

Journal of The Association of Physicians of India



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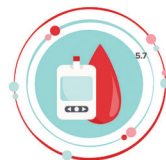
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Second and third trimesters of pregnancy. Biliary obstructive disorders. Severe hepatic impairment. The concomitant use of Telmisartan with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m²). **Warnings And Precautions - Fetal Toxicity** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. **Hypotension** In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. **Hyperkalemia** may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered particularly in patients at risk. **Impaired Hepatic Function** As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan should be initiated at low doses and titrated slowly in these patients. **Impaired Renal Function** as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function should be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System:** Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, combined use of drugs from different classes of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes in patients on Telmisartan and other agents that affect the RAS should be closely monitored. Aliskiren must not be co-administered with Telmisartan in patients with diabetes. Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m²) must be avoided. **Nondclinical Toxicology:** Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when Telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan. These same doses have been shown to provide average systemic exposures to Telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any Telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of Telmisartan. This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **Use In Specific Populations: Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. **Pediatric Use:** Safety and effectiveness of Telmisartan in pediatrics has not been established. Thus, the drug is not recommended in pediatrics. **Geriatric Use:** No dose adjustment is needed in elderly patients



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Telmisartan is an orally active and specific angiotensin II receptor (type AT1) blocker. **Contraindication:** The fixed dose combination of Bisoprolol fumarate and Telmisartan tablets is contraindicated in hypersensitivity to Bisoprolol and Telmisartan or to any of the excipients in the formulation. **Bisoprolol:** cardiogenic shock, AV block of second or third degree, symptomatic bradycardia and hypotension. **Telmisartan:** Second and third trimesters of pregnancy, Biliary obstructive disorders, severe hepatic impairment. The concomitant use of Telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²). **Warning & Precautions:** Bisoprolol-Especially in patients with ischaemic heart disease the cessation of therapy with Bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition. There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with coronary heart disease. Bisoprolol must be used with caution in bronchospasm, diabetes mellitus, AV block of first degree, Prinzmetal's angina, Peripheral arterial occlusive disease. **Telmisartan** is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since Telmisartan is mostly eliminated with the bile. Volume- and/or sodium-depleted patients: Volume and/or sodium depletion should be corrected prior to administration of Telmisartan. Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. **Drug Interactions:** Bisoprolol-Combination not recommended-Verapamil, Diltiazem, Methyldopa, Lidocaine. Combinations to be used with caution- Amlodipine, Amiodarone, Digoxin, NSAIDs. **Telmisartan-**When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. Concomitant use requiring caution- NSAIDs, Diuretics, ACEi, ARBs, Aliskiren. **Special Populations: Pregnancy:** Bisoprolol is not recommended during pregnancy unless clearly necessary and breast-feeding. **Telmisartan-**Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started. Telmisartan is not recommended in breast-feeding. **Hepatic or Renal impairment: Bisoprolol** - In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required. In patients with severe renal impairment (creatinine clearance < 20 mL/min) and in patients with severe liver function disorders it is recommended that a daily dose of 10 mg is not exceeded. **Telmisartan-**Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment. When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. **Adverse Reactions: Bisoprolol-** Most common adverse reactions include headache and dizziness. **Telmisartan-** sinus pain, stuffy nose, back pain. **Overdose: Bisoprolol:** With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, if overdose occurs, Bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Bradycardia: Administer intravenous atropine. Hypotension: Intravenous fluids and vasopressors should be administered. **Telmisartan:** The most prominent manifestations of Telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose.



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A Randomized Multicenter Double-blind Placebo-controlled Prospective Study to Evaluate the Efficacy and Safety of Magnesium + Vitamin D Supplement as an Add-on Therapy to Oral Hypoglycemic Agents in Type 2 Diabetic Patients

Sanjay Tandon^{1*}, GM Prasad², Dilip Kadam³
Received: 24 July 2025; Accepted: 17 October 2025

ABSTRACT

Background: Diabetes mellitus (DM) is a growing global concern, with India projected to have 124.9 million cases by 2045. Magnesium (Mg) and vitamin D (VitD) deficiencies are linked to poor glycemic control. Both nutrients play essential roles in glucose metabolism and insulin function, but their combined supplementation in diabetes management remains underexplored. This study evaluates the efficacy and safety of Mg + VitD supplementation as an adjunct to oral hypoglycemic agents (OHAs) in patients with type 2 diabetes mellitus (T2DM).

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Ref.: 1. Journal of the Association of Physicians of India (JAPI) 2026;74(5):42-47.

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IN26OZM00226 | Review Date: 25 Aug 2026





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Subscription Information

Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹15,000 (India). The Journal is dispatched within India by surface mail.

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Published and Edited by

Prof. Dr Jyotirmoy Pal, on behalf of **The Association of Physicians of India**, Journal of The Association of Physicians of India, Unit No. 3301, Prestige Turf Tower 'D', Shakti Mill Lane, Off. Dr. E. Moses Road, Near Mahalaxmi Station (West), Mumbai-400 011.

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Sleep, Quality of Life, and the Intricate Relationship with Good Health

Anupam Prakash^{1*}, Ghan Shyam Pangtey², Ramesh Aggarwal³

Keywords: Mental health, Noncommunicable diseases, Physical health, Sleep deprivation, Sleep disturbance.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1711

Sleep is the golden chain that ties health and our bodies together—Thomas Dekker

Sleep is an integral part of human life's daily cycle. A day or two without sleep reflects a restless mind. Loss of sleep, or even the lack of it, makes one perturbed. Good sleep is a dynamic, active biological process. It affects several domains, be it cognitive or emotional, and its effects contribute to maintaining good health. Sleep is the time when the brain's activity is at a lower level, and during this time, the accumulated toxins are cleared from the brain. One such accumulated toxin is amyloid-beta, which is linked to Alzheimer's disease. Sleep helps store daily memories and improves focus and decision-making. Apart from ensuring cognitive health, sleep also improves physical and metabolic health, since adequate rest lowers blood pressure, regulates stress hormones like cortisol, and also reduces inflammation.

Charlotte Brontë rightly remarked, "A ruffled mind makes a restless pillow."

In fact, chronic sleep deprivation can adversely impact the quality of life and, in the long run, contribute to adverse health consequences. In a Brazilian study,¹ among 1,650 randomly selected medical students, it was found that daytime sleepiness was observed in 46.5% of the students, significantly more among females. Students who had higher daytime sleepiness scores had poorer quality-of-life scores in all aspects examined (physical health, psychological health, social relationships, and environment). Moreover, higher daytime sleepiness scores were associated with lower perception of the educational environment and greater anxiety. Most students were having fewer hours of sleep on weekdays and appeared to compensate for their sleep during the weekends.

Chronic sleep deprivation is also linked to an increased risk of developing chronic noncommunicable diseases, namely, type 2 diabetes mellitus, obesity, and cardiovascular diseases. Besides, chronic sleep deprivation can also result in suppressed immunity. The

effect on mental health is paramount because of sleep deprivation. Unsettled sleep often results in irritability at work and hampers cordial interpersonal relations, apart from poor performance at the workplace.

The revered Tibetan religious leader, the Dalai Lama, had once said, "Sleep is the best meditation." Chronic sleep deprivation can also result in impaired emotional regulation, which can trigger or exacerbate conditions like anxiety and depression. It is also a well-known fact that psychiatric morbidities alter sleep patterns, reflecting that it is an intricate bidirectional relationship. The aforementioned health effects are bound to affect the quality of life.

The American Academy of Sleep Medicine (AASM) and Sleep Research Society (SRS) developed a consensus recommendation in 2015² on the amount of sleep needed to promote optimal health in adults. They used a modified RAND Appropriateness Method process.³ The consensus statement recommended that adults should sleep 7 or more hours per night on a regular basis to promote optimal health. The statement highlighted that <7 hours of sleep per night on a regular basis is associated with adverse health outcomes, namely, weight gain and obesity, diabetes, hypertension, heart disease and stroke, depression, and increased risk of death. It is also reported to be associated with impaired immune function, increased pain, impaired performance, increased errors, and greater risk of accidents. The consensus statement also emphasized that sleeping >9 hours per night on a regular basis may be appropriate for young adults, individuals recovering from sleep debt, and individuals with illnesses. However, the statement expressed uncertainty on whether sleeping >9 hours per night is associated with health risk in other segments of the population.

