score Median% (IQR)* | *p-value* |
|---|---|---|---|
| Review of literature | 37.5 (25–75) | 100 (60–100) | 0.000 |
| Results | 60 (40–80) | 100 (60–100) | 0.000 |
| Discussion | 25 (25–68.8) | 75 (25–100) | 0.000 |
| Conclusion | 100 (50–100) | 100 (50–100) | 0.214 |

**Table 2:** Qualitative analysis of feedback

| *What did you like most about the workshop?* | *Number of responses* | *Percentage (%)* | *Suggestions on how to improve the workshop* | *Number of responses* | *Percentage (%)* |
|---|---|---|---|---|---|
| Detailed information provided | 13 | 19.1 | No improvement required | 46 | 67.6 |
| Everything was perfect | 11 | 16.2 | To include more hands-on exercises | 12 | 17.6 |
| All the concepts were well explained | 10 | 14.7 | To be conducted more frequently | 8 | 11.8 |
| Helped to solve doubts | 7 | 10.3 | To be conducted over more time | 7 | 10.3 |
| Do's and don'ts of thesis writing made clear | 5 | 7.4 | To be conducted during the 1st year of postgraduation | 5 | 7.4 |
| Easy to understand | 5 | 7.4 | To be made more interactive | 3 | 4.4 |
| Good method of teaching | 4 | 5.9 | To include time management strategies for completion of thesis | 2 | 2.9 |
| Crisp and focused | 3 | 4.4 | To be conducted in multiple languages | 2 | 2.9 |
| Good faculty | 3 | 4.4 | To be conducted in hybrid mode (offline and online) | 1 | 1.5 |

felt that the workshop was very relevant for them and they perceived a definite improvement in their confidence and knowledge about various aspects of thesis writing. About 90% of the study population felt that focused training about thesis writing should be a part of the medical postgraduate training course. These results are in line with those seen by Singh et al., who found that 49.48% of students strongly agreed that contents discussed in the workshop were adequate, 61.85% agreed about better understanding of the topics of the workshop, 60.80% agreed that their queries and doubts were cleared, 53.6% agreed that the workshop motivates them to do research, and 44.3% agreed that they will attend the similar workshops in future.[13] In a study by Giri et al., it was found that majority of the enrolled (91.4%) students believed that patient outcome improves with continued medical research and 70.7% are willing to participate in workshop for research methodology.[7]

One of the major strengths of our study is that we have been able to demonstrate the utility of a single-day focused thesis writing workshop, which can be easily incorporated in the postgraduate teaching program of any institute and can be of definite benefit to the students. The involvement of postgraduate students from a wide variety of clinical and paraclinical specialties further reiterates the importance of holding such training sessions for medical postgraduate students across different disciplines. The mixed-method design added value to the study as there was an emergence of valuable feedback and suggestions from the postgraduate students, which might have gone unnoticed in a purely quantitative study. However, we acknowledge that the results may not be generalizable due to a moderate number of participants enrolled and it being a single-center study. Nevertheless, the results are still very important and need further validation in larger, multicentric studies. A 1-day workshop might be insufficient to expect a major change in thesis writing, but the confidence improvement definitely is an indicator that the workshop was an effective sensitizer and motivator, and these residents need to be followed up in the long term to assess the impact of this workshop on their teaching and assessment practices. Imparting more structured training about the various aspects of conducting and drafting a medical postgraduation thesis is definitely a need of the hour, and the medical regulatory bodies should consider making it a mandatory part of the medical postgraduation curriculum.

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ORIGINAL ARTICLE

# Prevalence of Allergic Bronchopulmonary Aspergillosis in Severe Asthma Patients Presenting to a Tertiary Care Hospital in North West India

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## Abstract

**Background/introduction:** The Indian subcontinent faces a substantial healthcare challenge with allergic bronchopulmonary aspergillosis (ABPA). While numerous investigations have explored ABPA's occurrence in the general asthmatic population, there remains a significant knowledge gap regarding its specific prevalence among individuals with severe asthma. Current Indian research demonstrates considerable variation in reported ABPA prevalence rates among severe asthmatics, highlighting the need for more comprehensive investigation.

**Objective:** This research initiative aimed to determine the precise prevalence of ABPA among severe asthma patients seeking treatment at a tertiary healthcare institution in northwestern India, with the goal of enhancing our understanding of this complex condition's burden in this specific patient population.

**Methodology:** We conducted a comprehensive cross-sectional investigation spanning August 2022 through July 2023. The study encompassed 247 patients diagnosed with severe asthma. Each participant underwent thorough clinical evaluation and provided blood samples for comprehensive analysis, including absolute eosinophil count measurement, total IgE quantification, and specific testing for *Aspergillus fumigatus*-related IgE antibodies. When clinically indicated, additional diagnostic procedures included *Aspergillus*-specific IgG testing and detailed chest imaging through X-ray or high-resolution computed tomography (HRCT).

**Results:** Our investigation revealed that 63.2% (156 out of 247) of severe asthma patients met the diagnostic criteria for ABPA. The affected population showed a mean age of 41.6 years, with a relatively balanced gender distribution (80 females, 76 males). Among those diagnosed with ABPA, we observed a notably higher prevalence of ABPA-B (92.3%, 144 patients) compared to ABPA-S (7.7%, 12 patients).

**Conclusion:** This research represents one of the most extensive investigations to date documenting such a high ABPA prevalence (63.2%) among severe asthma patients in northern India. These findings underscore the critical need for expanded research initiatives to investigate the underlying factors contributing to such elevated ABPA rates in this geographical region, ultimately aiming to develop and implement effective preventive strategies at the community level.


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## Introduction

The global healthcare landscape has witnessed a significant transformation in respiratory disease patterns, with bronchial asthma emerging as a critical concern characterized by chronic airway inflammation and variable airflow limitation.[1] This respiratory condition demonstrates increasing prevalence across all demographic groups worldwide, with recent decades showing a marked upward trend that healthcare experts project will continue to escalate.[1,2] The evolving nature of this condition presents mounting challenges for healthcare systems globally, emphasizing the urgent need for enhanced understanding of its complexities and the development of more effective management strategies.

Environmental factors play a crucial role in asthma progression, with fungal spore exposure emerging as a significant contributor to both symptom deterioration and declining pulmonary function. The *Aspergillus* species, in particular, represents a notable environmental trigger.[3] The interaction between fungal elements and severe asthma manifests through multiple pathways: direct triggering of asthma exacerbations through spore inhalation, development of fungal sensitization characterized by immediate cutaneous hyperreactivity or elevated specific IgE antibodies, and in severe cases, the emergence of allergic bronchopulmonary mycosis leading to permanent bronchopulmonary damage.[3]

Among fungal pathogens, *Aspergillus fumigatus* demonstrates particular clinical significance in asthma patients. This organism can affect the respiratory system through various mechanisms, including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma formation, and invasive aspergillosis.[3,4] ABPA represents a complex hypersensitivity response to *A. fumigatus*, characterized by a distinctive combination of clinical features: asthma exacerbations, recurrent pulmonary infiltrates, elevated eosinophil counts, increased total serum IgE levels, and elevated *Aspergillus*-specific IgE or IgG, with or without central bronchiectasis.[4]

The International Society for Human and Animal Mycology (ISHAM) established comprehensive diagnostic criteria for ABPA in 2013, requiring the presence of two mandatory criteria alongside at least two of three additional criteria.[5] However, despite these standardized diagnostic guidelines, the actual prevalence of ABPA among asthmatic populations remains subject to considerable variation across different studies and geographical regions.

A comprehensive systematic review conducted by Agarwal and colleagues revealed that ABPA prevalence in Indian asthma patients ranges from 3 to 41%, with an aggregate prevalence of 16.2%.[6] When specifically examining severe asthma cases, the reported prevalence demonstrates even greater variability. Previous research by Agarwal et al. documented ABPA prevalence rates ranging from 12.9 to 27.2% in severe asthma patients,[5,7] while another study reported a prevalence of 38.6% among patients hospitalized with acute severe asthma.[8]

The substantial burden of ABPA in India, evidenced by these varying prevalence estimates, underscores the critical importance

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of establishing precise epidemiological data, particularly among individuals with severe asthma. Accurate prevalence data can significantly inform the development and implementation of targeted screening protocols and management strategies within asthma care settings. Current literature reveals a notable gap in understanding ABPA prevalence specifically within the severe asthma population in the Indian context.

This research initiative aims to address this knowledge gap by conducting a detailed investigation into ABPA prevalence among severe asthma patients presenting to a tertiary care institution in northwestern India. The findings from this study will contribute valuable insights into the burden of ABPA in this high-risk population and help inform future screening and management approaches, ultimately working toward improving care outcomes for individuals with severe asthma in India.

## Methodology

This was a prospective institutional study, and a total of 247 patients presenting with a diagnosis of severe asthma to the outpatient clinic or emergency department were consecutively enrolled from August 2022 to July 2023. The patients were classified as severe asthma as per the Global Initiative for Asthma guidelines, 2022.[1] After taking informed consent, patients' detailed case history, examination, and other relevant workup were done.

### Collection of Sample

Under aseptic conditions, a venous blood sample was collected and serum was separated for further testing. Absolute eosinophil count and total IgE levels were tested in all 247 patients. Chemiluminescence immunoassay (CLIA)-based tests were performed for total IgE, and fluorescent enzyme immunoassay (FEIA)-based tests were done for *A. fumigatus*-specific IgE and IgG using the ImmunoCap Diagnostics kit.

Patients were diagnosed with ABPA according to ISHAM criteria and further classified into ABPA-B and ABPA-S. The results of all these tests were recorded and compiled.

Data analysis was performed using SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA). We employed descriptive statistical methods appropriate to the data distribution, presenting continuous variables as either mean with standard deviation or median with range, depending on the underlying distribution patterns.

### Inclusion Criteria

- Patients presenting to the outpatient clinic or emergency department who had been diagnosed with severe asthma.
- Older than 15 years.

### Exclusion Criteria

- Patients who had already been diagnosed with ABPA in the past or were currently being treated for ABPA.
- Pregnant women.
- Those who did not give consent.

## Results

Among the 247 patients enrolled, 55.5% ($n$ = 137) were female and 44.5% ($n$ = 110) were male, and the mean age of the patients was 46.3 ± 16.3 years. The mean AEC recorded was 901.8 ± 940.8 cells/µL, and mean IgE was 2874.9 ± 2701.5 IU/mL among the total 247 patients enrolled in the study.

Of the 247 severe asthma patients, 63.2% ($n$ = 156) were diagnosed with ABPA, while 36.8% ($n$ = 91) patients had no ABPA, according to ISHAM criteria. The mean age of the patients diagnosed with ABPA was 41.6 ± 15.2 years. Of these 156 ABPA patients, 80 (51.3%) were female and the remaining 76 (48.7%) were male. Twelve (7.7%) patients were diagnosed with ABPA-S and 144 (92.3%) patients with ABPA-B.

The mean absolute eosinophil count (AEC) in our patients was 1097.9 ± 951.9 cells/µL. The mean AEC values were higher in the ABPA-B group (1141.4 ± 974.6) as compared to the ABPA-S group (577.1 ± 317.2), and this difference was statistically significant ($p$ = 0.05) (Table 1).

The mean IgE in our ABPA patients was 3867.9 ± 2782.2 IU/mL. The mean IgE values were higher in the ABPA-B group (4041.4 ± 2798.2 IU/mL) as compared to the ABPA-S group (1785.9 ± 1470.2 IU/mL), and this difference was statistically significant ($p$ < 0.01) (Table 1).

## Discussion

Patients with severe asthma with recurrent attacks and those with persistent asthma with irreversible lung changes are at higher risk of fungal colonization and sensitization.[9]

In the current study group, 170 out of 247 patients had total IgE >1,000 IU/mL, with a mean value of 3867.9 ± 2782.2 IU/mL. Sarkar et al. reported higher serum total IgE levels in 8 out of 10 patients with ABPA,[10] while Nath et al. reported mean total serum IgE levels as 1970.5 IU/mL.[11]

In our study cohort, the overall prevalence of ABPA among patients with severe asthma was found to be 63.2% (156 of 247 patients). To date, very few studies have been carried out to estimate the prevalence of ABPA in severe asthma, wherein Bhankhur reported a prevalence of ABPA as high as 70%,[9] Agarwal reported a prevalence of 38.6% in acute severe asthma,[8] and Mathur found prevalence of ABPA to be only 2.7% in severe asthmatics.[12]

The mean age in our study was 41.6 years, which was slightly higher than that reported previously. Kumar and Gaur have reported the mean age of ABPA to be 34 years,[13] Agarwal et al. as 34.4 years,[14] and Sarkar et al. as 33.1 years.[10]

In our study, more females (51.3%, $n$ = 80) were diagnosed with ABPA than males (43.7%, $n$ = 76); however, this difference was not significant. Nath et al. have also reported no significant gender predisposition toward ABPA in their study.[11]

The mean AEC in ABPA patients in our study was 1097.9 ± 951.9 cells/µL, and the mean IgE was 3867.9 ± 2782.2 IU/mL; significantly higher values of both were seen in the ABPA-B variant. In a study done on 31 ABPA patients, Kumar reported significantly higher values of total IgE in ABPA-B than ABPA-S patients.[15] In their study done on 93 patients, Wang et al. reported higher, but not significant, values of both AEC and total IgE in ABPA-B patients when compared to ABPA-S.[16]

In our study, the prevalence of ABPA-B (92.3%) was found to be much higher than ABPA-S (7.7%). Kumar and Gaur have reported 75% prevalence of ABPA-B and 25% prevalence of ABPA-S.[13] Similar findings were reported by Agarwal et al. in their study done on 209 ABPA patients, wherein a high prevalence of ABPA-B (77.5%) was seen compared with ABPA-S (22.5%).[14] On the contrary, in their study

**Table 1:** Distribution of mean AEC and IgE with respect to types of ABPA

| *Characteristic* | *ABPA subcategory* | *Number of patients* | *Mean* | *SD* | *Minimum* | *Maximum* | *Median* | *p-value* |
|---|---|---|---|---|---|---|---|---|
| AEC (cells/µL) | ABPA—B | 144 | 1141.4 | 974.6 | 100 | 5100 | 940 | 0.05 |
| | ABPA—S | 12 | 577.1 | 317.2 | 115 | 1260 | 500 | |
| IgE (IU/mL) | ABPA—B | 144 | 4041.4 | 2798.2 | 189 | 15856 | 3200 | <0.01 |
| | ABPA—S | 12 | 1785.9 | 1470.2 | 269 | 5630 | 1291.5 | |

of 50 ABPA patients, Bhankhur et al. reported a prevalence of ABPA-S (68.5%) much higher than ABPA-B (31.5%).[9]

These diverse findings across multiple studies not only reflect regional variations but also highlight potential environmental and genetic factors that may influence ABPA manifestation in severe asthma patients. The remarkably high ABPA-B prevalence in our study population could be attributed to several factors unique to northwestern India, including climatic conditions, agricultural practices, and indoor air quality characteristics. Additionally, the timing of clinical presentation and diagnosis may play a crucial role, as patients with bronchiectasis often present at later stages of disease progression. The environmental conditions in this region, characterized by significant temperature fluctuations, agricultural activities generating organic dust, and specific housing conditions, might contribute to increased *Aspergillus* exposure and subsequent sensitization. Understanding these regional determinants could be instrumental in developing targeted preventive strategies and optimizing diagnostic protocols for early ABPA detection in severe asthma patients. This observation also raises important questions about the potential role of local environmental modifications and patient education in reducing ABPA burden in this geographical area.

## Conclusion

Our study highlights a high prevalence (63.2%) of ABPA in patients with severe asthma. Hence, it seems pertinent to evaluate all such patients for the presence of ABPA using standard guidelines. The importance of creating awareness among the physician community to achieve early diagnosis and institute timely management, so as to achieve better asthma control and avoid permanent lung damage, cannot be undermined. However, studies with a larger sample size are needed to assess the underlying causes of such a high burden of ABPA in this part of the world, so that preventive measures can be instituted at the community level.

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ORIGINAL ARTICLE

# Assessment of Nutritional Status Using Body Composition Analysis in Cardiac Surgery and Risk Association with Acute Kidney Injury

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## Abstract

Poor nutritional status prior to surgery in cardiac patients is one of the risk factors for acute kidney injury (AKI), morbidity, and mortality. There is a lack of data in patients undergoing cardiac surgery with regard to nutritional status and risk of AKI.

This study was conducted with the objective of assessment of the nutritional status of cardiac surgery patients using body composition measures (BCM) and other biochemical parameters.

This study was conducted at Madras Medical Mission Hospital, Chennai. Before enrolling, informed consent from the patients and ethical authorization were obtained. All patients >18 years of age undergoing cardiac surgery had a BCM analysis done on the pre- and postoperative day 5. Paired *t*-test was used to compare the pre- and postoperative data.

Preoperative body mass index (BMI) of the patients showed that the majority of them were overweight, with a mean BMI of ±26.55 kg/m$^2$. There were no significant changes in the BCM results for protein weight in either study group (no AKI group—preop: mean ± SD, 9.0316 ± 2.39, $p = 0.67$; postop: mean ± SD, 9.1919 ± 2.57, $p = 0.77$; AKI group—preop: mean ± SD, 9.57 ± 8.00, $p = 0.67$; postop: mean ± SD, 9.56 ± 8.07, $p = 0.77$). There was a significant loss of body fat in all patients, but it was higher in patients who developed AKI (preop: mean ± SD, 33.28 ± 10.96, $p = 0.11$ vs postop: mean ± SD, 31.83 ± 10.94, $p = 0.53$). The skeletal muscle mass in both groups showed no significant changes. Those who developed AKI postoperatively had a higher preoperative visceral fat area (VFA) (mean ± SD, 116.87) and percentage body fat (PBF) (33%) compared to patients who did not develop AKI (VFA ±102.36 and PBF 30%).

We found that patients had lost body fat postsurgically. Those who were diagnosed with AKI had overhydration, high waist circumference, and VFA preoperatively.


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## Introduction

Poor nutritional status prior to surgery in cardiac patients increases the risk of acute kidney injury (AKI), morbidity, and mortality. There is an excess paucity of data in cardiac surgery patients with regard to nutritional status and AKI outcomes. There is a lack of data in patients undergoing cardiac surgery regarding nutritional status and the risk of AKI. Older age-groups and patients requiring urgent surgical intervention may have protein-energy wasting (PEW), necessitating early assessment and intervention prior to adequate nutrition therapy. Therefore, assessment of nutritional status by body composition measures (BCM) and other biochemical parameters may provide adequate information to categorize patients as high, moderate, or low risk of malnutrition and AKI.[1] Cardiac surgery patients are often exposed to stressors and are at risk of inflammation, which may cause damage to the organ and can even lead to dysfunction. Cardiopulmonary bypass (CPB) may activate systemic inflammatory response syndrome (SIRS), which causes the release of reactive oxygen species (ROS), reactive nitrogen species (RNS), and pro-inflammatory cytokines.[2–4]

In the nutritional assessment of patients undergoing cardiothoracic surgeries, the percentage of overweight and obesity is high, which systematically increases the risk of complications, including AKI. Bioelectrical impedance analysis (BIA) is a noninvasive and easy technique for measuring body composition, including muscle, fat, and water content. The body composition equipment uses a three-compartment physiologic tissue model, which measures total body fluid water (TBW), extracellular water (ECW), intracellular volume (ICV), and helps in identifying fluid overload, euvolemia, or hypovolemia. AKI is a rare but significant complication of cardiac surgery. It occurs in up to 40% of all cases, with 1% of them requiring renal replacement therapy.[5,6] Even in individuals who have complete renal recovery, the risk of mortality related to AKI remains significant for 10 years following heart surgery, regardless of other risk factors. BCM can also be clinically used in the assessment and management of fluids in patients with end-stage kidney disease (ESKD) and heart disease.[6,7] Many times, a trained nutritionist is not available to assess preoperatively and postoperatively nutritional status and interact with the medical and surgical teams for a smooth postoperative course (R). In a critical care setting, cardiac surgery-related AKI is the second most common cause and is associated with increased mortality rates and increased length of hospital stay.[6] Several studies have found that preoperative, perioperative, and postoperative fluid assessment, blood pressure, and nutritional management have an impact on the postoperative course in preventing complications.[6,7] Therefore, preoperative technically assisted objective assessment of nutritional status and volume, electrolytes, acid-base balance, and albumin is useful to direct intra- and postoperative fluid and electrolyte administration. A previous observational study found that patients with a lower ECW had a greater risk of cardiac surgery-associated (CSA)-AKI compared to patients with stable coronary artery disease and lower ECW.[8,9] We, therefore, hypothesized that BIA-guided volume expansion could be inexpensive and effective in preventing CSA-AKI.

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## Methods and Materials

### Objective

The objective of the study is to assess the nutritional status and investigate the association between body composition, fluid volume, and biochemical parameters in patients undergoing cardiac surgery and their correlation with the risk of AKI and prognosis.

### Methods

This study was conducted at a tertiary cardiac care hospital in Chennai. Before enrolling, informed consent and approval from the Ethics Committee were obtained from all the patients and the institution. After informed consent, all adult patients underwent a BCM analysis performed by the trained nutritionist on the preoperative and postoperative day 5. The study period was 12 months.

### Inclusion Criteria

Elective cardiac surgery patients above 18 years of age ($N = 325$ patients).

### Exclusion Criteria

Those with no informed consent, those with metal implants, pacemakers, pregnant and lactating women, emergency surgery, and patients who underwent valvular cardiac surgery.

### Statistical Analysis

The collected data were statistically analyzed using the *t*-test, percentage, median, interquartile range, or as frequency percentages. Pre- and postoperative comparisons among patients were made using the paired *t*-test. The relationship between variables was analyzed using the Pearson correlation coefficient. AKI was diagnosed using KDIGO guidelines—Kidney Disease Improving Global Outcomes.

### Bioelectrical Impedance Analysis

Body composition monitor by Fresenius Medical Care, Germany, is a device based on multifrequency bioimpedance spectroscopy. The method of BIA consists of two components: (1) resistance and (2) reactance, and it is used to analyze body composition by sending a weak electric current through the five components of the body to calculate the impedance of the body fluid, fat, protein, and muscle mass. A low frequency (5 kHz) impedance reflects extracellular fluid because current does not flow through cell membranes. At frequencies above 100–200 kHz, the current will flow through the cell membrane, and the impedance will reflect both extracellular and intracellular fluids.[10] The edema index is defined as the ratio between intra- and ECW.

## Results

About 325 patients (M = 265; F = 60), median age 57 years, IQR 49–62 years, who had undergone elective cardiac surgery, were admitted to this study. The results showed that 38 (11.69%) patients developed AKI. Baseline characteristics, such as gender and comorbidities, showed no statistical differences. Patients who developed AKI had a median age of 62.5 years (IQR 54–68 years) vs no AKI (IQR 49.5–64 years), $p = 0.004$. The incidence of AKI was higher in females (17.2%) compared to males (12.3%, $p = 0.2481$). Patients with comorbidities such as diabetes mellitus (71.05%, $p = 0.2964$), hypertension (52.63%, $p = 0.5431$), and cerebrovascular diseases (2.63%) had a higher risk of developing CSA-AKI (Table 1). The preoperative mean serum albumin level was 4.09 gm/dL for those without AKI, compared to 3.97 gm/dL for those who had AKI ($p = 0.1872$). Postoperatively, serum creatinine values increased in patients with AKI, and analysis of variance (ANOVA) confirmed this, with $p = 0.0000$ (Table 2).

Sepsis incidence and mortality rate were higher in those who developed AKI, with 23.33 and 4% death rates, respectively. In the non-AKI category, the incidence of sepsis was 5.51%, and there were no deaths. There was no noted difference in the length of intensive care unit (ICU) and hospital stays in both groups. The *p*-value was 0.001 (Table 3), showing a significant difference in the mechanical ventilation days. The duration of mechanical ventilation was longer in patients who developed postoperative AKI, with a mean of 2.34 days.

Overhydration was maximum with the ECW/TBW >0.38 in patients with AKI compared to non-AKI patients (mean ± SD 0.4006 ± 0.0409, $p = 0.05$) (Table 4); however, it was not significant. Parameters such as body fat, ECW, WHR, and visceral fat area (VFA) were higher in patients with AKI.

As per the preoperative nutritional assessment, the majority of the patients were overweight, with a mean body mass index (BMI) of ±26.55 kg/m$^2$. The BCM results indicated no significant changes in the protein weight of both study groups (no AKI group—preop: mean ± SD, 9.0316 ± 2.39, $p = 0.67$; postop: mean ± SD, 9.1919 ± 2.57, $p = 0.77$; AKI—preop: mean ± SD, 9.57 ± 8.00, $p = 0.67$; postop: mean ± SD, 9.56 ± 8.07, $p = 0.77$). There was a significant loss of body fat in all the patients, but it was higher in patients who developed AKI (preop: mean ± SD, 33.28 ± 10.96, $p = 0.11$ vs postop: mean ± SD, 31.83 ± 10.94, $p = 0.53$). The skeletal muscle mass in both groups showed no significant changes. Those who developed AKI

**Table 1:** Demographic characteristics

| | *Patients without AKI* | | | | *Patients with AKI* | | | | *Difference = AKI – no AKI* | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Patient characteristics* | *N* | *Median* | *IQR* | | *N* | *Median* | *IQR* | | *Difference in means* | *ANOVA p-value* |
| Age in years | 287 | 57 | 49 | 64 | 38 | 62.5 | 54 | 68 | 5.8555 | 0.0043 |
| *Gender* | *N* | *%* | | | *N* | *%* | | | *Difference in %* | *Chi-square p-value* |
| Male | 236 | 82.23 | | | 29 | 76.32 | | | –5.91 | 0.2481 |
| Female | 51 | 17.77 | | | 9 | 23.68 | | | 5.91 | 0.2481 |
| | *N* | *Mean* | *95% Confidence interval* | | *N* | *Mean* | *95% Confidence interval* | | *Difference in means* | *ANOVA p-value* |
| BMI kg/m$^2$ (day 0) | 287 | 26.86 | 24.18 | 29.54 | 38 | 26.24 | 24.87 | 27.60 | –0.6231 | 0.8681 |
| *Comorbidities* | *N* | *%* | | | *N* | *%* | | | *Difference in %* | *Chi-square p-value* |
| Diabetes | 179 | 62.37 | | | 27 | 71.05 | | | 8.68 | 0.2964 |
| Hypertension | 136 | 47.39 | | | 20 | 52.63 | | | 5.24 | 0.5431 |
| CKD | 6 | 2.09 | | | 6 | 15.79 | | | 13.70 | 0.0000 |
| CVA | 8 | 2.79 | | | 1 | 2.63 | | | –0.16 | 0.4562 |

**Table 2:** Pre- and postoperative biochemical analysis

| *Parameters* | *Patients without AKI* | | | | *Patients with AKI* | | | | *Difference = AKI – no AKI* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | *Mean* | *95% Confidence interval* | | *N* | *Mean* | *95% Confidence interval* | | *Difference in means* | *ANOVA p-value* |
| Pre-operative parameters | | | | | | | | | | |
| Serum albumin gm/dL | 286 | 4.09 | 4.03 | 4.15 | 38 | 3.97 | 3.76 | 4.18 | –0.1216 | 0.1872 |
| Sodium mmol/L | 286 | 137.99 | 137.03 | 138.94 | 38 | 138.47 | 137.61 | 139.33 | 0.4877 | 0.7156 |
| Potassium mmol/L | 286 | 6.27 | 2.84 | 9.69 | 38 | 4.60 | 4.46 | 4.75 | –1.6655 | 0.7277 |
| Bicarbonate mmol/L | 283 | 27.43 | 26.97 | 27.89 | 38 | 26.24 | 24.44 | 28.04 | –1.1907 | 0.0976 |
| EGFR mL/minute | 287 | 100.59 | 97.45 | 103.73 | 38 | 61.53 | 54.85 | 68.22 | –39.0525 | 0.0000 |
| | *N* | *Median* | *IQR* | | *N* | *Median* | *IQR* | | *Difference in means* | *ANOVA p-value* |
| Post-operative parameters | | | | | | | | | | |
| Day 2 creatinine mg/dL | 287 | 0.72 | 0.61 | 0.82 | 38 | 1.14 | 0.95 | 1.26 | 0.3949 | 0.0000 |
| Day 3 creatinine mg/dL | 287 | 0.76 | 0.65 | 0.89 | 38 | 1.20 | 1.03 | 1.48 | 0.5380 | 0.0000 |
| Day 4 creatinine mg/dL | 287 | 0.75 | 0.65 | 0.87 | 38 | 1.24 | 0.91 | 1.48 | 0.5420 | 0.0000 |
| Day 5 creatinine mg/dL | 287 | 0.74 | 0.61 | 0.88 | 38 | 1.14 | 0.90 | 1.43 | 0.5012 | 0.0000 |
| Creatinine at discharge mg/dL | 287 | 0.75 | 0.62 | 0.87 | 38 | 1.09 | 0.90 | 1.31 | 0.3323 | 0.0000 |

**Table 3:** Surgical outcome

| *Parameters* | *Patients without AKI* | | | | *Patients with AKI* | | | | *Difference = AKI – no AKI* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | *%* | | | *N* | *%* | | | *Difference in %* | *Chi-square p-value* |
| Sepsis | 13 | 5.51 | | | 7 | 23.33 | | | 17.82 | 0.0005 |
| Death | 0 | 0.00 | | | 1 | 4.00 | | | 4.00 | 0.0046 |
| | *N* | *Median* | *IQR* | | *N* | *Median* | *IQR* | | *Difference in means* | *ANOVA p-value* |
| ICU stay | 287 | 3 | 2 | 3 | 38 | 3 | 2 | 3 | 0.6895 | 0.0442 |
| Duration of hospital stay in days | 287 | 10 | 9 | 11 | 38 | 10 | 8 | 10 | 0.0833 | 0.9045 |
| Days on mechanical ventilation | 287 | 1 | 1 | 2 | 38 | 1 | 1 | 1 | 1.0099 | 0.0013 |

**Table 4:** Body composition analysis—hydration

| *Parameters* | *Preoperative* | | | | *Postoperative* | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | *Mean* | *Std. deviation* | *p-value* | *N* | *Mean* | *Std. deviation* | *p-value* |
| ICW—AKI (L) | 38 | 20.8947 | 5.5312 | 0.6737 | 37 | 21.2757 | 5.9517 | 0.7854 |
| ICW—no AKI (L) | 287 | 22.1704 | 18.5273 | | 278 | 22.1173 | 18.6376 | |
| ECW—AKI (L) | 38 | 13.0842 | 3.4418 | 0.6815 | 37 | 13.4865 | 3.2201 | 0.8648 |
| ECW—no AKI (L) | 287 | 14.0516 | 14.4456 | | 278 | 13.8029 | 11.2150 | |
| ECW/TBW total—AKI (L) | 38 | 0.3858 | 0.0297 | 0.9958 | 37 | 0.3898 | 0.0152 | 0.7260 |
| ECW/TBW total—no AKI (L) | 287 | 0.3859 | 0.0138 | | 278 | 0.5006 | 1.9202 | |
| ECW/TBW (RA)—AKI (L) | 38 | 0.3777 | 0.0196 | 0.9885 | 37 | 0.3780 | 0.0158 | 0.6422 |
| ECW/TBW (RA)—no AKI | 287 | 0.3778 | 0.0156 | | 278 | 0.3766 | 0.0169 | |
| ECW/TBW (LA)—AKI (L) | 38 | 0.3807 | 0.0091 | 0.2591 | 37 | 0.3803 | 0.0098 | 0.5972 |
| ECM/TBW (LA)—no AKI (L) | 287 | 0.3778 | 0.0158 | | 278 | 0.3790 | 0.0146 | |
| ECW/TBW (TR)—AKI | 38 | 0.3879 | 0.0296 | 0.6530 | 37 | 0.3906 | 0.0160 | 0.2579 |
| ECW/TBW (TR)—no AKI (L) | 287 | 0.3866 | 0.0146 | | 278 | 0.3866 | 0.0202 | |
| ECW/TBW (RL)—AKI (L) | 38 | 0.3852 | 0.0432 | 0.8810 | 37 | 0.3891 | 0.0193 | 0.3115 |
| ECW/TBW (RL)—no AKI (L) | 287 | 0.3846 | 0.0208 | | 278 | 0.3838 | 0.0307 | |
| ECW/TBW (LL)—AKI | 38 | 0.3869 | 0.0334 | 0.1866 | 37 | 0.3956 | 0.0158 | 0.2127 |
| ECW/TBW (LL)—no AKI (L) | 287 | 0.3917 | 0.0190 | | 278 | 0.3905 | 0.0240 | |

postoperatively had higher VFA (mean ± 116.87) and percentage body fat (PBF) (33%) compared to patients who did not develop AKI (VFA ±102.36 and PBF 30%) (Table 5).

Those who developed AKI were overhydrated, as both intracellular water (ICW) (preop: mean ± SD, 20.89 ± 5.53, $p = 0.67$ vs postop: mean ± SD, 21.27 ± 5.95, $p = 0.78$) and ECW (preop: mean ± SD, 13.08 ± 3.44, $p = 0.68$ vs postop: mean ± SD, 13.48 ± 3.22, $p = 0.86$) increased during the postoperative state. They also had increased waist circumference

**Table 5:** Body composition analysis—fat and protein

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Protein—AKI kgs | 38 | 9.0316 | 2.3957 | 0.6760 | 37 | 9.1919 | 2.5750 | 0.7778 |
| Protein—no AKI kgs | 287 | 9.5787 | 8.0052 | | 277 | 9.5697 | 8.0712 | |
| FAT—AKI kgs | 38 | 23.1474 | 8.9104 | 0.1414 | 37 | 22.3649 | 9.2578 | 0.3387 |
| FAT—no AKI kgs | 287 | 20.9780 | 8.4742 | | 278 | 20.9421 | 8.3800 | |
| Skeletal muscle mass—AKI kgs | 38 | 25.2553 | 7.2265 | 0.6748 | 37 | 25.7405 | 7.7644 | 0.7692 |
| skeletal muscle mass—no AKI kgs | 287 | 26.9129 | 24.1575 | | 278 | 26.9241 | 24.3236 | |
| Percent body fat—AKI | 38 | 33.2895 | 10.9633 | 0.1138 | 37 | 31.8324 | 10.9414 | 0.5315 |
| Percent body fat—no AKI (%) | 287 | 30.5449 | 9.8993 | | 278 | 30.7183 | 10.0589 | |
| BMI—AKI kg/m$^2$ | 38 | 26.2368 | 4.1444 | 0.8681 | 37 | 26.2243 | 4.2194 | 0.8624 |
| BMI—no AKI kg/m$^2$ | 287 | 26.8599 | 23.0280 | | 278 | 26.8950 | 23.4314 | |
| Body cell mass—AKI kgs | 38 | 29.9289 | 7.9353 | 0.6740 | 37 | 30.4784 | 8.5231 | 0.8027 |
| Body cell mass—no AKI kgs | 287 | 31.7544 | 26.5372 | | 278 | 31.5870 | 26.7591 | |
| Waist cir—AKI | 38 | 89.3605 | 13.7119 | 0.2825 | 37 | 90.2270 | 13.4341 | 0.5678 |
| Waist cir—no AKI cms | 287 | 87.2031 | 11.3077 | | 278 | 88.9558 | 12.6030 | |
| VFA—AKI cms | 38 | 116.8737 | 63.2090 | 0.0972 | 37 | 115.0595 | 56.6129 | 0.3242 |
| VFA—no AKI cms | 287 | 102.3672 | 48.6376 | | 278 | 105.7712 | 53.3678 | |

(preop: mean ± SD, 89.36 ± 13.71, $p = 0.28$ vs postop: mean ± SD, 90.22 ± 13.43, $p = 0.56$), which may be due to overhydration.

## Discussion

This investigation examines the role of BCM with biochemical parameters in the assessment of nutritional status and its associated risk for AKI in pre- and postoperative cardiac surgery patients. The assessment consisted of patients in the older age-group with type 2 diabetes mellitus (T2DM), hypertension, and other comorbidities. Those patients with a mean eGFR of ≤61.8 mL/minute developed more AKI, which is not surprising, as their residual kidney reserve was low. Preoperative fluid status, body composition, and edema index were helpful markers in supporting patient management intraoperatively, perioperatively, and postoperatively, as it was not possible to measure the weight of the individuals. This assessment provided value-added information for better management of AKI and recovery. This information helped us reduce the dialysis requirement to a minimum of two patients. We suggest that the tools we used and the information we gathered can be used as a model for improving outcomes following cardiac surgery.