It is not only the amount of sleep that is important. It is also imperative to have a good quality of sleep, which includes undisturbed sleep with few awakenings. A systematic review examined the association between sleep timing, sleep consistency, and health

outcomes.⁴ The review indicated that later sleep timing and greater sleep variability were both associated with adverse health outcomes. Social jetlag was also found to be associated with adverse health outcomes. The systematic review designated eight health outcomes as critical or primary outcomes, namely, mortality, cardiovascular disease, type 2 diabetes, mental health (depression, anxiety, psychological distress), brain health (neurodegenerative diseases), cognitive function, falls, and accidents/injuries. Six secondary health outcomes were labeled as important and included adiposity, biomarkers of cardiometabolic risk, bone health, health-related quality of life, work productivity, and physical activity and sedentary behavior. The review emphasized that weekend catch-up sleep was associated with better health outcomes. The quality of evidence (on the basis of the studies included in the systematic review) varied from very low to moderate. The systematic review concluded that earlier sleep timing and regularity in sleep patterns with consistent bedtimes and wake-up times are favorably associated with good health.

It is also imperative to understand the concept of sleep hygiene,⁵ which is intricately associated with the quality of sleep. Although there is no universally accepted definition of sleep hygiene or its components, it encompasses three factors, namely, behavioral factors, environmental factors, and an aspect of control. The most commonly considered components of sleep hygiene in various studies include caffeine, alcohol, exercise, sleep timing, light, napping, smoking, noise, temperature, wind-down routine, stress, and stimulus control. All these factors, and perhaps some others too, not only help improve sleep quality but also improve sleep duration, and hence, sleep hygiene is an intricate factor in contributing to good sleep.

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How to cite this article: Prakash A, Pangtey GS, Aggarwal R. Sleep, Quality of Life, and the Intricate Relationship with Good Health. *J Assoc Physicians India* 2026;74(9):11–12.

The Centers for Disease Control and Prevention (CDC) emphasizes how to improve sleep quality.⁶ It advises going to bed and getting up at the same time every day. Keeping the bedroom quiet and relaxing, with a cool temperature, is also advised. It advises turning off electronic devices at least 30 minutes before bedtime. It advises against having large meals and alcohol before bedtime and against having caffeine in the afternoon or evening. Exercising regularly and maintaining a healthy diet are other recommendations to follow.

The American Heart Association in 2010 had talked about the concept of cardiovascular health (CVH). The initial definition of CVH was based on seven health behaviors and health factors, which, if they remain optimal, were associated with greater cardiovascular disease-free survival and total longevity and

higher quality of life. In 2022, the Presidential Advisory added the eighth component as sleep health.⁷ The components of Life's Essential Eight include diet, physical activity, nicotine exposure, sleep health, body mass index, blood lipids, blood glucose, and blood pressure. This is a real impetus on the value allocated to sleep, not only for cardiovascular diseases but for other chronic diseases in the times to come. Sleep remains a critical pillar of health, and disturbances in sleep can adversely impact quality of life and have a bearing on several noncommunicable diseases.

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A Needle through Time: Celebrating 21 Years of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration in Pulmonary Medicine!

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Keywords: Drug resistant tuberculosis, EBUS TBNA, Lung cancer, Mediastinal tuberculosis.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1710

Traditional methods with limited diagnostic yield and invasive surgical techniques prompted the development of minimally invasive, real-time, image-guided sampling of mediastinal and hilar lymph nodes *via* endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).^{1,2} Since its inception, EBUS-TBNA has grown exponentially and is now established as the standard of care in mediastinal sampling.³ EBUS-TBNA is a safe, minimally invasive outpatient procedure that can be completed under moderate sedation with minimal patient discomfort and achieves diagnostic accuracy exceeding 90% for both benign and malignant etiologies.^{3,4} It has significantly impacted treatment decisions in thoracic and extrathoracic malignancies, as well as in various inflammatory processes and infections.

Prior to the advent of EBUS-TBNA, mediastinal sampling was performed using conventional transbronchial needle aspiration (TBNA) and mediastinoscopy.⁵⁻⁷ Mediastinoscopy, a surgical procedure, was traditionally regarded as the gold standard for mediastinal sampling. By 2011, studies had reported the noninferiority of EBUS-TBNA to mediastinoscopy and its superiority to conventional TBNA.^{4,8,9} EBUS-TBNA can additionally sample N1 to N3 nodes, making it superior to mediastinoscopy for accurate lung cancer staging.^{10,11} When combined with endoscopic ultrasound with a bronchoscope-guided fine-needle aspiration (EUS-B-FNA) using the same bronchoscope, EBUS-TBNA allows for comprehensive mediastinal sampling. It is now considered the first-line modality of choice for sampling mediastinal or hilar lymphadenopathy. The feasibility of EBUS-TBNA is also reported in the pediatric population.¹²

Over the past 2 decades, the lung cancer treatment landscape has evolved significantly, especially with improved survival in advanced cases due to targeted and molecular therapies. Despite this advancement, EBUS-TBNA remains an indispensable diagnostic

tool. It can upstage a radiologically normal mediastinum and downstage lesions that are positron emission tomography (PET)-positive with high diagnostic accuracy.^{10,11} It is currently the only modality capable of simultaneously diagnosing and staging lung cancer in a single procedure.⁴ Subcentimeter lymph nodes, often non-FDG-avid on PET-computed tomography (PET-CT), can be safely and precisely sampled using EBUS-TBNA. EBUS-TBNA has also been reported as a safe modality in elderly patients and those with superior vena cava syndrome. Postsurgical mediastinal sampling, which remains challenging due to anatomical distortion, can be safely and accurately performed with EBUS-TBNA, facilitating restaging of lung cancer.⁴

Despite the emergence of screening programs, most lung cancers are diagnosed at an advanced and unresectable stage.¹³ The exponential evolution of medical oncology has increased the demand for high-quality cytological, histological, and molecular material from tissue samples. Consequently, these patients rely on minimally invasive diagnostic modalities expected to yield tissue suitable for molecular profiling. The emergence of molecular profiling and next-generation sequencing (NGS) in lung cancer has marked a pivotal shift toward precision oncology. NGS requires higher quantities of deoxyribonucleic acid (DNA) compared with conventional molecular testing, as it involves testing for hundreds of mutations. These mutations include both actionable alterations and those currently under investigation in clinical trials. International oncological guidelines now recommend concurrent diagnosis, staging, and acquisition of adequate material for genetic testing. Often, tissue samples from EBUS-TBNA are the only samples available at the time of diagnosis. These samples have been reported to have excellent adequacy and quality for these advanced tests.¹⁴⁻¹⁶ EBUS-TBNA is also referred to as endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-

TBNA) when core biopsies are obtained.^{17,18} There have been advances in EBUS-TBNA needles to obtain core biopsies; however, they can be obtained with 21-gauge needles as well.¹⁷ Its diagnostic yield further improves when core tissue biopsies are obtained using fine-gauge needles.^{17,19} Optimal processing of EBUS-TBNA cytological specimens also enhances diagnostic yield for lymphoma.²⁰

EBUS-TBNA maintains a high diagnostic yield in benign diseases as well. As with other interventional pulmonology techniques, bronchoscopic modalities discovered for lung cancer have led to a paradigm shift in nonmalignant diseases as well. An additional diagnostic dilemma that physicians often encounter, especially in tuberculosis (TB)-endemic regions like India, is fever and mediastinal lymphadenopathy. More often than not, these individuals are treated empirically without microbiological or pathological subtyping. The dilemma takes a turn for the worse when they do not respond to empiric treatment. The emergence of drug-resistant tuberculosis, from multidrug-resistant to extensively drug-resistant tuberculosis, makes it extremely difficult to achieve an accurate diagnosis in people with tuberculous mediastinal lymphadenopathy. Fortunately, microbiological tests such as BACTEC-MGIT techniques of acid-fast bacilli (AFB) culture and cartridge-based nucleic acid amplification tests (CB-NAATs) like GeneXpert have facilitated rapid diagnosis and management of drug-resistant tuberculosis. The feasibility of performing these tests on samples obtained by EBUS-TBNA has

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How to cite this article: Vaidya PJ, Chhajed PN. A Needle through Time: Celebrating 21 Years of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration in Pulmonary Medicine!. *J Assoc Physicians India* 2026;74(9):13-14.

significantly helped in accurately diagnosing and microbiologically subtyping these lethal infections.^{21,22} It enables timely therapy modification and individualized treatment regimens in patients with tuberculous mediastinal lymphadenopathy.²² Noninfective granulomatous inflammation confounds the clinical picture in both malignancy and tuberculosis. It becomes extremely challenging to differentiate sarcoidosis from active tuberculosis, especially in TB-endemic regions like India. EBUS-TBNA becomes crucial in these situations as well. EBUS-TBNA has demonstrated the highest diagnostic accuracy for sarcoidosis among available modalities.^{23,24} Owing to its high diagnostic yield, EBUS-TBNA is effective in diagnosing mediastinal lymphadenopathy in people living with human immunodeficiency virus (HIV).²⁵ The bronchoscopic ultrasound also aids in characterizing lymph nodes as malignant, granulomatous, or tuberculous in nature.^{26,27} However, while not definitive, this feature assists in targeting specific regions within the lymph node for sampling.

EBUS-TBNA is also evolving as a platform to facilitate cryobiopsy of mediastinal lymph nodes. EBUS-guided cryobiopsy improves its diagnostic yield for lymphoma to 91% while not increasing the rate of complications.^{20,28,29} Studies have also reported the feasibility of therapeutic interventions via EBUS-TBNA, such as intranodal cisplatin injections.^{30,31} EBUS-TBNA has also been used successfully to sample lymph nodes via transvascular approaches, including transaortic access.^{32,33} The role of EBUS-TBNA is expected to expand further with the increasing implementation of lung cancer screening programs and global initiatives like STOP TB. Its unmatched combination of diagnostic accuracy and safety continues to establish EBUS-TBNA as a cornerstone in pulmonary diagnostics.

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Integrated Genomic Phenotypic and Host-response Analysis of Multidrug-resistant Diabetic Foot Infections: A Tertiary Center Study from Kerala India

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Received: 02 November 2025; Accepted: 02 July 2026

[Visual Abstract](#)

ABSTRACT

Background: Diabetic foot infections (DFIs) are a primary driver of amputation, worsened by multidrug-resistant (MDR) organisms. The link between pathogen genomics, virulence (e.g., biofilm), and host immunity is poorly quantified. This study aimed to integrate these multi-omic data streams to identify predictors of treatment failure.

Materials and methods: This prospective, single-center cohort study enrolled 150 DFI patients. Deep-tissue and autologous healthy-skin biopsies were collected. Pathogens were identified (culture/16S rRNA), with susceptibility and biofilm capacity tested. MDR isolates ($n = 76$) underwent whole-genome sequencing (WGS). Host response was quantified using an eight-gene quantitative reverse transcription polymerase chain reaction (qRT-PCR) panel, normalized to autologous controls. The primary outcome was “healing failure” (amputation or persistent ulcer) at 12 weeks. A least absolute shrinkage and selection operator (LASSO)-penalized regression model was developed and cross-validated.

Results: The final analytical cohort included 112 culture-positive patients; 68/112 (60.7%) had an MDR infection. WGS identified high-risk clones (*Escherichia coli* ST131, *Klebsiella pneumoniae* ST258). Healing failure occurred in 34/112 (30.4%) patients. Strong biofilm production (adjusted OR 3.81, 95% CI 1.92–7.55) and a high host IL-10:TNF- α expression ratio (AOR 2.98, 95% CI 1.41–6.30) were independent predictors of healing failure. The LASSO model achieved an optimism-corrected area under the curve (AUC) of 0.79 (95% CI 0.71–0.87) with acceptable calibration (Brier score: 0.18; slope: 0.95).

Conclusion: In this DFI cohort, pathogen biofilm capacity and a modulated host immune signature were independently associated with treatment failure, highlighting potential new diagnostic and therapeutic targets.

Keywords: Biofilms, Diabetic foot infection, Host-pathogen interactions, Interleukin-10, Multidrug-resistant, Predictive model, Wound healing.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1693

INTRODUCTION

Diabetic foot infections (DFIs) are a leading cause of nontraumatic lower limb amputations and represent a significant global health burden, particularly in regions with a high prevalence of diabetes, such as Kerala, India.¹ The management of DFIs is increasingly complicated by their frequent polymicrobial nature and the rising prevalence of multidrug-resistant (MDR) organisms.^{2,3}

Current literature has extensively cataloged pathogen prevalence but often suffers from limitations.⁴ Many studies are descriptive, relying on standard culture techniques that may miss fastidious organisms or anaerobes. Crucially, they often fail to integrate key pathogenic determinants, such as the genomic drivers of resistance, virulence factor profiles, and critical phenotypic states, particularly the capacity to form biofilms.⁵

Furthermore, DFI represents an interaction between the pathogen and the

host. The local immune environment at the wound site—whether robust, impaired, or dysregulated—is a critical determinant of outcome. Most studies fail to characterize this response, and those that do often lack appropriate autologous control tissues, making interpretation of fold-change data difficult.

This study was undertaken to address these gaps by integrating three data streams at the patient level. The objectives were to: (1) characterize the aerobic/anaerobic bacteriological profile; (2) quantify biofilm-forming capacity as a key virulence phenotype; (3) define the genomic resistome and virulome of MDR pathogens using WGS; (4) characterize the in situ host immune-inflammatory response at the wound site relative to autologous healthy-skin controls; and (5) integrate these datasets to identify independent predictors and build a validated model for treatment failure.

MATERIALS AND METHODS

Study Design and Ethical Approval

This prospective, single-center cohort study was conducted over an 18-month period (January 2023 to June 2024) at a tertiary care teaching hospital in Kerala, India. The study was approved by the Institutional Ethics Committee (IEC No. 22/IEC/SUTAMS/2023). Written informed consent was obtained from all participants.

Patient Population and Outcomes

All consenting adult (≥ 18 years) patients with type 2 diabetes mellitus admitted with a new or worsening DFI [per Infectious Diseases Society of America (IDSA) guidelines] were enrolled. Antibiotic use within 14 days was recorded as a covariate.

The primary composite outcome was “healing failure” at 12 weeks, defined as either (1) the need for a major amputation (below- or above-knee) or (2) a persistent, unhealed ulcer at the 12-week follow-up visit. Patients who died from unrelated causes ($n = 3$) or were lost to follow-up ($n = 8$) were excluded from the final analytical cohort. All 112 patients in the analytical cohort completed the 12-week follow-up.

Data and Sample Collection

A standardized case report form captured demographics, metabolic control (HbA1c), comorbidities (PAD, neuropathy), wound classifications (PEDIS, WifI), and key covariates, including surgical debridement and revascularization status.

After debridement, four tissue samples were collected: (1) a deep-tissue biopsy for aerobic/anaerobic culture; (2) a second

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How to cite this article: Ibrahim K MJ. Integrated Genomic Phenotypic and Host-response Analysis of Multidrug-resistant Diabetic Foot Infections: A Tertiary Center Study from Kerala India. *J Assoc Physicians India* 2026;74(9):15–18.

deep-tissue biopsy for 16S rRNA sequencing if needed; (3) a 3 mm punch biopsy from the active wound edge, placed in RNAlater; and (4) a 4 mm punch biopsy from healthy, nonacral skin (proximal thigh) of the same patient as an autologous control.

Microbiological Analysis

Tissue was homogenized and plated for aerobic and anaerobic culture. Identification was performed by standard biochemical methods or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). 16S rRNA gene sequencing was used for difficult-to-identify isolates. Antimicrobial susceptibility testing (AST) was performed per Clinical and Laboratory Standards Institute (CLSI) guidelines. MDR was defined per Magiorakos et al.⁶

For polymicrobial infections, an “index pathogen” was designated for patient-level analysis based on a prespecified algorithm: (1) the isolate with the highest level of resistance (MDR > non-MDR), and (2) in cases of equivalent resistance, the isolate with the highest semiquantitative abundance.

Advanced Pathogen Analysis

Quantitative biofilm assay: All isolates were assessed in triplicate using a 96-well plate crystal violet assay. Absorbance (OD) was read at 570 nm. Isolates were categorized relative to a nonadherent control (*Escherichia coli* ATCC 25922) cutoff (OD_c): nonformer (OD ≤ OD_c), weak (OD_c < OD ≤ two × OD_c), moderate (two × OD_c < OD ≤ four × OD_c), or strong (OD > four × OD_c). The interassay coefficient of variation was <15%.