The biochemical parameters such as serum iron, sodium, bicarbonate, and albumin showed no significant changes among patients who developed AKI and those who did not. It is possible that patients who were on ACE inhibitors or ARBs had higher potassium, which was not statistically significant between the two groups. Hyperkalemia ≥5.5 mmol/L was carefully monitored and treated with insulin-glucose infusion or potassium-binding resins. There was an increase in the ECW, ICW, and edema index (EI) in the immediate postoperative period, which declined on postoperative day 5. This increase in ECW was greater than the ICW, and the decline in ECW was faster than in ICW. Cardiac surgery with CPB leads to a rise in the total body fluid due to the infusion of fluids such as intravenous fluids and priming solution. In addition, systemic inflammation was also caused by the interaction of extracorporeal circulation and priming volume with the endogenous body fluids.[11] The EI, defined as the ratio of ECW to TBW, is recognized as a surrogate marker for extracellular volume status. Studies showed that the EI was a useful marker for heart failure (HF), with an EI value of ≥0.390 being a predictor of HF readmissions and all-cause mortality in patients with acute decompensated HF.[12,13]

The preoperative BMI was ± 26.55 kg/m$^2$ for patients in both groups, indicating overweight. The cutoff BMI of World Health Organization (WHO) for Asian populations was used, which classified BMI into four groups: normal weight (18.5–22.9 kg/m$^2$), underweight (<18.5 kg/m$^2$), overweight (23.0–27.4 kg/m$^2$), or obese (≥27.5 kg/m$^2$). We observed increased loss of fat in the patients who developed AKI, suggesting augmented lipolysis. Lipolysis begins to dominate in patients who have undergone surgery, and fatty acids become the main source of energy. This can lead to insulin resistance and reduce the anabolic effect of insulin.[14] It was also found that the preoperative PBF, VFA, and waist circumference were higher in patients who developed AKI. Overweight and obese cardiac patients are at an increased risk of developing AKI postoperatively, due to a greater number of comorbidities and underlying structural changes that occur in the kidneys, such as oxidative stress, inflammation, and endothelial dysfunction.[14] There was no significant loss of muscle mass seen in both groups, as the study was limited to 5 days. Preoperative nutritional status and avoidance of increased hospitalization due to complications and comorbidities determine postoperative muscle proteolysis with skeletal muscle loss, which can be managed by appropriate counseling by a trained nutritionist providing protein, calories, and micronutrients.[15] Although a prospective study, the limitations are that it was time-limited to 5 days, accurate information on urine output and thoracic drain tube volumes were not considered, and valvular surgery and very sick patients with hypotension were excluded from our analysis.

## Conclusion

This study concludes that higher body fat, visceral fat, and body fat percentage are risk factors for developing AKI postcardiac surgery. The development of AKI after cardiac surgeries can have a significant effect on a patient's body composition. We assessed nutritional status and body fluid status using BCM and biochemical parameters pre- and postcardiac surgery, which helped us tailor nutrition therapy, fluid management, and prevention and management of AKI. The use of the BCM device is a simple and acceptable method to assess nutritional status.

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ORIGINAL ARTICLE

# Prosthetic Valve Thrombosis: Fibrinolysis, Surgery, or Percutaneous Manipulation?

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## Abstract

A total number of 20 cases of prosthetic valve thrombosis (PVT) involving left-sided bileaflet St Jude's prosthesis (16), Medtronic Hall (3), and pulmonary prosthesis (1) are reported. Streptokinase (STK) fibrinolysis provided excellent results in 66.6% of cases with thrombosed St Jude's mitral prosthesis and remains the preferred option for this subset. Percutaneous manipulation of the mitral disk proved a useful adjuvant. Reteplase produced gratifying results in pulmonary mechanical prosthesis. However, thrombosed aortic prosthesis responded unfavorably to fibrinolysis.

About six patients who failed to respond to thrombolysis had excellent results with valve replacement surgery. Two patients (10%) succumbed due to extremely high-risk clinical characteristics.


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## Introduction

Rheumatic heart disease (RHD) continues to be a common cause of multivalvular involvement requiring valve replacement at a young age.[1,2] Prosthetic valve thrombosis (PVT) is a rare but serious complication of valve replacement, mostly observed with mechanical prosthesis. The incidence of PVT for mechanical valves varies between 0.3 and 1.3% patient-years.[3] The outcome of PVT is determined by clinical status, degree of valvular obstruction, and valve location (left- or right-sided).

Obstructive left-sided PVT is generally considered an indication for surgery but is limited by excessive mortality and morbidity in patients with New York Heart Association (NYHA) class III or IV or cardiogenic shock.[4] The excessive cost of reoperation is also relevant in resource-constrained patients. Alternative therapeutic modalities include heparin and fibrinolysis. Interventional techniques have been utilized for hemodynamic stabilization in unstable patients.[5]

The present communication, a retrospective study, reports experience from a tertiary care unit in treating 20 cases involving mechanical PVT. The results of fibrinolysis, surgery, and interventional techniques are discussed.

## Materials and Methods

The material for this retrospective study was obtained from records of 20 cases of PVT diagnosed and treated during January 2021 to 2023 in a tertiary care referral teaching institution.

Diagnosis of PVT was based on clinical features, fluoroscopic, and transthoracic echocardiography (TTE) findings. Clinical criteria for PVT included progressive dyspnea, heart failure (HF), low output state, or systemic embolization. Muffling or disappearance of click sounds and appearance of new regurgitation or obstructive murmur were additionally recorded. Cinefluoroscopy findings in multiple views provided information about the type of valve (single or bileaflet) and its leaflet mobility.

Transthoracic echocardiography data, including color Doppler and pulse Doppler, were available in standard parasternal long-axis, short-axis, and four-chamber views. The following data were specifically analyzed:

- Transvalvular gradients across the prosthetic valve. For mitral prosthesis, a mean gradient >8 mm Hg and for aortic prosthesis, a mean gradient >45 mm Hg supported the diagnosis when PVT is suspected.[4]
- Prosthetic valve visualization for reduced mobility, valve thrombosis, or pannus. Thrombus was diagnosed as a soft, mobile mass or homogeneous echo located on the valve leaflet, whereas pannus was visualized as a fixed, calcific, bright echo density on the valve ring.[6]
- Pulmonary artery (PA) pressures and left ventricular (LV) function.

### Thrombolysis Protocol

The choice of the thrombolytic agent was decided by financial considerations and availability of the agent. One of the following thrombolytic regimens was used:

- Streptokinase (STK): 2,50,000 units intravenous (IV) for 30 minutes, followed by slow IV infusion at 1,00,000 units per hour for 48–72 hours.
- Tenecteplase (TNK): 0.5 mg/kg bodyweight as a bolus.
- Reteplase: 10 unit IV bolus over 2 minutes followed by 10 units IV after 30 minutes.

Fluoroscopy and TTE was performed at 24, 48, and 72 hours.

Depending on the response to thrombolysis, patients were categorized as responders and nonresponders. Responders were those individuals who had clinical improvement, accompanied by a reduction in transvalvular gradients by 70% and restoration of disk mobility on fluoroscopy.

Nonresponders had little or no clinical improvement, and transvalvular gradients were reduced by <50% from basal values, with sluggish or only single-leaflet mobility on fluoroscopy.

The complications of thrombolysis were classified as major or minor. Major complications included intracranial bleed, ischemic stroke, need for blood transfusion, anaphylactic shock, or inhospital mortality. Minor complications included hematoma, petechiae, access site bleeding, hematuria, hematemesis, or allergic reactions.

The nonresponders were subsequently treated either by interventional procedure or by surgical valve replacement. Two patients (case 11, 15) with mitral PVT underwent transcatheter manipulation of the prosthetic valve disk after transvenous transseptal cauterization using the protocol as described earlier.[5,7] A 6 F Judkins right (JR) coronary guiding catheter was manipulated thrice across the prosthetic valve disk under fluoroscopic guidance. Fragmentation of the thrombus was also attempted using a

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1.5 × 10 mm noncompliant (NC) balloon at 10 atm. Disk mobility changes were recorded on fluoroscopy, and gradients were recorded on TTE.[7]

Mitral valve replacement (MVR) and aortic valve replacement (AVR) were performed in six cases using conventional open-heart surgery.

## Results

The duration between PVT and valve replacement was 6.3 years for the mitral position and 16.6 years for the aortic position. The results of this study were analyzed depending on the response to thrombolytic therapy and percutaneous intervention and are shown in Tables 1 and 2 and Figures 1 and 2.

Table 1 (case number 1–9) shows data of responders, who all had St Jude's mitral prosthesis and were treated with STK. About 66% (6) were males, and the age range was 30–70 (m = 43.5 years). The clinical picture was dominated by dyspnea NYHA class II and III [5 (55.6%)], HF [3 (33.3%)], and atrial fibrillation (AF) [9 (100%)]. Subtherapeutic international normalized ratio (INR) was observed in the majority [8 (88.8%)] and ranged between 1.34 and 2.17 (mean: 1.68). Following thrombolysis, all nine patients with mitral PVT had rapid clinical and hemodynamic stabilization. Mitral gradients reduced as follows:

| | *Average mitral gradients (mm Hg)* | | |
|---|---|---|---|
| | *Peak* | *Mean* | *%Reduction* |
| Prethrombolysis | 32.5 | 15.3 | – |
| Postthrombolysis | 10.4 | 5.2 | 68% |

Cinefluoroscopy showed remarkable improvement in leaflet mobility (Fig. 1, panels C and D).

A 30-year-old female (case 10) with primary intracardiac repair for tetralogy of Fallot (TOF) underwent pulmonary valve replacement (PVR) in 2009 and 2021 using Bicor and St Jude's prosthesis, 21 mm respectively, for recurrent pulmonary regurgitation (PR). She presented with pulmonary PVT and responded to reteplase bolus after developing an allergic reaction to STK. Transpulmonary gradients reduced significantly (Table 1).

Table 2 summarizes data of the nonresponders. About six (60%) were females, and the age range was 33–74 years (mean 47.9). AF was observed in the majority, 7 (70%), and 1 (10%) patient had complete heart block (CHB). The clinical picture was dominated by NYHA class II and III dyspnea 6 (60%), 2 (20%) HF, and one patient had cardioembolic stroke, angina, and low output. Both St Jude's and Medtronic Hall prosthetic valves were involved irrespective of the location of PVT. Thrombolytic failure was seen both with STK and TNK. In the nonresponder with mitral PVT, gradients were:

| | *Average mitral gradients (mm Hg)* | | |
|---|---|---|---|
| | *Peak* | *Mean* | *%Reduction* |
| Prethrombolysis | 33 | 16 | – |
| Postthrombolysis | 17.4 | 8.5 | 47% |

Fluoroscopy showed one or both leaflets remaining stuck. Three cases (Sr. No. 12, 13, 14) underwent MVR. Figure 2 shows the thrombosed prosthesis with underlying pannus at surgery.

Two patients (Sr. No. 11, 15) were reluctant for a third surgery, and a transcatheter procedure was performed with reduction in Doppler gradients and complete or partial improvement in disk mobility on fluoroscopy (Table 2).

Aortic PVT (St Jude and Medtronic Hall) patients responded poorly to thrombolysis. Aortic gradients were as follows:

| | *Average aortic gradients (mm Hg)* | | |
|---|---|---|---|
| | *Peak* | *Mean* | *%Reduction* |
| Prethrombolysis | 85.3 | 46 | – |
| Postthrombolysis | 58 | 31.6 | 30% |

Case no. 17, 18, and 20 underwent successful AVR. One patient, Sr. No. 16, presented with cardioembolic stroke, CHB, and complex aortic root anatomy. Surgery was refused by the family, and the patient succumbed after a few days of conservative therapy, including heparin.

No major complications were observed. Minor bleeding complications were seen in four patients after thrombolysis, and one had an allergic reaction to STK. Two patients (16 and 19) had fatal outcomes due to progressive shock and extremely high-risk for surgery. All patients were discharged in stable condition with advice on INR monitoring during follow-up.

## Discussion

The present communication deals with 20 cases of PVT treated in a tertiary care center. PVT remains a serious condition with high mortality and morbidity. A rapid diagnosis is essential and can be promptly made by clinical history, cinefluoroscopy, and echo-Doppler techniques. This study includes 19 cases who had thrombosis of left-sided mechanical prosthesis and a case of pulmonary prosthesis. About 80% of patients with PVT had St Jude's bileaflet prosthesis, 15% Medtronic Hall, and one had bio-prosthesis. Obstructive PVT was common in young females with

**Table 1:** Clinical and investigative profile of responders

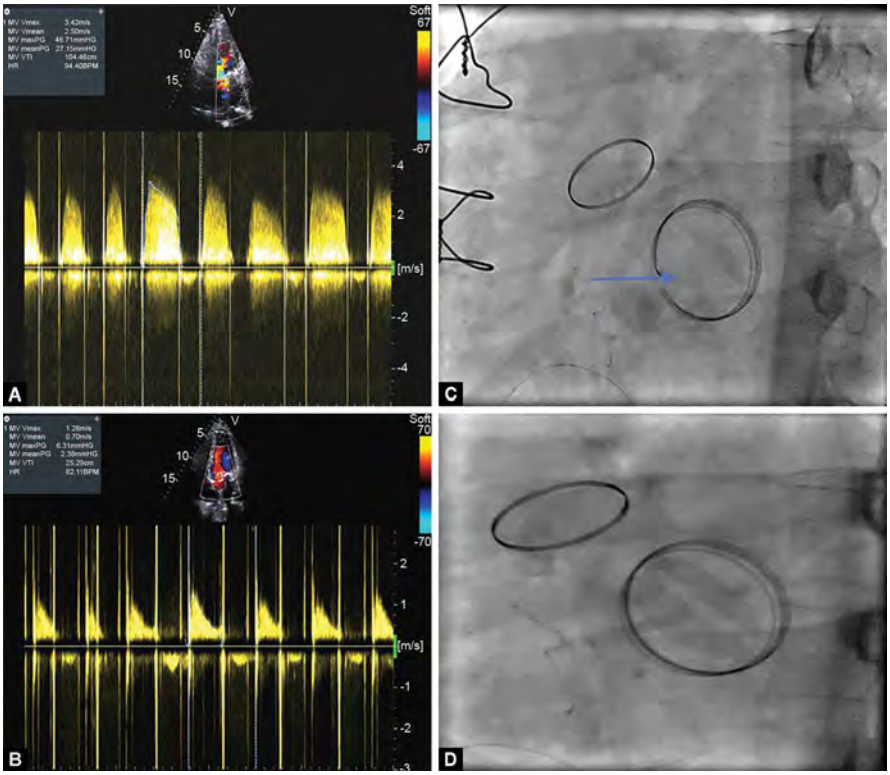
| *Sr. No.#* | *Age* | *Sex* | *Clinical presentation* | *INR (ratio)* | *Interval (months)** | *Thrombolytic agent* | *TTE gradient* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Peak* | *Mean* |
| 1 | 39 | M | HF, low output, AF | 2.03 | 6 | STK | 49 (6) | 21 (3) |
| 2 | 41 | F | NYHA III, AF | 1.9 | 96 | STK | 44 (13) | 20 (8) |
| 3 | 54 | F | NYHA III, AF | 2.17 | 108 | STK | 32 (14) | 15 (5) |
| 4 | 51 | M | NYHA III, ANGINA, AF | 2.0 | 108 | STK | 25 (6) | 8 (3) |
| 5 | 28 | M | NYHA II, ANGINA, AF | 1.3 | 12 | STK | 39 (17) | 20 (10) |
| 6 | 31 | F | NYHA III, AF | 1.85 | 12 | STK | 25 (12) | 12 (6) |
| 7 | 49 | M | HF, AF | 1.34 | 108 | STK | 33 (8) | 20 (3) |
| 8 | 70 | M | HF, low output, AF | 1.26 | 132 | STK | 20 (12) | 12 (6) |
| 9 | 30 | M | NYHA III, AF | 1.5 | 180 | STK | 25 (6) | 10 (3) |
| 10[#] | 30 | F | NYHA II, palpitation | 2.0 | 18 | Reteplase | 72 (31) | 40 (19) |

[#]Mitral valve PVT in all expect case 10 who has pulmonary valve involvement; *Interval between valve replacement and presentation with PVT; Gradients in () indicate values postthrombolysis; F, female; M, male; others as in text

**Table 2:** Clinical and investigative profile of nonresponders to thrombolysis

| *Sr. No.* | *Age* | *Sex* | *Clinical presentation* | *Valve (location, type)* | *Thrombolytic agent* | *TTE gradients* | | *Intervention* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Pre (P/M)* | *Post (mm Hg)* | | |
| 11 | 42 | M | NYHA III, SR | Mitral, ST Jude | STK | 35/20 | 19/10 | Transcath | Gradients reduced* |
| 12 | 45 | F | Angina, AF | Mitral, Med Hall | STK | 17/10 | 12/6 | MVR | Asymp |
| 13 | 57 | F | NYHA III, AF | Mitral, ST Jude | STK | 47/27 | 11/6 | MVR | NYHA I |
| 14 | 29 | M | NYHA III, AF, | Mitral, Med Hall | STK | 44/15 | 30/12 | MVR | NYHA I |
| 15 | 53 | F | NYHA II, AF | Mitral, ST Jude | STK | 22/8 | 15/8 | Transcath | Success# |
| 16 | 74 | M | CVA, NYHAIII, CHB | Aortic, ST Jude | Heparin | 94/65 | – | No | Expired |
| 17 | 33 | F | NYHA III, AF | Aortic, ST Jude | STK | 86/40 | 54/20 | AVR | NYHA I |
| 18 | 33 | F | HF, NYHA III, AF | Aortic, ST Jude | TNK | 90/50 | 60/40 | AVR | NYHA I |
| 19 | 63 | M | Low output, HF SR | Aortic, Med Hall | STK | 90/45 | 60/35 | No | Expired |
| 20 | 50 | F | NYHA III, AF | Aortic, ST Jude | STK | 80/48 | 60/35 | AVR | NHYA I |

*TTE gradients reduced to 14/8 mm Hg and one leaflet briskly moving; #TTE gradients reduced to 12/6 mm Hg and both leaflets mobile; Asymp, asymptomatic; CVA, cerebrovascular accident; Med Hall, Medtronic Hall; MG, mean gradient; PG, peak gradient; SR, sinus rhythm; Transcath, transcatheter; Other abbreviations as in text

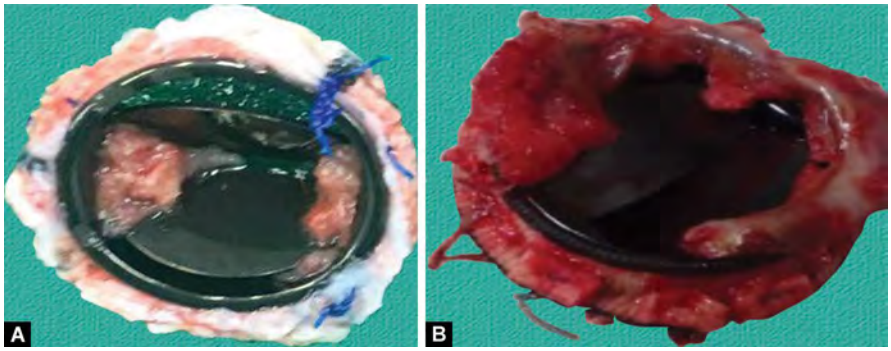



**Figs 1A to D:** Pre- and postthrombolysis echocardiographic continuous-wave Doppler and cinefluoroscopic views in a patient with mitral PVT: (A) Prethrombolysis peak gradient of 46 mm Hg and mean gradient of 27 mm Hg; (B) Postthrombolysis peak gradient of 6 mm Hg and mean gradient of 2 mm Hg; (C) Prethrombolysis left anterior oblique caudal views showing bileaflet tilting-disk valve in mitral position with one leaflet stuck (indicated by arrow); and (D) Postthrombolysis left anterior oblique caudal views showing bileaflet tilting-disk valve in mitral position with both leaflets mobile

AF and subtherapeutic INR, similar to the precipitating factors reported earlier.[8] It is noteworthy to note that despite widespread availability of pathological laboratories, subtherapeutic INR remains the underlying factor for PVT and was observed in 80% of patients. The Global Rheumatic Heart Disease Registry (the REMEDY study) reported no INR monitoring in 12.1%, limited monitoring in 34.1%, subtherapeutic values in 32.7%, and therapeutic values in only 28.3%.[1] About 60% of participants were unaware of the therapeutic range of INR values. It is worth emphasizing that current American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines recommend an INR range of 2–3 for aortic and 2.5–3.5 for mitral prosthesis to prevent thromboembolism.[9–11]

Obstruction of a mechanical prosthesis requires aggressive management. Surgery is the preferred therapy for left-sided PVT but can be associated with high-risk in sick patients.[4,12,13] Fibrinolytic therapy is an attractive alternative to surgery and was used in 95% of patients in this study. The response to this therapy depends on valve position, size, and characteristics of thrombus, type of the agent, and the comorbidities. There are reports in Indian literature using STK or TNK with varying success.[13–18] STK was preferred in this study due to its easy availability and low cost. STK produced gratifying results in patients with thrombosed St Jude's bileaflet prosthesis in the mitral position (Table 1). The overall success with STK was 66.6% in mitral PVT and 55.5% in the entire series. There was a low incidence of complications, and none had an embolic episode. It is possible that there was accumulation of small amounts of thrombus at the disk pivot points, which dissolved with thrombolysis. From the current study and previous data, it can be concluded that fibrinolytic therapy using STK can be used as a first-line therapy in thrombosed St Jude's mitral prosthesis.

On the contrary, STK administration failed to achieve thrombus dissolution in Medtronic Hall and St Jude's bileaflet valve in aortic position, resulting in fatal outcome or need for surgery. The aortic bileaflet mechanical St Jude's prosthesis has a low




**Figs 2A and B:** (A) Thrombosed bileaflet tilting-disk (ST Jude's valve) in mitral position, and (B) stuck bileaflet tilting-disk (ST Jude's valve) in mitral position

complication rate, with a thrombosis rate of 0.03% per patient year.[19] The valve design, which provides laminar flow, a low-pressure gradient, and a large orifice area, seems responsible for reduced risk of thrombus formation. The exact cause of aortic PVT and poor response to thrombolysis remain unclear but seems related to large valve area, longer period after valve replacement (16.6 years in this study), and subtherapeutic INR. Pulmonary prosthesis thrombosis is a serious and rare complication with high mortality in patients with operated TOF. Subtherapeutic INR and complex heart surgery with two previous PVR provided the nidus for thrombosis. Third-generation thrombolytic, reteplase, provided excellent symptomatic relief and dramatic reduction in echo gradients. A previous case report also describes successful results with reteplase.[20]

Percutaneous manipulation of a valve disk using a percutaneously placed cardiac catheter has been utilized to stabilize patients with mitral and aortic PVT.[5,7] We utilized this modality effectively in two patients with mitral PVT who did not respond to thrombolysis and were considered very high-risk for surgery. The conventional wisdom and teaching have been to avoid crossing of the prosthetic valve by guide wire or catheter due to potential complications like embolization or wire entrapment. The procedure proved safe and effective in both patients with all necessary precautions; however, large data are needed to support the use of this technique.

Surgery was performed in six patients with fibrinolytic therapy failure. Three patients each had MVR and AVR, with prompt restoration of valve function and hemodynamics. Excellent results could be obtained with improved surgical techniques and skills. High surgical success with excellent short- and long-term results has been reported.[4,21]

## Conclusion

Prosthetic valve thrombosis is common in females with AF, low output, and subtherapeutic INR. STK-based fibrinolysis can be therapy of first choice, with gratifying results in thrombosed St Jude's mitral prosthesis. Percutaneous transcatheter manipulation of the prosthetic disk is an alternative modality in high surgical risk patients. Valve replacement surgery was safe and lifesaving in individuals with thrombolysis failure.

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ORIGINAL ARTICLE

# Serum Liver Enzymes in Metabolic Syndrome and Nonmetabolic Syndrome Patients: A Case–Control Study

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## Abstract

**Background:** Metabolic syndrome (Met-S) is a major threat to human health all over the world due to a rise in obesity and sedentary lifestyle. It is associated with many cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. This study was conducted to determine the correlation of serum liver enzymes, especially serum gamma-glutamyl transferase (GGT), in Met-S and non-Met-S patients.

**Objectives:** To determine the correlation of serum liver enzymes, especially serum GGT, in Met-S and non-Met-S patients.

**Materials and Methods:** An observational case–control study was carried out on a total of 100 patients—50 cases of Met-S as defined by the International Diabetes Federation (IDF) 2005 and 50 age- and gender-matched controls (non-Met-S patients) aged >18 years—at a tertiary care hospital of Western India. Patients' history taking, general anthropometric, and systemic examination were done. Liver function tests [serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), GGT, alkaline phosphatase (ALP)], C-reactive protein (CRP), and ultrasonography (USG) for visualizing liver involvement were done.

**Results:** The maximum number of patients with Met-S were >50 years of age, with male predominance (78%) and a high prevalence of diabetes, hypertension, and central obesity among them as major components of Met-S. Liver function tests such as GGT, SGPT, SGOT, and CRP were significantly raised in Met-S patients compared to non-Met-S patients. The majority of the Met-S patients with deranged liver function tests had fatty liver on USG abdomen.

**Conclusion:** This study showed a significant association between elevated levels of GGT, SGPT, SGOT, CRP, and fatty liver in Met-S patients compared to non-Met-S patients.


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## Introduction

The term metabolic syndrome (Met-S) is also known as "syndrome X" and insulin resistance syndrome.[1] It refers to the co-occurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension.[2] Globally, Met-S is a major threat to human health all over the world.[3,4]

The worldwide prevalence of Met-S is on the rise, with the overall global prevalence estimated to be 20–25% of the adult population. A study conducted in 11 large urban cities of India during 2006–2010 reported the prevalence of Met-S as high as 35%.[5]

In 2005, the International Diabetes Federation (IDF) published new criteria for Met-S, which includes central obesity—waist circumference in male ≥90 cm and female ≥80 cm—plus two or more of the following: hypertriglyceridemia ≥150 mg/dL, with or without medications; low high-density lipoprotein (HDL) cholesterol <40 mg/dL in male and <50 mg/dL in female, with or without medications; hypertension ≥130/85 mm Hg, with or without medications; and fasting plasma glucose ≥100 mg/dL, with or without medications.[6]

Associated findings included fatty liver (especially in concurrent obesity) progressing to nonalcoholic fatty liver diseases (NAFLD), acanthosis nigricans, xanthoma and xanthelasma, arcus senilis, polycystic ovarian syndrome (PCOS) in females, elevated uric acid levels, etc.

Metabolic syndrome patients have simple fatty infiltration of the liver, steatohepatitis with necroinflammatory changes (NAFLD), and a variable degree of fibrosis, which may progress to liver cirrhosis. These changes of NAFLD due to Met-S lead to alteration of liver histology, morphology, and cellular dysfunction, which causes elevation of liver enzymes like gamma-glutamyl transferase (GGT), serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), and alkaline phosphatase (ALP). It is an independent risk factor for the mortality and morbidity of cardiovascular disease (CVD), along with diabetes mellitus, stroke, and hypertension in recent epidemiological and clinical studies due to its atherogenic property.[7]

According to certain studies, higher liver enzymes, especially GGT, occur due to low-grade hepatic inflammation induced by hepatic steatosis. Alternatively, excess fat in the liver could enhance oxidative stress, leading to overconsumption of glutathione with a compensatory increase in liver enzyme synthesis, along with high C-reactive protein (CRP) level, which reflects hepatic inflammation due to fatty liver.[8] Raised liver enzymes are relatively sensitive and easily obtained markers of fatty liver and reflect chronic ectopic fat deposition in the liver with Met-S association.

The prevalence of Met-S has progressively increased globally over several decades due to risk factors like sedentary lifestyle, addiction to smoking and alcoholism, mental stress, and obesity. According to IDF and National Cholesterol Education Program (NCEP), the prevalence of Met-S is estimated at >30% in the United States; however, by using adult treatment panel (ATP) criteria, prevalence is estimated at about 22%.[9–11]

It is of paramount importance to study the serum liver enzymes in metabolic and non-Met-S patients to treat it at early stages and prevent its further progression, which will help reduce the morbidity and mortality due to cardiovascular, cerebrovascular, and liver disease (fatty liver) in patients with Met-S.

## Materials and Methods

This observational case–control study was carried out on 50 metabolic and 50 non-Met-S patients of >18 years of age who were visiting the medical outpatient department (OPD) of Sir Sayajirao General Hospital or were admitted in general medicine wards. Study was carried out over 1 year, from January to December 2021.

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Patients having Met-S as defined by International Diabetes Federation criteria were included in the study. IDF criteria include central obesity with two or more of hypertriglyceridemia, low HDL, hypertension, and diabetes mellitus.[6] Age- and gender-matched non-Met-S patients visiting medical OPD or admitted in medicine wards of the hospital were included randomly as control. These controls (non-Met-S patients) were included randomly from medical OPD or wards and therefore they had none or few of the components of Met-S but not fulfilling all criteria of Met-S.

Exclusion criteria included chronic alcohol consumption, viral hepatitis, pregnant women, ischemic heart disease, cardiac failure, and other cardiovascular events, severely immunocompromised patients, subjects with history of abdominal or cardiac surgery, malignancy, thyroid disease, severe renal insufficiency, drugs like antiepileptics, oral contraceptive pills, erythromycin, cimetidine, acute infections, and inflammatory disorders.

A detailed history and clinical examination were done as per predesigned and pretested proforma.

Patients were subjected to detailed anthropometric examination and laboratory investigations like liver function test (SGPT, SGOT, GGT, ALP), renal function tests. Ultrasonography (USG) of abdomen for visualization of liver involvement for fatty changes for both metabolic and non-Met-S patients was done.

## Results

More numbers of males (78%) had Met-S compared to females (22%) as per Table 1.

Maximum numbers of patients were in the 51–60 years of age-group with a mean age of 58 years as shown in Table 1. It was inferred that the majority of the patients manifest Met-S later in life. In our study, all case and control patients were age- and gender-matched.

**Table 1:** Gender and age-wise distribution in metabolic and non-Met-S patients

| | *Met-S, n = 50, n (%)* | *Non-Met-S, n = 50, n (%)* |
|---|---|---|
| Gender | | |
| Female | 11 (22) | 16 (32) |
| Male | 39 (78) | 34 (68) |
| Age (years) | | |
| 31–40 | 3 (6) | 4 (8) |
| 41–50 | 7 (14) | 7 (14) |
| 51–60 | 19 (38) | 20 (40) |
| 61–70 | 16 (32) | 14 (28) |
| >71 | 5 (10) | 5 (10) |

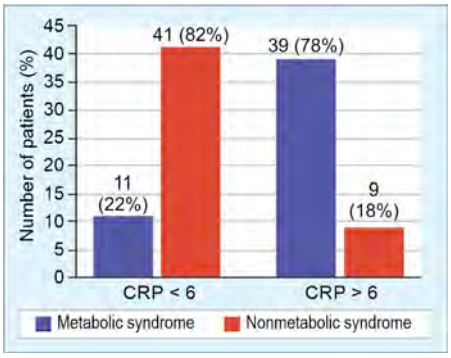


**Fig. 1:** Association of serum CRP value in both metabolic and non-Met-S patients

**Table 2:** Comparison of components of Met-S between patients with and without Met-S

| *Components of Met-S* | *Met-S (n = 50)* | *Non-Met-S (n = 50)* | *p-value* |
|---|---|---|---|
| Raised blood pressure (hypertension) | 48 (96%) | 10 (20%) | <0.0001† |
| Central obesity | 50 (100%) | 17 (34%) | <0.0001† |
| Fasting plasma glucose (≥100 mg/dL) | 50 (100%) | 31 (62%) | <0.0001† |
| Hypertriglyceridemia | 34 (68%) | 3 (6%) | <0.0001† |
| Low HDL | 12 (24%) | 6 (12%) | 0.118‡ |

†Fisher's exact test; ‡Chi-squared test

**Table 3:** Comparison of liver function test parameters between patients with and without Met-S

| *Liver function test* | *Met-S (n = 50)* | *Non-Met-S (n = 50)* | *Total* | *p-value* | *Odds ratio (95% CI)* |
|---|---|---|---|---|---|
| GGT(U/L) | | | | | |
| Normal (7–35 U/L) | 1 (2%) | 13 (26%) | 14 (14%) | 0.0008† | 1 |
| Deranged | 49 (98%) | 37 (74%) | 86 (86%) | | 11.88 (1.969–71.689) |
| SGPT(U/L) | | | | | |
| Normal (≤40 U/L) | 12 (24%) | 33 (66%) | 45 (45%) | <0.0001‡ | 1 |
| Raised | 38 (76%) | 17 (34%) | 55 (55%) | | 5.896 (2.471–14.07) |
| SGOT(U/L) | | | | | |
| Normal (≤45 U/L) | 7 (14%) | 28 (56%) | 35 (35%) | <0.0001‡ | 1 |
| Raised | 43 (86%) | 22 (44%) | 65 (65%) | | 7.347 (2.803–19.256) |
| ALP(U/L) | | | | | |
| Normal (≤110 U/L) | 2 (4%) | 9 (18%) | 11 (11%) | 0.051† | 1 |
| Raised | 48 (96%) | 41 (82%) | 89 (89%) | | 4.441 (0.977–20.176) |

†Fisher's exact test; ‡Chi-squared test

**Table 4:** Association of CRP with GGT (U/L) in Met-S patients

| *CRP* | *GGT ≤35 (n = 1)* | *GGT = 36–50 (n = 12)* | *GGT >50 (n = 37)* | *Total* | *p-value* |
|---|---|---|---|---|---|
| ≤6 | 0 (0%) | 6 (54.54%) | 5 (45.45%) | 11 (22%) | 0.03 |
| >6 | 1 (2.56%) | 6 (15.38%) | 32 (82.05%) | 39 (78%) | |
| Total | 1 (100%) | 12 (100%) | 37 (100%) | 50 (100%) | |

**Table 5:** Comparison of USG abdomen between patients with and without Met-S

| *USG abdomen* | *Met-S (n = 50)* | *Non-Met-S (n = 50)* | *Total* | *p-value* |
|---|---|---|---|---|
| Normal liver parenchyma | 8 (16%) | 46 (92%) | 54 (54%) | <0.0001[†] |
| Fatty liver | 42 (84%) | 4 (8%) | 46 (46%) | |
| Total | 50 (100%) | 50 (100%) | 100 (100%) | |

[†] Fisher's exact test

Table 2 shows distribution of components of Met-S among the study population. Controls (non-Met-S patients) were taken randomly from the OPD of the institute, so few of them had central obesity, raised blood pressure, raised blood sugar level, or dyslipidemia. On comparing these components of Met-S in patients with metabolic and non-Met-S, each individual component was more commonly seen in patients with Met-S (*p*-value < 0.05).

Among Met-S group patients, 98% had raised GGT, 76% had raised SGPT, 86% had raised SGOT, and 96% had raised ALP level. When comparing this with age- and gender-matched patients of non-Met-S, this was statistically significant (*p*-value < 0.05) (Table 3).

As per Figure 1, 78% (39) patients of Met-S had higher CRP value of >6 while only 22% (11) patients of non-Met-S had higher CRP value of >6 (*p*-value < 0.05).

Among 39 patients of Met-S with CRP value of >6, 32 patients had GGT level >50 U/L also. This shows strong correlation between CRP and GGT in patients of Met-S. It suggests the majority of patients with Met-S had high CRP and high GGT level with significant *p*-value of 0.03 among them (Table 4).

As per Table 5, 84% (42) patients of Met-S patients and 8% (4) patients of non-Met-S patients had fatty liver in USG. This shows strong association of Met-S and fatty liver changes in USG (*p*-value < 0.0001).

## Discussion

In our study, we found that 38% of patients with Met-S were of 51–60 years age. Krishnamoorthy et al. study observed that there was a steady increase in the burden across the age-groups from 13% in the 18–29 years group to 50% in the 50–59 years group. Prasad et al. study showed significantly higher rates of Met-S in older age-groups.[12]

In this study, male patients with Met-S were more than female patients with Met-S. However, Prasad et al. observed an age-standardized prevalence rate of Met-S of 33.5% overall, with 24.9% males and 42.3% females. The study done by Prasad et al. was a community-based study, and the present study was a hospital-based study. Kapoor et al. found gender discrimination in access to healthcare, with an overall sex ratio of 1.69 male to 1 female outpatient visit in a large referral public hospital of Delhi, India.[13] Gender discrimination in access to healthcare, along with reluctance of female patients to enroll in the study, may be the reason for a greater number of male patients with Met-S than females in this study compared to other studies.

Among the patients of Met-S, all 50 (100%) of them had central obesity with raised fasting plasma glucose level, 48 (96%) had raised blood pressure, 34 (68%) had hypertriglyceridemia, and 12 (24%) had low HDL level. Biadgo et al. estimated the prevalence of Met-S among diabetic patients using NCEP-ATP III and IDF criteria and found the most prevalent component of Met-S was elevated triglyceride (56.6% in NCEP-ATP III and 62.3% in IDF criteria), followed by abdominal obesity (61%) in IDF and elevated blood pressure (55.4%) in NCEP-ATP III criteria.[14]

In our study, 49 (98%) out of 50 patients with Met-S had raised GGT (>35 U/mL) level, compared to 37 (74%) out of 50 non-Met-S patients who had raised GGT level. Apart from that, SGPT was raised in 38 (76%) of Met-S patients and 17 (34%) of non-Met-S patients. SGOT level was raised in 43 (86%) patients with Met-S and 22 (44%) patients with non-Met-S. All the above values signify that liver function test parameters have a strong correlation with Met-S patients in comparison to non-Met-S patients. Wang et al. revealed that liver function tests, especially GGT level, showed a significantly positive correlation in Met-S patients as an early predictive marker of Met-S, CVD, heart failure, and all-cause mortality.[15] Rantala et al. revealed a highly significant relationship between GGT and the components of the Met-S even after adjustment for age, body mass index, and alcohol consumption.[16] GGT level is associated with the development of CVD risk factors, including diabetes, hypertension, and the Met-S.[17]

In our study, 78% of Met-S cases had higher CRP value of >6 compared to non-Met-S controls. This was suggestive of an inflammatory condition of the liver due to ectopic fat deposition in the liver. Rutter et al. suggested that CRP level was significantly positive in Met-S patients compared to non-Met-S patients.[18]

Krishnamoorthy et al. and Akbaraly et al. observed that circulating GGT and transaminase activities are elevated in patients with Met-S. GGT plays an important role in glutathione homeostasis, which is an antioxidant defense mechanism for the cell. Elevated GGT levels could be a marker of oxidative stress, subclinical inflammation, and proatherogenic molecules in patients with Met-S. Ultimately, this leads to increased levels of CRP in them.[5,19] Similar correlation between CRP and GGT was also noted in our study, with significant *p*-value of 0.03. In our study, 82.05% of Met-S patients had GGT value of >50 U/L with CRP levels of >6, while 45.45% of Met-S patients had GGT value of >50 U/L with CRP levels of <6. It showed strong positive correlation between CRP and GGT in Met-S patients.