Whole-genome sequencing (WGS): Genomic DNA from all MDR isolates was sequenced on an Illumina NovaSeq 6000. Reads were quality-trimmed (Trimomatic), assembled (SPAdes), and assessed for quality (QUAST). WGS libraries achieved a mean read depth of >80× and a mean N50 of >55 kb. Contamination was screened (Kraken2). Resistomes (ResFinder) and virulence factors (VFDB) were identified. Multilocus sequence typing (MLST) (v2.0) was determined.

Host Immunological Analysis

Total RNA was extracted from wound-edge and autologous skin biopsies (RNeasy kit). cDNA was synthesized, and quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed for a targeted eight-gene panel (TNF-α, IL-1β, IL-6, IL-10, CD4, CD68, MMP-9, TGF-β) and two reference genes (GAPDH, B2M). Relative expression was calculated using the $\Delta\Delta C_t$ method, normalized to the geometric mean

of the reference genes, and expressed as fold-change relative to the patient’s own healthy skin sample. Primer efficiencies were verified (95–105%). Assay precision was high (mean SD of Ct triplicates = 0.21 Ct).

Statistical Analysis

All analyses were performed in R (v4.3.1). The primary analytical cohort consisted of 112 culture-positive patients with 12-week outcome data.

Missing data: Missingness in covariates (<5%) was handled using multiple imputation by chained equations (MICE, five imputed datasets).

Risk factor analysis: A multivariable logistic regression model was built to identify risk factors for “MDR infection” (patient-level). Variables were selected a priori (age, HbA1c, PAD, prior DFI, duration of DM). Continuous variables were modeled using restricted cubic splines.

Outcome analysis: A separate multivariable logistic regression model assessed predictors of “healing failure.”

Host response: Gene expression fold-changes were log₂-transformed. *p*-values for the eight-gene panel were adjusted for multiple comparisons [Benjamini-Hochberg false discovery rate (FDR)].

Predictive model: A least absolute shrinkage and selection operator (LASSO)-penalized logistic regression model was built using 22 candidate variables. Performance was validated using 10-fold cross-validation, repeated 10 times. Model optimism was assessed via 200 bootstrap resamples.

Sensitivity analyses: Six prespecified sensitivity analyses were conducted to test robustness, including modeling biofilm as a continuous variable, using “amputation only” as the outcome, and an inverse probability of censoring weighting (IPCW) analysis to assess selection bias.

RESULTS

Patient Cohort

A total of 150 patients were enrolled. Thirty-eight were excluded (27 culture-negative, 8 lost to follow-up, 3 died of unrelated causes), leaving a final analytical cohort of 112 patients. Mean age was 62.4 ± 11.2 years, 66.2% were male, and mean HbA1c was 8.9% ± 1.4%. Baseline wound severity was high (45% Wifl stage 3 or 4).

Bacteriological Profile and Multidrug-resistant Prevalence

The 112 patients yielded 131 bacterial isolates; 58/112 (51.8%) infections were polymicrobial. Gram-negative organisms were predominant

(55.0% of isolates). At the patient level, the most common index pathogens were *Staphylococcus aureus* (*n* = 25, 22.3%), *E. coli* (*n* = 21, 18.8%), and *Klebsiella pneumoniae* (*n* = 18, 16.1%) (Table 1).

Overall, 76/131 (58.0%) of isolates were MDR. At the patient level, 68/112 (60.7%) patients had an infection involving at least one MDR organism.

Genomic Analysis of Multidrug-resistant Isolates

WGS was performed on all 76 MDR isolates. This analysis confirmed the genomic basis for resistance and identified the circulation of high-risk international clones (Table 2).

Among 28 MDR *E. coli* isolates, 12 (42.9%) belonged to the ST131 clone, all carrying bla_{CTX-M-15}. Among 22 MDR *K. pneumoniae* isolates, 7 (31.8%) were ST258, and 3 carried bla_{KPC-2}. Carbapenem resistance was also driven by bla_{NDM-5} (identified in 5 *K. pneumoniae* and 2 *Acinetobacter baumannii*). All 14 MRSA isolates were ST239-SCCmecIII, and 5 (35.7%) carried genes for the Pantone-Valentine Leukocidin (pvl) toxin.

Risk Factors for Multidrug-resistant Infection

The a priori multivariable logistic regression model (Table 3) identified two significant independent predictors for having an MDR infection (*n* = 68 events): previous DFI (AOR 4.05, 95% CI 1.85–8.87) and baseline HbA1c (AOR 1.41, 95% CI 1.10–1.82). A sensitivity analysis confirmed that antibiotic use in the last 14 days was also a predictor (AOR 2.45, 95% CI 1.15–5.21) but did not meaningfully alter the main findings.

Primary Outcome and Integrated Analysis

The primary composite outcome, healing failure at 12 weeks, occurred in 34 of

Table 1: Distribution of 112 index pathogens from DFIs

Bacterial isolate (index)	Frequency (n)	Percentage (%)
<i>S. aureus</i>	25	22.3%
<i>E. coli</i>	21	18.8%
<i>K. pneumoniae</i>	18	16.1%
<i>Pseudomonas aeruginosa</i>	14	12.5%
<i>Acinetobacter</i> spp.	9	8.0%
Other*	25	22.3%
Total	112	100%

*Other includes: Anaerobes (*n* = 7), *Enterococcus* spp. (*n* = 6), *Proteus* spp. (*n* = 5), and other (*n* = 7)

Table 2: Key genomic characteristics of the 76 MDR isolates

Organism (n = 76)	Common sequence types (STs) (n)	Key AMR genes detected (n)	Key virulence factors (n)
<i>E. coli</i> (n = 28)	ST131 (12)	_bla_CTX-M-15 (20)	<i>iutA</i> (aerobactin) (15)
	ST648 (4)	<i>aac(6')-Ib-cr</i> (11)	<i>fimH</i> (adhesion) (26)
<i>K. pneumoniae</i> (n = 22)	ST258 (7)	_bla_KPC-2 (3)	<i>rmpA</i> (hypermucoidity) (4)
	ST11 (5)	_bla_NDM-5 (5)	<i>ybtS</i> (yersiniabactin) (9)
<i>S. aureus</i> (n = 14)	ST239 (14)	<i>mecA</i> (SCC_mec_III) (14)	<i>pvl</i> (PVL toxin) (5)
		<i>aac(6')-Ie</i> (8)	<i>icaA</i> (biofilm) (11)
<i>P. aeruginosa</i> (n = 6)	ST235 (3)	_bla_VIM-2 (2)	<i>lasR</i> (quorum sensing) (6)
<i>Acinetobacter</i> spp. (n = 6)	ST2 (4)	_bla_OXA-23 (5)	<i>cpaA</i> (adhesion) (4)

AMR, antimicrobial resistance; pvl, Panton-Valentine leucocidin; ST, sequence type

Table 3: Multivariable logistic regression model for risk factors associated with MDR infection (n = 112 patients, 68 MDR events)

Predictor variable	Adjusted odds ratio (AOR)	95% confidence interval (CI)	p-value
Prior DFI (yes vs no)	4.05	1.85–8.87	<0.001
HbA1c (per 1% increase) ¹	1.41	1.10–1.82	0.007
Peripheral arterial disease (yes vs no)	1.33	0.71–2.49	0.38
Age (per 10-year increase) ¹	1.05	0.89–1.24	0.55
Duration of diabetes (per 5 years)	1.12	0.95–1.32	0.18

¹Modeled using restricted cubic splines. Results pooled from 5 multiply imputed datasets

Table 4: Multivariable logistic regression model for predictors of healing failure at 12 weeks (n = 112 patients, 34 failure events)

Predictor variable	Adjusted odds ratio (AOR)	95% confidence interval (CI)	p-value
Strong biofilm (vs non/weak/mod)	3.81	1.92–7.55	<0.001
IL-10:TNF-alpha ratio (per log ₂ -unit)	2.98	1.41–6.30	0.004
Wifl score (per stage increase)	2.15	1.45–3.19	<0.001
MDR status (yes vs no)	1.89	0.88–4.06	0.101
Surgical source control (achieved vs not)	0.45	0.22–0.92	0.028
HbA1c (per 1% increase) ¹	1.20	0.98–1.47	0.08

¹Modeled using restricted cubic splines. Model adjusted for age and PAD. Results pooled from 5 multiply imputed datasets

Table 5: Clinical utility of the LASSO model at different risk thresholds (from 10-fold cross-validated predictions)

Risk threshold	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
20%	88.2% (72.6–96.7)	65.4% (53.5–76.0)	48.4% (35.6–61.4)	93.1% (83.3–97.9)
30%	70.6% (52.5–84.9)	82.1% (71.3–90.2)	58.5% (42.1–73.7)	88.4% (78.4–94.9)
40%	52.9% (35.1–70.2)	91.0% (82.4–96.4)	66.7% (46.0–83.5)	84.1% (74.4–91.3)

Thresholds for intervention based on predicted probability of healing failure. Prevalence of outcome = 30.4%. 95% confidence intervals calculated via the bootstrap method

112 patients (30.4%), including 22 major amputations and 12 persistent ulcers.