We found a strong correlation between USG changes of fatty liver in patients with Met-S (84%) compared to non-Met-S patients (8%). Goyal et al. found fatty liver in 73% of cases of Met-S and in 38% of controls. It shows a strong correlation between fatty liver and Met-S.[20]

The positive correlation between GGT and CRP is suggestive of likely inflammation, atherosclerosis, and fatty liver, and it is a risk factor for high cardiovascular morbidity and mortality in upcoming years in patients with Met-S.

Our study findings are limited primarily by the small sample size. Other than that, the long-term outcome on the patients was not studied. Moreover, the study individuals were taken only from one center and hence may not represent the whole population.

## Conclusion

Most of the patients with Met-S had deranged liver enzymes (GGT, SGPT, SGOT, ALP) and fatty changes of liver in USG. The majority of Met-S patients had raised CRP level due to low-grade hepatic inflammation and atherogenic property in view of increased oxidative stress and reduced glutathione reductase level, which causes more damage to liver cells and alteration of its function. It is a risk factor for high cardiovascular and cerebrovascular morbidity and mortality in future.

We can prevent cardiovascular and cerebrovascular morbidity and mortality by identifying components of Met-S in the population at an early age and preventing further progression of Met-S in them. We can reduce the prevalence of Met-S by educating people about all high-risk factors causing the disease as primordial prevention, along with regular medication and checkup of the particular disease, and educating them on how to prevent further complications.

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ORIGINAL ARTICLE

# Beliefs and Perceptions of Nonintensivists towards the Role of Intensivist Leadership in the Intensive Care Unit and the Impact of Intensivists on Patient-driven Outcomes in India: A Descriptive Survey

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## Abstract

**Aim:** To study the perception of nonintensivists of Indian intensive care units (ICUs) about the role of intensivists as leaders of the ICU, their impact on patient outcomes, including length of stay on the ventilator, cost of care, and evidence-driven quality care using a survey questionnaire.

**Materials and methods:** This study employed an online survey conducted using a Google Form and distributed *via* WhatsApp to nonintensivists taking care of ICU/high dependency unit (HDU) patients in public and private hospitals all over India. It consisted of 24 questions related to perceptions about the role of an intensivist in the ICU, their impact on patient-driven outcomes, ICU processes, and ICU structure.

**Results:** There was a statistically significant difference in responses from respondents working in closed and semi-open ICUs vs open ICUs. Overall, the presence of an intensivist was perceived to be associated with improvements in patient outcomes, smoother decision-making for complex cases, reduced costs by avoiding unnecessary tests, and reduced litigation by patient families, especially in closed and semi-open ICUs vs open ICUs.

**Conclusion:** This is the first-ever survey done to understand the role of an intensivist in the ICU in India in the eyes of a nonintensivist/admitting physician or surgeon. It shows that intensivists are considered to play a significant role in impacting patient outcomes, such as facilitating smoother decision-making in complex cases, improving decision-making efficiency, reducing costs associated with unnecessary tests, and preventing litigation by families. The survey results are very encouraging and should pave the way for conducting large-scale surveys in the developing world.

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## Introduction

Dual providers in the intensive care unit (ICU) provide care of critically ill patients in India, one who admits the patient, that is, the admitting consultant, and the other being the consultant intensivist. Most ICUs in India are semi-open/open ICUs. The Indian Society of Critical Care Medicine guidelines recommend that the responsibility for patient care be shared between the admitting consultant (i.e., physician/surgeon) and the consultant intensivist.[1]

Only 58% of Indian ICUs have 24-hour trained intensivist coverage, as per a study by Kashyap et al.[2] This may be due to multiple synergistic factors, for example, a lack of information about the role of the intensivist, a lack of trained intensivists, or a lack of finances to pay the intensivist. There is no published information on the perception and beliefs of nonintensivists, that is, admitting physicians/surgeons, regarding the roles and impact of an intensivist in managing critically ill patients, especially with regard to their understanding of the impact that an intensivist can make on the outcome of patients in terms of length of stay, cost of care, communication to families, end of life care, and palliation. This survey was therefore created to understand the beliefs and perceptions of the admitting consultant, that is, the nonintensivist, in ICUs in India. This information may help the intensive care community foster better relationships with the admitting consultant/nonintensivist.

## Materials and Methods

This survey was conducted using an online Google form (https://forms.gle/qP6TbRjGxepqUW8d7, supplement), which was distributed through WhatsApp by the 15 group members responsible for data collection *via* personal messages/group chats. No particular web portal was used to get access to these nonintensivists. It was sent to all nonintensivists managing critically ill patients in India, including post-MS specialists and superspecialists working in both public and private hospitals. General practitioners, that is, MBBS doctors who were caring for critically ill patients in the ICU/high dependency unit (HDU), were not sent the survey and were excluded from the study. No personal identifiers were collected during the study. As this study was an anonymous survey, ethics approval was not sought. The survey data were collected over 3 months, from February to April 2024. The survey consisted of 24 questions, six of which pertained to the respondent's demographics. A closed ICU was defined as one in which the intensivist leads the care of the patient, with all treatments, including ventilatory support, nutrition, and extubation, being managed by them. An open ICU is one in which different specialists provide input, but there is no overall in charge of the patient. A semi-open ICU is one in which both the intensivist and the admitting

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physician/surgeon can institute treatments. One question was related to the perception of care of acutely ill patients requiring special skills and knowledge, four were related to the role of the intensivist as a leader of ICU, code blue team, trauma team, and antibiotic stewardship team. One question was related to early referral of deteriorating patients in the general ward to the intensivist to prevent cardiac arrest. Four were related to outcomes, including patient outcomes, evidence-based quality care, extubation, and the cost of care. Two questions pertained to end-of-life care communication and litigation. Three questions were related to systems and processes of ICU, including utility of combined ICU-HDU, role of specialized ICUs (e.g., cardiac ICU, nephrology ICU), and clinical privileges of the intensivist in the ICU to do procedures and report them (e.g., bronchoscopy, echocardiogram). Three more questions were related to the presence of an intensivist and its impact on the dynamics of the team, including the stress on the admitting team, smoother decision-making for complex patients, and reducing conflict between multiple teams. A Likert scale was used, with points ranging from 1 (strongly agree) to 5 (strongly disagree). The survey questions were designed after discussions between the study group, which included intensivists from India, Singapore, Oman, and Dubai. All the intensivists involved in designing the survey were qualified intensivists working independently in their own countries, with >10 years of clinical experience. The study was conducted and reported in accordance with the published STROBE guidelines.[3]

### Statistical Analysis

The data analysis was conducted using SPSS v25.0 to perform descriptive statistics, factor analysis, and analysis of variance (ANOVA) with Tukey's *post hoc* tests. Factor analysis, using principal component analysis (PCA) with varimax rotation, was applied to identify underlying components within the survey items, grouping them based on shared variance to reveal key factors influencing perceptions of intensivist-led care. ANOVA was then used to compare the mean survey scores across ICU types (open, semi-open, and closed ICUs) for each question to determine if perceptions varied significantly depending on the ICU model. Where significant differences were identified, a *post hoc* Tukey test was applied to identify specific pairwise differences, providing detailed insights into how each ICU type compared across survey items. For items with <5% missing data, mean imputation was used, assuming that the missingness was random and would not introduce bias.

## Results

A total of 319 responses were received for the survey; however, for individual questions some respondents did not answer all questions. Of the 319 responders, 103 (32.2%) nonintensivist responders belonged to a surgical specialty, and 213 (66.7%) were from a medical specialty. Table 1 shows the clinical specialty of the responders.

About 57.3% of the respondents were senior consultants in their specialty, followed by 12.7% being the head of department, 10.5% being the junior/associate consultant, 10.2% marked as others, and 9.2% were professor/assistant professor. Five respondents did not answer this question.

A total of 54.5% of respondents worked in a semi-open ICU, 26.1% worked in a closed ICU, and 19.4% of respondents worked in an open ICU. Five respondents did not answer this question.

About 59.2% of respondents surveyed did not manage their critically ill patients independently without involvement of an intensivist, whereas 22.3% of respondents did manage their critically ill patients independently without involvement of an intensivist. 18.7% of respondents managed their critically ill patients independently without an intensivist sometimes. Three respondents did not answer this question.

Again 60.5% of respondents cared for <2 HDU/ICU patients daily, whereas 23.9% cared for 2–5 critically ill patients. 9.2% of respondents cared for 5–10 patients, and 6.4% cared for >10 ICU/HDU patients. Five respondents did not answer this question.

The responses to the remaining 18 questions have been tabulated in Table 2. The number of respondents who strongly agreed or agreed with the question on the Likert scale was totaled; similarly, the respondents who strongly disagreed or disagreed were added together.

The number of respondents who could not decide and marked the question as neither agreeing nor disagreeing, as well as those who did not answer the question, has also been displayed in Table 2.

A PCA was performed to identify underlying factors in participants' responses regarding the effectiveness and management of intensivist-led care. Using an eigenvalue criterion of >1, two principal components (PCs) were extracted (Table 3), accounting for 62.51% of the variance and explaining a significant portion of the variance in responses. Question 21 and 24 were not included in any PC as they both had a poor loading of <0.6. The missing data rate was <5% in our survey.

Principal component 1 (PC1) has a mean overall score of 3.81 [standard deviation (SD) = 1.11], indicating moderate agreement on perceptions related to the effectiveness of intensivist-led care. PC2 has a higher overall mean score of 4.29 (SD = 0.86), indicating stronger agreement on cost-effectiveness, resource management, and specialized roles in ICU care. Closed ICUs had the highest mean score for PC1 (mean = 4.17, SD = 0.99), followed by semi-open ICUs (mean = 3.70, SD = 1.07) and open ICUs (mean = 3.62, SD = 1.26). Semi-open ICUs had the highest mean score for PC2 (mean = 4.28, SD = 0.85), followed closely by closed ICUs (mean = 4.25, SD = 0.79) and open ICUs (mean = 4.18, SD = 0.95). The ANOVA test for PC1 revealed a significant difference across ICU types ($F(2, 298) = 5.824$, $p = 0.003$), indicating that perceptions related to the effectiveness and impact of intensivist-led care varied significantly among the different ICU models. However, for PC2, the ANOVA was not significant ($p = 0.237$), suggesting that there were no significant differences in perceptions related to cost-effectiveness and resource management across the ICU types.

The ANOVA analysis was also performed for each question of the survey to compare responses across ICU types. Mean scores, standard errors, and significance levels ($p$-values) are presented for each question in Table 4. A statistically significant difference was found between ICU types for five questions. Respondents in closed ICUs reported a significantly higher mean score ($4.32 \pm 0.13$) than those in semi-open ($3.84 \pm 0.11$) and open ICUs ($3.62 \pm 0.21$), with intensivist-led care being perceived as reducing cost by avoiding unnecessary tests and treatments. Regarding patient outcomes, there was a significant effect of

**Table 1:** Specialty of the responder

| *Specialty of the responder* | *Number (%)* |
|---|---|
| General medicine | 97/319 (30.4) |
| General surgery | 19/319 (5.9) |
| Nephrology | 12/319 (3.7) |
| Pulmonology | 21/319 (6.5) |
| Orthopedics | 13/319 (4.0) |
| Trauma surgery | 3/319 (0.9) |
| Gastrointestinal (GI) surgery | 13/319 (4.0) |
| Gastroenterology | 9/319 (2.8) |
| Obstetrics and gynecology | 22/319 (6.8) |
| Ear, nose, and throat surgery | 4/319 (1.2) |
| Cardiology | 8/319 (2.5) |
| Cardiac surgery | 3/319 (0.9) |
| Urology | 9/319 (2.8) |
| Others | 81/319 (25.3) |
| Unknown | 5/319 (1.5) |

**Table 2:** Responses of the survey

| *Question 7–24* | *Number of respondents who strongly agreed* | *Number of respondents who strongly disagreed* | *Number of respondents who did not agree/ disagree* | *Number of respondents who did not answer this question* |
|---|---|---|---|---|
| Do you believe acute care, that is, looking after critically ill patients, is different from the care of stable, noncritically ill patients (nonacute care), which requires a special set of skills, knowledge, and training? | 279/319 (87.4%) | 23/319 (7.2%) | 15/319 (4.7%) | 2/319 (0.6%) |
| Do you believe an intensivist should be the administrative and clinical lead for critically ill patients in an ICU/HDU? | 213/319 (66.7%) | 52/319 (16.3%) | 50/319 (15.6%) | 4/319 (1.2%) |
| Do you believe that an intensivist-led treatment leads to a reduction in the cost of care by avoiding unnecessary laboratory tests and inappropriate treatments? | 147/319 (46.0)% | 92/319 (28.8%) | 77/319 (24.1%) | 3/319 (0.9%) |
| Do you believe that an intensivist-led treatment delivery leads to improvements in patient outcomes? | 229/319 (71.7%) | 41/319 (12.8%) | 43/319 (13.4%) | 6/319 (1.8%) |
| Do you believe an intensivist-led treatment leads to faster extubation and thus a reduction in ventilator days in the ICU? | 232/319 (72.7%) | 42/319 (13.1%) | 39/319 (12.2%) | 6/319 (1.8%) |
| Do you believe an intensivist-led treatment of critically ill patients reduces stress on the admitting team? | 263/319 (82.4%) | 28/319 (8.7%) | 24/319 (7.5%) | 4/319 (1.2%) |
| Do you believe that an intensivist-driven treatment is more evidence-based and up-to-date? | 209/319 (65.5%) | 46/319 (14.4%) | 60/319 (18.8%) | 4/319 (1.2%) |
| Do you believe that an intensivist-led care reduces conflict among multiple care teams? | 200/319 (62.6%) | 48/319 (15.0%) | 67/319 (21.0%) | 4/319 (1.2%) |
| Do you believe that an intensivist-led care of critically ill patients reduces the risk of litigation by patients' families? | 204/319 (63.9%) | 50/319 (15.6%) | 59/319 (18.4%) | 6/319 (1.8%) |
| Do you believe that the hospital should grant intensivist clinical privileges to perform bedside bronchoscopy and report transthoracic echocardiograms if they are trained to do so? | 238/319 (74.6%) | 41/319 (12.8%) | 36/319 (11.2%) | 4/319 (1.2%) |
| Do you think a closed ICU, led by intensivists, can lead to smoother decision-making for complex, critically ill patients, thereby resulting in efficient and timely care? | 201/319 (63.0%) | 59/319 (18.4%) | 54/319 (15.4%) | 5/319 (1.5%) |
| Do you believe that an intensivist should lead the communication with families regarding end-of-life care and palliation? | 217/319 (68.0%) | 38/319 (11.9%) | 59/319 (18.4%) | 5/319 (1.5%) |
| Do you believe an intensivist should lead the code blue team in a hospital? | 276/319 (86.5%) | 19/319 (5.4%) | 20/319 (6.2%) | 4/319 (1.2%) |
| Do you believe an early referral of a deteriorating patient in the surgical/medical ward to an intensivist can lead to earlier recognition of critical illness and thus avoid cardiac arrests in the general ward? | 265/319 (83.0%) | 26/319 (8.1%) | 23/319 (7.2%) | 5/319 (1.5%) |
| Do you believe an intensivist should be the leader of a trauma team? | 192/319 (60.1%) | 53/319 (16.6%) | 69/319 (21.6%) | 5/319 (1.5%) |
| Do you believe that an intensivist should lead the antibiotic stewardship program in the ICU in order to minimize antibiotic resistance and unnecessary costs, as well as side effects of prolonged antibiotic use? | 238/319 (74.6%) | 39/319 (12.2%) | 34/319 (10.6%) | 8/319 (2.5%) |
| Do you believe there should be a combined ICU and HDU in a hospital to facilitate the smoother transition of care for critically ill patients and better utilization of resources? | 261/319 (81.8%) | 26/319 (8.1%) | 26/319 (8.1%) | 6/319 (1.8%) |
| Do you believe that there should be specialized ICUs/HDUs, such as neurology ICUs, cardiac ICUs, gastroenterology ICUs, nephrology ICUs, etc.? | 236/319 (73.9%) | 37/319 (11.5%) | 38/319 (11.9%) | 8/319 (2.5%) |

the type of ICU. Respondents in closed ICUs had a higher level of agreement (3.75 ± 0.15) compared to those in semi-open ICUs (3.08 ± 0.11) and open ICUs (3.18 ± 0.20). A significant difference in perceptions regarding decision-making efficiency was also observed. Closed ICUs received the highest mean score (4.27 ± 0.12), followed by semi-open (3.47 ± 0.10) and open ICUs (3.62 ± 0.20). For the item addressing litigation risk, a significant difference was found between ICU types. The role of the intensivist in closed ICUs was rated higher (4.15 ± 0.12) compared to semi-open (3.72 ± 0.10) and open ICUs (3.63 ± 0.18). The ANOVA analysis revealed a significant effect on perceptions of treatment efficiency ($p = 0.018$). Closed ICUs had a higher mean score (4.33 ± 0.12) compared to semi-open (3.96 ± 0.09) and open ICUs (3.75 ± 0.19). *Post hoc* Tukey analysis revealed similar significant differences in comparisons of responses from nonintensivists between closed ICU and semi-open ICU, and between closed ICU and open ICU. Closed ICUs

**Table 3:** PCA

| *PC1* | *PC2* |
|---|---|
| VAR00008: "Do you believe an intensivist should be the administrative and clinical lead for critically ill patients in an ICU/HDU?" | VAR00007: "Do you believe acute care (i.e., looking after critically ill patients) is different from the care of stable noncritically ill patients (nonacute care) requiring a special set of skills, knowledge, and training?" |
| VAR00009: "Do you believe an intensivist-led treatment leads to a reduction in the cost of care by avoiding unnecessary laboratory tests and inappropriate treatments?" | VAR00012: "Do you believe an intensivist-led treatment of critically ill patients reduces stress on the admitting team?" |
| VAR00010: "Do you believe an intensivist-led treatment delivery leads to improvement in patient outcomes?" | VAR00016: "Do you believe that the hospital should give an intensivist clinical privileges to do bedside bronchoscopy and report transthoracic echocardiograms if trained to do so?" |
| VAR00011: "Do you believe an intensivist-led treatment leads to faster extubation and thus reduction in ventilator days in ICU?" | VAR00018: "Do you believe that an intensivist should lead the communication with families regarding end-of-life care and palliation?" |
| VAR00013: "Do you believe that an intensivist-driven treatment is more evidence-based and up-to-date?" | VAR00019: "Do you believe an intensivist should lead the code blue team in a hospital?" |
| VAR00014: "Do you believe an intensivist-led care reduces conflict among multiple care teams?" | VAR00020: "Do you believe an early referral of a deteriorating patient in the surgical/medical ward to an intensivist can lead to earlier recognition of critical illness and thus avoid cardiac arrests in the general ward?" |
| VAR00015: "Do you believe an intensivist-led care of critically ill patients reduces the risk of litigation by patients' families?" | VAR00022: "Do you believe that an intensivist should lead the antibiotic stewardship program in the ICU to minimize antibiotic resistance, costs, and side effects?" |
| VAR00017: "Do you think a closed ICU, which is intensivist-led, can lead to smoother decision-making for complex critically ill patients, thus leading to efficient, timely care? | VAR00023: "Do you believe there should be a combined ICU and HDU in a hospital to facilitate smoother transitions of care for critically ill patients and better resource utilization?" |

**Table 4:** ANOVA across different ICU types

| *Variable* | *Overall* | *Open (n = 61)* | *Semi-open (n = 171)* | *Closed (n = 82)* | *p-value* |
|---|---|---|---|---|---|
| Special skills required for acute care vs nonacute care | 4.54 ± 0.60 | 4.34 ± 0.17 | 4.58 ± 0.08 | 4.59 ± 0.11 | 0.297 |
| Cost reduction by avoiding unnecessary tests | 3.93 ± 0.78 | 3.62 ± 0.21 | 3.84 ± 0.11 | 4.32 ± 0.13 | 0.006* |
| Improvement in patient outcomes | 3.28 ± 0.08 | 3.18 ± 0.20 | 3.08 ± 0.11 | 3.75 ± 0.15 | 0.003* |
| Improvement in treatment efficiency | 4.02 ± 0.07 | 3.75 ± 0.19 | 3.96 ± 0.09 | 4.33 ± 0.12 | 0.018* |
| Faster extubation and reduced ventilator days due to intensivist-led care | 4.07 ± 0.69 | 3.82 ± 0.18 | 4.04 ± 0.09 | 4.29 ± 0.12 | 0.075 |
| Reduction in stress on the admitting team with intensivist-led care | 4.33 ± 0.06 | 4.31 ± 0.14 | 4.26 ± 0.09 | 4.48 ± 0.11 | 0.353 |
| Intensivist leadership effectiveness | 3.83 ± 0.07 | 3.62 ± 0.19 | 3.76 ± 0.09 | 4.10 ± 0.12 | 0.053 |
| Reduction of conflicts among care teams with intensivist-led care | 3.78 ± 0.07 | 3.67 ± 0.18 | 3.68 ± 0.09 | 4.05 ± 0.13 | 0.075 |
| Reduction in litigation risk | 3.82 ± 0.07 | 3.63 ± 0.18 | 3.72 ± 0.10 | 4.15 ± 0.12 | 0.021* |
| Clinical privileges for intensivists for bedside procedures | 4.07 ± 0.07 | 3.90 ± 0.17 | 4.09 ± 0.09 | 4.19 ± 0.13 | 0.393 |
| Smoother decision-making for complex cases | 3.72 ± 0.08 | 3.62 ± 0.20 | 3.47 ± 0.10 | 4.27 ± 0.12 | <0.001* |
| Intensivist-led communication with families on end-of-life care | 3.99 ± 0.07 | 3.98 ± 0.17 | 3.87 ± 0.10 | 4.25 ± 0.13 | 0.079 |
| Intensivist as leader of the code blue team | 4.51 ± 0.06 | 4.58 ± 0.11 | 4.53 ± 0.08 | 4.43 ± 0.11 | 0.631 |
| Early referral to intensivists to prevent deterioration in general wards | 4.36 ± 0.06 | 4.12 ± 0.17 | 4.39 ± 0.08 | 4.50 ± 0.12 | 0.118 |
| An intensivist as the leader of a trauma team | 3.75 ± 0.07 | 3.62 ± 0.18 | 3.77 ± 0.10 | 3.81 ± 0.14 | 0.659 |
| Intensivist-led antibiotic stewardship to reduce resistance and costs | 4.11 ± 0.07 | 3.93 ± 0.17 | 4.11 ± 0.10 | 4.23 ± 0.13 | 0.389 |
| Combined ICU and HDU to improve patient transitions and resource use | 4.31 ± 0.06 | 4.32 ± 0.15 | 4.33 ± 0.08 | 4.27 ± 0.13 | 0.902 |
| Need for specialized ICUs (e.g., neurology, cardiac) for specific patient needs | 4.12 ± 0.07 | 3.88 ± 0.18 | 4.12 ± 0.09 | 4.27 ± 0.14 | 0.193 |

*Indicates *p*-value is statistically significant

consistently exhibited higher ratings across questions related to the role of intensivists in leadership effectiveness, patient outcome improvements, cost efficiency, and litigation risk reduction when compared with both semi-open and open ICUs.

## Discussion

One of the reasons for conducting this study was that intensive care, as a specialty, is still underrecognized and undervalued by the medical fraternity, hospital administration, and society in low- and middle-income countries. Although, intensive care units developed in some countries in Asia in the 1960s; the specialty of intensive care is still not recognized in many developing countries, such as Nepal and Pakistan. This is compounded by the fact that training for the specialty, that is, the critical care fellowship programs, existed in only 34, 65, and 67% of ICUs in low-, middle-, and high-income countries, respectively, in 2013–2014, as per the data published by Phua et al. in their study of Asian ICUs.[4] About 87% of nonintensivists surveyed in this study strongly believed that acute care, which involves taking care of critically unwell patients, requires special skills, knowledge, and training, which lends support to the Indian Society of Critical Care Medicine's initiative of putting forth guidelines that standardize the definition of an intensivist.[1] The presence of dual providers in Indian ICUs, that is, the admitting physician/surgeon as well as the intensivist looking after patients, may lead to conflict or disagreements in everyone's roles and responsibilities. The results of our survey indicate that ICU type has a significant impact on the perceptions of nonintensivists about intensivist-led care. The results of our survey also provide reassurance that the nonintensivist in India does understand the role of an intensivist as effective in impacting patient care, especially in closed and semi-open ICUs, in terms of smoother decision-making in complex cases, reduction of cost of care by avoiding unnecessary tests, reducing litigation by patient families, improving treatment efficiency, and better patient outcomes. The impact of closed ICUs on patient outcomes has been studied.

Pronovost et al.,[5] in their systematic review of 26 studies conducted in North America, Europe, and Asia, also found that high-intensity intensive care staffing, that is, in closed ICUs or mandatory ICU consultation, was associated with reduced ICU and hospital mortality, as well as reduced length of stay in ICU and hospital, when compared to ICUs with low-intensity intensive care staffing.[5] A recent systematic review by Vahedian-Azimi et al.[6] looked at 90 studies comparing open vs closed ICUs from around the world and concluded that ICU mortality and length of stay were reduced in a closed ICU model as compared to an open ICU model.[6] The staffing of ICUs in North America has dramatically improved over the last 25 years. In a survey published recently by Gershengorn et al.,[7] out of 554 ICUs, 93% had intensivist coverage, with 53% being present onsite 24 hour/day. However, the situation in developing countries, such as India, is different. In the Intensive Care Unit Needs Assessment Survey (ININ18) by Kashyap et al., which was an extensive national semi-structured needs assessment survey conducted in 134 ICUs across India, 82% were open ICUs, and only 58% had 24-hour in-house intensivist coverage.

Most nonintensivist responders in our survey were senior consultants of medicine who cared for critically ill patients while working in semi-open ICUs, which correlates with data from studies in India.

Most nonintensivists in this survey strongly believed that the intensivist should be the clinical and administrative lead of the ICU, lead the code blue team and trauma team in the hospital. This is a very encouraging finding, which should empower intensivists in taking up these leadership roles in the hospital. Most nonintensivists surveyed also believed that early referral of deteriorating patients to the intensivist can prevent cardiac arrests in the hospital, which is also consistent with the data from the rapid response studies from the UK and Australia.[8,9]

Stress and burnout in healthcare workers in the ICU are a well-recognized worldwide phenomenon, and various critical care societies are undertaking measures to prevent it and avoid loss of workforce.[10–14] The results of this survey also indicate strong agreement among nonintensivist respondents regarding the role of intensivists in reducing stress on the admitting team. There may be multiple reasons for this, due to the centralized leadership of a closed ICU, which can provide seamless care through a single decision-maker with focused insight and prompt, timely decisions.

Care of critically ill patients is complex and dynamic, requiring input from multiple teams and decision-makers regarding therapeutic interventions. This requires effective interdisciplinary communication. Medical malpractice cases have shown that a breakdown of communication is a significant contributing factor in litigation by patient families.[15] The results of this survey highlight the important role an intensivist can play in smoothing out communication with families, which may be an important factor to consider, as litigation cases contribute significantly to the economic burden on the hospital. The potential short-term cost of employing an intensivist by a hospital may bring benefits in the long term, not only to the patients but also to hospital systems.

This study has several drawbacks. The survey tool we used has not been validated in any previous study. We were unable to find any previous surveys on this topic in our PubMed search, so we developed this survey tool. We were unable to accurately calculate the response rate as the survey was widely distributed through WhatsApp. Additionally, the difference in responses from respondents working in various ICU models, which was found to be statistically significant in our study, had not been planned a priori. Although closed ICUs were perceived to have a better impact on patient outcomes due to the presence of an intensivist, only 26.1% of respondents in our survey worked in closed ICUs. This survey tool may be tested in other developing countries where intensive care is still a growing specialty to understand the needs, perceptions, and biases of the nonintensivists toward trained intensivists and their role in managing critically ill patients. By doing this, one can further the cause of improved care and outcomes for these vulnerable, critically ill patients, with the trained intensive care specialist serving as the leader and collaborator. This may be a small step in helping intensive care societies in the developing world build the critical care specialty as an important entity in itself by championing for its own self.

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ORIGINAL ARTICLE

# Utility of $CHA_2DS_2$-VASc Score in Predicting Contrast-induced Nephropathy in Patients with Acute Myocardial Infarction Following Percutaneous Coronary Angiography: A Cross-sectional Study in South India

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## Abstract

**Background:** Contrast-induced nephropathy (CIN) is an iatrogenic impairment to the kidneys that can occur in susceptible persons after intravascular injections of contrast agents. Individuals undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) often bear the risk of developing CIN. The likelihood of CIN can be predicted using several techniques, although none of them are very accurate. $CHA_2DS_2$-VASc score is used to predict unfavorable clinical outcomes in patients with ACS and atrial fibrillation. The score comprises preprocedural variables and is simple to calculate and can be used for predicting CIN. This study aims to validate $CHA_2DS_2$-VASc score to predict occurrence of CIN among patients undergoing PCI.

**Materials and methods:** This cross-sectional research has been carried out at a tertiary care hospital. The study comprised a total of 182 patients who were admitted with ACS and underwent PCI. CIN incidence was computed. The study population was divided into two groups (the CIN group and the non-CIN group) based on the incidence of CIN. The $CHA_2DS_2$-VASc score was computed for every patient. The best cutoff values of the $CHA_2DS_2$-VASc score to predict the development of CIN were found using receiver operating characteristic (ROC) curve analysis. The incidence of CIN was computed both above and below the $CHA_2DS_2$-VASc score's optimal cutoff point.

**Results:** The incidence of CIN among patients undergoing PCI was 14.3%, and the ROC value for the $CHA_2DS_2$-VASc score was 0.896. Statistically significant increases in the incidence of CIN were observed in patients undergoing PCI who had a $CHA_2DS_2$-VASc score of >2. Additionally, a significant relationship was discovered between CIN and age, diabetes, hypertension, prior coronary artery disease (CAD), and Killip class ≥2.

**Conclusion:** Patients with $CHA_2DS_2$-VASc score of >2 had higher incidence of CIN. $CHA_2DS_2$-VASc score was found to be useful in predicting contrast nephropathy among patients with acute myocardial infarction undergoing angiography.


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## Introduction

An iatrogenic kidney injury referred to as contrast-induced nephropathy (CIN) or contrast-induced acute kidney injury (CI-AKI) may occur in individuals who are vulnerable following an intravascular injection of radio-opaque dyes or contrast agents. CIN is defined as a rise in serum creatinine >0.5 mg/dL or >25% from baseline levels 48–72 hours after contrast agent administration, provided that all other possible causes of renal impairment have been ruled out.[1,2]

Patients suffering from both chronic coronary artery disease (CAD) and acute coronary syndromes (ACS) have been reported to develop CIN after percutaneous coronary intervention (PCI). CIN can lead to prolonged hospitalization, need of hemodialysis, and sometimes permanent impairment of kidney function.[3] The incidence of CIN was found to be in the range of 7–25% in various subgroups of patients.[4,5] Therefore, high-risk patients who may develop CIN need to be identified, and preventive therapies to such individuals should be initiated before administration of contrast agents.

The occurrence of CIN has been predicted using numerous risk prediction models. Because of their complexity, these models are impractical for everyday use. The risk factors for the development of CIN are also present among the components of the $CHA_2DS_2$-VASc score. The $CHA_2DS_2$-VASc score has been routinely used to predict the risk of embolic stroke in patients having atrial fibrillation.[6] The $CHA_2DS_2$-VASc score has been known to predict unfavorable clinical events in patients with ischemic heart disease with or without atrial fibrillation.[7–11] It is a scoring system comprising the variables summarized in Table 1.

$CHA_2DS_2$-VASc score has components like presence of hypertension, diabetes mellitus, vascular diseases, cardiac failure, occurrence of transient ischemic attack, and advancing age. These parameters are also the risk factors for developing AKI. $CHA_2DS_2$-VASc score comprises preprocedural variables and is simple to calculate and can be used for predicting CIN. This study aims to validate $CHA_2DS_2$-VASc score to predict CIN among patients undergoing PCI.

## Materials and Methods

### Study Design

A hospital-based cross-sectional study.

### Study Period

February 2021 to October 2022.

### Source of Data

Patients admitted to a tertiary care center in South India for acute myocardial infarction undergoing PCI.

### Study Subjects

Patients admitted with ACS undergoing PCI were included in the study after obtaining informed consent. The study was approved by the Institutional Ethics Committee (MSRMC/EC/PG-01-2021).

### Methods of Collecting Data

A thorough clinical history was obtained. Physical examination was done and recorded. Specific history like symptoms of

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cardiac disease and presence of risk factors like smoking or tobacco use was asked. Comorbidities like diabetes, hypertension, family history of CAD, previous history of CAD, previous atherosclerotic cerebrovascular events, and ongoing medications were taken. Serum creatinine level was measured at admission and was repeated daily up to 48 hours after PCI. Baseline investigations like complete blood count, fasting blood sugar (FBS) and postprandial blood sugar, and fasting lipid profile were done. Two-dimensional (2D) echocardiography was used to calculate the left ventricular ejection fraction (LVEF). CIN was defined as a rise in serum creatinine >0.5 mg/dL or >25% from baseline levels after 48–72 hours of contrast agent administration, provided that all other possible causes of renal impairment had been ruled out.[1,2] The study population was divided into two groups (the CIN group and the non-CIN group) based on the incidence of CIN. The $CHA_2DS_2$-VASc score was computed for every patient. The best cutoff values of the $CHA_2DS_2$-VASc score to predict the development of CIN were found using receiver operating characteristic (ROC) curve analysis.

After ROC curve analysis, enrolled patients were further divided into two groups according to $CHA_2DS_2$-VASc score. The incidence of CIN above and below the optimum cutoff value of $CHA_2DS_2$-VASc score was calculated.

**Table 1:** $CHA_2DS_2$-VASc parameters and the scores

| *$CHA_2DS_2$-VASc score and its parameters* | *Score* |
|---|---|
| C: Congestive cardiac failure | 1 |
| H: Hypertension | 1 |
| A: Age >75 years | 2 |
| D: Type 2 diabetes mellitus | 1 |
| S: Prior history of stroke or transient ischemic attack | 2 |
| V: Vascular disease | 1 |
| A: Age 65–74 years old | 1 |
| Sc: Sex category (female) | 1 |

## Inclusion Criteria

Patients aged ≥18 years with ACS comprising both ST-elevation myocardial infarction (STEMI) and non-STEMI planned (elective or emergency) for PCI. Age ≥18 years, received iodinated contrast media during PCI.

## Exclusion Criteria

Patients who did not give informed consent to take part in the study; patients with end-stage renal disease (ESRD) on dialysis; AKI prior to PCI (confounds CIN diagnosis); use of nephrotoxic drugs during the CIN risk window (e.g., aminoglycosides, amphotericin B); patients with known contrast allergy (may receive special precautions affecting contrast dose and hydration); pregnancy (different renal physiology and ethical considerations); and severe hemodynamic instability or cardiogenic shock prior to PCI (may independently affect kidney function and increase bias) were excluded.

## Sample Size Estimation

As per the study by Chaudhary et al.,[12] which included 300 patients, CIN was reported in 41 patients (13.7%). The $CHA_2DS_2$-VASc score was found to be an excellent predictor of CIN, according to ROC curve statistics [area under the curve (AUC) 0.81, 95% CI: 0.73–0.90]. Individuals with a score of four or higher were more likely to have CIN than those with a score of <3 ($p = 0.0001$). In the present study, expecting a similar result with 5% level of significance, 5% absolute precision, and 90% power, it was estimated that a minimum of 182 patients need to be recruited for the study.

## Statistical Analysis

Frequencies and proportions are utilized to present categorical data. The Fisher's exact test or the Chi-squared test is used for assessing the statistical significance of qualitative data. Continuous data is represented in the form of mean and standard deviation. For the $CHA_2DS_2$-VASc score and the incidence of CIN in patients following PCI, ROC curves were generated. Values for specificity, sensitivity, and positive and negative predictiveness were calculated. An area under the ROC curve of 0.5 indicates that a test predicts an outcome no better than chance. A ROC curve area <0.8 signified a well-predicted outcome. The significance of two quantitative variables was tested using the independent *t*-test. Assuming that all statistical test rules are followed, a *p*-value (probability that the result is true) of <0.05 was deemed statistically significant.

## Statistical Software

MS Excel and SPSS version 22 (IBM SPSS Statistics, Somers, NY, USA) were used to analyze data.

# Results

The study comprised 182 patients with age-group ranging from 28 to 89 years. Mean age of patients studied is 62 years [standard deviation (SD) 13]. Age-group from 61 to 70 years accounts for 31.9% of the study population ($N = 58$). About 71.4% ($N = 130$) of the patients were males, and 28.6% ($N = 52$) were females. A total of 14.3% ($N = 26$) developed CIN after PCI, while 85.7% ($N = 156$) did not develop CIN after PCI ($p = 0.002$). About 53.8% ($N = 14$) among the age-group of 61–70 years developed CIN, and 38.5% ($N = 10$) in the age-group of 71–80 years developed CIN, while none of the patients <40 years developed CIN (Table 2).

About 76.9% ($N = 20$) of male patients and 23.1% ($N = 6$) of female patients developed CIN. This gender difference was not statistically significant ($p = 0.065$). Mean age of patients who developed CIN was 69 ± 10 years (SD). Subjects with a mean ejection fraction of 42 ± 5% developed CIN ($p < 0.001$); however, subjects with a mean ejection fraction of 52 ± 4% did not develop CIN. Subjects with mean baseline estimated glomerular filtration rate (eGFR) of 71.26 ± 17.7 mL/minute were at risk of developing CIN ($p < 0.002$). In this study, it was also noted that the volume of contrast used in PCI was directly linked with the risk of developing CIN. Mean contrast volume of 200 ± 73 mL had a statistically significant risk of developing CIN ($p < 0.001$) (Table 3).

**Table 2:** Distribution of subjects according to CIN and age-group

| *Age-group (years)* | *Non-CIN* | | *CIN* | | *p-value* |
|---|---|---|---|---|---|
| | *N* | *%* | *N* | *%* | |
| <40 | 13 | 8.3 | 0 | 0.0 | 0.002 |
| 41–50 | 17 | 10.9 | 2 | 7.7 | |
| 51–60 | 46 | 29.5 | 0 | 0.0 | |
| 61–70 | 44 | 28.2 | 14 | 53.8 | |
| 71–80 | 36 | 23.1 | 10 | 38.5 | |

Of the total 54 diabetic patients, 19 patients developed CIN ($p < 0.001$). Among 82 hypertensive patients, 19 patients developed CIN ($p < 0.01$). Ten out of 24 patients with previous CAD developed CIN ($p < 0.001$) (Table 4).

Among the 182 subjects, 168 patients received iohexol as contrast media for PCI, and 14 patients received iodixanol as contrast media. All patients who developed CIN ($N = 26$) in this study had iohexol used as the contrast media for PCI. None of the patients where iodixanol was used developed CIN. These findings are summarized in Table 4.

Area under the ROC curve was 0.896, standard error of 0.0248 (95% CI: 0.842–0.936) with $p < 0.0001$. Optimal cutoff point of $CHA_2DS_2$-VASc score for predicting CIN is 2, with a sensitivity of 92.3% and specificity of 75.6% (Table 5 and Fig. 1).

About 33 out of 77 patients with multiple vessel CAD and 38 out of 91 patients with multiple vessel stenting had a $CHA_2DS_2$-VASc score >2, which had a statistically significant correlation ($p = 0.04$). Again 32 out of 69 patients using ACE inhibitors and 26 out of 42 patients using metformin had a $CHA_2DS_2$-VASc score >2, which was statistically significant ($p = 0.01$ and <0.001, respectively) (Table 6).

**Table 5:** Sensitivity, specificity, PPV, and NPV of $CHA_2DS_2$-VASc in predicting CIN

| | *Value* | *95% CI* |
|---|---|---|
| Sensitivity | 92.31% | 74.9–99.1% |
| Specificity | 75.64% | 68.1–82.1% |
| PPV | 38.7% | 26.6–51.9% |
| NPV | 98.3% | 94.1–99.8% |

PPV, positive predictive value; NPV, negative predictive value

**Table 3:** Comparison of age and laboratory parameters according to CIN

| | *Non-CIN* | | *CIN* | | *p-value* |
|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | |
| Age (years) | 61 | 13 | 69 | 10 | 0.005 |
| LVEF (%) | 52 | 4 | 42 | 5 | <0.001 |
| Hemoglobin (gm/dL) | 12.63 | 1.58 | 12.56 | 0.99 | 0.824 |
| Baseline serum creatinine (mg/dL) | 0.87 | 0.34 | 1.05 | 0.28 | 0.015 |
| Creatinine at 48 hours | 0.9212 | 0.365 | 1.57 | 0.4539 | <0.001 |
| Baseline eGFR (mL/minute) | 87.37 | 24.94 | 71.26 | 17.72 | 0.002 |
| Contrast volume (mL) | 127 | 44 | 200 | 73 | <0.001 |

**Table 4:** Comparison of various factors according to CIN

| | *Non-CIN* | | *CIN* | | *p-value* |
|---|---|---|---|---|---|
| | *N* | *%* | *N* | *%* | |
| Diabetes | 35 | 22.4 | 19 | 73.1 | <0.001 |
| Hypertension | 63 | 40.4 | 19 | 73.1 | 0.003 |
| Dyslipidemia | 32 | 20.5 | 7 | 26.9 | 0.447 |
| Smoking | 50 | 32.1 | 13 | 50.0 | 0.117 |
| Tobacco use | 25 | 16.0 | 5 | 19.2 | 0.775 |
| Previous CAD | 14 | 9.0 | 10 | 38.5 | <0.001 |
| Previous CABG | 4 | 2.6 | 1 | 3.8 | 0.542 |
| PVD | 4 | 2.6 | 6 | 23.1 | <0.001 |
| Killip class ≥2 | 16 | 10.3 | 18 | 69.2 | <0.001 |
| NSTEMI | 101 | 64.7 | 9 | 34.6 | <0.005 |
| STEMI | 55 | 35.3 | 17 | 65.4 | |
| Iohexol | 142 | 91.0 | 26 | 100.0 | 0.226 |
| Iodixanol | 14 | 9.0 | 0 | 0.0 | |
| Multivessel CAD (no. of vessels ≥2) | 54 | 34.6 | 23 | 88.5 | <0.001 |
| Use of ACE inhibitors/ARB | 56 | 35.9 | 13 | 50.0 | 0.194 |

**Table 6:** Comparison of angiographic and medical therapy related factors according to $CHA_2DS_2$-VASc score

| | *<2 score* | | *>2 score* | | *p-value* |
|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | |
| Age | 56 | 11 | 73 | 8 | <0.001 |
| LVEF (%) | 52 | 5 | 48 | 6 | <0.001 |
| Hb (gm/dL) | 12.9492 | 1.5858 | 12.0032 | 1.1491 | <0.001 |
| Baseline serum creatinine (mg/dL) | 0.8838 | 0.3712 | 0.9437 | 0.2772 | 0.265 |
| Creatinine at 48 hours | 0.9280 | 0.3944 | 1.1823 | 0.4820 | <0.001 |
| Baseline eGFR (mL/minute) | 91.6356 | 25.1958 | 72.3802 | 17.8258 | <0.001 |
| Contrast volume (mL) | 131 | 46 | 151 | 69 | 0.043 |
| Multivessel CAD (no. of vessels ≥2) | 44 | 36.7% | 33 | 53.2% | 0.040 |
| Use of ACE inhibitors/ARB | 37 | 30.8% | 32 | 51.6% | 0.010 |
| Previous use of metformin | 16 | 13.3% | 26 | 41.9% | <0.001 |

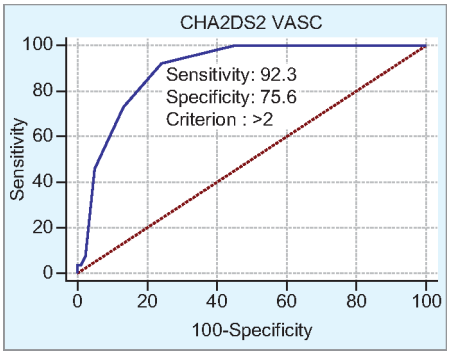


**Fig. 1:** ROC curve for $CHA_2DS_2$-VASc in predicting CIN

## Discussion

Contrast-induced nephropathy is a major complication and can lead to increased morbidity and mortality among patients following PCI for ACS.[13,14]

Early detection of CIN is important as patients will require closer monitoring of vital parameters and fluid control.[15] Congestive heart failure (CHF), renal impairment, age, female sex, and diabetes mellitus are known risk factors for CIN.[16–19] The parameters are also the components of $CHA_2DS_2$-VASc score.[1] Its use can be extended to nonatrial fibrillation populations[7–11,20,21] to help in risk stratification of high-risk individuals. In individuals with stable CAD and ACS, an elevated $CHA_2DS_2$-VASc score has been predictive of unfavorable clinical outcomes.[7–11,22,23] The purpose of this study was to ascertain whether the $CHA_2DS_2$-VASc score could be utilized to predict CIN in ACS patients receiving PCI.

This study indicated that 14.3% of patients undergoing PCI for ACS had CIN, which was similar to the study conducted by Chaudhary et al.,[12] where the incidence of CIN was found to be 13.7%. Similarly, the incidence of CIN was 11.3% in a study by Kurtul et al.[1] and 16.3% in a study by Wang et al.[23] However, the incidence was higher in a study conducted by Cicek and Yıldırım,[24] which was 23.3% compared to our study, and the incidence was lower in a study conducted by Kumar et al.,[25] where it was 9.1%.

The present study showed that the incidence of CIN increased with the age of the patients. This result corresponded with those of Wang et al.[23] and Kumar et al.[25] The study conducted by Chaudhary et al.,[12] however, did not show any statistically significant difference between age-groups and the development of CIN. There was no statistical correlation between gender distribution and CIN.

Presence of comorbidities like diabetes and hypertension showed a positive correlation with the development of CIN. About 73.1% of patients who developed CIN in the study were diabetic and hypertensive. This finding was consistent with previous studies[1,14,22–26] and shows that patients with these comorbidities are at high risk of developing CIN, and appropriate preventive strategies should be employed in these patients.

Other comorbidities, like a previous history of CAD and peripheral vascular disease, accounted for 38.5 and 23.1% of patients who developed CIN, respectively. History of CAD also had a similar relationship with CIN in studies conducted by Chaudhary et al.[12] and Cicek and Yıldırım.[24]

This study was the first to compare the risk of CIN with multiple comorbidities, which was statistically significant ($p$-value < 0.001). About 92.3% of the patients who had CIN had a history of multiple comorbidities.

Killip class >2, multivessel CAD, multivessel PCI, and CIN showed a $p$-value of <0.001, which was significant. Studies like Chaudhary et al.[12] also ascertained this relationship.

Interesting to note that in the study, of the 14 patients who received iodixanol as the contrast agent, none developed CIN. With regard to the volume of contrast media administered, in the CIN group, the volume of contrast was 200 ± 73 mL, and for the non-CIN group, 127 ± 44 mL was used ($p$ < 0.001). Patients in whom a higher amount of contrast volume is used are prone to CIN. It was observed that the patients with CIN had a lower baseline eGFR. Mean eGFR in Kurtul et al.[1] and Chaudhary et al.[12] was 52.4 ± 19.5 and 83.76 ± 19.22 mL/minute, respectively.

Receiver operating characteristic curve analysis of the study data showed a good predictive value of $CHA_2DS_2$-VASc score for predicting CIN in patients undergoing PCI for ACS, with AUC of 0.896 (0.842–0.936). $CHA_2DS_2$-VASc score of >2 had a sensitivity of 92.31% (CI: 74.9–99.19) and specificity of 75.64% (CI: 68.1–82.1), with a $p$-value of <0.001. Patients with $CHA_2DS_2$-VASc score of >2 had a significantly higher incidence of CIN.

Patients with $CHA_2DS_2$-VASc score of >2 had a significantly higher number of patients with diabetes (51.6%), hypertension (72.6%), history of CAD (25.8%), CVA (24.2%), Killip class ≥2 (35.5%) with $p$-value < 0.001, and PVD (11.3%) with $p$-value of 0.033.

In patients with normal renal function, the course of CIN is often benign and is almost always followed by full recovery.[12] In this study, two patients out of the 26 CIN cases required dialysis. Two sessions of hemodialysis were needed in these patients, but both recovered from CIN eventually.

Several risk models have been developed to predict CIN following PCI.[27–29] Mehran risk score is one such score, which includes multiple clinical and procedural parameters such as hypotension, use of intraaortic balloon pump, and contrast volume. Though robust and validated, the Mehran score requires data that may not always be readily available before the procedure. Other models, like the age, creatinine, ejection fraction (ACEF) score and the National Cardiovascular Data Registry (NCDR) risk score (age, diabetes, anemia, CHF, renal function, contrast volume), also incorporate laboratory and echocardiographic findings, which may not be feasible to calculate quickly in all clinical settings. In contrast, the $CHA_2DS_2$-VASc score is simple, bedside-friendly, and composed entirely of clinical variables that are routinely available, particularly in settings where rapid and simple risk stratification is needed.

The confounding factors were controlled in the study. Due to the limited sample size and the observational nature of the study, multivariate regression was not conducted. However, the results provide valuable initial evidence supporting the predictive role of $CHA_2DS_2$-VASc score in this population. Although a statistically significant association was observed between the $CHA_2DS_2$-VASc score and CIN, causality cannot be firmly established. The study was conducted at a single center with a modest sample size of 182 patients, which may limit generalizability. Nevertheless, the findings provide important preliminary evidence suggesting the potential utility of the $CHA_2DS_2$-VASc score as a simple and effective tool to stratify CIN risk in patients undergoing PCI.

The significant association between higher $CHA_2DS_2$-VASc scores and CIN observed in this study highlights the potential of this scoring system beyond its traditional use in atrial fibrillation. The ease of calculating the score and the availability of its components at the bedside make it a practical option for early risk stratification in the Indian clinical setting, particularly where access to more sophisticated predictive tools may be limited. While our results are consistent with findings from studies conducted in other countries, they also reflect local demographic and clinical characteristics that may influence CIN risk. Further research involving larger populations and multivariate modeling is required to establish the independent predictive value of the score.

## Conclusion

According to this study, in patients with ACS undergoing PCI, $CHA_2DS_2$-VASc score of more

than two is independently correlated with the incidence of CIN. To predict CIN risk, $CHA_2DS_2$-VASc score is an innovative and inexpensive scoring system.

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ORIGINAL ARTICLE

# Clinical Biochemical Profile and Outcomes of Cerebral Venous Thrombosis in Puerperal and Nonpuerperal Presentation: A Prospective Observation Study from Northwest India

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## Abstract

**Background:** Cerebral venous thrombosis (CVT) is a rare but treatable cause of stroke, predominantly affecting younger individuals, particularly women during the puerperal period. Despite increased recognition through advanced imaging, clinical diagnosis remains challenging due to its diverse presentation and varying etiological factors.

**Objective:** To evaluate the clinical profile, etiological factors, treatment outcomes, and prognosis of CVT patients, with a focus on comparing puerperal and nonpuerperal cases in a tertiary care setting in Northwest India.

**Materials and methods:** This prospective observational study included 80 adult patients diagnosed with CVT *via* computed tomography venography (CTV) or magnetic resonance venography (MRV) over a 2-year period. Participants were categorized into male, puerperal female, and nonpuerperal female groups. Detailed clinical, laboratory, and radiological evaluations were performed. Modified Rankin Scale (mRS) was used to assess neurological outcomes. Statistical analyses were conducted using analysis of variance (ANOVA) and Chi-squared tests with significance at $p < 0.05$.

**Results:** Puerperal females were younger than other groups. Common symptoms included headache (85%), seizures (45%), and focal deficits (47.5%). Hyperhomocysteinemia (65%) and vitamin B12 deficiency (51.25%) were prevalent, particularly among males and nonpuerperal females. Anemia was significantly more common in females. No significant difference was noted in clinical outcomes across groups. Poor prognosis was associated with Glasgow Coma Scale (GCS) <8, focal deficits, and low vitamin B12 levels. In-hospital mortality was 6.25%; 97% of survivors had favorable outcomes (mRS <3) at 3 months.

**Conclusion:** CVT in Northwest India affects a significant number of males and nonpuerperal females. Nutritional deficiencies, particularly vitamin B12 and anemia, play a crucial role. Early diagnosis and appropriate anticoagulation therapy are critical for favorable outcomes.


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## Introduction

Cerebral venous thrombosis (CVT) is a rare cause of stroke, with an annual incidence of 2–4 per million, and accounts for 0.5–1% of strokes.[1] CVT is more prevalent among women aged 20–35 due to pregnancy, puerperium, and contraceptive use.[2,3] Enhanced awareness and imaging have led to more frequent diagnoses, though clinical recognition remains difficult due to its wide presentation spectrum. CVT aligns with Virchow's triad—stasis, endothelial injury, and hypercoagulability. Risk factors include acquired (e.g., pregnancy, trauma, and cancer) and genetic (e.g., Factor V Leiden, protein C/S deficiency) causes.[2,4] The superior sagittal sinus (72%) and lateral sinuses (70%) are most frequently affected,[2] often with multisinus involvement.[5] Pregnancy and puerperium significantly increase thrombotic risk due to hypercoagulability and volume depletion.[6] Up to 80% of CVT patients have identifiable risk factors,[7] while 10–15% have hereditary thrombophilia[8]; 20–30% remain idiopathic.[2]

Common symptoms include headache (~90%), focal deficits such as hemiparesis and aphasia, and sometimes isolated mental status changes—especially with deep venous thrombosis.[5,9] Diagnosis relies on imaging: noncontrast computed tomography (CT) may show hyperdensity; contrast-enhanced CT can reveal the "empty delta" sign.[8,10] Magnetic resonance imaging (MRI)/magnetic resonance venography (MRV) offers higher sensitivity, with evolving thrombus signals over time.[11] Computed tomography venography (CTV) and contrast MRV are used when plain MRV is inconclusive.[2,12]

Coagulation profiles are important for unexplained or familial cases and must be timed appropriately[4] Historically diagnosed postmortem with high mortality (30–50%), modern diagnosis and treatment have reduced mortality to 5.5–18%, with 57–86% achieving full recovery. Poor outcomes are linked to infancy, older age, coma, and deep venous involvement.[3,7,13–15]

In India, particularly northwest regions, CVT incidence is uncertain due to lack of population-based studies. This study explores CVT cases from a tertiary hospital in Northwest India, comparing puerperal and nonpuerperal cases and evaluating clinical patterns, causes, outcomes, and treatment response.

## Materials and Methods

This hospital-based, descriptive, prospective observational study was conducted at a tertiary care teaching hospital and research institute, from Northwest India. All patients aged ≥18 years diagnosed with CVT, confirmed *via* MRV or CTV, presenting over the 2-year study period were included. Patients <18 years, those who left against medical advice before the outcome endpoint, or had incomplete data, were excluded.

The sample size was calculated at a 95% confidence level, assuming a seizure prevalence of 29.4% in CVT cases,[16] requiring a minimum of 80 subjects at 10% allowable error. Ethical approval was obtained from the Institutional Ethics Committee prior to study initiation, and written informed consent was taken from all patients prior to inclusion in the study.

Participants were categorized into male and female groups, with the latter subdivided into puerperal (within 6 weeks postpartum)

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and nonpuerperal subgroups. A detailed history (lifestyle, comorbidities, and family history), physical examination, and relevant laboratory and imaging investigations were recorded on a structured proforma.

Investigations included routine blood tests [complete blood count (CBC), erythrocyte sedimentation Rate (ESR), electrolytes, glucose, liver function tests (LFTs), and renal function tests (RFTs)], human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), antinuclear antibody (ANA), venereal disease research laboratory (VDRL), folate, vitamin B12, homocysteine, antiphospholipid antibodies (APLA), electrocardiogram (ECG), chest X-ray, and MRV/CTV. Cerebrospinal fluid (CSF) analysis was done when clinically indicated. Neurological deficits or disability were assessed using mRS. "Best mRS" was recorded within the first 3 days of admission to avoid postictal bias. Only clinically discharged patients (fit for home care) were included in the outcome analysis.

Statistical analysis was performed using MedCalc v16.4. Continuous variables were analyzed using analysis of variance (ANOVA); categorical variables using Chi-square or Fisher's exact test. A $p$-value < 0.05 was considered statistically significant.

## Results

Puerperal females were relatively younger in age. Alcohol was used by 10/38 (26.32%) male patients. History of oral contraceptive pill (OCP) use was given by 6/28 (21.43%) of the nonpuerperal females (Table 1). Headache (85%), seizure (45%), and focal deficit (47.5%) were the most common clinical features among patients with CVT. Papilledema was noticeable in 21 (26.3%) cases. No significant difference was seen in clinical presentation among male and female cases. No significant difference was seen in APLA positivity among male and female cases (Table 2). Mean hemoglobin level and hematocrit were significantly lower among females (both puerperal and nonpuerperal) as compared to males ($p < 0.001$). ESR was significantly higher among females (both puerperal and nonpuerperal). Homocysteine level was significantly higher in males (39.3%). No significant difference was seen in vitamin B12 and folate levels (Table 3). No significant difference was seen in mRS at admission, discharge, or 3 months between males, puerperal, and nonpuerperal females (Table 4). Glasgow Coma Scale (GCS) <8, presence of focal deficit, and lower vitamin B12 were significantly associated with poor prognosis at 3 months follow-up (Table 5).

## Discussion

This study was a prospective, single-center study done in a tertiary care hospital in Northwest India. A total of 80 patients were included, and a detailed evaluation of all the patients was done, including demographic data, clinical features, radiological findings, and prothrombotic workup. To the best of our knowledge, this is the first study on CVT from Northwest India, particularly Rajasthan. Panagariya and Maru published a study from this region limited only to puerperal females and did not include other etiological or demographic features of CVT.[17]

Our study showed a large number of male (47.5%) and nonpuerperal female (35%) patients. A study conducted in the West (ISCVT trial) showed a female predominance with a 3:1 female-to-male ratio.[8] However, Indian studies, including those by Pai et al., Christopher et al., and Khelaeni et al., reported higher male predominance, similar to our findings.[18–20] This may be explained by cultural factors, differing risk profiles, and possibly genetic or environmental variations.

The mean age of patients in our study was 34 years, which is in accordance with Indian data.[20,21] Puerperal CVT was noted in 17.5% of patients with a mean age of 27.85 years, younger than the overall cohort, due to the early age of marriage and childbirth in this region.

Hyperhomocysteinemia was found in 65% of patients, which is much higher than in Western and Indian studies.[17,22,23] In our study, 51.25% of patients had vitamin B12 deficiency, which likely contributes to this

**Table 1:** Demographics

| *Parameters* | *Male (N = 38)* | *Puerperal females (N = 14)* | *Nonpuerperal females (N = 28)* | *p-value* | *p-value* | | |
|---|---|---|---|---|---|---|---|
| | | | | | *A vs B* | *A vs C* | *B vs C* |
| Age | 34.79 ± 14.45 | 24.29 ± 2.95 | 38.04 ± 12.47 | 0.005 | 0.002 | 0.262 | 0.010 |
| Alcohol | 10 (26.32%) | 0 | 0 | 0.002 | 0.046 | 0.004 | NA |
| OCPs | | 0 | 6 (21.43%) | | | | |
| Gravid | | | | | | | |
| Nulli | | 0 | 3 (10.71%) | | | | |
| Primi | | 5 (35.71%) | 2 (7.14%) | | | | 0.042 |
| Multi | | 9 (64.29%) | 23 (82.14%) | | | | |

A, males; B, puerperal females; C, nonpuerperal females

**Table 2:** Clinical profile

| *Parameters* | *Male (N = 38)* | *Puerperal females (N = 14)* | *Nonpuerperal females (N = 28)* | *Total* | *p-value* |
|---|---|---|---|---|---|
| Headache | 33 (86.8%) | 13 (92.9%) | 22 (78.6%) | 68 (85%) | 0.430 |
| Seizure | 17 (44.7%) | 5 (35.7%) | 14 (50%) | 36 (45%) | 0.680 |
| Focal deficit | 18 (47.4%) | 6 (42.9%) | 14 (50%) | 38 (47.5%) | 0.908 |
| Altered sensorium | 7 (18.4%) | 1 (7.1%) | 4 (14.3%) | 12 (15%) | 0.595 |
| Idiopathic intracranial hypertension (IIH)-like presentation | 2 (5.3%) | 2 (14.3%) | 1 (3.6%) | 5 (6.3%) | 0.377 |
| Papilledema | 11 (28.9%) | 4 (28.6%) | 6 (21.4%) | 21 (26.3%) | 0.772 |
| APLA positive | 4 (10.53%) | 0 | 3 (10.71%) | 7 (8.8%) | 0.443 |

**Table 3:** Laboratory profile and hospital stay among CVT patients

| *Parameters* | *Male (N = 38)* | *Puerperal females (N = 14)* | *Nonpuerperal females (N = 28)* | *p-value* |
|---|---|---|---|---|
| Hemoglobin | 14.1 ± 2.46 | 10.58 ± 2.25 | 10.89 ± 2.72 | <0.001 |
| Hematocrit | 42.59 ± 5.76 | 34.44 ± 7.28 | 35.71 ± 7.71 | <0.001 |
| ESR | 20.5 ± 13.03 | 44.57 ± 30.4 | 45.75 ± 31.53 | <0.001 |
| Body mass index (BMI) | 23.1 ± 1.54 | 22.81 ± 1.06 | 25.53 ± 4.03 | <0.001 |
| Homocysteine | 39.3 ± 32.28 | 11.16 ± 4.49 | 18.97 ± 10.15 | <0.001 |
| Vitamin B12 | 252.33 ± 134.24 | 266.92 ± 45.65 | 233.65 ± 70.52 | 0.064 |
| Folate | 4.02 ± 2.06 | 3.95 ± 1.48 | 4.96 ± 2.6 | 0.185 |
| Hospital stay (days) | 12.35 ± 11.02 | 10.07 ± 6.08 | 10.63 ± 5.13 | 0.608 |

**Table 4:** Comparison of mRS among different groups

| | | *Group* | | | | | | *Total* | | *p-value* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Male* | | *Puerperal* | | *Nonpuerperal* | | | | |
| | | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | |
| mRS at admission | <3 | 22 | 57.89 | 9 | 64.29 | 20 | 71.43 | 51 | 63.75 | 0.527 |
| | ≥3 | 16 | 42.11 | 5 | 35.71 | 8 | 28.57 | 29 | 36.25 | |
| mRS at discharge | <3 | 32 | 84.21 | 13 | 92.86 | 23 | 82.14 | 68 | 85.00 | 0.645 |
| | ≥3 | 6 | 15.79 | 1 | 7.14 | 5 | 17.86 | 12 | 15.00 | |
| mRS at 3 months | <3 | 29 | 93.55 | 13 | 100.0 | 24 | 100.0 | 66 | 97.06 | 0.292 |
| | ≥3 | 2 | 6.45 | 0 | 0.00 | 0 | 0.00 | 2 | 2.94 | |

**Table 5:** Factors associated with poor prognosis at 3-month follow-up

| *Variable* | *Good prognosis mRS <3 (N = 73)* | *Poor prognosis mRS ≥3 (N = 7)* | *p-value* |
|---|---|---|---|
| GCS <8 | 3 (4.1%) | 3 (42.9%) | 0.003 |
| GCS ≥8 | 70 (95.9%) | 4 (57.1%) | |
| Focal deficit | 31 (42.5%) | 7 (100%) | 0.012 |
| Vitamin B12 level | 269.1 ± 199.1 | 169.9 ± 16.89 | 0.028 |

high prevalence. Vitamin B12 deficiency was found exclusively in males and nonpuerperal females, possibly due to antenatal B12 supplementation in pregnant females. An inverse relationship between vitamin B12 and homocysteine levels was found, supporting the role of nutritional deficiency in thrombosis risk.[24,25]

Antiphospholipid antibodies was positive in 8.75% of patients, consistent with other studies.[17,22,26] Anemia was found in 43.75% of patients and in 64.29% of female patients. The high incidence of anemia, particularly in females, is a modifiable risk factor for CVT and should be addressed through nutritional and public health interventions.

Among males, alcohol intake was the second most common risk factor after hyperhomocysteinemia and was not reported in any female patients. This is consistent with the cultural pattern of alcohol consumption in the region. OCP intake was reported in 20% of females, similar to other Indian studies,[20,27] and lower than Western studies.[8] No significant seasonal variation was found, though most cases presented in summer and monsoon seasons, possibly due to dehydration or other climatic factors.[28]

Headache was the most common presenting symptom, followed by seizures and focal deficits, aligning with prior studies.[17,20,22] Papilledema was present in 25% of patients, indicating that its absence should not exclude the diagnosis. Neuroimaging showed that the superior sagittal sinus, transverse sinus, and sigmoid sinus were the most commonly involved sinuses, consistent with other studies.[17] Hemorrhagic infarcts were found in 21.25% of patients.

Most patients received anticoagulation, including those with hemorrhagic infarcts, following standard recommendations.[17] Decompressive craniectomy was done in five patients; two of them died. The relatively high mortality in these cases emphasizes the importance of early recognition of increased intracranial pressure and prompt neurosurgical intervention.

The in-hospital mortality was 6.25%, which is comparable with other studies.[17,20,21] On follow-up, 97% of patients had an mRS <3, indicating a good outcome. Poor outcome was associated with low GCS at admission and focal neurological deficits, as supported by earlier studies.[29]

In conclusion, our study provides valuable insights into the demographic and etiological profile of CVT in Northwest India. Male and nonpuerperal female patients represent a significant burden of the disease. Hyperhomocysteinemia, vitamin B12 deficiency, and anemia were common, especially in males and nonpuerperal females. Early diagnosis, appropriate anticoagulation, and identification of poor prognostic indicators are key to improving outcomes.

## Conclusion

Cerebral venous thrombosis is a treatable cause of stroke with a generally favorable prognosis. Our study highlights its higher incidence in males and nonpuerperal populations, with hyperhomocysteinemia and vitamin B12 deficiency as key risk factors, along with anemia, oral contraceptive use, and alcoholism. The most common symptoms were headache, seizures, focal deficits, and

altered sensorium, with papilledema being the most frequent sign. Poor outcomes were linked to focal deficits and low GCS scores at admission. Anticoagulation therapy, even with hemorrhagic infarction, is recommended. Early imaging and screening for hyperhomocysteinemia and vitamin B12 deficiency are essential for diagnosis and treatment. This study, the first broad hospital-based analysis from Rajasthan, underscores regional variations in CVT's pathophysiology and presentation.

## Key Message

Cerebral venous thrombosis, increasingly recognized in both puerperal and nonpuerperal patients, often presents with reversible risk factors such as vitamin B12 deficiency and anemia, underscoring the importance of early diagnosis and targeted treatment for favorable outcomes.

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ORIGINAL ARTICLE

# Usage of Guideline-directed Medical Therapy in Patients with Heart Failure and Reduced Ejection Fraction in a Tertiary Care Hospital

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## Abstract

**Objective:** To assess the prevalence of guideline-directed medical therapy (GDMT) and identify reasons for nonprescription and dose optimization in heart failure patients with reduced ejection fraction (HFrEF) in a tertiary care hospital in southern India.

**Methods:** A cross-sectional study was conducted in a tertiary care hospital involving HFrEF patients. Patients with heart failure were categorized based on GDMT prescriptions. Reasons for nonprescription and suboptimal dosing were identified.

**Results:** The study included 102 HFrEF patients with a mean age of 54 ± 11.7 years, predominantly male (89%). Only 10.8% of patients received GDMT at optimal doses. Although 62% were on triple therapy, many had one or more medications at suboptimal doses. Additionally, 26% of patients were not prescribed all recommended drug classes. Notably, the majority of patients with renal impairment fail to receive triple therapy. Barriers identified included hemodynamic issues and renal dysfunction.

**Conclusion:** GDMT adherence in HFrEF patients is significantly lower than expected, with only 10.8% receiving therapy at recommended doses. Key issues include suboptimal dosing and incomplete prescription of drug classes, influenced by patient-specific factors and systemic barriers.


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## Introduction

Heart failure (HF) is a common and serious health condition that significantly impacts morbidity and mortality worldwide. With >64 million individuals affected globally and an increasing incidence in India, estimated between 0.5 and 1.7 per 1,000 persons annually and a prevalence of 1.3–4.6 million, the burden of HF is substantial.[1–3]

For individuals with heart failure with reduced ejection fraction (HFrEF), clinical guidelines from both the American Heart Association (AHA) and the European Society of Cardiology (ESC) advocate for the use of guideline-directed medical therapy (GDMT). This typically includes angiotensin receptor–neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs), along with beta-blockers and mineralocorticoid receptor antagonists (MRAs).[4,5] More recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors have been added to the GDMT regimen due to their proven effectiveness in managing heart failure.[6] Following these clinical guidelines is essential, as individuals who do not receive GDMT face a 37% higher risk of death compared to those who do.[6] Additionally, not initiating GDMT prior to the placement of a primary prevention implantable cardioverter-defibrillator (ICD) has been linked to notably reduced survival rates within the 1st year.[7]

Despite well-established evidence supporting GDMT for improving outcomes and minimizing hospital admissions,[8] many HFrEF patients remain undertreated or do not attain the recommended therapeutic doses. Studies indicate that only 25–50% of HF patients reach target dosages.[9] The reasons for nonprescription and suboptimal dosing of GDMT are not well understood, highlighting the need for further investigation into these gaps. This study aims to assess the prevalence of GDMT prescriptions, evaluate adherence to recommended dosages, and identify potential factors contributing to GDMT nonprescription and suboptimal dosing in a tertiary care hospital setting.

By analyzing these factors, the study seeks to provide insights into improving GDMT adherence and optimizing patient outcomes in HFrEF management.

## Methods

A cross-sectional study was carried out at a tertiary care hospital in southern India, which included HFrEF patients attending the cardiology OPD over a 2-month period (December 2023–January 2024).

### Study Procedure

The investigator identified patients meeting the inclusion and exclusion criteria from those attending the cardiology OPD. Information collected from case sheets and electronic medical records included are mentioned below.

Patient parameters such as age, gender, hospital number, pulse rate, blood pressure, serum creatinine, serum potassium, cause of HF, duration of treatment, ejection fraction, and comorbidities.

Drugs prescribed along with dosages.

Based on the drugs prescribed, patients were categorized into three groups:

1. Category 1: HFrEF patients receiving all 3 recommended drug classes (ACEi/ARBs/ARNIs, beta-blockers, MRAs) at ≥50% of the target dose (optimal dose).
2. Category 2: HFrEF patients receiving all 3 recommended drug classes, but 1 or more drugs prescribed at <50% of the target dose.
3. Category 3: HFrEF patients not receiving all 3 recommended drug classes.

Target doses for the drugs were based on the effective dose as studied in major clinical trials. The target doses used for the different drugs are listed in Table 1.

The patient categories were later analyzed in terms of potential factors to determine their role in GDMT prescription and dose optimization.

### Inclusion Criteria

Patients aged 18 years and above diagnosed with symptomatic heart failure and reduced

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ejection fraction (≤40%) (HFrEF) attending the cardiology outpatient department (OPD).

Patients who had been on treatment for heart failure for at least 3 months from the cardiology OPD.

### Exclusion Criteria

Heart failure patients classified as NYHA class IV.

### Sample Size Calculation

Assuming that 40% of HFrEF patients are prescribed all recommended drugs at optimal doses, the study required a sample size of 102 patients to estimate the proportion with 8% absolute precision and 90% confidence.

### Statistical Analysis

Categorical variables were presented as frequencies and percentages, while continuous variables were described as mean and standard deviation or median and interquartile range (IQR), depending on the data distribution. The Chi-squared test (or Fisher's exact test for expected cell counts <5) was used to compare categorical variables. A two-tailed significance level of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA version 16.1 (Stata Corporation, College Station, TX, USA).

**Table 1:** Target dose for the heart failure drugs

| *Drug* | *Target dose* |
|---|---|
| ACEi | |
| Enalapril | 10 mg BID |
| Lisinopril | 20 mg OD |
| Ramipril | 10 mg OD |
| ARNi | |
| Sacubitril/valsartan | 97/103 mg BID |
| ARB | |
| Losartan | 50 mg OD |
| Valsartan | 160 mg BID |
| Beta-blockers | |
| Bisoprolol | 10 mg OD |
| Carvedilol | 25 mg BID |
| Metoprolol succinate | 200 mg OD |
| Nebivolol | 10 mg OD |
| Mineralocorticoid receptor antagonist | |
| Spironolactone | 25 mg OD |
| Eplerenone | 50 mg OD |
| SGLT2i | |
| Dapagliflozin | 10 mg OD |
| Empagliflozin | 10 mg OD |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BID, bis in die (twice daily); GDMT, guideline-directed medical therapy; OD, omne in die (once daily); SGLT2i, sodium glucose cotransporter 2 inhibitor; TID, ter in die (three times a day)

### Ethics Approval

This cross-sectional study did not include any invasive procedures or clinical trials. Informed consent was obtained from all participants, and their personal information was kept confidential. The study received approval from the institute ethics committee prior to initiation and adhered to widely recognized ethical guidelines for human research.

## Results

A total of 102 HFrEF patients who had been on treatment for at least 3 months were recruited from the cardiology outpatient department (OPD) during the course of the study. The baseline demographics of the study participants are detailed in Table 2. The average age of participants was 54 ± 11.7 years, with males comprising 89.2% of the sample. Most patients had heart failure due to ischemic causes (84.3%). The average left ventricular ejection fraction was 32.8 ± 5.6%.

### Prevalence of Guideline-directed Medical Therapy

Among the 102 patients, 11 (10.8%) were receiving all 3 recommended classes of medications at optimal dosages (≥50% of target dose), classified as category 1. In contrast, 64 patients (62.7%) were on all 3 classes but with 1 or more medications at suboptimal dosages (<50% of target dose), categorized as category 2. Additionally, 27 patients (26.5%) did not receive all 3 recommended classes of medications, falling into category 3 (Fig. 1).

GDMT distribution by patient subgroups is presented in Table 3. The majority of patients with renal impairment (creatinine ≥1.5 mg/dL) failed to receive all 3 classes of medications (category 3). Patients with low blood pressure (<100/60 mm Hg) and abnormal potassium levels (<3.5 and >5.1 mmol/L) were either on suboptimal dosing (category 2) or did not receive all 3 classes of drugs (category 3). Of the 102 patients, 64 (62.7%) had been on treatment for 1 year or more. Patients in Category 1 were more likely to have been on treatment for >1 year compared to those in categories 2 or 3.