In the multivariable model for healing failure (n = 34 events, Table 4), strong biofilm production by the index pathogen was the most significant pathogen-related predictor, stronger than MDR status alone.

Host-immune Signature

After FDR correction, patients who failed to heal showed significantly higher expression of IL-10 (mean log₂ fold-change 2.9, q = 0.008) and significantly lower expression of TNF-α (mean log₂ fold-change -1.8, q = 0.015) compared to those who healed. The IL-10:TNF-α expression ratio was also an independent predictor of healing failure (see Table 4).

Predictive Model for Healing Failure

A LASSO-penalized regression model was built using 22 candidate variables, retaining 7 predictors. Performance, assessed by 10-times repeated 10-fold cross-validation, achieved a mean AUC of 0.81 (95% CI 0.74–0.88). The optimism-corrected AUC was 0.79 (95% CI 0.71–0.87). The model was well calibrated (mean cross-validated Brier score: 0.18, 95% CI 0.14–0.22; optimism-corrected calibration slope: 0.95, 95% CI 0.88–1.03).

Decision curve analysis showed a net benefit over default strategies. The clinical utility of the model at specific thresholds is presented in Table 5.

Sensitivity Analyses

The primary findings were robust across all six sensitivity analyses. Modeling biofilm OD as a continuous variable (AOR 1.9, p = 0.002) and using “major amputation only” as the outcome (AOR 3.1, p = 0.003) confirmed the association. The findings also held in the complete-case analysis, the polymicrobial-only cohort, when the index pathogen was defined by abundance, and in the IPCW analysis.

DISCUSSION

This prospective study integrated pathogen genomics, virulence phenotyping, and host

transcriptomics to identify predictors of DFI treatment failure. We found that 60.7% of patients harbored an MDR organism, with prior DFI and poor glycemic control (HbA1c) being key risk factors. The WGS analysis (Table 2) confirmed that this burden is driven by high-risk, globally disseminated clones such as *E. coli* ST131 and *K. pneumoniae* ST258.

The primary finding is that while MDR status is a risk factor, it was not the strongest independent predictor of 12-week healing failure. Instead, the phenotype of the index pathogen ("strong biofilm production") and the host immune response (a high IL-10:TNF- α ratio, suggestive of a "blunted" immune state) were independent and clinically relevant predictors. This supports the hypothesis that the bacteria's ability to protect itself *via* biofilm and modulate the local immune environment is a critical pathogenic mechanism.

Our predictive model, which integrated these novel markers, achieved a robust, optimism-corrected AUC of 0.79 with good calibration. This demonstrates the potential utility of an integrated approach. However, given the borderline events-per-variable ratio (34 events/22 candidate predictors), the model coefficients may be unstable. Furthermore, the sample size provided limited precision for detecting smaller effect sizes.

Therefore, these findings and the model require mandatory external validation in a separate, larger cohort before any clinical consideration.

This study has several limitations. It is a single-center study, limiting the generalizability of specific pathogen prevalences. The "index pathogen" definition, while prespecified and robust to sensitivity analyses, simplifies complex polymicrobial dynamics. We also acknowledge that by excluding 3 patient deaths, we did not formally model the competing risk of mortality. A Fine-Gray competing risk analysis was considered but was underpowered due to the small number of events.

An independent multicenter cohort validation is planned for 2025 (protocol under development) to assess transportability of the LASSO model.

CONCLUSION

This study demonstrates that DFI outcomes are associated with a complex triad of pathogen resistance, virulence phenotype, and host immune response. Strong biofilm production and a high IL-10:TNF- α ratio at the wound site are independent predictors of treatment failure. These findings suggest that future DFI management strategies may

be improved by incorporating diagnostics that assess biofilm and host response. These findings and the proposed model must be validated in external cohorts.

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Feasibility of a Model-based HbA2 Prediction for Low-cost Screening of β -thalassemia Trait Using Blood-derived Indices: Opportunities and Challenges

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Received: 02 February 2026; Accepted: 06 July 2026

[Visual Abstract](#)

[Supplement Material](#)

ABSTRACT

Background: β -thalassemia trait (β -TT) is a common genetic condition with significant public health implications, particularly in regions with high prevalence. Diagnosis conventionally relies on HbA2 quantification using high-performance liquid chromatography or Hemoglobin electrophoresis, which are costly and inaccessible in resource-limited settings. Developing low-cost screening/triage tools is therefore essential.

Materials and methods: A retrospective single-center cross-sectional study was conducted at the Department of Pathology, Apollo Institute of Medical Sciences & Research, Hyderabad, between February 2023 and December 2025. Data from 129 patients with complete blood counts, iron profiles, and HbA2 measurements were analyzed. LASSO method was applied to identify salient predictors of HbA2 from demographic, hematological, and iron parameters. Two ordinary least squares regression models (OLS) were constructed: one excluding iron parameters (model 1) and another incorporating iron parameters (model 2). LASSO-then-OLS approach was used for both 5-fold cross-validation and final model development. ROC analysis was also done.

Results: Of the 129 patients, 15 (11.6%) had β -TT (HbA2 >3.5%). The 5-fold cross-validation found lower root mean squared error (RMSE) and superior variable selection stability with an iron parameter-inclusive model. Salient predictors in the final model were age, RBC count, MCV, and RDW-CV in model 1, while model 2 additionally included serum ferritin, transferrin saturation, and total iron binding capacity (TIBC). Age and RBC count were positively associated with HbA2, while MCV, RDW-CV, serum ferritin, and TIBC were negatively associated. Model 1 explained 40% of HbA2 variance, while model 2 explained 47% variance. Model imprecision was more pronounced for β -TT cases. ROC analysis showed an area under the curve (AUC) value of 0.868 (0.766–0.969) for model 1 and 0.904 (0.829–0.98) for model 2. Optimal cutoff (3.31% from model 1 and 3.26% from model 2) for β -TT detection was lower than the conventional threshold.

Conclusion: Regression-based machine learning models have the potential to estimate HbA2 using routine blood indices, offering a cost-effective screening/triage before specialized assays. Such models are particularly valuable in populations with prevalent iron deficiency anemia (serum ferritin <12 ng/ml), where fixed HbA2 cutoffs are unreliable. Larger studies incorporating peripheral smear image analysis are needed to improve the predictive accuracy of models before they can be deployed clinically.

Keywords: β -thalassemia trait, Least absolute shrinkage and selection operator, Machine learning, OLS regression, ROC analysis, Screening.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1706

INTRODUCTION

Globally, the burden of β -thalassemia is considerable. A recent systematic review and meta-analysis has revealed that nearly 3–5% of the population are carriers of thalassemia genes, called β -thalassemia trait (β -TT).¹ The progeny of such carriers are at a high risk of full-blown β -thalassemia, underscoring the importance of accurate screening and diagnosis of the β -TT. In regions with high prevalence,² such as India and other South Asian countries, the Middle East, and the Mediterranean, Population-level screening and detection of β -TT are challenging and have profound public health implications. Failure to identify carriers of β -TT not only

affects individual patient management but also hampers preventive strategies aimed at reducing the incidence of severe thalassemia syndromes in future generations. The β -TT is conventionally diagnosed by HbA2 >3.5% with high-performance liquid chromatography (HPLC) or hemoglobin electrophoresis.³ Both techniques are expensive and not widely available in the remote, resource-limited settings in low- and middle-income countries, posing a formidable public health challenge. It is therefore imperative to develop low-cost mass screening tools for β -TT.