**Table 2:** Baseline characteristics of patient

| *Parameter* | | *Values* |
|---|---|---|
| Age | | 54 ± 11.7 |
| Sex | Males | 91 (89.2%) |
| | Females | 11 (10.7%) |
| Cause of heart failure | Ischemic | 86 (84.3%) |
| | Nonischemic | 16 (15.7%) |
| Ejection fraction (%) | | 32.8 ± 5.6 |

### Treatment Patterns

The prescription rates for ACEi/ARBs/ARNi, beta-blockers, and MRAs were 94 (92.1%), 95 (93.1%), and 85 (83.3%), respectively. Optimal dosing was achieved in 43 (45.7%) for ACE inhibitors/ARBs/ARNi, 19 (20%) for beta-blockers, and 85 (100%) for MRAs (Fig. 2). Among ACE inhibitors/ARBs/ARNi, enalapril and losartan were prescribed in 94.7 and 5.3% of cases, respectively. Metoprolol was the most commonly prescribed beta-blocker (75.8%), followed by carvedilol (22.1%) and bisoprolol (2.1%). Spironolactone was prescribed to all patients receiving MRAs. However, 5 patients (4.9%) were prescribed atenolol, a beta-blocker not recommended under GDMT guidelines.

SGLT2 inhibitors, recently introduced into clinical practice, were prescribed to 36 patients (35.3%). Of these, 5 patients received all drugs at optimal dosage, while 27 patients were on quadruple therapy with 1 or more drugs at suboptimal dosages.

## Discussion

This study aimed to assess the prevalence and adequacy of GDMT in patients with HFrEF in a tertiary care setting in southern India and to explore reasons behind nonprescription and suboptimal dosing. The results highlight notable discrepancies between guideline recommendations and real-world clinical practice.

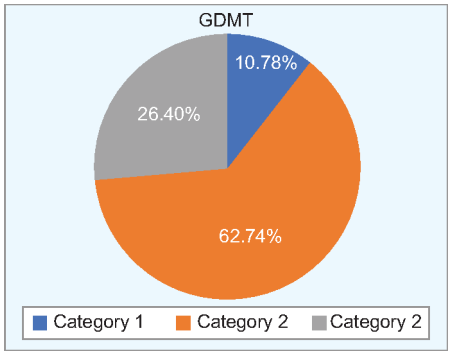


**Fig. 1:** Prevalence of GDMT in HFrEF patients. 10.78% of patients received all three drug classes at optimum dose (category 1) compared to 62.74% of patients who received all three classes with one or more drugs at suboptimum dose (category 2). 26.4% of patients were not on triple therapy (category 3). GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction

**Table 3:** GDMT with respect to patient subgroups

| *Subgroups* | | *Overall (n = 102)* | *Category 1 and 2 (n = 75)* | *Category 3 (n = 27)* | *p-value* |
|---|---|---|---|---|---|
| Duration of treatment (≥1 year) | | 64 | 46 | 18 | 0.623 |
| Diabetes mellitus | | 48 | 37 | 11 | 0.443 |
| Renal impairment (creatinine level ≥1.5mg/dL) | | 13 | 5 | 8 | 0.001 |
| Blood pressure | High (≥140/90 mm Hg) | 43 | 32 | 11 | 0.862 |
| | Low (<100/60 mm Hg) | 5 | 3 | 2 | 0.606 |
| Potassium levels | High (>5.1 mmol/L) | 6 | 3 | 3 | 0.146 |
| | Low (<3.5 mmol/L) | 4 | 3 | 1 | 1.000 |

mm Hg, millimeters of mercury; mmol/L, millimole per liter;

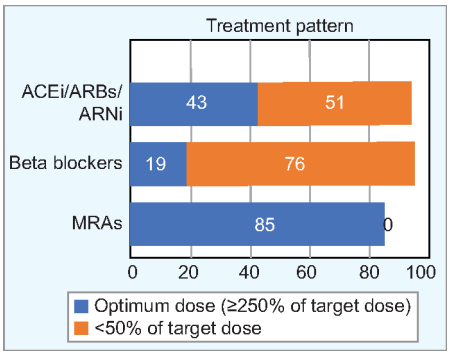


**Fig. 2:** Prescription rates and optimal dosing of heart failure medications. The prescription rates for ACEi/ARBs/ARNi, beta-blockers, and mineralocorticoid receptor antagonists (MRAs) were 94 (92.1%), 95 (93.1%), and 85 (83.3%), respectively. Optimal dosing was achieved in 43 (45.7%) patients for ACEi/ARBs/ARNi, 19 (20%) for beta-blockers, and 85 (100%) for MRAs. ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNis, angiotensin receptor neprilysin inhibitors; MRAs, mineralocorticoid receptor antagonists

## Prevalence and Adequacy of Guideline-directed Medical Therapy

Our study observed that only 10.8% of HFrEF patients received all three recommended classes of drugs (ACEi/ARBs/ARNi, beta-blockers, and MRAs) at optimal dosages. This figure is notably lower than the optimal adherence rates seen in some international studies, such as the 22.1% reported by the CHAMP-HF study and the 39.2% observed in the CHECK-HF registry.[10,11] This discrepancy highlights a substantial gap in adhering to GDMT, indicating that only a minority of patients receive treatment according to guideline recommendations. The setting was a cardiology OPD in a tertiary care center. GDMT rates may be lower in patients not treated in a specialist OPD in other centers.

In our cohort, 62.7% of patients were prescribed all 3 classes of recommended medications, though at suboptimal doses, aligning with results from other studies that also report high levels of under-dosing.[12–14] This under-dosing can have significant implications for patient outcomes, as inadequate dosing is associated with poorer clinical results and increased mortality risk.[6] Furthermore, 26.5% of patients failed to receive all recommended classes of drugs, a situation observed in other studies and indicative of systemic issues in achieving comprehensive GDMT coverage.[15]

## Factors Influencing Guideline-directed Medical Therapy Prescription

Several patient-specific factors were identified as barriers to achieving optimal GDMT. Notably, patients with renal impairment and those with blood pressure abnormalities were less likely to receive all 3 classes of drugs, and when they did, the dosing was often suboptimal. This aligns with other research indicating that medical conditions, particularly renal dysfunction and hypotension, frequently lead to reluctance or limitations in prescribing certain GDMT agents.[13,15]

The duration of treatment was another important factor, with patients who had been on treatment for over 1 year more likely to achieve optimal dosing. This suggests that longer treatment duration may be associated with better optimization of therapy, possibly due to increased familiarity with the patient's condition and ongoing adjustments to therapy.

## Treatment Patterns and Medication Adherence

Our study found high prescription rates for ACEi/ARBs/ARNi, beta-blockers, and MRAs, but only a minority of these prescriptions were at optimal doses. This reflects a broader issue observed in other research where, despite high prescription rates, target doses are often not achieved.[11,16,17] The choice of specific medications also varied, with enalapril and losartan being the most commonly prescribed ACEi/ARBs and metoprolol being the predominant beta-blocker, reflecting typical prescribing patterns observed in practice.

The introduction of SGLT2 inhibitors in a small percentage of patients indicates a gradual incorporation of newer therapies into practice. However, their limited use suggests potential barriers to their widespread adoption, such as cost or lack of familiarity.

This study has a few limitations:

- Only the prevalence of GDMT prescription at the physician or health facility level was assessed; patient adherence to GDMT and its impact on clinical outcomes were not evaluated. Further prospective studies on these patients will provide a better understanding of GDMT prevalence and other potential factors influencing patient adherence.
- The sample size of patients in this study was small. Further studies with larger sample sizes are required.
- Recently introduced SGLT2 inhibitors were not included while categorizing the patients due to their nonavailability from the hospital pharmacy. However, they were still prescribed to some patients; hence, further prospective studies involving quadruple therapy can be conducted to analyze their enhanced role in HFrEF patients.

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ORIGINAL ARTICLE

# A Cross-sectional Study of Medication Identification Patterns among Patients Attending the Medicine Outpatient Department in a Tertiary Hospital in Rural Gujarat

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## Abstract

**Background:** The number of people living with multiple chronic medical conditions has risen, and with it, the number of medications taken by them. In addition to adherence to medications, it is extremely important to correctly identify the medications. Medication errors occur at all steps, with polypharmacy, low literacy, language barriers, old age, and lack of communication as contributing factors. Many of the patients may not be identifying medications themselves or may be doing so incorrectly. Hence, this study is aimed to check the methods used by patients to identify medications.

**Materials and methods:** A total of 150 patients attending the outpatient department (OPD) of the medicine department were interviewed using a structured questionnaire, which had multiple-choice questions and one open-ended question. Sociodemographic data, level of education, data on type and number of clinical conditions, groups of medications taken, and methods used for identification of medications were collected. Statistical analysis was done using Stata 14.2.

**Results:** Most (85.33%) of the patients had a chronic medical condition, out of which 37.33% had two or more clinical conditions. Physical attributes of the tablets (60%) and packaging (39.33%) were used most commonly to identify medications. About 10.67% did not identify the medications themselves. Again 45.33% of the patients depended on the doctor's prescription for the dosing of medications. Patients felt that identification of medications would be easier if the content on packaging included indication, was written in the local language, and was in bold font. They also felt that healthcare professionals spending more time explaining would help them.

**Conclusion:** Irrespective of the level of education, language known, and number of comorbidities, physical attributes and packaging were most commonly used to identify medications.


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## Introduction

India's population stands at 142.86 crores. With average life expectancy at birth of 67.74 years in 2022,[1] the burden of chronic diseases is increasing. Over 100 million people in India are living with diabetes[2] and an estimated 220 million adults with hypertension.[3] Furthermore, the prevalence of prediabetes ranges from 6 to 14.7%.[4] According to the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study, the overall prevalence of dyslipidemia was 81.2%.[5] To add to this burden, coronary artery disease and strokes occur earlier in Indians compared to the West.[6] Multimorbidity is common, which necessitates lifelong use of medications, mostly polypharmacy. Polypharmacy is defined as regular use of five or more medications at the same time[7] or intake of more than prescription or intake of more drugs than clinically appropriate.[8] It is estimated to be high in our country. A study showed it to be 8.37% among patients in Bhopal, Madhya Pradesh.[9] Another study focusing on elderly population found that polypharmacy, hyperpolypharmacy, and potentially inappropriate medication use were present in 49, 31, and 28%, respectively.[10] Polypharmacy elevates the risks of medication errors. Errors can occur at any stage of medication delivery—from manufacturing and prescribing to dispensing and administration. It is very important to identify these errors or the scope for them so that corrective steps can be taken. A particularly vulnerable step is the identification of medications by patients or caregiver prior to administration. This step relies heavily on the individual's capacity to interpret and process basic health information, and low level of health literacy in our country may interfere with this.[11] Health literacy is defined as the degree of ability of individuals to obtain, process, and understand basic health information and services which are needed to make appropriate healthcare decisions.[12] Individuals with adequate health literacy demonstrate a combination of functional skills (ability to read and understand educational written materials), interactive skills (ability to communicate with healthcare professionals), critical skills (ability to make appropriate health decisions), and numeracy skills (ability to measure medication dosages).[13,14] Low health literacy hence may interfere with medication self-management.

While multiple studies have assessed the prevalence of polypharmacy, its health outcomes, and the role of health literacy at a global level, there remains a significant gap in the Indian context with regard to how patients identify and differentiate medications. The present study aims to evaluate the strategies employed by patients in India to identify medications, the challenges faced by them in doing so, and the impact of literacy and language barriers on this process. Studying this may give valuable inputs for improving pharmaceutical labeling, medication packaging, prescription practices, and patient education methods in the Indian healthcare system.

## Materials and Methods

### Study Design

The study employed a cross-sectional design and was conducted using a researcher-administered, questionnaire-based survey. The survey was administered to patients attending the outpatient department (OPD) of the general medicine unit at a tertiary care hospital affiliated with a medical college in rural Gujarat, India.

### Sample Size, Data Collection, and Analysis

The study is a type of survey. It followed a nonprobability sampling approach, specifically judgment sampling. Eligible participants were interviewed using a

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structured questionnaire after verbal informed consent. Data were collected under sociodemographic details, number and type of medications the patients reported to be taking, number and nature of clinical conditions reported by patients, and methods used by patients to identify the medications. The majority of the questions were multiple-choice questions, allowing for multiple responses. One open-ended question was included to gather qualitative insights. Data collected were entered into an Excel sheet and analyzed using Stata version 14.2.

### Ethics Committee Approval

The study protocol was reviewed and approved by the Institutional Ethics Committee. Participation in the survey was voluntary, and the participants did not receive any monetary or material compensation for participating.

## Results

A total of 150 patients participated in the study. Of them, 56 were males and 94 were females. The average age of the participants was 57.8 years, and age ranged from 27 to 98 years. Table 1 shows the sociodemographic characteristics of the participants. It is important to note that 54% of the participants had less than secondary education, and only 25.33% had English reading skills.

Table 2 lists the clinical history of participants, with hypertension as the most common clinical condition at 68%. About 14.67% were either not aware of what clinical condition they had or reported that they did not have any chronic medical condition. The number of clinical conditions reported by each participant may not reflect the actual picture, as many may not have been aware of all the clinical conditions for which they were being treated.

Table 3 lists the medications reported to be taken by participants, with antihypertensives being the most common group at 68.67%. It also reports the awareness about medications observed among participants. Awareness here means the ability to identify the indication and group of the medication correctly. It is worth noting that none of the medications were identified correctly by 20% of the participants.

Table 4 lists information about the personnel who provided information about medications to the participants. Here, providing information means explaining the indication, group, and dosing of the medications.

Table 5 gives data on the methods used by participants to identify medications. It is to be noted that the physical attributes of the tablet and packaging of the medication were used as methods for identification much more commonly than the content of the medication.

Table 6 lists the methods used by participants to know the dosing of the medications. Data reveal that they relied on the doctor's prescription, followed by the pharmacy label, for the same.

Data was also collected on the methods used to identify medications by participants and the language read. Table 7 lists the data regarding the same. It is to be noted that irrespective of the language reading ability, physical attributes of the tablet and/or packaging were most commonly used to identify medications rather than content and brand name.

Data collected on methods used to identify medications and the education level of the participants shows that irrespective of the education level, physical attributes of tablets and/or packaging were most commonly used to identify medications rather than content and brand name. Table 8 lists the data regarding the same.

Table 9 shows that irrespective of the number of clinical conditions present,

**Table 1:** Sociodemographic characteristics of participants

| *Variables* | *Frequency* | *Percentage (%)* |
|---|---|---|
| Age-group | | |
| 25–50 | 44 | 29.33 |
| 51–75 | 93 | 62 |
| 76–100 | 13 | 0.086 |
| Minimum age: 27 years | | |
| Maximum age: 98 years | | |
| Median age: 57.8 years | | |
| Gender | | |
| Male | 56 | 37.33 |
| Female | 94 | 62.67 |
| Education | | |
| Postgraduate | 5 | 3.33 |
| Graduate | 24 | 16 |
| Secondary school | 40 | 26.67 |
| Primary | 64 | 42.67 |
| Not educated | 17 | 11.3 |
| Languages read | | |
| Gujarati | 40 | 26.67 |
| Gujarati and English | 2 | 1.33 |
| Gujarati and Hindi | 51 | 34 |
| Gujarati, English, and Hindi | 31 | 20.67 |
| Hindi | 4 | 2.67 |
| Hindi and English | 5 | 3.33 |
| None | 17 | 11.33 |

**Table 2:** Clinical history of participants

| *Variables* | *Frequency* | *Percentage (%)* |
|---|---|---|
| Clinical conditions reported | | |
| Hypertension | 102 | 68 |
| Diabetes | 70 | 46.67 |
| Dyslipidemia | 3 | 2 |
| CAD | 11 | 7.33 |
| Stroke | 7 | 4.6 |
| CKD | 3 | 2 |
| CLD | 3 | 2 |
| Thyroid disorder | 28 | 18.66 |
| Malignancy | 3 | 2 |
| PAD | 1 | 0.67 |
| Not known/ none | 22 | 14.67 |
| Number of clinical conditions reported | | |
| 1 | 72 | 48 |
| 2 | 46 | 30.67 |
| 3 | 7 | 4.67 |
| 4 | 2 | 1.33 |
| 5 | 1 | 0.67 |
| Not known/ none | 22 | 14.67 |

**Table 3:** Medication history and awareness among participants

| *Variables* | *Frequency* | *Percentage (%)* |
|---|---|---|
| Medication groups reported to be taking | | |
| Antihypertensives | 102 | 68.67 |
| Oral antidiabetics | 65 | 43.33 |
| Insulin | 8 | 5.33 |
| Antiplatelets and anticoagulants | 17 | 11.33 |
| Statins | 9 | 6 |
| Thyroid medications | 26 | 17.33 |
| Diuretics | 1 | 0.6 |
| Antibiotics | 5 | 3.33 |
| Pain killers | 5 | 3.33 |
| Multivitamins | 9 | 6 |
| Antacids | 12 | 8 |
| Awareness about medications—expressed as percentage—50% means participant could correctly identify 50% of the total medications | | |
| 0% | 30 | 20 |
| 25% | 2 | 1.33 |
| 50% | 7 | 4.67 |
| 75% | 1 | 0.6 |
| 100% | 110 | 73.33 |

physical attributes and packaging were most commonly used to identify medications.

**Table 4:** Personnel who provided information about medications

| *Variables* | *Frequency* | *Percentage (%)* |
|---|---|---|
| Doctors | 119 | 79.33 |
| Doctor and pharmacist | 18 | 12 |
| Doctor and family member | 2 | 1.33 |
| Nurse | 2 | 1.33 |
| Doctor, nurse, and pharmacist | 1 | 0.67 |
| Pharmacist | 6 | 4 |
| Family member | 2 | 1.33 |

**Table 5:** Methods used by patients to identify medications

| *Variables* | *Frequency* | *Percentage (%)* |
|---|---|---|
| Packaging | 59 | 39.33 |
| Content | 10 | 6.6 |
| Physical attribute of tablet | 90 | 60 |
| Brand name | 41 | 27.33 |

Note: 16 (10.67%) did not identify the medications by themself

Participants were asked if they had difficulty reading the print on the package and if a bigger and bolder font size on the packaging would help them overcome the problem. About 60.67% replied in the positive. Table 10 shows the data related to this.

The participants were asked to respond to an open-ended question on what they thought would help them identify medications better. They were allowed to give more than one response. Most felt that having content in the local language on the packaging and having the indication mentioned would help them identify medications better. Many others felt that content in bold font would help them, while a few felt that healthcare personnel spending more time explaining and a self-explanatory pharmacy label would help (Table 11).

**Table 6:** Methods used by patients to know the dosing of medications

| *Variables* | *Frequency* | *Percentage (%)* |
|---|---|---|
| Doctor's prescription | 68 | 45.33 |
| Doctor's prescription and pharmacy label | 26 | 17.33 |
| Pharmacy label | 56 | 37.33 |

**Table 7:** Methods used by patients to identify medications and language (reading ability)

| *Variables (Language)* | *Number of patients* | *Identification methods* | | | | |
|---|---|---|---|---|---|---|
| | | *Packaging* | *Content* | *Physical attributes of tablets* | *Brand name* | *Not identifying by themselves* |
| Gujarati | 40 | 20 | 0 | 26 | 3 | 5 |
| Gujarati and English | 2 | 0 | 0 | 0 | 2 | 0 |
| Gujarati and Hindi | 51 | 23 | 2 | 36 | 11 | 4 |
| Gujarati, English, and Hindi | 31 | 9 | 8 | 15 | 21 | 0 |
| Hindi | 4 | 1 | 0 | 3 | 0 | 0 |
| Hindi and English | 5 | 1 | 0 | 0 | 4 | 0 |
| None | 17 | 5 | 0 | 10 | 0 | 7 |
| Total | 150 | 59 | 10 | 90 | 41 | 16 |

**Table 8:** Methods used by patients to identify medications and education level

| *Variables (Education)* | *Number of patients* | *Identification patterns* | | | | |
|---|---|---|---|---|---|---|
| | | *Packaging* | *Content* | *Physical attributes of tablets* | *Brand name* | *Not identifying by self* |
| Postgraduate | 5 | 1 | 2 | 0 | 3 | 0 |
| Graduate | 24 | 6 | 6 | 9 | 18 | 0 |
| Secondary | 40 | 13 | 0 | 20 | 13 | 6 |
| Primary | 64 | 36 | 2 | 51 | 7 | 3 |
| No formal education | 17 | 3 | 0 | 10 | 0 | 7 |
| Total | 150 | 59 | 10 | 90 | 41 | 16 |

**Table 9:** Methods used by patients to identify medications and number of clinical conditions

| *Variables (No. of clinical conditions)* | *Number of patients* | *Identification patterns* | | | | |
|---|---|---|---|---|---|---|
| | | *Packaging* | *Content* | *Physical attributes of tablets* | *Brand name* | *Not identifying by self* |
| 0 | 22 | 13 | 3 | 18 | 8 | 3 |
| 1 | 72 | 26 | 4 | 42 | 17 | 7 |
| 2 | 46 | 15 | 2 | 24 | 14 | 5 |
| 3 | 7 | 5 | 0 | 5 | 1 | 0 |
| 4 | 2 | 0 | 1 | 1 | 1 | 0 |
| 5 | 1 | 0 | 0 | 0 | 0 | 1 |
| Total | 150 | 59 | 10 | 90 | 41 | 16 |

**Table 10:** Response to close-ended question

| *Question* | *Response* | | | |
|---|---|---|---|---|
| | *Yes* | | *No* | |
| | *Number of patients* | *Percentage (%)* | *Number of patients* | *Percentage (%)* |
| Did you find difficulty in reading the print on the packaging and do you think it would help if the font size was bigger and bolder? | 91 | 60.67 | 59 | 39.33 |

**Table 11:** Response to open-ended question

| *Question* | *Responses* | *Number* | *Percentage (%)* |
|---|---|---|---|
| What do you think will help you identify your medications better? | Nurses spending more time in explaining | 1 | 1.33 |
| | Self-explanatory pharmacy label | 5 | 3.33 |
| | Doctors spending more time in explaining | 10 | 6.67 |
| | Content written in bold font | 55 | 36.67 |
| | Indication written in bold on packaging | 105 | 70 |
| | Content on packages written in local language | 118 | 78.67 |

## Discussion

With increasing population and improved life expectancy in our country, a substantial number of individuals are living with one or more chronic health conditions, resulting in high pill burden. Accurate identification of medications is critical for this population, as errors in medication use can lead to significant harm—even in high-income countries. In the Indian context, low levels of literacy and health literacy can interfere with these skills. In addition, old age, polypharmacy, decreased vision, and decreased ability to read English, a language in which the content on packaging of medications is written, may further hinder patients' ability to safely manage their medications.

To explore how patients identify their medications and the difficulties faced by them, a cross-sectional study was conducted at our hospital, a 900-bedded tertiary hospital attached to a medical college in rural Gujarat. The aim was to understand patients' practices and perceptions regarding medication identification and to assess the impact of factors such as literacy and language barriers.

Review of literature reveals that while many studies have been conducted to understand medication errors, very few focus on the patients. A review studying patients' role in errors highlighted that, though they are the people most affected by them, little is known about how they make attributions of the adverse effects that arise from medication errors and suggested that better communication is needed between healthcare providers and patients.[15] Our study chose to fill this gap and involved interaction with the patients through a questionnaire-based interview, which allowed patients to give suggestions through open-ended questions, giving insight into what they feel would help reduce errors. Most of our patients felt that having the content on the packaging in the local language and the indication for the drug written in bold letters would help them identify medications better. Many felt that having the content in bold font would help, while a few opined that doctors and nurses spending more time to explain and self-explanatory pharmacy labels would make identification easy. With content on all medicine packaging in English in our country and a significant number of people with no ability to read the language, it would be worth considering adding content in Hindi on the packaging and mentioning the indication along with it. In general, the packaging needs to be more informative and clear, considering the fact that patients rely on it when no professionals are around for advice. The need to bring in more effective communication between patients and doctors and/or nurses during drug reconciliation cannot be stressed enough and is the need of the hour.

The results of studies on medication errors have varied based on where they are conducted. While one in South India reported an overall prevalence of medication errors to be 80%,[16] another in Austria found at least one error in 56.2% of the studied population.[17] Another descriptive observational study to estimate the types and incidence of dispensing errors found 1.4% of dispensing errors, concluded that the incidence was higher for prescriptions on chronic diseases, and noted that there were fewer prescription errors when the average number of drugs in the prescription was <5.[18] It may be noted that most studies focus on dispensing and prescription errors, and there are no studies that aim to see how patients identify their

medications and if this has the potential to be a reason for medication errors. Our study goes beyond the steps of prescription or dispensing and focuses on methods used by patients to identify medications. This information can be a valuable tool to redesign the steps of the drug delivery chain—from manufacturing to the doctor's desk and from the doctor's desk to the patient's mouth.

Level of literacy contributes to errors directly or indirectly, and studies have been done in this area. A cross-sectional study with the aim to identify medication self-administration errors (MSE) and the contributing factors among illiterate and low-literate, community-dwelling older adults with polypharmacy found the frequency of MSE over 6 months to be 69.2%, with 18% reporting adverse events following their mistakes.[19] Another multisite cross-sectional study to identify the role of health literacy in chronic disease self-management found that 15% of the patients could not identify their medications despite the fact that half of them had adequate literacy levels.[20] In our study, we saw if the level of education among literates affected the way they identified medications and hence classified them into those with primary education, secondary education, graduate, and postgraduate education. We found that irrespective of the level of literacy, physical attributes and packaging were used to identify medications most commonly, which is similar to other studies. This finding underscores the importance of the appearance of pills and packaging and stresses the need to have a standardized system pertaining to the physical attributes of tablets and packaging. This also shows why look-alike, sound-alike drugs contribute to medication errors.

Further to these findings, a review of the literature showed studies that have explored whether the appearance of pills affected adherence and reduced medication errors. These studies have called for instituting a more organized and consistent system of appearance, which would increase adherence, simplify medical regimens, reduce medication errors, and encourage the rational use of bioequivalent generic drugs.[21] Our study endorses the same. Another study that explored the utility of using color and shape to differentiate drug strength information on over-the-counter medicine packages found that it improved drug strength identification performance.[22] In our study, we also noted that most patients relied on the physical attributes of pills to identify them, and by bringing in policies to standardize and regularize the appearance of pills, one can reduce medication errors.

A study to analyze the medication self-management process in polypharmacy revealed that patients continue to have problems in medical management, among other areas. The study suggested that improving medication literacy would help patients integrate medication management into their daily life and that future research should focus on developing effective intervention strategies to further enhance self-management abilities.[23]

While most of the studies are centered around quantifying medication errors and their point of occurrence, they stop short of studying what patients think and how they themselves identify medications. The study reveals that current practices are often unscientific, inconsistent, and a significant proportion of patients rely on others to identify or administer their medications. These findings, together with polypharmacy, low literacy, vision impairment, old age, and inability to read a nonnative language, create a high-risk environment for medication errors. Importantly, our study captures patient-driven insights and practical suggestions for improving medication identification—from using local language and including indication on packaging to using bold font for content; from better communication to self-explanatory pharmacy labels, patients provide us with starting points from which newer strategies can begin.

### Strengths

The study was conducted in a rural area, where most of India's population lives, and hence the findings can be said to be relevant and applicable to real-world settings. By taking a patient-centered approach, we have addressed a critical yet overlooked component in the prevention of medication errors. Our study provides valuable contextual information that can be used to design patient-friendly medication management systems. It also contributes to raising awareness of how medication packaging design and communication practices can impact patient safety.

### Limitations

It was conducted in a specific geographic region, and the findings may not be entirely generalizable to the urban population or other countries. Self-reporting by patients may have introduced recall bias or underreporting. The sample size was small, and studies with larger sample size may help increase the representativeness of the findings.

## Conclusion

Medication errors have remained a significant challenge in the healthcare system. Time and again, we have quantified them; the need of the hour, however, is to develop and implement strategies to minimize their occurrence. A critical step toward this is to understand how the consumers of these medications—our patients—identify them. This study represents a step in that direction. The findings underscore the need to reevaluate and reconsider multiple facets of medication management, including the physical appearance and packaging of medications, the clarity and language on the packaging, the design and format of prescriptions, communication practices among healthcare providers, the process of drug reconciliation, and the labeling practices used by pharmacists. A comprehensive and patient-centered approach is essential to enhance medication safety and reduce the risk of errors.

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ORIGINAL ARTICLE

# Assessment of Hemoglobinopathies in Antenatal Females

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## Abstract

**Introduction:** Hemoglobinopathies, a group of inherited disorders characterized by abnormal hemoglobin (Hb) production or structure, pose significant health risks during pregnancy. This study aims to assess the prevalence of hemoglobinopathies among antenatal females and establish guidelines for effective screening and management.

**Materials and methods:** An observational cross-sectional study was conducted over 18 months at Dr DY Patil Medical College, Hospital and Research Centre, involving 800 antenatal women. Demographic data, medical history, and blood samples were collected for complete blood count (CBC) and Hb electrophoresis. Statistical analysis was performed using SPSS software.

**Results:** A study evaluated 800 antenatal females aged 20–39 years, with an almost equal distribution between age-groups 20–29 (49.23%) and 30–39 (50.77%) years. Peripheral blood smear analysis revealed 97.69% had microcytic hypochromic anemia, indicating a high prevalence of iron deficiency, while 2.31% exhibited normocytic normochromic anemia. Hb electrophoresis identified hemoglobinopathies in 1.72% of cases, with 1.53% cases identified as beta-thalassemia carriers, and 0.19% with sickle cell trait (SCT). Among the abnormal cases, beta-thalassemia (55.56%) was found to be the most common, followed by HbE heterozygous (11.11%), HbE homozygous (11.11%), and double heterozygous (11.11%), with a single case (11.11%) of sickle cell disease (SCD). Beta-thalassemia was the most prevalent hemoglobinopathy. CBC parameters showed significant variations among hemoglobinopathy types, with analysis of variance (ANOVA) *p*-values of 0.0001 for Hb, mean corpuscular volume (MCV), and mean corpuscular Hb. These findings underscore the significance of microcytic hypochromic anemia and the relatively low prevalence of hemoglobinopathies in the antenatal population.

**Discussion:** The low prevalence of hemoglobinopathies in this region contrasts with higher rates reported elsewhere in India, indicating potential regional genetic factors. The predominant finding of microcytic hypochromic anemia underscores the urgent need for targeted interventions addressing iron deficiency in antenatal care.

**Conclusion:** This study emphasizes the importance of routine screening for hemoglobinopathies in pregnant women, particularly in regions with known genetic predispositions. Increased awareness and follow-up molecular analysis are recommended for accurate diagnosis and management, ultimately improving maternal and fetal health outcomes. Future research should expand to larger, multicentric studies to further validate these findings.


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## Introduction

Hemoglobinopathies constitute a heterogeneous group of single-gene disorders that are inherited. They are characterized by either abnormal production or structure of the hemoglobin (Hb) molecule. The abnormality may be quantitative or qualitative.

Qualitative defects can occur due to genetic mutations that involve globin protein chains. These defects include either amino acid deletions or substitutions, which cause structural variations of the globin chain that manifest in the form of HbS, HbD, HbE, etc.[1]

Quantitative defects can lead to a decrease in the synthesis of structurally normal globin chains.

These include disorders such as:

Thalassemia, which is a genetically heterogeneous autosomal recessive disorder of Hb synthesis caused by germline mutations, is characterized by the absence or decreased synthesis of alpha or beta globin chains of Hb. Thus, it leads to anemia, tissue hypoxia, and red cell hemolysis connected to an imbalance in globin chain synthesis.[2]

Alpha-thalassemia is characterized by deficient synthesis of alpha globin chains. Beta-thalassemia is caused by a deficient synthesis of beta globin chains. Two alpha chains in HbA are encoded by an identical pair of alpha globin genes present on chromosome 16. Beta chains are encoded by a single globin gene on chromosome 11.

World literature states that heterozygous carriers of hereditary disorders of Hb are >270 million. Among them, at least 3,00,000 affected homozygotes or compound heterozygotes are born each year.[3] The purpose of this document is to review the most common hemoglobinopathies and to formulate policies and guidelines for screening and clinical management of hemoglobinopathies during pregnancy. Alpha-thalassemia is distributed in Southeast Asia, the Eastern Mediterranean region, and the Middle East.[4] Beta-thalassemia is distributed in the Mediterranean region, Africa, the Middle East, India, Pakistan, and Southeast Asia.[5]

Sickle cell disease (SCD) and thalassemia are the common hemoglobinopathies caused by mutations in genes for Hb, resulting in significant morbidity and mortality. There is usually a great disparity in the outcome of these diseases between resource-rich and resource-poor nations.

The aim of this study was to assess the frequency and prevalence of hemoglobinopathies in antenatal mothers in Western India.

The objective was to evaluate the hematological parameters and Hb electrophoresis in different hemoglobinopathies and to study the demographic profile of antenatal females with hemoglobinopathies.

## Materials and Methods

An observational cross-sectional analytical study was performed in the Department of Pathology in collaboration with the Department of Obstetrics and Gynecology, Dr DY Patil Medical College, Hospital and Research Centre, Pimpri, Pune, for a period of 18 months. An Institutional Ethics Committee Clearance (IECC) was obtained before the start of the study.

Informed and written consent was taken from the antenatal females who were included in the study. The study included 800 antenatal females as cases. Antenatal females during their first visit to the antenatal OPD, irrespective of their gestational age, in the Department of

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Obstetrics and Gynecology, were included as cases. Patients with a previous history of blood transfusion were excluded from the study for a year. Relevant history was taken regarding their demographic profile, past, and family history. A 3 mL blood sample of antenatal females was collected in vacuum collection tubes containing ethylenediaminetetraacetic acid (EDTA), and 2 mL of blood sample was collected in a plain vial.

Complete blood cell count was done by a five-part cell counter. Peripheral blood smears were prepared and analyzed. EDTA samples were stored at 2–8°C for 4 days. They were allowed to reach room temperature prior to analysis.

Automated cation-exchange high-performance liquid chromatography (HPLC) was used for the detection of hemoglobinopathies. About 2 mL of blood sample, which was collected in plain vials, was used for the HPLC machine: D-10 Dual HbA2/F/A1c Program 220-0201, manufacturer: Bio-Rad Laboratories, model: D-10 Hemoglobin Testing System. The principle of the procedure is based on chromatographic separation of the analytes by ion-exchange HPLC. The data obtained is displayed as a chromatogram and converted into peaks as per the retention time. The separated Hb with the percentage is displayed.

Data were collected and entered into Microsoft Excel and were analyzed using SPSS software version 26. Quantitative data were expressed in mean and standard deviation. Categorical variables were expressed in numbers and percentages. An independent *t*-test was applied to compare means. A *p*-value < 0.05 was considered statistically significant. Antenatal females were called and counselled for further screening of their spouse for prevention and emphasizing the need for early detection and screening of their offspring for hemoglobinopathies.

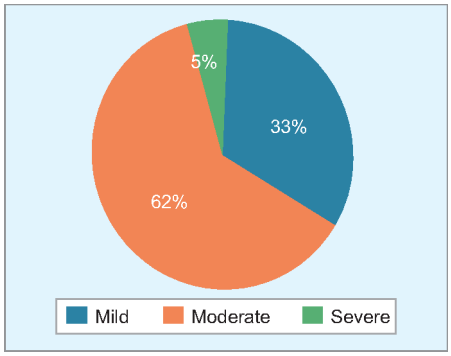


**Fig. 1:** Distribution of cases according to anemia grading

## Results

A total of 800 antenatal females were screened. The females with an age range between 20 and 29 years were 394 (49.21 %), whereas those between 30 and 39 years were 406 (50.77%). Thus, showing a nearly equal distribution among the two age-groups. Among the total 800 cases, 520 (65%) were diagnosed with anemia, while 280 (35%) showed normal Hb levels.

In terms of anemia grading, the majority of cases fell into the moderate anemia category (Hb levels between 7.1 and 9.9 gm/dL), with 323 cases making up 62% of the total. Mild anemia (Hb levels between 10 and 10.9 gm/dL) was observed in 172 (33%) cases. Severe anemia (Hb levels of 7 gm/dL or lower) was noted in 25 cases, representing 4.80% of the total, as shown in Figure 1.

**Table 1:** Distribution of cases according to findings on Hb electrophoresis

| *Hb electrophoresis* | *Number* | *Percentage (%)* |
|---|---|---|
| SCT | 01 | 0.19 |
| Normal | 511 | 98.26 |
| Thalassemia | 08 | 1.53 |
| Total | 520 | 12.50 |

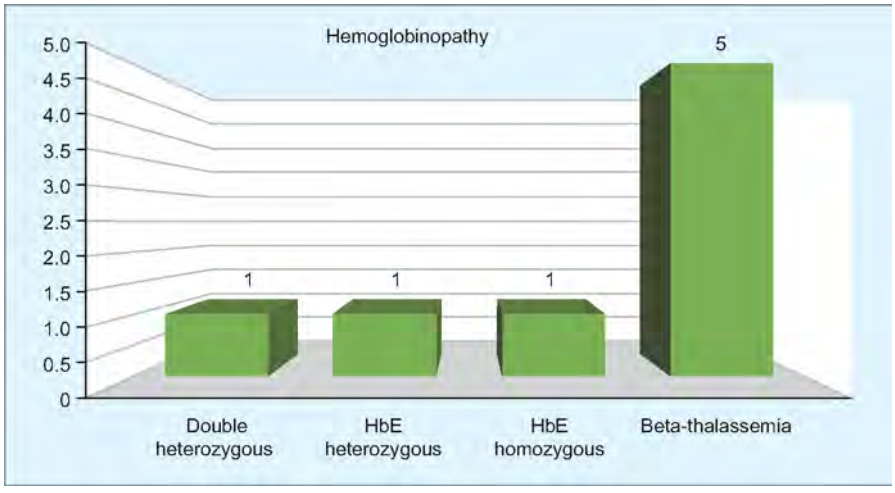


**Fig. 2:** Distribution of thalassemia and variants on Hb electrophoresis

On evaluating the peripheral blood smears, 508 (97.69%) antenatal females had microcytic hypochromic anemia, and 12 (2.31%) had normocytic normochromic anemia. This significant predominance of microcytic hypochromic findings underscores the commonality of iron deficiency in the study population.