β -thalassemia is due to mutations in both of the β -globin genes, leading to reduced or no production of β -globin protein,

while the α -globin synthesis continues unabated, leading to excess accumulation of α -globin chains that form toxic precipitates in developing RBC precursor cells in the bone marrow. This leads to excessive cell death (apoptosis) of erythroid precursors (ineffective erythropoiesis) and premature hemolysis of the RBC in the spleen. Serious consequences include chronic anemia, hypoxia, bone marrow expansion, skeletal deformities, and a lifelong requirement of periodic blood transfusions and their attendant adverse consequences like systemic iron overload. The affected patients may overproduce fetal hemoglobin, which reduces the severity of the disease. In contrast, β -TT is associated with a single mutated β -globin gene, which reduces but does not eliminate β -globin production, leading to a milder and very often asymptomatic clinical phenotype.^{4,5} The progeny of two such β -TT individuals has a 25% risk of major β -thalassemia and a 50% risk of carrier state. The β -TT individuals overproduce HbA2 as a compensatory strategy to mitigate the imbalance in α - β synthesis. This high HbA2 (>3.5%) is the diagnostic hallmark of β -TT. Iron deficiency anemia (IDA), widely prevalent in India,⁶ can mask β -TT by reducing HbA2 levels. IDA is defined as serum ferritin <12 ng/ml and low hemoglobin for the age and sex.^{7–9} On the other hand, mild-to-moderate pure IDA causes a similar clinical and hematological profile and renders the task of

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How to cite this article: Peraka R, Reddy MPK, Vanajakshi S, et al. Feasibility of a Model-based HbA2 Prediction for Low-cost Screening of β -thalassemia Trait Using Blood-derived Indices: Opportunities and Challenges. *J Assoc Physicians India* 2026;74(9):19–24.

β -TT screening challenging. Co-existing β -TT and IDA will further lower HbA2, complicating the interpretation using a fixed cutoff (like $\text{HbA2} > 3.5\%$). Hence, it is necessary to characterize the factors affecting HbA2 levels to support its judicious interpretation in a clinical context. Identification of all the salient sources of variability in HbA2 is also a prerequisite for devising a robust and reliable machine learning model for the estimation of HbA2 levels.¹⁰

Several discriminant indices based on routine blood count parameters have been proposed as a screening test of β -TT, including Mentzer's Index (MI).¹¹ The MI (MCV/RBC count), introduced in 1973, remains one of the most widely used indices, and values greater than 13 suggest IDA and less than 13 indicate β -TT. While simple and cost-effective, these discriminant indices alone are not universally reliable, as overlap between IDA and β -TT cases can occur. Consequently, there is a growing interest in refining predictive models by integrating multiple hematological parameters. In this work, we devise and assess the feasibility of combining traditional red blood cell indices¹² with predictive machine learning algorithms,¹⁰ to develop models that estimate HbA2 levels indirectly, thereby offering an accessible adjunct to specialized laboratory techniques. Such models could serve as valuable triage tools in primary care and resource-limited settings, enabling clinicians to make informed decisions regarding further testing, treatment, and genetic counseling. By leveraging readily available hematological data, this model has the potential to improve patient outcomes, optimize resource utilization, and contribute to global efforts in reducing the burden of thalassemia.

Although HbA2 testing is available at referral laboratories, access remains inconsistent across India. Many peripheral facilities lack HPLC/capillary gel electrophoresis capability, and referral requires temperature-controlled transport and multi-day turnaround times; high ambient temperatures frequently compromise sample integrity and HbA2 accuracy. Because most referral pathways lack reliable cold-chain support, test quality is variable, and delays disrupt antenatal screening workflows. Moreover, while the per-test price is modest, the logistical and programmatic costs of scaling population-level screening are substantial. These constraints explain the limited uptake of HbA2 testing in many regions and support the need for low-cost triage tools. In addition, IDA can confound HbA2 interpretation as discussed previously. Our model is intended for preliminary screening

in such settings, and not as a replacement for definitive laboratory testing. This study has two-fold objectives: 1. To examine the feasibility of a machine-learning model to predict HbA2 from blood-derived parameters for β -TT screening. 2. To determine the factors affecting the variability of HbA2.

MATERIALS AND METHODS

This retrospective single-center cross-sectional study was conducted at the Department of Pathology, Apollo Institute of Medical Sciences and Research (AIMSR), Hyderabad. Inpatients and outpatients of all age groups, both males and females, who visited AIMSR between February 2023 and December 2025 for whom the complete blood picture, iron profile, and HbA2 were available, were included in the study. Thalassemia major and other hemoglobinopathies were excluded from the study. Routine screening of medical records identified the participants, and their data were retrieved from the hospital databases. The institutional ethics committee-Apollo Institute of Medical Sciences and Research (AIMSR), Hyderabad (EC/NEW/INST/1527/2025/12/010 dated December 23, 2025) approved the study.

Following enrollment, the following data were collected from hospital databases:

HbA2 estimated by hemoglobin capillary gel electrophoresis; Complete blood picture was done using Mindray 7-part Coulter. The Coulter-derived parameters are:

- RBC parameters, i.e., RBC count, Hemoglobin (Hb), Hematocrit (Hct), red cell distribution width (RDW-CV%), Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). From the MCV and the RBC count, MI was computed.
- WBC parameters: total WBC count, absolute (Absolute neutrophil, lymphocyte, monocyte, eosinophil, and basophil count) and differential cell counts (neutrophil%, lymphocyte%, monocyte%, eosinophil%, basophil%).
- Platelet indices: platelet count, mean platelet volume (MPV), and platelet distribution width (PDW).

Serum iron profile^{1,3,13}: Serum iron, serum ferritin, Total iron binding capacity (TIBC), unsaturated iron binding capacity, and transferrin saturation (%).

Raw continuous variables were summarized as mean $\pm$ standard deviation (SD), while categorical variables were represented as frequencies. Missing data-related information is summarized in

Supplementary information, Table S1. Missing data were statistically recovered using multiple imputation analysis under a missing at random (MAR) assumption in accordance with the STROBE guidelines for missing data. Continuous hematological predictors were imputed using PMM (predictive mean matching) ($m = 1, 40$ iterations). Categorical variables (sex, β -TT status) were excluded from the imputation model. PMM was chosen because it preserves the observed distribution and avoids implausible values. The completed dataset was used for all subsequent analyses.

As the analysis involved a large number of variables, a two-stage modeling approach was adopted to predict HbA2 from blood and demographic variables. The approach consisted of: 1. Least Absolute Shrinkage and Selection Operator (LASSO) based feature-selection followed by: 2. Post-selection ordinary least squares (OLS) regression. This two-stage approach was used for both *Model validation* (5-fold cross-validation) and *Final model development*. In the first stage, salient variables were identified from the large variable set using the LASSO technique. All continuous variables were first scaled to unit variance and zero mean before the LASSO. The LASSO was implemented with a 5-fold inner cross-validation within the training dataset to determine the optimal penalty parameter (λ). As the dataset contains a small number of β -TT cases relative to non- β -TT patients, it creates an inherent class imbalance. This imbalance was addressed by using observation-level weighting within the LASSO framework, assigning higher weights ($w = 5$) to β -TT cases and lower weights ($w = 1$) to non- β -TT cases during model training. This weighted penalized regression model increases the influence of minority observations while preserving the original data distribution. All the variables with nonzero regression coefficients were considered salient variables for the prediction of HbA2. Using the salient predictors determined by the LASSO method, two multiple linear regression models (OLS regression) were devised from the training dataset to predict HbA2, the first model without iron parameters and the second one including iron parameters.

Overall model performance and generalization were assessed using 5-fold cross-validation. The dataset was randomly divided into five approximately equal subsets; in each iteration, four subsets were used for training and one for validation, with each subset serving as the validation set once. For each fold, the partitioning was done, ensuring that β -TT patients were divided in a 70:30 ratio between the training and validation sets, respectively. Within each fold,

the full modeling pipeline outlined above, consisting of LASSO followed by OLS-fit on selected features, was implemented. Predictive performance was evaluated using the root mean squared error (RMSE), computed between observed and predicted values in each validation fold. The overall performance was summarized by reporting the mean RMSE across folds along with its standard deviation. The stability of feature selection was assessed by recording the frequency with which each predictor was selected across the 5-fold cross-validation. This provides an indication of the consistency of variable selection under different data partitions.