The obstetric history of the study subjects showed G2P1L1 as the most common category, representing 188 cases (36.15%), indicating women with one pregnancy and one live birth. On Hb electrophoresis, the majority of the cases, that is, 511 out of 520 (98.26%), showed a normal pattern, while 9 cases (1.7%) showed abnormal results. Among these, there were eight cases (1.55%) identified with thalassemia, and only one case (0.19%) was sickle cell trait (SCT) as depicted in Table 1. This data indicates a relatively low prevalence of hemoglobinopathies in the study population. Among the cases with hemoglobinopathies, beta-thalassemia was the most prevalent type, with five out of eight cases (62.50%). The remaining types included double heterozygous (12.50%), HbE heterozygous (12.50%), and HbE homozygous (12.50%). This suggests that beta-thalassemia is the most common hemoglobinopathy in this study population (Fig. 2).

The mean complete blood count (CBC) parameters were found to be significantly lower than normal. The RBC indices were found to be statistically significantly across different types of hemoglobinopathies as depicted in Table 2. The analysis of variance (ANOVA) test *p*-value for Hb, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) parameters was 0.0001, indicating significant differences across hemoglobinopathy types as depicted in Table 2.

## Discussion

In our study, the age distribution showed a nearly equal division between the third- and fourth-decade age-groups, with a slight majority in the older group (50.77 %). A study by Udho et al.[6] showed anemia in women aged ≥30 years age-group (37%). A study by Siddiqui et al. in New Delhi also highlighted a high prevalence of anemia (70%) among women older than 35 years.[7]

The reason for this slight predominance in the older age-group may be attributed to cumulative nutritional deficits and higher parity in this demographic, factors that have been well-documented in literature.

**Table 2:** Mean CBC parameters in different types of hemoglobinopathy on Hb electrophoresis

| *Type of hemoglobinopathy* | *Hb* | *RBC* | *MCV* | *MCH* | *Mentzer's index* |
|---|---|---|---|---|---|
| Double heterozygous | 6.8 | 5.1 | 55.3 | 29.6 | 55.3/5.1 = 10.84 |
| HbE heterozygous | 5.50 | 5.8 | 48.60 | 32.1 | 48.60/5.8 = 8.38 |
| HbE homozygous | 7.90 | 6.2 | 66.2 | 24.8 | 66.2/6.2 = 12.29 |
| Beta-thalassemia: mean ± SD | 7.75 ± 1.31 | 6.5 | 61.15 ± 8.83 | 25.0 ± 0.70 | 61.15/6.5 = 9.21 |
| Case 1 | 9.8 | 6 | 56.3 | 25.6 | |
| Case 2 | 7.8 | 5.8 | 57.8 | 23.8 | |
| Case 3 | 6.2 | 5.3 | 76.3 | 25.3 | |
| Case 4 | 7.2 | 6.2 | 54.2 | 25.3 | |
| SCT | 6.5 | 4.9 | 54.8 | 26.8 | 54.8/4.9 = 11.18 |
| ANOVA test *p*-value | 0.0001* | 0.0001 | 0.0001* | 0.0001* | 0.0001* |

*Indicates clinical significance

Our study found that 65% of antenatal women were anemic, indicating a high prevalence of anemia, which may be attributed to multiple contributing factors, including nutritional deficiencies (especially iron and folic acid), poor dietary intake, increased physiological demands during pregnancy, and socioeconomic factors.

Furthermore, the 35% of antenatal females without anemia in our study indicate that a fraction of the population has access to proper nutrition, iron supplementation, and overall better healthcare facilities.

Udho et al.[6] highlighted a slightly lower prevalence of anemia (24.7%).

In our study, moderate anemia (hemoglobin levels between 7.1 and 9.9 gm/dL) was the most prevalent, observed in 54.62% of the cases. This is comparable to the findings of Toteja et al.,[8] highlighting the prevalence of moderate anemia to be 60.1% in pregnant women. Severe anemia was less common in our study (4.42%).

A study from Uganda by Udho et al.[6] indicated the prevalence of severe anemia to be significantly lower (2.2%), indicating successful preventive strategies in Uganda.

The overwhelming majority of cases in our study exhibited a microcytic hypochromic pattern (97.69%), indicative of iron deficiency anemia (IDA). This finding is consistent with studies by Patra et al.[9] who found microcytic hypochromic anemia to be the commonest type, found in 49% of the severely anemic women.

There were no cases of megaloblastic anemia found in our study.

In contrast, Khanduri and Sharma[10] reported cobalamin deficiency in 78 patients (65%) out of 120 women diagnosed with megaloblastic anemia.

The most common obstetric history in our study was G2P1L1, accounting for 36.15% of the cases. This pattern reflects the reproductive behavior in the population studied. Balarajan et al. stated that anemia is more prevalent in women with multiple pregnancies.[11] High parity is a known risk factor for anemia, as repeated pregnancies can deplete iron stores and other essential nutrients, exacerbating the risk of anemia. Severe anemia was observed mainly in G2P2L1 females.

The Mentzer index calculated in our study was <13 for all types of hemoglobinopathies. A study conducted at Sri Guru Ram Das Charitable Hospital in Amritsar evaluated the efficacy of the Mentzer index in screening for beta-thalassemia trait (BTT) among 130 pregnant women with anemia. The findings revealed that the Mentzer index had a sensitivity of 80% and specificity of 95.65% for detecting BTT. For IDA, the sensitivity was 95.33% and the specificity was 86.96%.[12] These results suggest that the Mentzer index is a useful, cost-effective tool for distinguishing between IDA and BTT in resource-limited settings.

Among the cases with hemoglobinopathies, beta-thalassemia was the most prevalent type, consistent with findings from studies such as Verma et al.,[13] which reported beta-thalassemia as the most common single gene disorder hemoglobinopathy in India. The mean CBC parameters varied significantly across different types of hemoglobinopathies, with beta-thalassemia cases showing the lowest mean Hb levels, which aligns with global findings on the hematological profile of thalassemia patients.

In another study from Uttarakhand by Singh et al.,[14] the prevalence of BTT and HbD-Punjab trait among pregnant women was found to be 2.6 and 0.2%, respectively. In contrast, a study done in Central India by Balgir[15] depicted 12.26% prevalence of hemoglobinopathies, with SCT being the most common (7.45%).

Kate and Lingojwar screened major communities from Maharashtra state and found high prevalence among SC, ST, and OBC with an overall carrier frequency of approximately 10%. Highest rates are reported from the eastern region (Vidarbha), parts of north Maharashtra, and the Marathwada belt. Among tribal communities, several groups exhibit alarmingly high frequencies. The Otkar tribe in Gadchiroli reports a prevalence of 35%, followed by the Pardhan tribe in Gadchiroli, Chandrapur, and Yavatmal at 32%, and the Pawara tribe in Nandurbar and Jalgaon at 25%. Other tribes with significant prevalence include the Bhill and Madia (each at 20%), Halbi (13%), Rajgond (11%), Korku (10%), and both Kolam and Warli tribes.[16]

It is estimated that Maharashtra has approximately 2.5 million carriers of the sickle cell gene and about 1,25,000 sufferers (HbSS), based on 2001 census data. The disease is especially concentrated in rural areas where awareness and medical resources are limited.[16]

In the case of BTT, a study conducted by Satpute et al. in South-western Maharashtra (covering Satara, Sangli, and Kolhapur districts) analyzed 126 beta-thalassemia carriers. The most common mutation found was intervening sequence (IVS) I-5 (G–C), present in 65.07% of cases, making it the dominant variant in the region. The second most prevalent was IVS I-1 (G–T), found in 9.52% of subjects. Other mutations included codon 8/9 (+G) and codon 15 (G–A), both occurring in 6.34% of the sample, followed by codon 41/42 (–TCTT) at 3.96% and 619 bp deletion at 2.38%. Additionally, 6.34% of the subjects had uncharacterized mutations. This data emphasizes the regional genetic variation in beta-thalassemia mutations and the importance of targeted screening and counselling strategies in these districts.[17]

All the above findings reinforce the significant geographical variation of hemoglobinopathies across India as well as within individual states. Such high regional figures justify the implementation of screening protocols as public health mandates.

As per the National Health Mission (NHM) and WHO recommendations, hemoglobinopathy screening during

antenatal care is particularly essential in regions with high carrier frequency. The Indian Council of Medical Research (ICMR) also recommends early identification and counselling of carriers in high-prevalence zones to curtail the burden of severe inherited hemoglobin disorders.

The limitations of this study were that the study was conducted with a sample size of 800 antenatal females from a single center, which may limit the generalizability of the findings to broader populations. A larger, multicentric study would provide more representative data. Further molecular studies may be needed in order to detect certain other hemoglobinopathies which may have been missed.

## Conclusion

An observational cross-sectional study conducted on antenatal females revealed a high prevalence of anemia. The majority of participants were in their second or third decade of life, with nearly equal distribution between the two age-groups. Most cases were of moderate severity, with peripheral blood smear findings predominantly indicating microcytic hypochromic anemia, suggestive of iron deficiency. A significant proportion of the participants belonged to lower-middle-income backgrounds, highlighting the socioeconomic influence on maternal health. Additionally, obstetric history analysis showed that the most common parity status was among women with one previous pregnancy and one living child. These findings emphasize the need for targeted interventions to address anemia in antenatal care.

This study assessed the prevalence of hemoglobinopathies among antenatal females in a specific region, revealing a low prevalence (1.55%), with beta-thalassemia being the most common type identified. The high rate of microcytic hypochromic anemia underscores the need for targeted interventions to address iron deficiency and improve maternal health outcomes.

## Acknowledgment

We extend our sincere thanks to Dr DY Patil Medical College, Hospital and Research Centre, Pimpri, Pune, for providing resources, facilities, and funding for the project.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author, Mallika Agarwal (MA), upon reasonable request.

## Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the females have given their consent for the clinical information to be reported in the journal. The females understand that their name and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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ORIGINAL ARTICLE

# The Function of Platelet-to-lymphocyte Ratio and Neutrophil-to-lymphocyte Ratio in Assessing Disease Activity in Rheumatoid Arthritis Patients

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## Abstract

**Aim:** To ascertain the function of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as biomarkers in evaluation of disease activity in rheumatoid arthritis (RA) patients.

**Materials and methods:** This cross-sectional research was performed in a hospital and included 381 patients who met the 2010 ACR/EULAR criteria for RA. The clinical disease activity assessment (CDAI) was used to evaluate activity of disease in addition to demographic and disease-related variables. Based on preestablished CDAI cutoff values, the participants were categorized into four groups. For each patient, laboratory analysis included the following: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and complete blood count (CBC). The conventional procedure was followed in the appropriate computation of PLR and NLR. The four patient groups' NLR and PLR values were compared, and the relation among disease activity indices and NLR and PLR was investigated using Pearson correlation analysis.

**Results:** In patients, the mean PLR was 132.8 ± 127.7 and the mean NLR was 3.66 ± 2.6. Patients with low disease activity had a substantially lower mean PLR ($p = 0.021$) in comparison to those with higher disease activity. The mean NLR in relation to CDAI was not observed to be statistically significant ($p = 0.69$) across the four groups. While there was a weak positive association between PLR and the physician visual analog scale (VAS) ($r = 0.22$), patient VAS ($r = 0.12$), and CDAI ($r = 0.17$), there was no correlation among CDAI and specific disease indices with NLR, according to Pearson correlation analysis.

**Conclusion:** PLR, but not NLR, may be an effective biomarker for evaluating the disease activity level in RA patients, particularly higher disease activity.

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## Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease with an incidence of 0.75–1% in the Indian population, impacting synovial joints and extra-articular organs.[1] At present, with the treat-to-target strategy, every patient is treated aggressively, aiming at the achievement of remission. Thus, patient assessment is an important part that guides treatment. The predominant methods for evaluating disease activity are composite indices, including the simplified disease activity index (SDAI), disease activity score (DAS), and clinical disease activity assessment (CDAI). These composite indices include joint inspection of tender and swollen joints, laboratory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and patient-reported outcomes. But these measurements also have drawbacks, including the unpredictability of physician and patient assessments and the impact of coexisting illnesses on laboratory parameters.[2,3]

There has been a rising demand for innovative biomarkers to assess disease activity in RA. Two indices have attracted attention as potential indicators of inflammation: the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR).[4] They are easily collected from complete blood count (CBC) and are inexpensive. Neutrophils are among the first responders to inflammatory sites, causing tissue damage and worsening inflammation, while lymphocytes, particularly T and B cells, are central to autoimmune processes underlying RA.[5] Platelets also are increasingly known for their involvement in inflammation and immune modulation.[6] Increased PLR and NLR have been recognized as markers of systemic inflammation in a number of autoimmune and inflammatory diseases.[7,8]

Data on their clinical utility in RA disease assessment, however, are debatable. Studies with a majority of participants have reported greater NLR and PLR in RA patients than in controls.[9] However, other research that also linked PLR and NLR to the activity of RA produced contradictory findings.[10] There is some Indian data in this regard by Chandrashekara et al., wherein they found that NLR correlates well with disease activity and also serves as an effective measure to predict sustained remission.[11,12] The present research seeks to address this gap by investigating the significance of PLR and NLR in evaluating disease activity in a clearly defined cohort of RA patients. The current work compares these ratios across various disease activity levels and examines their correlation with clinical and laboratory markers in an effort to elucidate their potential as adjuncts to traditional disease activity assessments.

## Materials and Methods

A cross-sectional research was performed at the rheumatology clinic of the department of medicine at the Hind Institute of Medical Sciences from January 2023 to December 2023. The institutional ethics committee approved the informed consent and research procedures. The research encompassed 381 individuals aged 18 and older who satisfied the 2010 American College of Rheumatology (ACR) criteria for RA. Patients with active infections, autoimmune diseases other than RA, significant major organ failure, and abnormalities in the hematocrit were not allowed to take part in the study.

A comprehensive clinical examination, standard laboratory testing, and a full history were used to evaluate each study participant. Disease activity was calculated by utilizing the CDAI. Patients were then classified using predefined CDAI cutoff values (Table 1).[13]

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### Assessment of Platelet-to-lymphocyte Ratio and Neutrophil-to-lymphocyte Ratio

Peripheral venous blood was obtained at the time of enrollment from each patient, and the total blood count was determined using a BC-5130 auto hematology analyzer. The total and differential WBC counts were subsequently utilized to determine the absolute neutrophil count and the absolute lymphocyte count. The overall platelet count was divided by the total lymphocyte count (TLC) to calculate the PLR, while the total neutrophil count was divided by the TLC to ascertain the NLR.[14]

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 26th version was utilized for statistical analysis. The quantitative variables were presented as mean and SD, while the qualitative variables were expressed as percentages. The Chi-squared test was utilized for categorical variables, while the *t*-test was employed for continuous variables. Pearson correlation analysis was employed to evaluate the association among NLR, PLR, and disease activity variables related to RA.

## Results

Three hundred eighty patients participated in the research, comprising 336 females and 44 males with an average age of 43 ± 11 years. The patients' demographic profile and the core set of variables' mean values are summarized in Table 2. Most patients exhibited moderate to low disease activity, with a mean CDAI of 14.72 ± 11.62. Table 1 presents the patient distribution based on CDAI.

### Hematological Indices

The mean NLR in the patients was 3.6 ± 2.1, and the mean NLR in relation to CDAI was as follows: remission, 3.44 ± 2.16; low activity, 3.83 ± 2.82; moderate activity, 3.66 ± 2.05; and high activity, 3.48 ± 1.55. The observed difference in the mean NLR in relation to disease activity was not found to be significant ($p = 0.6$). The mean PLR in the patients was 132.84 ± 127.75, and the mean PLR in relation to CDAI was as follows: remission, 120.35 ± 77.2; low activity, 131.1 ± 60.25; moderate activity, 119.25 ± 57.2; and high activity, 174.6 ± 267.96. The observed difference in the mean PLR in relation to disease activity was found to be significant ($p = 0.021$).

**Table 1:** Predefined cutoff values for CDAI and distribution of patients according to the level of the disease

| *CDAI | *n (%)* |
|---|---|
| Remission ≤2.8 | 32 (8.4%) |
| Low activity >2.8 and ≤10 | 111 (29.2%) |
| Moderate activity >10 and ≤22 | 168 (44.2%) |
| High activity >22 | 69 (18.2%) |

*Clinical Disease Activity Index

### Hematological Parameters and Disease Activity Indices Correlation

Using a Pearson correlation analysis, the association among disease activity indices and hematological indices was investigated. NLR did not correlate with any of the disease activity indicators, though there was a weak positive association—though not a statistically significant one—between PLR and patient visual analog scale (VAS), physician VAS, and CDAI. Table 3 enumerates the details.

## Discussion

This study's primary objective was to analyze the role of NLR and PLR in evaluating disease activity in patients with RA, in comparison to conventional disease assessment tools and laboratory markers. PLR specifically correlated with high disease activity in the patients with RA, whereas NLR did not correlate with disease activity.

Although previous research suggests NLR to be a good inflammatory marker for RA, the present study did not find any relation of NLR with CDAI-defined disease activity groups or with any individual indices.[4,9] The variability in NLR may be due to various confounders that were not adjusted during analysis, such as age, obesity, and medications the patients were taking for RA that may affect neutrophil

**Table 2:** Demographic data of patients and core set of disease variables

| *Parameter (n = 380)* | *Value* |
|---|---|
| Age in years (mean ± SD) | 43 ± 11.5 |
| BMI (kg/m$^2$) | 24.24 ± 1.93 |
| Males *n* (%) | 44 (11.6%) |
| Females *n* (%) | 336 (88.4%) |
| Postmenopausal females *n* (%) | 170 (49.4%) |
| Positive rheumatoid factor *n* (%) | 284 (75%) |
| Positive anticyclic citrullinated peptide *n* (%) | 309 (81%) |
| Duration of disease in months (mean ± SD) | 42.6 ± 54 |
| Disease activity indices (mean ± SD) | |
| Tender joint count (0–28) | 4.99 ± 5.47 |
| Swollen joint count (0–28) | 2.19 ± 3.90 |
| Physician VAS (0–10) | 4.20 ± 2.25 |
| Patient VAS (0–10) | 3.32 ± 2.13 |
| CDAI (0–76) | 14.72 ± 11.62 |
| ESR (in mm/hour) | 35.64 ± 27.74 |
| CRP (mg/dL) | 5.29 ± 12.80 |

**Table 3:** Hematological and disease activity parameters in RA are correlation

| | *Hematological indices* | | | |
|---|---|---|---|---|
| *Disease activity indices* | *NLR* | | *PLR* | |
| | *r* | *p* | *r* | *p* |
| Individual indices | | | | |
| ESR | 0.025 | 0.62 | 0.02 | 0.61 |
| CRP | 0.04 | 0.43 | 0.002 | 0.9 |
| TJC | 0.05 | 0.3 | 0.03 | 0.5 |
| SJC | 0.02 | 0.6 | 0.08 | 0.11 |
| Physician VAS | 0.01 | 0.7 | 0.12 | 0.01 |
| Patient VAS | 0.04 | 0.3 | 0.12 | 0.01 |
| Composite indices | | | | |
| CDAI | 0.04 | 0.376 | 0.09 | 0.07 |

By using a Pearson correlation analysis, *p*-values were determined. Data have a correlation coefficient assigned to them (*r*). A few examples of abbreviations are: CDAI, clinical disease activity index; TJC, tender joint count; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; and VAS, visual analog scale

and lymphocyte counts independently of RA disease activity.[15]

On the other hand, PLR did correlate with CDAI-defined activity state and mainly with high disease state, suggesting that PLR is associated with severe disease. This supports the knowledge that platelets have been linked with immunological response and inflammation.[16]

Previous studies have reported that high platelet count and reduced lymphocyte count indicate high disease activity in RA patients.[17,18] Although the correlation of PLR with physician and patient VAS was weak, PLR can be used along with existing standard biomarkers in regular disease assessment in patients with RA. Similarly, with CDAI, PLR also had a modest correlation; thus, PLR could be integrated along with routine evaluations to provide a more comprehensive picture of disease activity.[18]

### Clinical Implications

The outcomes of the research proposed that NLR might not be a helpful marker in disease assessment, but PLR can be used to assess patients, and high PLR does indicate high disease activity, which helps in putting patients on more aggressive treatment from the beginning. Also, PLR is a cheap biomarker and can be calculated easily using the standard medical tests done for regular evaluation of patients with RA.

### Limitations

It is necessary to recognize that the study has several limitations. It is challenging to determine a causal association between NLR, PLR, and RA disease activity because this study is cross-sectional. A longitudinal study is required to verify these findings and the relation of these markers with time. Also, the results may have been affected by confounders such as age, weight, medication use, and concomitant diseases, which were not adjusted during analysis.

## Conclusion

The study's findings indicate that PLR, but not NLR, has the potential to be a biomarker for determining the RA patient's disease activity. PLR's usefulness in clinical practice is highlighted by its strong connection with clinical assessments and considerable link with high disease activity. Subsequent investigations ought to concentrate on long-term studies to confirm PLR's function and explore its predictive significance in the handling of RA.

## Author Contributions

All the authors contributed equally to the manuscript, compiling, writing, and collection of data.

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REVIEW ARTICLE

# Fosfomycin Tromethamine: A Urinary Antibiotic

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## Abstract

Urinary tract infection (UTI) is the second most common type of infection in the human body. It is one of the most prevalent conditions in medical practice, with approximately 150 million cases occurring globally each year. Approximately 50% of women will experience at least one episode of UTI during their lifetime, and between 20 and 40% will have recurrent episodes. The discovery of a broad-spectrum antibiotic, fosfomycin tromethamine, occurred in Spain in 1969 and is prominently used in the management of uncomplicated UTIs. As a phosphonic acid derivative, fosfomycin acts by disrupting bacterial cell wall synthesis by inhibiting the enzyme MurA, demonstrating effective activity against a wide variety of gram-negative and gram-positive pathogens, comprising multidrug-resistant strains such as *Escherichia coli* and *Klebsiella pneumoniae*. Fosfomycin is not metabolized and is predominantly excreted unchanged in the urine through glomerular filtration. Mean peak urinary concentrations of fosfomycin ranging from 1053 to 4415 mg/L occur within 4 hours of administration of a single oral dose of fosfomycin tromethamine correspondent to fosfomycin 3 gm. Urinary concentrations >128 mg/L, which are adequate to inhibit most urinary pathogens, are maintained for 24–48 hours following a single oral dose of fosfomycin tromethamine. This makes it particularly advantageous for uncomplicated UTIs, where it offers a convenient and effective single-dose treatment option. Clinical trials and observational studies have consistently shown high cure rates and patient compliance, attributing this to its minimal side effects and broad-spectrum efficacy. A single oral dose of fosfomycin tromethamine, equivalent to 3 gm of fosfomycin, is indicated for treating acute uncomplicated lower UTIs in adults. It is classified as pregnancy category B. Various clinical guidelines, such as the Infectious Diseases Society of America (IDSA), European Association of Urology (EAU), and National Institute for Health and Care Excellence (NICE), also recommend fosfomycin tromethamine for the treatment of UTI. In conclusion, fosfomycin tromethamine remains a robust and indispensable antibiotic in the management of uncomplicated UTIs, with a distinct pharmacological profile that ensures both efficacy and safety, and patient compliance due to its single-dose regimen.


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## Introduction

In India, patients suffering from lower urinary tract infections (UTIs) can be managed not only by urologists but also by family physicians/general practitioners (GPs), geriatricians, pediatricians, and gynecologists. The global pooled incidence of UTI accounted for 1.6%. With respect to a systematic review and meta-analysis, the prevalence of UTIs in India has been rising, with *Escherichia coli* being the most commonly isolated pathogen, found in 49.6% of cases, followed by *Klebsiella* spp. at 12.8%.[1] Uncomplicated UTIs occur at a rate of 50 per 1,000 women per year. Approximately 50% of all women will experience at least one UTI during their lifetime, and between 20 and 40% of women will have recurrent UTI episodes.[2] During pregnancy, UTIs are highly prevalent, affecting approximately 20% of pregnant women.[3]

Treating UTIs in India presents several significant challenges, including:

- Antimicrobial resistance: One of the most pressing issues in treating UTIs in India is the high prevalence of antimicrobial resistance (AMR) among common uropathogens like *E. coli* and *Klebsiella pneumoniae*. The misuse and overuse of antibiotics contribute significantly to this problem.
- Diagnostic challenges: In India, the accuracy of UTI diagnosis is often compromised due to reliance on less sensitive methods, which can lead to both false positives and negatives. Proper diagnostic infrastructure is crucial for identifying the specific causative agents and their resistance patterns to tailor effective treatments.
- Socioeconomic factors: Many patients may not complete their prescribed antibiotic courses due to financial constraints, leading to incomplete eradication of the infection and increased resistance. Additionally, there is a lack of awareness about proper hygiene practices and the importance of adhering to prescribed treatments, which can contribute to recurrent infections and resistance issues.
- Right selection of antibiotic: Right selection of antibiotic while treating UTI is a key factor in clinical practice. Different factors should be considered while choosing antibiotic therapy for treating UTI, including: (1) pharmacokinetic (PK) properties of antibiotic—antibiotics with renal excretion should be preferred, (2) activity of the antibiotic against pathogens causing UTI, (3) local resistance pattern against causative pathogens, (4) dosing frequency (simplified dosing regimen or frequency is always preferred), (5) safety and efficacy, and (6) consideration of patient compliance.[4]

## Developmental Aspect of Fosfomycin

Fosfomycin is an old antibiotic. Merck, Sharp, and Dohme (MSD) and Compañía Española de Penicilina y Antibióticos (CEPA) discovered fosfomycin in 1969. Fosfomycin is a derivative of phosphonic acid, isolated from *Streptomyces* spp. Originally called phosphonomycin, fosfomycin has a broad bactericidal spectrum that acts by interfering with cell wall synthesis of both gram-negative and gram-positive bacteria.

Fosfomycin is available in three different formulations. When it is combined with calcium, it is called fosfomycin calcium. When combined with tromethamine (trometamol), it is called fosfomycin tromethamine, and both are for oral treatment, and when combined with sodium, it is called disodium fosfomycin and is for intravenous treatment.[5]

### Difference between Fosfomycin Calcium and Fosfomycin Tromethamine/Trometamol

The oral bioavailability of fosfomycin tromethamine/trometamol is 34–58%, with absorption predominantly occurring in the small intestine. Absorption of fosfomycin tromethamine is six times more than that of

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fosfomycin calcium during the first 2 hours and three to four times more in the first 12 hours; the probable explanation could be that the calcium salt is hydrolyzed and inactivated by gastric enzymes.[6]

## Ideal Urinary Antibiotic

Ideal antibiotics for treating UTIs are the dream of clinicians and should possess several key properties to ensure efficacy, safety, and minimal resistance development (Fig. 1).

These properties help ensure that antibiotics for UTIs are both effective and practical for widespread use, reducing the incidence of complications and the spread of resistant bacteria.

## Fosfomycin Tromethamine

Though the name fosfomycin ends with "-omycin," it does not belong to the macrolide class of antibiotics. Instead, it is classified as phosphonic acids or phosphonic antibiotics, a novel class of antibiotics.[7]

## Chemical Structure

Fosfomycin trometamol is a monobasic hydrosoluble fosfomycin salt. After absorption, fosfomycin is released from fosfomycin trometamol through hydrolysis.[7]

## Mechanism of Action

Fosfomycin acts by inhibiting the bacterial cell wall, thereby inactivating the enzyme enolpyruvyl transferase.[7,8] This action blocks the condensation of uridine diphosphate *N*-acetylglucosamine with phosphoenolpyruvate, an essential step in peptidoglycan synthesis, which is crucial for bacterial cell wall formation. This inhibition leads to a bactericidal effect, particularly in the urinary tract, as fosfomycin is highly concentrated in the urine after administration.[8]

## Microbiology

Fosfomycin is effective against a broad range of gram-negative and gram-positive bacteria.[7,9] It has shown activity against *E. coli*, *Enterococcus faecalis*, and other pathogens involved in UTIs. It is bactericidal in urine at therapeutic doses with MIC: *E. coli* ($MIC_{90}$ ≤12.3 µg/mL). Its lack of cross-resistance with other antibiotic classes makes it a valuable option in the treatment of resistant infections.

## Pharmacokinetic Properties of Fosfomycin Tromethamine

### *Absorption*

Fosfomycin tromethamine is well absorbed after oral administration, although its bioavailability is <50% (absorption of fosfomycin occurs primarily in the small intestine) (Table 1). The absorption of the drug may reduce when coadministered with food. Concomitant administration of metoclopramide should be avoided, as it fails to maintain adequate drug levels for therapeutic efficacy.

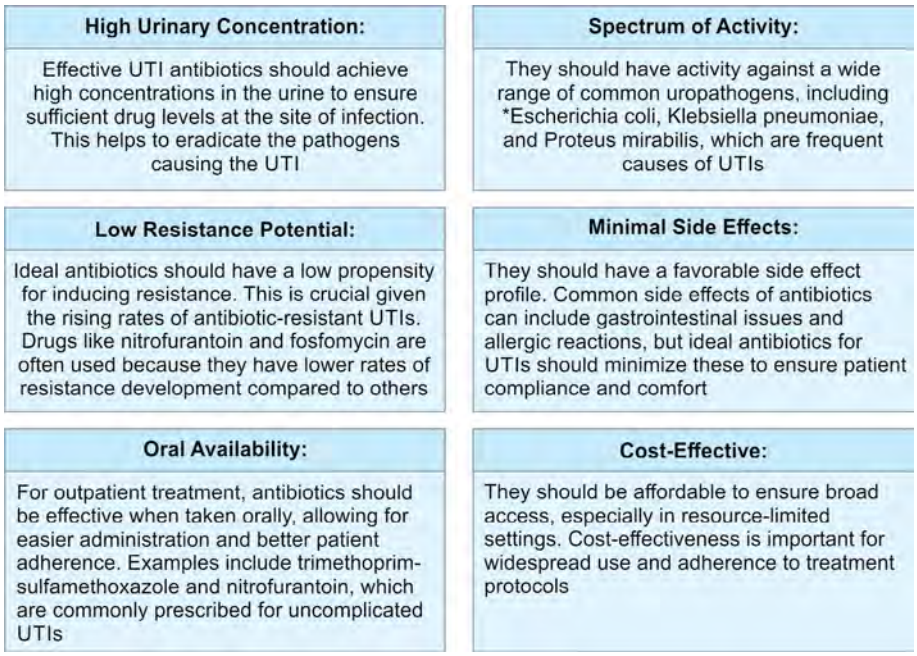


**Fig. 1:** Properties of ideal urinary antibiotic

### *Distribution*

Once absorbed, fosfomycin is widely distributed in body tissues, including the kidneys, bladder wall, and prostate, which is beneficial for treating UTIs. It does not bind to plasma proteins, facilitating its rapid action at infection sites. The evidence shows that a single 3 gm dosage of oral fosfomycin trometamol achieves adequate concentrations in noninflamed prostatic tissue.

### *Metabolism and Excretion*

Fosfomycin is primarily excreted unchanged in the urine. The half-life of fosfomycin trometamol is 5.7 hours in patients with normal renal function but can be significantly prolonged in those with renal impairment (up to 50 hours). After oral dosing, urinary concentrations exceed the MICs of susceptible pathogens for over 24 hours. A total of 32–43% of fosfomycin is excreted renally within 48 hours, and about 85–95% is excreted in the first 24 hours. Concentrations >128 mg/L, sufficient to inhibit most urinary pathogens, are maintained for 24–48 hours after a single oral dose of fosfomycin. After a single 3 gm dose, >99% of common urinary pathogens are eradicated. Additionally, bacterial adhesiveness to uroepithelial mucosa decreases significantly within 1 hour of exposure to fosfomycin at a concentration of 1000 mg/L.[7,9]

## Special Populations

### *In Geriatric Patients*

No dose adjustment is necessary, as there are no significant differences in the PK of fosfomycin.

### *Renal Impairment*

In patients with varying degrees of renal impairment, the elimination half-life of fosfomycin trometamol increases, and its excretion in urine decreases significantly.

**Table 1:** PK properties of fosfomycin trometamol[7,9]

| *Parameters* | *Serum/plasma* | *Parameters* | *Urine* |
|---|---|---|---|
| Bioavailability | 34–41% | | |
| Maximum plasma concentration ($C_{max}$) | 22–32 µg/mL | Maximum urinary concentration ($U_{max}$) | 1053–4415 µg/mL |
| Time to $C_{max}$ ($T_{max}$) | 2–2.5 hours | Time to $U_{max}$ (urinary $T_{max}$) | 4 hours |
| Half-life ($t_{1/2}$) | 5.7 hours | Urinary concentration at 48 hours | ~100 µg/mL |

*Fosfomycin in Pregnancy*[7,9,10]

Pregnant women are more prone to develop UTIs in the third trimester, with *E. coli* being the most common pathogen. Around 20–40% of *E. coli* cases are resistant to ampicillin and amoxicillin, making these antibiotics less effective. Fosfomycin is a valuable alternative treatment.

The US FDA classified fosfomycin in pregnancy category B, that is, "no evidence of risk in humans and can be used in pregnancy if clearly needed." Fosfomycin is excreted in breast milk.[7]

### Indication and Approval Status

Fosfomycin is approved in major countries like the US, UK, and India (Fig. 2).

*Approval Status*

Fosfomycin has been available in several European countries, as well as in Japan, South Africa, and Brazil, in both oral and parenteral formulations, for four decades. In India, the Drug Controller General of India (DCGI) approved fosfomycin in 2008.[12]

### Safety and Tolerability of Fosfomycin

Fosfomycin is generally well tolerated, with few common side effects such as diarrhea, nausea, and abdominal pain. It should be avoided in individuals with a known allergy to the drug, children under 12 years old, those with severe renal insufficiency (CLcr <10 mL/min), or patients undergoing hemodialysis.[7,11]

### Dosage of Fosfomycin

The rationale for using a single dose of fosfomycin trometamol is based on its PK properties (Table 2).[7] After single oral administration, the maximum concentration of 22–32 µg/mL is achieved in about 2 hours, with an elimination half-life of 2.4–7.3 hours and an area under the curve of 145–228 µg/mL·hour. This results in high urinary concentrations (1000–4000 µg/mL), maintaining levels above 100 µg/mL for 30–48 hours.

### Method of Administration

- It is advisable to take fosfomycin on an empty stomach.[7]
- About 2–3 hours before or 2–3 hours after meals, and preferably before bedtime after emptying the bladder.
- A sachet has to be dissolved in a glass of water and consumed immediately after preparation.

### Clinical Efficacy and Safety

Fosfomycin tromethamine is clinically effective for treating uncomplicated UTIs. A meta-analysis comparing fosfomycin to other antibiotics like nitrofurantoin and ciprofloxacin found that a single dose of fosfomycin achieved similar clinical and microbiological cure rates. It is particularly effective against common uropathogens, including multidrug-resistant *E. coli*. Studies show that fosfomycin is generally well tolerated, with fewer gastrointestinal side effects compared to other treatments.[13]

## Guidelines Recommending Fosfomycin Use in Clinical Practice

Fosfomycin tromethamine is recommended for the treatment of uncomplicated UTIs due to its effectiveness, safety, and convenient single-dose administration. It is particularly beneficial against a broad range of uropathogens, including multidrug-resistant strains like *E. coli* and *E. faecalis*.