Two final models, with and without iron profile parameters, were constructed using the full dataset, with both the 5-fold cross-validation and final model development performed separately for each predictor set. The goodness-of-fit for each model was expressed as adjusted R^2 and AIC (Akaike Information Criterion). The results of the multiple regression models are expressed as regression coefficients, their standard errors,

and 95% confidence intervals (95% CI), t -values, and the p -values for each variable. A $p < 0.05$ was considered statistically significant. The ability of the model-fitted values from models 1 and 2 to correctly classify β -TT (defined as measured HbA2 $> 3.5\%$) was assessed using ROC (receiver operating characteristic) analysis. The area under the curve was estimated, and Youden's index-based optimal cutoff for the model fit value was determined. From the optimal cutoff, sensitivity, specificity, positive predictive value, and negative predictive value were determined. Statistical analysis was done using R software version 4.5.2. Multiple imputation for missing data was done using the mice R package. Weighted LASSO with 5-fold cross-validation was implemented using the glmnet R package with weights passed directly to the penalized regression objective function. ROC analysis was implemented using the pROC package.

RESULTS

The data of 129 participants were included in the study. Of them, 15 patients (11.6%) had

β -TT, based on the HbA2 cutoff of $> 3.5\%$. The demographic and hematological profile of the cohort is summarized in Table 1, and the iron profile results are shown in Table 2. Missing data are summarized in supplementary information, Table S1.

The 5-fold cross-validation was performed separately for predictor sets including and excluding iron profile parameters. The model including iron parameters demonstrated improved predictive performance, with a mean RMSE of 1.03 (SD: 0.14), compared to a higher RMSE of 1.09 (SD: 0.15) for the model without these variables. Fold-wise RMSE values ranged from 0.83 to 1.18 in the iron-inclusive model and from 0.98 to 1.35 in the model excluding iron parameters. The number of predictors selected by the LASSO was more consistent in the model with iron parameters (8–9 variables across folds) than in the model without iron parameters (5–9 variables). Feature selection stability analysis showed that age, RBC count, RDW-CV, and MCHC were consistently selected across all folds in both models, indicating robust associations with the outcome. In the iron-

Table 1: Demographic and hematological characteristics of the Non- β -TT and the β -TT group

S. no	Variable	Non- β -TT (HbA2 $\leq 3.5\%$) Mean (SD)	β -TT (HbA2 $> 3.5\%$) Mean (SD)
1	Age (years)	15.1 (14.8)	27.8 (12.4)
2	WBC count (/ μ L)	9967.2 (4953.0)	8972.2 (2843.2)
3	Neutrophil%	49.2 (20.3)	62.0 (13.1)
4	Lymphocyte%	41.4 (20.2)	28.0 (14.6)
5	Monocyte%	6.4 (2.7)	8.6 (6.1)
6	Eosinophil%	2.8 (3.6)	2.1 (1.4)
7	Basophil%	0.3 (0.6)	0.2 (0.4)
8	Absolute neutrophil count (/ μ L)	4646.2 (4140.7)	5570.0 (2020.8)
9	Absolute lymphocyte count (/ μ L)	3960.7 (3165.4)	2651.8 (2261.5)
10	Absolute monocyte count (/ μ L)	581.7 (359.2)	778.8 (682.5)
11	Absolute eosinophil count (/ μ L)	278.2 (521.2)	148.8 (101.3)
12	Absolute basophil count (/ μ L)	30.5 (59.5)	18.2 (31.6)
13	RBC count (millions/ μ L)	4.5 (0.9)	5.5 (0.9)
14	Hemoglobin (gm/dL)	9.1 (2.6)	10.5 (2.2)
15	Hematocrit (Hct)%	29.9 (7.5)	33.9 (6.1)
16	Mean corpuscular volume (MCV) (fL)	67.5 (13.0)	62.0 (7.3)
17	Mean corpuscular hemoglobin (MCH) (pg)	20.6 (5.5)	19.1 (2.5)
18	Mean corpuscular hemoglobin concentration (MCHC) (gm/dL)	30.1 (2.8)	30.8 (1.4)
19	Red cell distribution width-coefficient of variation (RDW-CV)%	22.0 (7.8)	17.8 (3.5)
20	Mentzer's index (MI) (MCV/RBC count)	15.8 (5.7)	11.7 (3.1)
21	Platelet count ($\times 10^3$ cells/ μ L)	309.3 (155.5)	291.5 (63.2)
22	Mean platelet volume (MPV) (fL)	9.8 (8.0)	10.1 (1.3)
23	Platelet distribution width-coefficient of variation (PDW-CV)%	15.6 (0.6)	15.5 (0.5)
24	Hemoglobin A2 (HbA2)%	1.97 (0.49)	4.73 (0.43)
	Sample size (total = 129)	114 (females = 61)	15 (females = 9)

SD: Standard deviation

Table 2: Iron profile of the non- β -TT and β -TT groups

S. no	Variable	Non- β -TT Mean (SD)	β -TT Mean (SD)
1	Serum ferritin (ng/mL)	133.3 (318.0)	103.0 (178.7)
2	Serum iron (μ g/dL)	22.7 (39.5)	78.0 (85.9)
3	Unsaturated iron binding capacity (μ g/dL)	398.4 (127.9)	291.8 (136.9)
4	Total iron binding capacity (TIBC) (μ g/dL)	421.0 (120.7)	369.8 (51.5)
5	Transferrin saturation%	6.0 (8.7)	24.1 (28.1)

Table 3: Regression model 1 to predict HbA2 from hematological (excluding iron profile) parameters selected by LASSO (AIC = 428.93)

Model no.	Model	Model parameters					R^2
		Variables	Regression Coefficients (SE)	Regression Coefficients 95% CI	t-value	p-value	
1	HbA2 ~ age + RBC count + MCV + MCHC + RDW-CV	Age	0.492 (0.115)	(0.264, 0.720)	4.272	$3.83 \times 10^{-5***}$	0.40 (model 1)
		RBC count	0.291 (0.104)	(0.085, 0.497)	2.801	0.00592**	
		MCV	-0.498 (0.149)	(-0.793, -0.202)	-3.335	0.00113***	
		MCHC	0.241 (0.149)	(-0.054, 0.536)	1.62	0.10782	
		RDW-CV	-0.549 (0.121)	(-0.789, -0.309)	-4.532	$1.37 \times 10^{-5***}$	

SE: Standard error of the regression coefficient; 95% CI: 95% confidence intervals; R^2 : adjusted coefficient of determination; AIC: Akaike information criterion; *** p -value ≤ 0.001 ; ** $0.001 < p$ -value ≤ 0.01 .

Table 4: Regression model 2 to predict HbA2 from hematological (including iron profile) parameters selected by LASSO (AIC = 417.03)

Model no.	Model	Model parameters					R^2
		Variables	Regression Coefficients (SE)	Regression Coefficients 95% CI	t-value	p-value	
2	HbA2 ~ age + RBC count + MCV + MCHC + RDW-CV + serum ferritin + transferrin saturation + TIBC	Age	0.413 (0.124)	(0.170, 0.660)	3.349	0.00108**	0.47 (model 2)
		RBC count	0.179 (0.104)	(-0.030, 0.383)	1.730	0.08626	
		MCV	-0.469 (0.145)	(-0.755, -0.182)	-3.234	0.00158**	
		MCHC	0.225 (0.151)	(-0.073, 0.523)	1.493	0.13796	
		RDW-CV	-0.401 (0.123)	(-0.645, -0.157)	-3.255	0.00147**	
		Serum Ferritin	-0.363 (0.132)	(-0.624, -0.102)	-2.757	0.00675**	
		Transferrin saturation	0.093 (0.097)	(-0.100, 0.285)	0.995	0.34158	
		TIBC	-0.403 (0.126)	(-0.653, -0.153)	-3.192	0.00181**	

SE: Standard error of regression coefficient, 95% CI: 95% confidence intervals, R^2 : adjusted Coefficient of determination, AIC: Akaike information criterion. ** $0.001 < p$ -value ≤ 0.01 .

inclusive model, additional predictors viz., serum ferritin, TIBC, and transferrin saturation, were also consistently selected in all folds, suggesting added predictive value from iron profile variables. In contrast, predictors such as Hct, MCV, and MI exhibited moderate selection frequency, while Hb showed low stability when iron parameters were excluded. Overall, inclusion of iron profile parameters improved model performance and enhanced the stability of predictor selection.