### European Association of Urology Guidelines

The European Association of Urology (EAU) guidelines for the management of uncomplicated UTIs recommend fosfomycin as one of the first-line options for empirical treatment in regions with low rates of resistance (<10–20%). Fosfomycin is particularly favored for the treatment of acute uncomplicated cystitis in women, owing to its high efficacy and favorable safety profile.[14]

### Infectious Diseases Society of America Guidelines

The Infectious Diseases Society of America (IDSA) guidelines for the treatment of uncomplicated cystitis in adult women recommend fosfomycin as one of the first-line agents, particularly in settings where the prevalence of multidrug-resistant pathogens is low. Fosfomycin is recommended as a single-dose regimen for uncomplicated cystitis caused by susceptible pathogens, such as *E. coli*.[15]

### Society of Infectious Diseases Pharmacists Recommendations

The Society of Infectious Diseases Pharmacists (SIDP) recommendations for the management of complicated urinary tract infections (cUTIs) and acute pyelonephritis (AP) highlight the role of fosfomycin in combination therapy for the treatment of multidrug-resistant pathogens, including extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* and carbapenem-resistant organisms. Fosfomycin is often recommended in combination with other agents, such as aminoglycosides or carbapenems, for the treatment of cUTIs and AP caused by difficult-to-treat pathogens.[16]

### As per National Institute for Health and Care Excellence (NICE) and Public Health England (PHE)

Fosfomycin is recommended for uncomplicated UTI caused by ESBL-producing *E. coli* in adults. Guidelines suggest a single dose of 3 gm in women and two 3 gm doses at an interval of 3 days in men.[17]

**Table 2:** Dosing schedule of fosfomycin

| *Availability* | *Dose* |
|---|---|
| Fosfomycin is available as sachet of 3 gm | A single oral dose of fosfomycin trometamol is suggested for treating acute uncomplicated lower UTIs in adults |

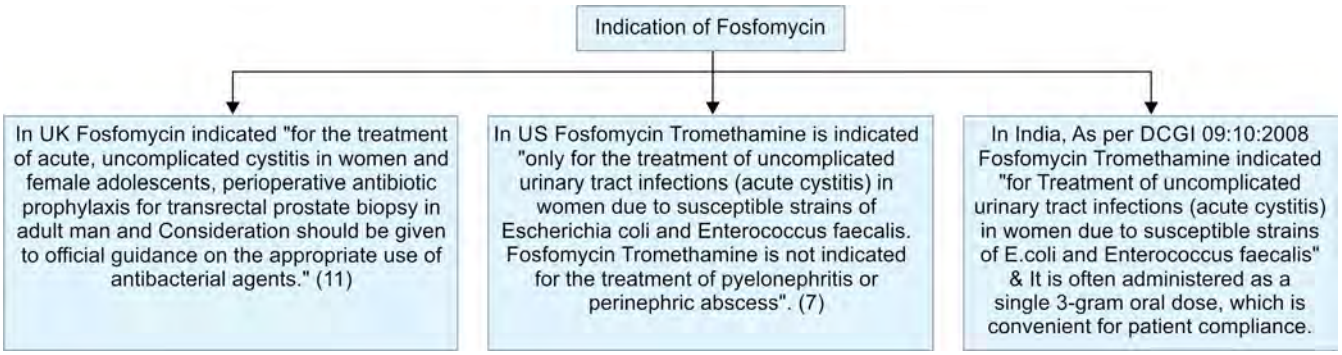


**Fig. 2:** Indications approval of fosfomycin in various countries like US, UK, and India

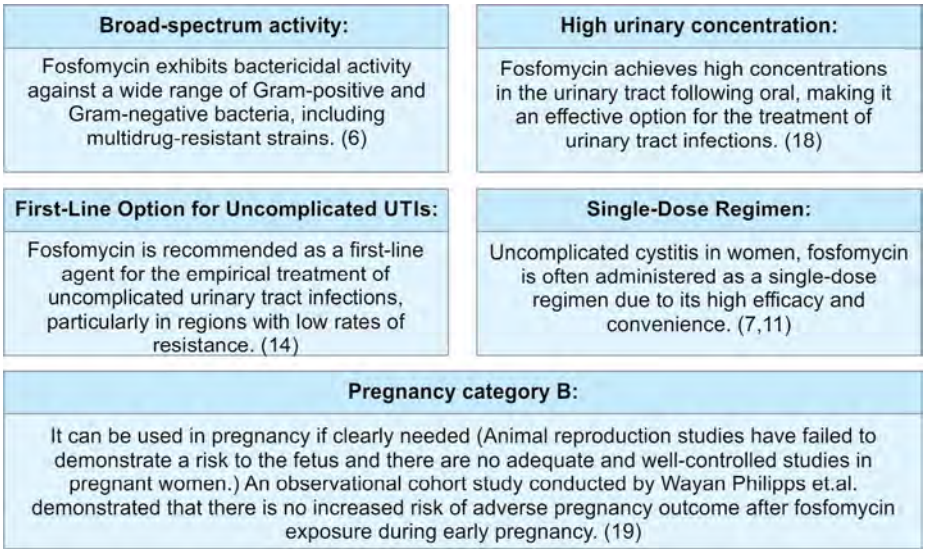


**Fig. 3:** Important pointers on fosfomycin from a clinical perspective

Important points regarding fosfomycin from a clinical perspective can be seen in Figure 3.

## Conclusion

Fosfomycin tromethamine is a broad-spectrum antibiotic prominently used in the management of uncomplicated UTIs. This agent is highly valued for its unique mechanism of action, which involves the inhibition of bacterial cell wall synthesis by blocking the initial step in peptidoglycan formation. Its efficacy against both gram-positive and gram-negative bacteria, including multidrug-resistant strains like ESBL-producing *Enterobacteriaceae*, makes it an essential option in antimicrobial therapy. Clinically, fosfomycin tromethamine is administered as a single-dose regimen, enhancing patient compliance compared to traditional multidose therapies. Its PK profile allows for high urinary concentrations, which is critical for effectively targeting urinary pathogens. Furthermore, the drug demonstrates a favorable safety profile with minimal adverse effects, making it suitable for a broad patient population. Given the rising issue of antibiotic resistance, fosfomycin tromethamine's role in the therapeutic landscape is increasingly significant. It offers a viable alternative in instances where other antibiotics may fail due to resistance or adverse reactions. A recent systematic review and network meta-analysis published in World Journal of Urology 2024 confirmed that fosfomycin is the most effective antibiotic in treating uncomplicated UTIs with respect to microbiological cure, clinical cure, and adverse events profile.[20]

In conclusion, fosfomycin tromethamine remains a robust and indispensable antibiotic in the management of uncomplicated UTIs, with a distinct pharmacological profile that ensures both efficacy and safety. Its relevance is further underscored in the current era of escalating AMR, positioning it as a critical tool in contemporary infectious disease therapy. Appropriate antibiotic therapy is essential for achieving clinical cure and preventing complications. However, the increasing prevalence of antibiotic resistance necessitates a thoughtful, evidence-based approach to antibiotic selection and management.

## Conflict of Interest

Dr Abhijit A Trailokya is associated with Indoco Remedies Limited, Mumbai.

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REVIEW ARTICLE

# Achieving Diabetes Remission: Current Guidelines and Emerging Pharmacotherapies in India

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## Abstract

Type 2 diabetes mellitus (T2DM) remission has emerged as a critical area of research and clinical interest, especially in India, where diabetes prevalence is rising at an alarming rate. Achieving remission through pharmacologic, dietary, and surgical interventions is now an attainable goal for a subset of patients. This systematic review synthesizes evidence from clinical trials, emerging pharmacologic interventions, and current guidelines for diabetes remission. We explore the mechanisms of diabetes reversal, highlighting novel agents such as glucagon-like peptide-1 (GLP-1) receptor agonists, dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 agonists, and sodium–glucose cotransporter 2 (SGLT2) inhibitors. This review also addresses the long-term sustainability of remission, epidemiological trends in India, and current treatment recommendations, integrating data from major studies. The findings underscore the need for a patient-centered, evidence-based approach to diabetes management. Additionally, we discuss the role of continuous glucose monitoring (CGM), dietary interventions, and the benefits of millet consumption in diabetes remission.


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## Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and chronic hyperglycemia. The burden of diabetes in India has been increasing at an unprecedented rate, with an estimated 77 million adults diagnosed and an additional 25 million exhibiting impaired glucose tolerance (IGT).[1] If this trajectory continues, the prevalence is expected to reach 134 million by 2045 [International Diabetes Federation (IDF), 2021].[1] Given this growing public health concern, the concept of diabetes remission is being increasingly recognized as an alternative therapeutic goal beyond standard glycemic control. Achieving remission through structured lifestyle interventions, intensive pharmacotherapy, or metabolic surgery could significantly reduce the long-term complications associated with diabetes.

The definition of diabetes remission is based on achieving a glycated hemoglobin (HbA1c) level below 6.5% (48 mmol/mol) for at least 3 months in the absence of glucose-lowering medications..[2] Current research efforts are focused on identifying effective interventions that can help patients attain sustained remission, particularly in populations with a high genetic predisposition, such as in India (Fig. 1).

Here is the bar graph showing the increasing prevalence of diabetes in India based on IDF projections. The data is sourced from the IDF.[1]

## Methodology

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. While this review was not registered with PROSPERO, all efforts were made to ensure transparency, reproducibility, and adherence to systematic standards. The decision not to register was due to early-stage resource constraints; however, the methodology followed remains robust and reproducible.

Although no formal meta-analysis was performed, methodological quality was reviewed based on study design and clinical relevance. Risk of bias was noted during screening, prioritizing peer-reviewed randomized controlled trials (RCTs) and well-structured trials.

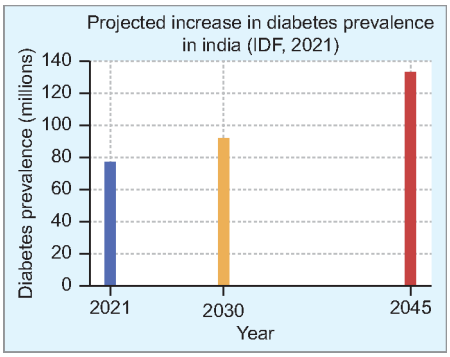


**Fig. 1:** Diabetes prevalence in India (2021–2045 projections)[1]

A comprehensive literature search was performed using PubMed, Embase, Cochrane Library, and Scopus databases to identify relevant studies published in the last 10 years. The search terms included "diabetes remission," "pharmacotherapy for diabetes reversal," "India diabetes guidelines," "glucagon-like peptide-1 (GLP-1) receptor agonists," "sodium–glucose cotransporter 2 (SGLT2) inhibitors," "combination therapy for diabetes remission," and "bariatric surgery for diabetes" (Table 1).

### Inclusion Criteria

- RCTs, meta-analyses, cohort studies, and systematic reviews on T2DM remission.
- Studies evaluating pharmacologic interventions, lifestyle modifications, or metabolic surgery.
- Studies conducted in both global and Indian populations.

### Exclusion Criteria

- Case reports and opinion articles.
- Studies lacking objective remission criteria.
- Studies with small sample sizes (<50 participants).

Data extraction was performed independently by two reviewers, and discrepancies were resolved by consensus. The extracted data included study design, intervention type, sample size, remission criteria, follow-up duration, and key findings.

## Clinical Trials

### Very Low-calorie Diets

The Diabetes Remission Clinical Trial (DiRECT) (2018, UK): The DiRECT trial was a landmark study that demonstrated the

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effectiveness of very low-calorie diets (VLCDs) in achieving diabetes remission. Participants who adhered to an 825–853 kcal/day diet for 3–5 months experienced a 46% remission rate at 1 year. Sustained weight loss of 10 kg or more was a key predictor of success.[3]

### GLP-1 Receptor Agonists and Dual GIP/GLP-1 Agonists

The SURPASS-1 trial (2023): The SURPASS-1 trial investigated the efficacy of tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist. Approximately 52% of participants reached an HbA1c level below 5.7%, which is within the normal range for individuals without diabetes.[4]

The STEP 2 trial (2021): This trial showed participants receiving semaglutide 2.4 mg weekly experienced significant weight loss and improved glycemic control. Specifically, 67.5% of participants achieved HbA1c levels of ≤6.5%, and 45.6% achieved a ≥10% reduction in baseline body weight at week 68.[5]

**Table 1:** Prisma flow table

| *Stage* | *Count* |
|---|---|
| Records identified through database searching (PubMed, Embase, Cochrane, and Scopus) | 1,240 |
| Records after duplicates removed | 980 |
| Records screened (title + abstract) | 980 |
| Records excluded (irrelevant, not focused on T2DM remission) | 865 |
| Full-text articles assessed for eligibility | 115 |
| Full-text articles excluded (e.g., poor methodology, <50 participants, not meeting remission criteria) | 87 |
| Studies included in final review | 28 |

### SGLT2 Inhibitors

A multicenter, RCT is currently underway to evaluate the remission effect of canagliflozin in patients with newly diagnosed T2DM. Participants will maintain their medication for 3 months after achieving target blood glucose levels and then discontinue it, with a follow-up period of 1 year to assess remission rates. The results of this trial are pending.[6]

### Metabolic Surgery

The STAMPEDE trial (2017): This trial demonstrated that Roux-en-Y gastric bypass led to diabetes remission in 70–80% of cases (Table 2).[7]

## Current Guidelines for Diabetes Remission in India

Diabetes management guidelines in India are predominantly influenced by global frameworks, with adaptations to meet local healthcare needs. The Research Society for the Study of Diabetes in India (RSSDI)[8] and the Indian Council of Medical Research (ICMR)[9] provide clinical guidelines that align with those issued by the American Diabetes Association (ADA)[10] and the European Association for the Study of Diabetes (EASD).[11] The 2024 ICMR guidelines emphasize a multifaceted approach, including lifestyle modifications, pharmacotherapy, and surgical options where applicable. These guidelines underscore the importance of individualized care plans, integrating patient preferences, and comorbid conditions into therapeutic decisions.

### Pharmacotherapy Guidelines

- First-line therapy: Lifestyle modification and metformin remain the cornerstone of initial management.
- GLP-1 receptor agonists and dual GIP/GLP-1 agonists: Recommended for patients with obesity [body mass index (BMI) ≥ 30 kg/m$^2$] or insulin resistance, and those failing to achieve glycemic control with metformin alone.
- SGLT2 inhibitors: Preferred in patients with chronic kidney disease (CKD), heart failure, or established atherosclerotic cardiovascular disease (ASCVD). These agents can be initiated in patients with HbA1c > 7% despite metformin therapy.
- Combination therapy: The use of metformin, pioglitazone, and repaglinide as a combination. These combinations are recommended for individuals with HbA1c > 8% at diagnosis.
- Insulin therapy and early intensification: In newly diagnosed individuals with severe hyperglycemia (HbA1c > 10% or fasting plasma glucose > 300 mg/dL), short-term insulin therapy may be required before transitioning to oral or injectable agents.

### Lifestyle and Surgical Guidelines

- Very low-calorie diets: Recommended for individuals with recent-onset diabetes (<6 years), with potential remission benefits if sustained for at least 12 weeks.
- Bariatric surgery: Recommended for individuals with BMI > 35 kg/m$^2$ with uncontrolled diabetes, or BMI > 30 kg/m$^2$

**Table 2:** Summary of clinical trials

| *Trial name* | *Objective* | *Methodology* | *Findings* | *Reference* |
|---|---|---|---|---|
| DiRECT trial (2018, UK) | Assess whether structured weight management can induce diabetes remission | Low-calorie total diet replacement (825–853 kcal/day), structured food reintroduction, and long-term support | 46% remission at 12 months; 36% sustained remission at 24 months | Lean et al.[3] |
| ARMMS-T2D trial | Compare metabolic surgery vs medical/lifestyle intervention for diabetes remission | Participants randomized to metabolic surgery (gastric bypass, sleeve gastrectomy) or medical/lifestyle management | 37.5% remission in the surgical group vs 2.6% in the medical/lifestyle group at 3 years | Kirwan et al.[12] |
| SURPASS-1 trial (2023) | Evaluate tirzepatide's role in glycemic control and remission | Participants randomized to receive 5, 10, or 15 mg of tirzepatide vs placebo for 40 weeks | 52% of participants on 15 mg achieved normoglycemia (HbA1c < 5.7%) without additional medication | Rosenstock et al.[4] |
| STEP 2 trial (2021) | Assess semaglutide's impact on T2DM remission in overweight/obese individuals | Participants received semaglutide 2.4 mg weekly for 68 weeks | Significant weight loss and glycemic control; remission rates not explicitly stated | Davies et al.[5] |
| STAMPEDE trial (2017) | Compare bariatric surgery vs intensive medical therapy for T2DM remission | Participants randomized to Roux-en-Y gastric bypass, sleeve gastrectomy, or medical therapy | 29% of surgical group achieved HbA1c ≤ 6.0% without diabetes medications at 5 years | Schauer et al.[7] |

with significant obesity-related complications.[8,12]
- Microbiome-based therapies: Although not yet part of standard guidelines, emerging evidence suggests that gut microbiota modulation through probiotic therapy, fecal microbiota transplantation (FMT), and prebiotic dietary interventions may enhance insulin sensitivity and glycemic control.

## Dietary Interventions for Diabetes Remission

Diet remains the cornerstone of diabetes remission strategies. The DiRECT trial demonstrated that VLCDs could induce remission in nearly 50% of patients. However, for Indian populations, dietary modifications must be tailored to cultural preferences and traditional food habits.

- Caloric restriction: VLCDs (800–900 kcal/day) have been effective in achieving remission. Intermittent fasting and time-restricted eating are emerging approaches.[3]
- Macronutrient modifications: High-fiber, low-glycemic index (GI) diets are recommended.[13] Increased intake of plant-based proteins and healthy fats (RSSDI, 2023).
- Role of millets in diabetes remission: The World Health Organization (WHO) declared 2023 as the International Year of Millets, recognizing their nutritional value. Millets, such as *jowar* (sorghum), *bajra* (pearl millet), and *ragi* (finger millet), are gaining prominence in diabetes management due to their high-fiber content and low GI properties—Jowar (Sorghum): Rich in polyphenols and resistant starch, improves insulin sensitivity.[13] Bajra (pearl millet): Lowers postprandial glucose spikes.[9] Ragi (finger millet): High calcium content and slow digestion rate aid in glucose control.[13]

Dietary guidelines for Indian populations: Replace refined grains with whole grains and millets.[8] Increase intake of legumes and vegetables.[9] Limit processed foods and sugar intake.[14] Include probiotic-rich foods to improve gut microbiome health.[13] Studies by Saboo et al. emphasize that dietary modifications incorporating millets can significantly improve glycemic control and aid in long-term remission.[13]

The Diabetes Surgery Summit II (DSS-II) 2016 guidelines, endorsed by international organizations, support surgical intervention as a therapeutic alternative for diabetes remission in specific cases.[15]

### Dosage Guidelines for Approved Agents

- Semaglutide (GLP-1 agonist): Recommended dose escalation from 0.25 to 1.0 mg weekly, with some studies exploring 2.4 mg weekly for weight loss benefits.
- Tirzepatide (dual GIP/GLP-1 agonist): Initiation at 2.5 mg weekly, with gradual titration to 15 mg weekly.
- Canagliflozin (SGLT2 inhibitor): Standard dose 100 mg daily, increasing to 300 mg daily based on renal function.

## Lantidra

Lantidra (donislecel): Approved by the Food and Drug Administration (FDA) in June 2023, Lantidra is the first allogeneic cellular therapy for adults with type 1 diabetes who experience severe hypoglycemia despite intensive management. It involves infusing donor pancreatic islet cells into the patient's liver, enabling insulin production. Clinical trials demonstrated that some patients achieved insulin independence posttreatment.[16]

## Continuous Glucose Monitoring in Diabetes Remission

Continuous glucose monitoring (CGM) is an essential tool for monitoring glucose levels and optimizing diabetes remission strategies. It provides real-time data, allowing for early detection of glycemic variability and aiding in personalized dietary and pharmacologic interventions. The ADA and the RSSDI recommend CGM for individuals aiming for remission, particularly those undergoing intensive lifestyle interventions or using insulin-sensitizing agents. CGM enables: Continuous tracking of glucose fluctuations, identification of early signs of relapse, tailoring dietary and exercise interventions, and adjusting pharmacologic regimens dynamically. Studies have shown that CGM use in remission strategies leads to better long-term glycemic control and increased adherence to lifestyle modifications (Table 3).[13]

## Relevance in the Indian Population

The relevance of diabetes remission strategies in India is profound due to the high prevalence of central obesity and insulin resistance. Genetic predisposition plays a significant role in the progression of T2DM, making lifestyle interventions challenging for many individuals. The dietary patterns in India, which are often carbohydrate-rich, further complicate adherence to low-calorie and

**Table 3:** Clinical guidelines comparison table: India vs Global

| *Aspect* | *RSSDI/ICMR (India)* | *ADA/EASD (Global)* |
|---|---|---|
| Definition of remission | HbA1c < 6.5% for ≥3 months without glucose-lowering medication | Same definition (per ADA Consensus Report 2021) |
| First-line therapy | Lifestyle + Metformin | Lifestyle + Metformin |
| GLP-1 receptor agonists | Recommended for BMI ≥ 30 kg/m$^2$ or insulin resistance | Recommended for ASCVD, obesity, or when weight loss is a priority |
| SGLT2 inhibitors | Preferred in patients with CKD, heart failure, or HbA1c > 7% | Same; strong evidence for cardiovascular and renal benefits |
| Combination therapy | Metformin + pioglitazone + repaglinide in patients with HbA1c > 8% | Metformin + GLP-1 RA or SGLT2i or sulfonylureas, depending on comorbidities |
| Insulin | Short-term insulin for HbA1c > 10% or FPG > 300 mg/dL | Same recommendation |
| VLCDs | Recommended for recent-onset diabetes (<6 years) | Recommended but with close medical supervision |
| Metabolic surgery | Recommended for BMI > 35 or BMI > 30 with comorbidities | BMI > 30 with inadequate control, especially in Asian populations |
| Continuous glucose monitoring (CGM) | Recommended in intensive interventions or insulin use | Widely recommended for type 1 and insulin-requiring type 2 diabetes |

*Note*: ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; ICMR, Indian Council of Medical Research; RSSDI, Research Society for the Study of Diabetes in India

low-carbohydrate interventions. Therefore, pharmacologic interventions, such as GLP-1 receptor agonists and SGLT2 inhibitors, have gained importance in remission strategies. Moreover, the high cost of metabolic surgery limits accessibility for a significant portion of the population, necessitating cost-effective and sustainable alternatives. Thus, socioeconomic factors also play a crucial role, as cost-effective pharmacologic alternatives, such as SGLT2 inhibitors and combination therapies, may be more viable than bariatric surgery for many patients.[8]

## Future Directions

Research into β-cell regeneration, microbiome modulation, and artificial pancreas systems offers promising avenues for diabetes remission. PDX-1 targeting drugs aimed at improving β-cell function are under investigation, while FMT is being explored as a potential intervention for metabolic diseases. The development of smart insulin delivery systems integrating CGM with insulin pumps may revolutionize diabetes management in the near future.

## Ongoing Clinical Trials

Several ongoing trials are investigating novel pharmacologic interventions for diabetes remission: Phase 3 trials of high-dose GLP-1/GIP receptor agonists (e.g., Tirzepatide) evaluating long-term remission potential, trials exploring combination therapies, including SGLT2 inhibitors with GLP-1 receptor agonists, aiming for superior glycemic control and weight loss, and β-cell regeneration studies utilizing novel peptide therapies to enhance insulin secretion.

## Conclusion

Diabetes remission is a tangible goal, with a growing body of evidence supporting structured lifestyle interventions, pharmacotherapy, and metabolic surgery as viable pathways. The adoption of new pharmacological agents, including GLP-1 receptor agonists, SGLT2 inhibitors, and combination therapies, provides an expanded toolkit for clinicians. CGM plays a critical role in monitoring and sustaining remission. Dietary interventions, particularly incorporating millets, provide a culturally appropriate and effective strategy for the Indian population. In India, addressing sociocultural and economic barriers remains crucial for achieving widespread remission outcomes. Future research should focus on personalized treatment strategies that cater to the unique metabolic profile of the Indian population.

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REVIEW ARTICLE

# Review of Safety and Efficacy of Polmacoxib: A Novel Dual Inhibitor of Cyclo-oxygenase 2 and Carbonic Anhydrase in Osteoarthritis and Acute Painful Conditions

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## Abstract

Osteoarthritis (OA) is a chronic degenerative joint disorder and a leading cause of pain and disability among the elderly. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs), though effective in symptom relief, pose significant risks of gastrointestinal, cardiovascular, and renal complications, especially in long-term use. Polmacoxib (CG100649) is a newer NSAID with its dual inhibitory role on cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA), planned to offer higher therapeutic efficacy and safety. This review critically examines the pharmacodynamic and pharmacokinetic properties of polmacoxib, along with its clinical efficacy and safety in OA and acute pain conditions. Clinical trials across phases I–III consistently show polmacoxib to be well tolerated and effective in pain relief and efficient improvement of the joint, with a safety profile comparable to or better than traditional COX-2 inhibitors like celecoxib. Recent trials also explore its role in combination therapies for acute pain management, including dental and postoperative settings, showing noninferiority to standard regimens and fewer adverse events. Its innovative mechanism and pharmacological profile support its potential as a next-generation NSAID for OA and pain management, particularly in populations at high risk for NSAID-induced adverse effects. Further larger long-term studies are warranted to confirm its medical benefits and broader therapeutic applications.


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## Introduction

Osteoarthritis (OA) is the most common type of arthritis leading to chronic pain and long-term disability in adults. It is associated with articular cartilage loss and hypertrophic bone. It predominantly affects load-bearing joints such as the hips and knees.[1] The World Health Organization (WHO) Global Ageing and Health Report (2015) underscores it as the fourth leading cause of disability among adults aged 60 years and older.[1,2] In 1990 nearly 23.46 million Indians were affected by OA, while by 2019 it had risen to 62.35 million.[3] OA can be categorized into two types: primary OA, which arises without an identifiable cause, and secondary OA, which develops due to factors such as injury or underlying medical conditions. Risk factors for OA include advancing age, female sex, obesity, certain anatomical traits, muscle weakness, and joint injuries, particularly those resulting from occupation-related activities or sports.[4]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been the cornerstone of symptomatic treatment for OA, helping to alleviate pain and inflammation. However, traditional NSAIDs, while effective, are associated with significant adverse effects, including gastrointestinal (GI) toxicity, cardiovascular (CV) risk, and renal impairment, which limit their long-term use, especially in older adults.[5]

Recent therapeutic advancements have aimed to develop safer alternatives with improved efficacy and reduced side effects. Polmacoxib is an innovative dual inhibitor of cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA), a promising new class of NSAID that has garnered attention for its potential to provide effective pain relief with a more favorable safety profile.[6] Its dual mechanism of action targets both the inflammatory pathway mediated by COX-2 and the dysregulated CA enzyme activity often seen in OA, offering a more comprehensive approach to managing the disease.

This review aims to critically appraise the safety and efficacy of polmacoxib in the treatment of OA. We will explore preclinical and clinical studies, focusing on its pharmacokinetics (PK), pharmacodynamics (PD), clinical outcomes, and adverse event profile. By comparing polmacoxib to traditional NSAIDs and other novel treatments, this review seeks to provide a comprehensive understanding of its role as a next-generation therapeutic option for OA.

## Polmacoxib (CG100649)

Polmacoxib is a synthetic novel NSAID inhibiting both COX-2 and CA enzymes. It was developed by CrystalGenomics Inc. and first approved in South Korea in 2015 for the treatment of colorectal cancer and OA.[7] On 14th February 2023, the Drug Controller of India approved polmacoxib for the management of idiopathic primary OA of the hip and knee.[8] Its chemical structure and pharmacological properties are shown in Figure 1 and Table 1, respectively.

## Pharmacodynamics of Polmacoxib

NSAIDs are a class of drugs commonly used to relieve pain, control inflammation, and reduce fever. They act through cyclooxygenase (COX) enzyme inhibition. There are two types of COX isoenzymes: COX-1, which is constitutively expressed and plays a protective role in the gastric mucosa and platelet function, and COX-2, which is induced in inflammation and is responsible for producing prostaglandins mediating pain and inflammation.[10] Most traditional NSAIDs are nonselective,

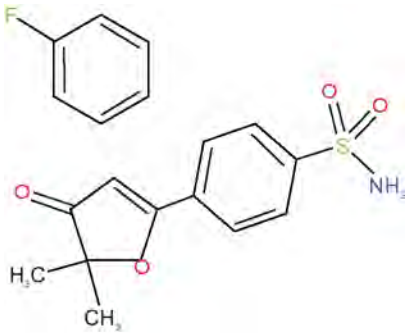


**Fig. 1:** Chemical structure of polmacoxib

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**Table 1:** Features and properties of polmacoxib[9]

| | |
|---|---|
| Alternative names | CG100649, CG-100649, Acelex®, Polmakem™ |
| Class | Nonsteroidal anti-inflammatory drugs |
| Route of administration | Oral |
| Recommended dosage | 2 mg once daily after a meal. The dose should not exceed 2 mg/day |
| Pharmacodynamics | Dual inhibitor of cyclo-oxygenase 2 and carbonic anhydrase |
| Pharmacokinetics | Mean $T_{max}$: 5.6 hours; mean $C_{max}$: 3.5 ng/mL; mean $t_{1/2}$: 131 hours; Excretion: primarily *via* the fecal route |
| Approved therapeutic indication | OA of the hip or knee |
| Adverse events | Epigastric pain, diarrhea, indigestion, nausea, abdominal pain, chest discomfort, facial swelling, edema, peripheral swelling |
| WHO ATC code | M01AH07 |
| Molecular formula | $C_{18}H_{16}FNO_4S$ |
| CAS registry number | 301692-76-2 |

CAS, chemical abstracts service; WHO ATC, World Health Organization Anatomical Therapeutic Chemical

inhibiting both COX-1 and COX-2, and can lead to GI adverse effects. Selective COX-2 inhibitors specifically target the COX-2 isoenzyme, reducing GI damage but sparing the gastroprotective effects of COX-1.[11] Hence, it is usually recommended to use selective COX-2 inhibitors over nonselective NSAIDs for patients with OA and GI comorbidities.[12] However, certain COX-2 inhibitors, such as rofecoxib and valdecoxib, have been withdrawn from the market due to concerns about increased CV risks linked to their inhibition of COX-2 in the circulatory system.[13]

Polmacoxib stands out from other NSAIDs due to its dual mechanism of action, which includes both COX-2 inhibition and inhibition of CA-I and CA-II. Unlike most conventional COX-2 inhibitors, which do not significantly affect CA activity, polmacoxib shows a higher affinity for CA than COX-2, particularly in CV tissues. This dual inhibition reduces COX-2 activity in the CV system, potentially minimizing the CV risks typically seen with selective COX-2 inhibitors.[14] Moreover, low-dose administration has negligible impact on overall CA function in the CV system. In contrast, inflamed tissues, which have low CA levels and elevated COX-2 expression, benefit from its ability to effectively inhibit COX-2, thus reducing inflammation and pain, particularly in conditions like OA.[14]

## Pharmacokinetics of Polmacoxib

The transport of polmacoxib across the biological membrane principally involves red blood cells (RBCs). RBCs act as a reservoir, carrying the drug in an inactive form to tissues with low CA activity, for example, inflamed joints in OA. The drug concentration in RBCs is 85- to 100-fold higher than in plasma, where CA is absent.[15] This unique transport system ensures that polmacoxib remains active in the inflamed joints while minimizing systemic exposure, thereby reducing its potential impact on the CV, renal, and GI systems. Pharmacokinetic data show that after oral administration of polmacoxib at 2 and 8 mg doses, maximum plasma concentrations (Cmax) were 3.5 and 14.1 ng/mL, respectively, with elimination half-lives of 131 hours and 127 hours.[15] Polmacoxib also demonstrates a longer retention time in the inflamed joint tissues compared to blood, suggesting its sustained therapeutic effect at the target site while limiting prolonged exposure to other body systems. Polmacoxib is metabolized by the hepatic microsomal enzyme CYP3A4 and is principally excreted in the feces, with only traces found in the urine. Any impairment in liver function could potentially affect its clearance.[14]

## Preclinical Pharmacology

Lee et al. (2008) conducted an experimental *in vivo* and *in vitro* evaluation of polmacoxib.[16] The study reported that polmacoxib has moderate selectivity for COX-2 compared to COX-1, with selectivity ratios ranging from 15-fold in human cells (whole blood, macrophages, and platelets) to 45-fold in mouse peritoneal macrophages. In *ex vivo* assays (rat whole blood), it showed a lower COX-1 inhibition potential compared to indomethacin. It showed potent anti-inflammatory effects in animal models, with paw swelling $ED_{50}$ of 0.10 and 0.22 mg/kg/day in adjuvant-induced and collagen-induced arthritis in Lewis rats, respectively. Indomethacin and polmacoxib exhibited parallel efficacy in rat paw edema and mouse acute air pouch models, but the latter was 5 times more potent compared to indomethacin in a thermal hyperalgesia rat model and displayed higher antipyretic activity than ibuprofen. Polmacoxib inhibited human CA I and II with $IC_{50}$ values of 0.336 µM and 0.062 µM, respectively, compared to acetazolamide (0.68 µM and 0.0091 µM). The CA-blocking activity of polmacoxib likely does not interfere with its therapeutic effects, as it is believed to detach from CA and concentrate in tissues with low CA activity (inflamed joints). However, its high affinity toward CA may influence its tissue distribution, potentially reducing COX-2 inhibition in CA-rich tissues like the GI tract, blood, and kidneys, thereby mitigating NSAID-associated toxicities in these organs. Additionally, its CA-binding affinity could lead to blood pressure reduction, similar to the effects of acetazolamide, a potent CA inhibitor.[16]

## Clinical Pharmacology

A phase I clinical trial conducted by Hirankarn et al. (2013) characterized the pharmacokinetics (PK) of polmacoxib in healthy volunteers. After single oral doses of 2 mg or 8 mg, polmacoxib exhibited long half-lives in whole blood and plasma (mean ± SD: 127 ± 33 hours and 131 ± 19 hours, respectively) and a high whole blood-to-plasma concentration ratio (78 ± 23), indicative of biodistribution similar to other strong CA inhibitors. While absorption rate constants between plasma and whole blood were comparable, significant differences were observed in clearance (3.29 vs 0.04 L/hour/70 kg) and in volume of distribution (559 vs 7.6 L/70 kg). These findings highlight unique pharmacokinetic parameters of polmacoxib compared to other COX-2 inhibitors, warranting further studies to explore its clinical implications.[17]

Similarly, a randomized, placebo-controlled, double-blind, multiple ascending dose (MAD) study was conducted by Kim et al. (2015)[18] and evaluated polmacoxib's safety, PK, and PD. This study included 48 healthy Korean volunteers (8 males and 8 females in each dose cohort). Participants received either polmacoxib—administered as loading doses of 8, 10, or 12 mg followed by 2, 4, or 8 mg daily for 6 days—or a placebo. Results showed that polmacoxib achieved significantly higher whole blood concentrations (50–70 times plasma levels), with a median $T_{max}$ of 3–10 hours and a terminal half-life of 121–203 hours in blood. Adverse events were mild, with no significant changes in blood pressure. The

study concluded that polmacoxib was well tolerated and effective in suppressing COX activity markers at multiple doses.[18]

A phase II double-blind randomized controlled trial (RCT) (NCT00530452)[19] was conducted by CrystalGenomics Inc. to study the safety and efficacy of polmacoxib in treating OA pain over 21 days. This placebo-controlled study randomized eligible participants, who recorded an average daily pain intensity (DPI) of 4–8 during a washout period, to receive one of three dose levels of polmacoxib or placebo. Participants were prohibited from using other NSAIDs, COX-2 inhibitors, opioids, or corticosteroids during the study, with acetaminophen allowed for breakthrough pain. Efficacy was assessed using differences in the Western Ontario and McMaster Universities OA (WOMAC OA) index at baseline and days 7, 14, 21, 28, and 35, along with DPI, functional interference–Brief Pain Inventory (BPI) scales, and pain relief evaluations recorded in subject diaries at scheduled visits. The study findings are not available in the public domain but are suggestive of promising efficacy and safety of polmacoxib.[19]

Later, a phase IIa randomized double-blind trial conducted by Schmidt et al. (2009)[20] evaluated the efficacy and safety of polmacoxib. The study involved 248 male patients with OA across 25 sites in Germany, Ukraine, and Hungary. The participants received high (8 mg), medium (4 mg), or low doses (2 mg) of either polmacoxib or placebo over a 21-day treatment period. The 8 mg group showed more than twice the improvement in WOMAC scores compared to the placebo group (37 vs 17%; $p = 0.01$), with significant benefits observed across pain, stiffness, and physical function subscales ($p < 0.05$) throughout the treatment as well as during the follow-up periods. Early and sustained pain relief was evident by day 7 and persisted through day 28. Importantly, polmacoxib showed no treatment-related changes in blood pressure, electrocardiogram (ECG) parameters, or GI bleeding across all doses, highlighting its safety profile. The study concluded that polmacoxib provides significant analgesic and functional benefits as a dual COX-2 and CA inhibitor and lacks GI or CV adverse effects.[20]

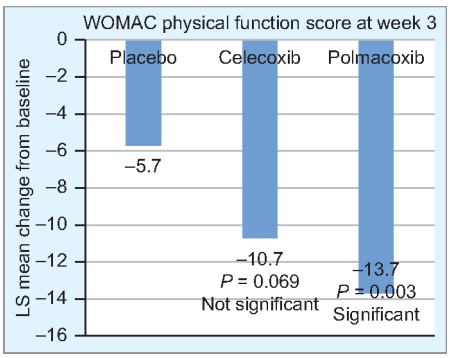


**Fig. 2:** WOMAC physical function score

In 2017, Lee et al.[21] reported the study findings of a phase III RCT of 6 weeks, followed by an open-label extension study (for 18 weeks) which evaluated the safety and efficacy of polmacoxib compared to placebo (superiority) and celecoxib (noninferiority) in patients with OA. Of 362 patients randomized, 324 completed the 6-week treatment phase, and 220 continued into the extension. Polmacoxib (2 mg) demonstrated significantly greater pain reduction than placebo, as reflected by the WOMAC pain subscale (mean difference: −2.5; 95% CI: −4.4 to −0.6; $p = 0.011$), and was found to be noninferior to celecoxib 200 mg (mean difference: 0.6; 95% CI: −0.9 to 2.2; $p = 0.425$). Additionally, physician assessments indicated that a higher proportion of patients treated with polmacoxib were rated as "much improved" by week 3. Surprisingly, polmacoxib demonstrated statistically significant superiority over placebo ($p = 0.003$), whereas celecoxib did not show a statistically significant difference from placebo ($p = 0.069$) at week 3, as shown in Figure 2. Adverse events, particularly GI and general disorders, were more frequent with polmacoxib and celecoxib than with placebo. The study concluded that polmacoxib 2 mg is an effective and safer option for the treatment of OA, demonstrating a safety profile similar to that of celecoxib.[21]

Recently, in 2024, a phase III multicentric RCT by Sinha et al.[22] reported the efficacy and safety of polmacoxib (2 mg) vs celecoxib (200 mg) in 294 Indian adult patients with idiopathic knee or hip OA diagnosed per the American College of Rheumatology (ACR) criteria. Patients were randomized with an allocation ratio of 1:1 and received either polmacoxib or celecoxib. Pain assessment scores were recorded at weeks 3 and 6 using the WOMAC pain subscale, WOMAC OA index, and global evaluations by subjects and physicians. It demonstrated comparable improvements in pain scores for both groups, with mean changes of 4.88 (polmacoxib) vs 4.49 (celecoxib) in the ITT population and 4.90 vs 4.50 in the PP population ($p < 0.0001$). Of the 40 adverse events (AEs) reported, 30 were treatment related, with a slightly lower incidence in the polmacoxib group (13 AEs vs 17 AEs for celecoxib). The study concluded that polmacoxib is noninferior to celecoxib in terms of both safety and efficacy, potentially offering a safer alternative to traditional NSAIDs by reducing GI and CV side effects.[22]

The clinical evolution of polmacoxib is summarized in Table 2.

## Clinical Evidence on Drug–Drug Interactions

A study was conducted by Choi et al. (2013)[23] to find the effect of a strong CYP3A inhibitor (ketoconazole) on the pharmacokinetics of polmacoxib. This was a randomized open-label two-period crossover trial involving 30 healthy Korean male volunteers. Participants received a single 6 mg dose of polmacoxib alone or in combination with 400 mg of ketoconazole, with a washout period of 42 days between the treatments. The results showed that concurrent ketoconazole administration increased the AUClast of polmacoxib by 29% (2074.0 vs 2685.8 ng·hour/mL; $p < 0.05$), while the Cmax values were comparable (10.7 vs 11.0 ng/mL). No significant differences were observed in safety outcomes, including vital signs, clinical laboratory results including ECGs, or adverse events (AEs), with 17 mild AEs reported and resolved without sequelae. The study concluded that although ketoconazole increases exposure to polmacoxib, the combination does not alter its safety profile, suggesting no need for dosage adjustments.[23]

## Clinical Research with Concomitant Administration of Other Analgesics

A multicentric parallel RCT (CTRI/2023/11/060049)[24] evaluated the efficacy and safety of a fixed-dose combination (FDC) of polmacoxib (2 mg) and paracetamol (325 mg) vs an FDC of etoricoxib (60 mg) and paracetamol (325 mg) in Indian adults (18–65 years) experiencing acute pain following dental extraction. This study was conducted at 10–12 sites across India, and a total of 144 patients (72 per group) were randomized in a 1:1 ratio. The study reported noninferiority of polmacoxib + paracetamol to etoricoxib + paracetamol in percent change in mean pain intensity assessed by the Numeric Pain Rating Scale (NPRS) at 6, 24, and 48 hours. There was better control of pain at 24 and 48 hours in polmacoxib + paracetamol vs etoricoxib + paracetamol in mean pain relief (five-point scale), total pain relief, and Patient's Global Impression of Improvement (PGI-I). Of 25 AEs reported, only 6 were treatment related, with a lower incidence in the polmacoxib + paracetamol group (2 AEs vs 4 AEs for etoricoxib + paracetamol). All AEs were grade 1–1 and resolved without sequelae. The study concluded that polmacoxib + paracetamol is noninferior to etoricoxib +

**Table 2:** Summary of clinical trials

| *Phase* | *Authors* | *Year* | *Study design* | *Population* | *Intervention* | *Efficacy* | *Safety* |
|---|---|---|---|---|---|---|---|
| I | Hirankarn et al.[17] | 2013 | Randomized, prospective, single dose pharmacokinetic (PK) study | *N* = 13 healthy human participants | Polmacoxib 2 and 8 mg | PK profile:<br>Comparable absorption rate constants in plasma and whole blood<br>High whole blood-to-plasma concentration ratio (78 ± 23)<br>Volume of distribution –559 vs 7.6 L/70 kg)<br>Clearance –3.29 vs 0.04 L/hour/70 kg)<br>Half-lives in whole blood and plasma (mean ± SD: 127 ± 33 hours and 131 ± 19 hours, respectively) | |
| I | Kim et al.[18] | 2015 | Randomized, double-blind, placebo-controlled, multiple ascending dose study | *N* = 48 healthy Korean volunteers | Polmacoxib (8, 10, or 12 mg loading doses followed by 2, 4, or 8 mg daily for 6 days) or placebo | Suppressed serum thromboxane B2 (68–91%) and *ex vivo* lipopolysaccharide-stimulated prostglandin E2 (89–96%; $p < 0.001$) at all doses<br>8 mg dose also reduced urinary prostacyclin metabolite excretion by 64% ($p < 0.001$) | Adverse events (AEs) were mild, with no significant changes in blood pressure |
| II | NCT00530452[19] | 2007 | Randomized, double-blind, placebo-controlled study | *N* = 240 adult, normotensive patients of osteoarthritis (OA) | Polmacoxib 2, 4, or 8 mg daily for 21 days or placebo | Not yet publicly available | Not yet publicly available |
| IIa | Schmidt et al.[20] | 2009 | Randomized, double-blind, placebo-controlled study | *N* = 248 male patients with OA | Polmacoxib 2, 4, or 8 mg daily for 21 days or placebo | 8 mg group showed >2 folds improvement in WOMAC scores compared to placebo (37 vs 17%; $p = 0.01$), with significant benefits observed across pain, stiffness, and physical function subscales ($p < 0.05$) throughout the treatment and follow-up periods | No treatment-related changes in blood pressure, ECG parameters, or gastrointestinal bleeding across all doses, highlighting its safety profile |
| III | Lee et al.[21] | 2017 | Randomized, double-blind trial of 6-week, followed by an open-label extension study (for 18 weeks) | *N* = 362 patients of OA | Polmacoxib 2 mg compared to placebo (superiority) and celecoxib 200 mg (noninferiority) | Polmacoxib showed superior pain reduction compared to placebo (WOMAC-pain subscale difference: –2.5; 95% CI, –4.4 to –0.6; $p = 0.011$) and was noninferior to celecoxib (difference: 0.6; 95% CI, –0.9 to 2.2; $p = 0.425$)<br>Physician's assessments showed higher proportion of patients opted for "much improved" at week 3 with polmacoxib | AEs, particularly gastrointestinal and general disorders, were more frequent with polmacoxib and celecoxib than with placebo |
| III | Sinha et al.[22] | 2024 | Randomized, multicentric, double-blind, active-controlled study | *N* = 294 adult Indian patients with idiopathic knee or hip OA | Polmacoxib (2 mg) vs celecoxib (200 mg) | Improvements in pain scores (WOMAC pain subscale, WOMAC-OA index, and global evaluations by subjects and physicians) for both groups, with mean changes of 4.88 (polmacoxib) vs 4.49 (celecoxib) in the ITT population and 4.90 vs 4.50 in the PP population ($p < 0.0001$) | Of the 40 AEs reported, 30 were treatment-related, with a slightly lower incidence in the polmacoxib group (13 AEs vs 17 AEs for celecoxib) |

AEs, adverse events; CI, confidence interval; ITT, intention to treat; OA, osteoarthritis; PK, pharmacokinetics; PP, per protocol; WOMAC, Western Ontario and McMaster Universities Arthritis Index

paracetamol in terms of both safety and efficacy, potentially offering a safer and more efficacious alternative in acute pain.[24] Based on the study findings, the fixed-dose combination (polmacoxib 2 mg plus paracetamol 325 mg) received marketing approval for short-term use in acute somatic mild-to-moderate painful inflammatory conditions by DCGI on 6th August 2024.[25]

Another randomized parallel controlled clinical trial was initiated in August 2024, evaluating the efficacy of concomitant administration of polmacoxib 2 mg once daily with Ultraset ER Semi [containing tramadol (18.75 mg) + paracetamol (162.5 mg), as required] vs Ultraset ER Semi perioperatively in 150 patients with OA undergoing surgery for rotator cuff tear. The primary endpoint is cumulative administration frequency of narcotic analgesics at postoperative day 3. The secondary endpoints are cumulative number of doses of nonopioid analgesics excluding NSAIDs, range of motion, pain scores [Visual Analog Score, American Shoulder and Elbow Surgeons Score, and University of California, Los Angeles (UCLA) Score] perioperatively, and rotator cuff retear status at 12 weeks

postsurgery. The estimated study completion is August 2025.[26]

Finally, to summarize, polmacoxib is an innovative first-in-class orally administered NSAID with dual inhibition of COX-2 and CA enzymes. Being a selective COX-2 inhibitor, it reduces the risk of GI side effects typically seen with traditional nonselective NSAIDs. Clinical studies indicate that polmacoxib delivers significant analgesic and functional benefits, making it a promising option for effective and well-tolerated long-term pain relief in OA management as well as effective in acute painful conditions such as toothache. Additionally, its unique tissue-specific transport mechanism may help reduce the CV risks often linked to COX-2 inhibition. However, further larger RCTs are necessary to comprehensively assess its long-term safety and efficacy.

## Conclusion

In conclusion, polmacoxib emerges as a promising dual-action NSAID with distinct advantages for managing osteoarthritis and acute painful conditions. By selectively inhibiting both COX-2 and carbonic anhydrase enzymes, polmacoxib offers a targeted mechanism that minimizes gastrointestinal, cardiovascular, and renal side effects commonly associated with traditional NSAIDs. Clinical studies across phases I–III consistently demonstrate its noninferiority to established treatments like celecoxib, with favorable safety and efficacy profiles. Its pharmacokinetic properties—including prolonged half-life and red blood cell-mediated tissue-specific delivery—enable sustained therapeutic effect while reducing systemic toxicity. Moreover, recent data from Indian and international trials underscore its potential utility not only in chronic OA management but also in acute pain scenarios such as postoperative and dental pain. The availability of fixed-dose combinations further enhances its clinical versatility. While current findings are encouraging, further long-term multicenter studies are essential to substantiate its safety and broaden its therapeutic applications across diverse patient populations.

## Orcid

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CONSENSUS GUIDELINE

# Consensus Recommendations on Home Maintenance Nebulization with Focus on Obstructive Airway Diseases: An Update on Best Practices and Future Directions

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Asthma and chronic obstructive pulmonary disease (COPD) are obstructive airway diseases (OADs) that contribute significantly to the burden on healthcare systems in low- and middle-income countries like India.[1,2] Inhaler therapy (primarily involving pressurized metered-dose inhalers and dry powder inhalers) remains the cornerstone of maintenance therapy; however, not all patients can use them effectively.[3] Home maintenance nebulization (HMN) has been increasingly used as an alternative in appropriately identified patients, particularly those with advanced disease, physical or cognitive limitations, or suboptimal inspiratory flows. This expert consensus is an update from the 2017 recommendations, which provide evidence-informed recommendations on the use of HMN in OADs.[4] By incorporating recent research findings and clinical expertise, the updated consensus addresses current gaps in knowledge, optimizes therapeutic protocols, and supports healthcare providers in delivering high-quality, patient-centered care. It is aimed at aiding clinicians involved in the management of OADs, including asthma and COPD, and evaluating the suitability of nebulization therapy as long-term maintenance treatment in home care settings.

This consensus recommendation has been developed using the traditional method of consensus development and addresses patient selection criteria, appropriate drug-device combinations, therapy duration, adherence monitoring, and infection control practices. The message given by the panel clearly states that HMN should not replace handheld inhalers indiscriminately but should be considered only in specific situations, which have been clearly called out in the document. The various types of nebulizers that can be used for the management of OAD patients, along with their advantages and disadvantages, and the appropriate drugs that can be used as a part of HMN have been comprehensively detailed.

The panel has given the recommendations for the effective use of HMN (Table 1).

The panel has also shared its views on the future developments in nebulization therapy, which aim at making nebulization therapy more effective, user-friendly, and tailored to individual patient needs, ultimately improving the management of chronic respiratory conditions.

## Conclusion

Home nebulization is a critical component of respiratory disease management, offering convenience and improved medication adherence for patients with chronic conditions as a valuable alternative for drug delivery, though it should not be viewed as a substitute for handheld inhalers. Ensuring proper usage technique, monitoring adverse effects, and providing individualized treatment plans are essential for maximizing the benefits of home nebulization therapy. Future research should focus on evaluating long-term efficacy, patient-reported outcomes, and technological advancements in nebulization devices. By adhering to evidence-based recommendations, healthcare providers can enhance the safety and effectiveness of home-based respiratory therapy, ultimately improving patients' quality of life. These recommendations should be viewed as a reference by practicing clinicians for prescribing maintenance nebulization.

**Table 1:** Recommendations for the use of Home Maintenance Nebulization (HMN)

| *S. No.* | *Consensus recommendation* |
|---|---|
| 1. | HMN should be defined as the physician-prescribed administration of long-term maintenance medications in nebulized form (≥3 weeks) in appropriately selected patients within a properly managed home environment. |
| 2. | Selecting patients for maintenance nebulization requires a thorough clinical evaluation of disease severity, treatment response, cognitive status, and individual patient needs (dexterity, coordination, assistance availability, comorbidities, and symptom burden). The physician should determine the duration of maintenance nebulization and assess the possibility of introducing handheld inhalers whenever possible. Regular evaluations are essential to ensure treatment adherence and optimize patient outcomes. |
| 3. | The minimum duration for maintenance nebulization in patients with OADs should be at least 3 weeks, but the maximum duration remains undefined and should be individualized based on disease severity, treatment response, safety concerns, and patient needs. The prescribing physician must regularly assess therapy effectiveness and safety to determine its continuation or discontinuation. |
| 4. | The selection of a nebulizer for maintenance therapy should be individualized based on drug compatibility, particle size, ease of use, patient-specific factors, and cost-effectiveness to achieve optimal drug delivery and adherence. Prescribers are advised to refer to the exact indications, posology, and administration methods available in the prescribing information of the selected drugs. |
| 5. | Regular monitoring of symptoms, lung function, and nebulizer techniques are keys to measuring the effectiveness of treatment. Adherence to therapy and infection control measures should be reinforced through routine follow-ups to attain better patient outcomes. |
| 6. | Patients/caregivers should be advised to follow aseptic techniques, clean accessories every day, disinfect weekly, store parts in a dry environment, and replace components as per manufacturer guidelines. |
| 7. | The effectiveness of maintenance nebulization should be assessed through factors such as effectiveness of the treatment (objective and subjective), treatment adherence, and symptom monitoring. |
| 8. | Patients on maintenance nebulization should receive proper training on device use, assembly, and cleaning, with regular reassessment to prevent technique errors. Special precautions, including infection control measures and patient-specific considerations, should be strictly followed to ensure safety and efficacy. |
| 9. | Maintenance nebulization should be discontinued when patients show significant symptom improvement, can effectively use inhalers, or experience adverse effects. Transitioning to inhalers should be gradual, with proper training, close monitoring, and continued education to ensure effective symptom control and adherence. |
| 10. | Beyond OADs, maintenance nebulization plays a crucial role in treating various diseases/conditions, including structural lung diseases, lower respiratory infections, pulmonary hypertension, and in palliative care. The physician's judgment is essential in determining the need for maintenance therapy. |
| 11. | Well-trained caregivers assist in medication administration, equipment maintenance, and symptom monitoring. Structured training programs and emotional support to caregivers can improve caregiver effectiveness and reduce burnout. |
| 12. | While using nebulizers in patients on noninvasive ventilation (NIV), ensure to use them between NIV cycles. Selection of an appropriate interface and dose adjustments after carefully following manufacturer guidelines are important. Avoid using oxygen-driven nebulizers at home. |

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POINT OF VIEW

# Prediabetes: To Be Treated or Not?

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## Abstract

Prediabetes (PD) is a bridge between normoglycemia and hyperglycemia or diabetes mellitus (DM) characterized by higher than normal blood glucose but not fulfilling the criteria for type 2 DM (T2DM). PD is defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and/or hemoglobin A1c (HbA1c) above 5.7% but <6.4%. Individuals with PD are at increased risk of progressing to T2DM at a pace of 5–10% every year and other micro- and macrovascular complications, including cardiovascular diseases. Prevalence of IGT and IFG in 2021 was 9.1% (about 464 million), which is projected to increase to 10.0% (638 million) in 2045; that of IFG was 5.8% (about 298 million), projected to increase to 6.5% (414 million) in 2045 globally. That is why we must seriously take aggressive steps to prevent progression to T2DM and to reduce the morbidity and mortality associated with DM, its complications, and healthcare burden. Why PD is important? Why PD to be treated? Individuals with PD have a 5–10% annual risk of progressing to T2DM and are associated with increased risk of micro- and macrovascular complications like nephropathy, retinopathy, neuropathy, and cardiovascular risks, myocardial infarction, and stroke. To prevent progression or conversion of PD to DM, we must be very aggressive. These are sufficient reasons for treatment of PD by lifestyle intervention or pharmacotherapy, as intensive lifestyle modifications, dietary modification, and enhanced physical activity have been shown to reduce the progression of PD to T2DM by 40–70%. These measures also lead to weight loss and better cardiovascular health. PD develops due to insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Therefore, pharmacotherapy with metformin, pioglitazone, α-glucosidase inhibitors (AGIs), dipeptidyl peptidase IV (DPP IV) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP1 RA) targeting these defects are efficacious in preventing T2DM in PD. Diabetes Prevention Program (DPP) has shown 31% reduction in DM incidence with metformin. There is increasing evidence for prevention of DM in adults with PD by pharmacotherapy, but options other than metformin have adverse effects, and there is no unanimity for their use in PD. The role of pharmacotherapy is still debatable, and no consensus is made. We recommend that patients who are at high risk, having a strong family history of DM, signs of severe insulin resistance like acanthosis nigricans, severe obesity, or associated comorbidities, must be considered for disease-modifying pharmacotherapy like SGLT2 inhibitors, DPP IV inhibitors, and GLP1 RA. Those who do not have the above risk factors should be followed up at regular intervals, at least every year. Why PD not to be treated? When we treat DM, our "treat to target" is HbA1c of 7% or less, and organizations like the European Association for the Study of Diabetes (EASD) recommend a stricter target of 6.5%, which is above the diagnostic criteria for PD. Then the million-dollar question arises: are we justified in treating PD, as diagnostic criteria for PD are lower than the DM treatment target of 7% or less? There is another issue of overdiagnosis and overmedication; labeling individuals as PD and treating them with pharmacotherapy may lead to increased medication and healthcare costs, as well as stigma associated with a chronic disease and its treatment. Long-term studies are required to evaluate the risk-benefit of pharmacotherapy. We suggest that persons identified to have PD must be under vigilance and investigated at regular intervals. If they are found to have incremental blood glucose and HbA1c and a high risk of progression or conversion to DM, it is logical to treat. Those who are stable in the prediabetic range without associated comorbidities should be observed regularly and advised lifestyle modification (diet and exercise) and weight reduction.


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## Introduction

Prediabetes (PD) is a bridge between normoglycemia and hyperglycemia, characterized by higher than normal blood glucose but less than the diagnostic criteria for type 2 diabetes mellitus (T2DM). PD is a conglomeration of impaired fasting glucose (IFG), defined as fasting plasma glucose (FPG) 100–125 mg/dL; impaired glucose tolerance (IGT), defined as plasma glucose (PG) 140–199 mg/dL after 2 hours of 75 gm oral glucose administration; and/or hemoglobin A1c (HbA1c) of 5.7–6.4%.[1,2] Prediabetics are at increased risk of progressing to T2DM at the rate of 5–10% per annum and of micro- and macrovascular complications.[3]

We are aware that IGT starts much before the diagnosis of diabetes mellitus (DM), as do various micro- and macrovascular complications. That is why it is important to implement interventions in high-risk populations at the PD stage, much before the diagnosis of T2DM, to prevent DM and its complications.

## Discussion

Impaired fasting glucose, IGT, and HbA1c alone or in combination constitute PD. Prevalence of IGT and IFG in 2021 was 9.1%, approximately 464 million, which is projected to increase to 10.0%, approximately 638 million, in 2045; and that of IFG was 5.8%, approximately 298 million, which is projected to increase to 6.5%, approximately 414 million, in 2045 across the globe. PD prevalence was high in developed countries with higher per capita income, and the highest growth for PD would be in lower-per capita income regions. This is an inference from a review of >7,000 publications for PD in the 20–79-year age-group from 40 countries.[4]

Prevalence of DM, PD, and cardiovascular disease (CVD) was found to be high in an observational, retrospective study, "Progression of PD to DM at Veterans Health at Columbia, South Carolina," based on HbA1c criteria by American Diabetes Association (ADA) at 1 and 2 years and thereafter in 72,604 people with PD, with a mean age of 66 years and mean HbA1c of 5.9%. About 55% were hypertensive, and 13% had atherosclerotic cardiovascular disease (ASCVD). A total of 10,710 subjects were lost to follow-up, and the remaining 61,894 patients with PD included 21,954 (35%) who developed T2DM, while 39,940 (65%) remained prediabetic. Older persons and those with higher baseline HbA1c, ASCVD, and hypertension (HT) progressed more to DM. After 2 years, 60% of them developed DM. That is why we must take aggressive steps to prevent progression to T2DM, reduce the morbidity and mortality associated with DM and its complications, and cut the cost of healthcare.

The prevalence of PD is increasing worldwide, and it is projected that >470 million people will have PD in 2030.[5]

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The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study, cross-sectional urban and rural population-based survey of >20 years of age from 31 states, union territories, and the National Capital Territory of India. Diabetes and PD were diagnosed using the World Health Organization (WHO) criteria [IFG 110–125 mg/dL PG and IGT as 2-hour post 75 gm glucose (140–199 mg/dL PG)]; WHO does not use HbA1c as criteria for diagnosis of PD.[3] Total 1,13,043 individuals (79,506 rural and 33,537 urban areas) participated in this study. Overall weighted prevalence of diabetes was 11.4%, PD 15.3%, HT 35.5%, generalized obesity 28.6%, abdominal obesity 39.5%, and dyslipidemia 81.2%. All metabolic and noncommunicable diseases (NCDs), except PD, were more frequent in urban than rural areas.[6]

## Why Prediabetes is Important? Why Prediabetes is to be Treated?

Prediabetes progresses to DM at the rate of 5–10% annually and is associated with increased risk of various complications, like nephropathy, retinopathy, neuropathy (microvascular), and cardiovascular risks, myocardial infarction, and stroke (macrovascular complications). To prevent progression or conversion of PD to DM, we must be very aggressive.

Diabetes Prevention Program (DPP) has shown lifestyle intervention prevents more conversion of PD to DM compared to metformin.[3] There are sufficient reasons for treatment of PD by lifestyle intervention, as we know that intensive lifestyle modifications, dietary modification, and enhanced physical activity have been shown to reduce the progression of PD to T2DM by 40–70%. These measures also lead to weight loss and better cardiovascular health.[5,7]

In a study of 577 IGT adults from 33 clinics in China, participants were randomly divided into a control group and three lifestyle intervention groups (diet, exercise, or diet plus exercise). They were followed up with active intervention for 6 years to see the long-term effect of the interventions. The primary outcomes were incidence of DM, CVD, CV, and all-cause mortality. Combined lifestyle intervention groups had a 51% lower incidence of DM during intervention and a 43% lower incidence over the period of 20 years. DM incidence was 7% lower in the intervention group vs 11% in the control group annually. Intervention group participants were 3.6 years less exposed to T2DM compared to controls. No statistically significant difference was found in the first CV event, CV mortality, and all-cause mortality in this study, having limited statistical power. About 6 years of lifestyle interventions may delay DM for 14 years.[8]

Etiopathogenesis of PD is the same as T2DM—insulin resistance, insulin insufficiency, increased hepatic glucose production, incretin defect, lipotoxicity, hypertriglyceridemia, and many more,[5] and therefore metformin, pioglitazone, and α-glucosidase inhibitors (AGIs), dipeptidyl peptidase IV (DPP IV) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP1 RA) are found efficacious in reversing the conversion of PD to DM. DPP has shown the efficacy of lifestyle interventions and also metformin, reducing 31% conversion to T2DM. There is increasing evidence for prevention of DM in PD by various drugs, but Food and Drug Administration (FDA) has not approved any medication other than metformin.[3] Pharmacotherapy is debatable, and no consensus has been made. Obesity is a key factor in the etiopathogenesis of T2DM, so weight loss medication like GLP1 RA (semaglutide, tirzepatide) and SGLT2 inhibitors seems to be promising in reversing PD to normal glucose tolerance. Diabetes remission or reversal is a futuristic goal, evident from DIRECT and SOUL trials.

What we recommend is those who are at high risk of developing DM, having a strong family history of DM, signs of severe insulin resistance like acanthosis nigricans, severe obesity, HT, dyslipidemia, history of gestational diabetes mellitus (GDM), and associated comorbidities must be considered for pharmacotherapy with SGLT2 inhibitors, DPP IV inhibitors, and GLP1 RA, and those who do not have the above risk factors should be followed up at regular intervals, or at least every year.

## Why Prediabetes Not to be Treated?

Prediabetes includes IFG, IGT, and/or HbA1c of 5.7–6.4%.[1,2] But there are different criteria for the diagnosis of PD by different organizations, like the WHO, which does not consider HbA1c as a criterion for the diagnosis of PD, and FPG is higher than ADA criteria of 100–125 mg/dL. While the National Institute for Health and Care Excellence (NICE) guideline uses the same FPG criteria as WHO, HbA1c is higher than ADA criteria at 6–6.4%. There is unanimity for IGT, and there is no difference between the PG values for IGT. Prediabetics are at increased risk of progressing to T2DM at the rate of 5–10% per annum, as well as micro- and macrovascular complications.[3]

When we treat DM, our "target HbA1c" is 7% or less, and organizations like the European Association for the Study of Diabetes (EASD) recommend a stricter target of 6.5%, which is above the diagnostic criteria for PD. Then the million-dollar question arises: "Are we justified in treating PD," as the diagnostic criteria for PD are lower than the DM treatment target of 7% or less?

Overdiagnosis and overmedication by labeling individuals as PD may lead to increased medication and healthcare costs, as well as stigma associated with a chronic disease, and its treatment is another important issue. Long-term studies are required for evaluating the risk–benefit of pharmacotherapy in PD.

## Conclusion

Prediabetes is more prevalent than DM, and the conversion rate of PD to DM is significant, and lifestyle interventions are no doubt helpful and unanimously recommended.

The drug treatment of PD remains a subject of debate, and drug therapy should be individualized based on patient characteristics and risk factors. Further research is needed to evaluate the long-term benefits and risks of various treatment modalities.

But at the same time, when we treat DM, our "target HbA1c" is 7% or less, and EASD recommends a stricter target of 6.5%, still above the diagnostic criteria for PD by HbA1c. Then the question arises: "Are we justified in treating PD?"

What we suggest: people having PD must be under vigilance and investigated at regular intervals, and if they are found to have incremental blood glucose and HbA1C and risk of progression or conversion to DM is high, it is logical to treat. But those who are stable and remain in the prediabetic range without associated risk factors and comorbidities should be screened regularly for progression as well as risk factors and advised lifestyle modification (diet and exercise) and weight reduction.

"Golden Rule is Prevention is better than Cure."

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# Association of Physicians of India
## Election Results of API, PRF and ICP

Results of the election of the Association of Physicians of India, Physicians Research Foundation and Indian College of Physicians for 2026–2029.

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5. Dr. R. Chandni, Kozhikode
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Dr. Ajay Mahajan, Hisar

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***Central Zone***
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Dr. A. K. Singh, Varanasi

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Dr. K. R. Jawaharlal, Kakinada

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**Vice Dean:** Dr. Prakash Keswani, Jaipur

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**Dr. G. Narsimulu**
*Chairman – Election Committee*

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*Hon. General Secretary*

# Mental Health Lessons from a Stranded Space Mission: An Epitome of Hope, Human Resilience, and Mental Fortitude

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## Introduction

The story of astronauts Sunita Williams and Butch Wilmore, who endured 286 days in space instead of the planned 8 days, offers a profound example of human resilience, patience, and persistence. Their extended mission aboard the International Space Station (ISS) highlights not only the physical demands of space travel but also the immense psychological challenges faced by astronauts. Space travel is not just a test of physical endurance but also mental resilience. Astronauts are trained extensively for psychological challenges, but unforeseen mission extensions, as in the recent case of astronauts stranded for nearly 10 months, push human adaptability to its limits. This article delves into the mental health aspects of such missions, and how they offer lessons for coping with adversity in everyday life.

## Psychological Challenges in Prolonged Space Missions

- Isolation and confinement: Astronauts face extreme isolation, confined to small spaces with limited social interaction. This can lead to feelings of loneliness, homesickness, and emotional strain. Research shows that long-term isolation can result in anxiety, depression, and even cognitive decline due to the lack of normal social supports and environmental stimuli.[1]
- Stress from uncertainty: The unexpected extension of Wilmore and Williams' mission due to technical issues with the Boeing Starliner spacecraft would have added significant stress. Such uncertainty can exacerbate feelings of helplessness and require immense mental fortitude to stay focused on tasks.[2]
- Physical and cognitive challenges: Prolonged exposure to microgravity impacts physical health (e.g., muscle atrophy and bone loss), while high noise levels and disrupted circadian rhythms can impair cognitive performance.[3]

## Psychological Resilience in Extreme Isolation

Resilience is the ability to withstand and recover from adversity. Astronauts undergo rigorous psychological training to develop coping mechanisms for isolation, uncertainty, and stress. Studies have shown that long-duration space missions, like those planned for Mars exploration, will require even greater mental fortitude.

## Coping Mechanisms and Stress Management

- Mental preparation: Astronauts undergo rigorous psychological training before missions to build resilience. This includes simulations of stressful scenarios, mindfulness techniques, and coping strategies for isolation.[4]
- Structured routines: Daily schedules provide predictability, reducing stress. Maintaining a daily schedule that mimics Earth routines helps astronauts stay grounded. This includes 2 hours of exercise daily to combat physical effects of microgravity and promote mental health.[5]
- Mindfulness and cognitive reframing: These techniques help in shifting perspective and maintaining a positive outlook. Astronauts practice deep breathing, meditation, and mindfulness to manage acute stress during emergencies or high-pressure tasks.[1] Journaling provides an emotional outlet and helps researchers understand behavioral patterns in isolation.
- Team dynamics and communication: Strong interpersonal relationships among crew members are essential. NASA emphasizes team compatibility during selection and training to minimize conflicts in confined environments.[4] Open communication within the crew and with ground teams helps address emotional challenges early.[6]
- Support systems: Ground teams play a vital role in monitoring astronauts' mental health and providing real-time psychological support through communication channels.[7] Virtual reality simulations of relaxing environments help mitigate psychological distress.[7]
- Sense of purpose: Engaging in meaningful work, such as conducting scientific experiments or maintaining the spacecraft, gives astronauts a sense of purpose that boosts morale and reduces stress.[5]
- Postmission support: Astronauts receive psychological care after returning to Earth to aid their reintegration into society.[5]

## Mental Health Lessons from Astronauts for People on Earth

The patience and persistence demonstrated by these astronauts provide valuable insights for managing stress and uncertainty in daily life. Here are some key mental health lessons:

- Cognitive flexibility: Adapting to unexpected changes without panic and developing a mindset of problem solving.
- Patience and endurance: Learning to accept delays and setbacks as part of life while staying focused on long-term goals.
- Social support and communication: Maintaining strong relationships and open communication as a buffer against stress.
- Self-discipline and routine: Structuring daily life with set goals, healthy habits, and consistent activities to maintain mental stability.
- Mindfulness and stress management: Practicing techniques such as meditation, controlled breathing, and journaling to stay calm under pressure.
- Focusing on controllables: Instead of worrying about uncertain outcomes, directing energy toward tasks and goals that can be influenced.

From healthcare professionals managing chronic conditions to individuals facing personal crises, the astronaut experience underscores the importance of structured coping strategies, emotional intelligence, and resilience.

## Conclusion

The 286-day mission extension tested the limits of human endurance, yet the astronauts' ability to persist despite isolation, uncertainty, and extreme conditions stands as an inspiring testament to mental strength. Sunita Williams and Butch Wilmore's experience epitomizes human endurance under extreme conditions. Their journey serves as a testament to the power of preparation, teamwork, and mental strength in overcoming adversity—qualities that resonate far beyond the confines of space exploration.

These lessons, grounded in space psychology research, hold relevance far beyond the cosmos, offering guidance for mental health challenges on Earth. By embracing patience, persistence, and resilience, individuals can navigate adversity

with the same fortitude displayed by those who ventured beyond our planet.

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# Recurrent Rusty Pipe Syndrome: A Case Report

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*Sir*,

The first milk after delivery is a boon to the newborns. The onset of lactation also plays a crucial role in strengthening the bond between the baby and mother. During the lactation period, bleeding from nipples can cause severe maternal anxiety. In literature, secretion of bloody milk from the breast has been described as rusty pipe syndrome (RPS), which is a rare condition with a prevalence rate of 0.1%. It is a benign physiological condition that causes painless bloody discharge or milk from nipples in pregnant and postpartum women. RPS commonly occurs in primiparous women and is usually bilateral. Apart from RPS, other common causes of bloody discharge from nipples are cracked nipples, mastitis, and ductal papilloma.[1] It usually appears during the first few days of breastfeeding and self-resolves within 3–7 days.[2] No treatment is required. Diagnosis is based upon history and examination of the breast, followed by investigations, cytological analysis, and breast ultrasound to rule out other pathological conditions.[3] RPS is much more common than its presence in the published literature.

A 25-year-old second gravid patient delivered a baby boy with a weight of 2.92 kg at 37 weeks 4 days gestational age *via* cesarean section. The indication for her lower segment cesarean section (LSCS) was tenderness in the previous LSCS scar. The mother noticed painless bloody discharge from both breasts when she expressed milk at the time of initiation of the first breastfeed (Fig. 1). She reported a history of similar discharge during her last pregnancy. There was no apparent history of trauma or nipple manipulation. She did not report any occurrences of pruritus over or around the nipple area that could have led to traumatic scratching or manipulation. On gross examination, no abnormality was observed. On palpation, neither breast revealed tenderness, engorgement, or any mass/lump. Dermatological examination revealed no cracks, erosions, or ulcers over both nipples. Cytological analysis of the expressed milk showed scattered polymorphs, small lymphocytes, foamy macrophages, fat droplets, and red blood cells. Ultrasonography revealed a few bilateral dilated retro-alveolar ducts containing moving echoes. Based on the presenting clinical symptoms and normal cytological and radiographical assessment, the diagnosis of RPS was made. The patient was advised to express milk from both breasts every 2–3 hours to avoid breast engorgement. Bloody discharge gradually changed from dark to light color and became normal by the 5th postnatal day (Fig. 2). During the period of active discharge, exclusive breastfeeding was continued.

The RPS is a benign and self-resolving condition, which is characterized by the asymptomatic blood-tinged discharge in the breast milk during the immediate postpartum period.[1–6]

Bloody nipple discharge is also a common feature of various breast malignancies and is one of the common symptoms (8–30%) of malignancy in nonpregnant patients.[5] Any discharge containing blood is always frightening to the patients, irrespective of gender. During the postpartum period, the discharge could be physiological, which resolves on its own (RPS). However, in the absence of proper counseling, RPS can lead to the discontinuation of exclusive breastfeeding in apprehensive mothers.

The etiology of RPS remains elusive. It has been proposed that physiological injuries to the fragile and fast-proliferating ductal epithelium due to hormonal stimulation during pregnancy and the postpartum period can lead to it.[1,5] Increased capillary permeability in RPS can coexist with nasal and gum bleeds simultaneously.[4]

The RPS has been predominantly observed among primiparous women, and recurrence in subsequent pregnancies has not been described before. In our case, the patient developed RPS in both of her pregnancies.[1–6] During the follow-up visits, the infants gained the expected weight as

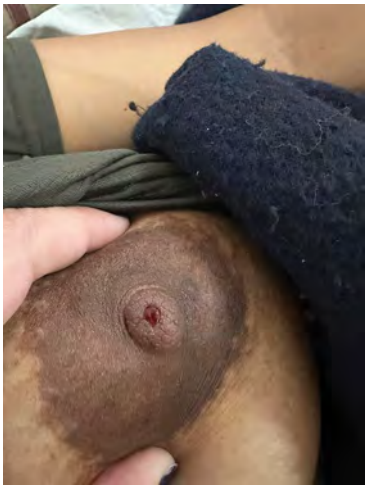

**Fig. 1:** Oozing of the blood-tinged nipple discharge at the time of presentation

**Fig. 2:** The expressed breast milk admixed with the self-resolving bloody discharge of RPS

per age. There was no discharge after the 1st week from delivery.

The current case is aimed to increase awareness among healthcare professionals about the benign and self-resolving nature of the RPS. As RPS is noticed by the mother either while expressing the milk or in the vomitus of her newborn, it can undeniably cause severe psychological burden to the mother and family. The unawareness among healthcare professionals can potentially lead to inadequate counseling about postnatal care (exclusive breastfeeding) and unnecessary investigations, further aggravating the psychological and financial burden to the family of the newborn. RPS does not require treatment and resolves completely within 3–7 days of the onset.[1–6] During this period, the mother should be encouraged for continued exclusive breastfeeds through active listening, understanding her concerns, and explaining to her the nature of her presenting symptoms.

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