The final weighted regression models were constructed on the full dataset for predictor sets with and without iron profile parameters. In the model excluding iron parameters (model 1), LASSO selected five predictors: age, RBC count, MCV, MCHC, and RDW-CV. In the subsequent weighted OLS analysis (Table 3), age and

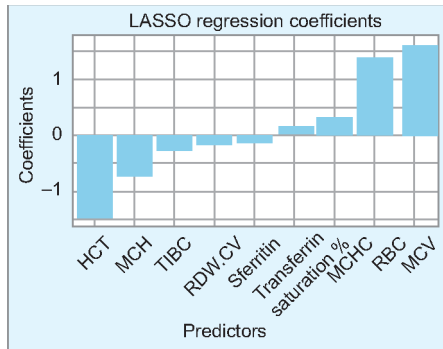
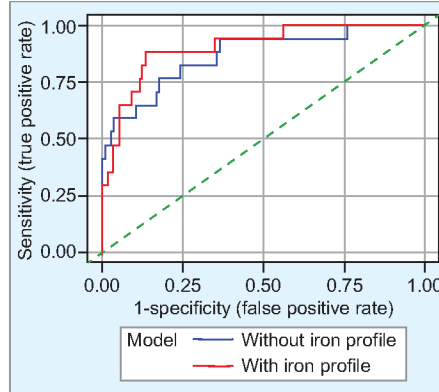
RBC count were positively associated with the outcome (HbA2); MCV and RDW-CV were negatively associated, while MCHC did not have a significant association. This model demonstrated moderate explanatory power (adjusted $R^2 = 0.40$). Similarly, the model including iron parameters (Model 2) had eight predictors selected by LASSO: age, RBC count, MCV, MCHC, RDW-CV, serum ferritin, TIBC, and transferrin saturation. The subsequent OLS regression analysis results are summarized in Table 4. Age was positively associated with HbA2; MCV, RDW-CV, serum ferritin, and TIBC were negatively associated; no significant association was seen for RBC count, MCHC, and transferrin saturation in this model. Overall, the inclusion of iron profile parameters enhanced both predictive performance (adjusted $R^2 = 0.47$) and model

stability, supporting their added value in the final model.

We show the relationship between measured and model-predicted HbA2 for both models in Figure 1. The scatterplots comparing measured and predicted HbA2 illustrate that the model exhibits modest imprecision in normal/non- β -TT individuals, and it's particularly more pronounced with elevated HbA2. The RMSE between measured and model-predicted HbA2 is 1.014 for Model 1 and 0.928 for Model 2. The ROC analysis curves are shown in Figure 2. The optimal cutoff and the other ROC metrics for the model-derived multivariate regression estimator of HbA2 (model fit) are summarized in Table 5. It can be seen that inclusion of iron and hematology parameters reduced the optimal cutoff for the detection of β -TT.

Table 5: ROC analysis metrics for classification of β -TT (HbA2 > 3.5%) using model fit-based estimator of HbA2

Metric	Model 1	Model 2
Optimal cutoff (based on Youden's index)	3.32%	3.26%
Sensitivity	76.5%	88.3%
Specificity	82.1%	86.6%
Positive predictive value	40%	50%
Negative predictive value	96%	98%
ROC AUC (95% CI)	0.868 (0.766–0.969)	0.904 (0.829–0.98)

**Fig. 1:** Scatter plot showing the relationship between measured and model-predicted HbA2 for models 1 (without iron parameters) and 2 (with iron parameters)**Fig. 2:** ROC curves for the final models without and with iron parameters

DISCUSSION

The present study has explored the feasibility of designing a machine learning-based regression model and the relevant variables to predict the HbA2 levels for screening of β -TT using blood-derived indices. In the study cohort, HbA2 was found to be positively associated with age, RBC count, while it was negatively associated with MCV, RDW-CV, serum ferritin, and TIBC.

HbA2, a tetramer of α - and δ -globin chains, is a marker of β -TT. The decrease in β -globin synthesis due to a mutation in one copy of the gene is known to induce compensatory δ -globin overproduction to reduce the toxic effects of α - β imbalance on developing and mature RBC. This accounts for elevated HbA2 in β -TT. Positive association of HbA2 with RBC count reflects compensatory overproduction of RBC, triggered by ineffective erythropoiesis characterized by increased apoptosis of RBC precursors due to the toxic effects of α -globin precipitates.^{5,14} Ineffective hemoglobin synthesis delays the cytoplasmic maturation of RBC precursors, while nuclear maturation continues unabated, leading to a greater number of cell divisions before maturation is completed, resulting in smaller-sized RBCs. This explains the low MCV values (Table 1) and negative relationship between HbA2 and MCV seen in the study. Because MCHC is known to be preserved in β -thalassemia trait,¹⁵ the absence of a significant association with HbA2

in our model is consistent with the underlying pathophysiology. The RDW-CV¹⁶ reflects the variability in red blood cell size (anisocytosis). In β -TT, most red cells are uniformly small and hypochromic because the defect is genetic and affects all cells consistently, reducing the size variability. This explains the negative association between HbA2 and RDW-CV. A negative regression coefficient with TIBC and serum ferritin reflects coexisting anemia in the cohort. Several studies found that β -TT is associated with low MI^{4,6,11,15,17,18} characterized by high RBC and low MCV. Our study found a positive association between HbA2 and RBC counts and a negative association with MCV, although MI was not selected by LASSO to be included in the model. Patients have higher RBC counts with β -TT. Our RDW-CV Results are concordant with other studies, which also found similarly diminished RDW-CV in β -TT. The negative association between HbA2 and TIBC found in our study is consistent with the results of other studies.^{6,19} We did not find any significant association between HbA2 and serum iron and transferrin saturation. Although HbA2 is physiologically stable beyond infancy, the regression model showed a positive association between age and HbA2. This likely reflects a statistical rather than biological relationship. Age may be acting as a proxy for unmeasured factors such as referral patterns, comorbidities, or cohort differences in laboratory testing, rather than exerting a direct effect on HbA2. Such associations

are well-recognized in multivariable models when predictors share correlations or when residual confounding is present. Moreover, the average age of β -TT patients is higher than that of the non- β -TT patients, explaining the positive association with HbA2. Therefore, the observed age coefficient should be interpreted as a modeling and sampling-related artifact rather than a true physiological effect.

Several studies have attempted to devise a binary classification type of machine learning^{10,20–23} to distinguish the β -TT group from the non- β -TT group based on a fixed cutoff value for HbA2. The present study and other studies discussed previously have shown the dependence of HbA2 on various blood indices, which are also sensitive to other conditions, like concurrent iron deficiency. ROC analysis in our study also has found a lower cutoff compared to the conventional HbA2 threshold for β -TT detection. Therefore, the use of a fixed cutoff value renders the models biased and unreliable in the assessment of β -TT. By using regression-based machine learning models, the present study offers a novel and cost-effective adjunct to the determination of HbA2 that does not suffer from the pitfalls of using a fixed cutoff value.

The study has the following limitations. A key limitation of this study was the presence of missing data, which may have influenced the completeness of the analyses and the generalizability of the findings. A few predictors had substantial missingness (3 had ~40%, one had 53.5%), but most had <15% missing data, because certain laboratory tests were not uniformly ordered. Although multiple imputation was used to retain sample size (by estimating missing data) and reduce bias, imputed values cannot fully replace observed measurements, and some residual uncertainty may remain. The average age of the β -TT patients is higher than that of the control group due to the liberal selection criteria and the observational nature of the study. The number of β -TT cases in the dataset was small, resulting in a limited predictor-to-event ratio. This tends to reduce model stability and increase the risk of overfitting. To mitigate this, we used LASSO methods for variable selection and evaluated model performance using 5-fold cross-validation. However, we acknowledge that the small number of β -TT cases remains a key limitation of the study and contributes to the reduced predictive accuracy that was more pronounced in β -TT patients, as shown in Figure 1. Larger β -TT cohorts will enable more precise and accurate model estimates of HbA2. The two-stage LASSO-then-OLS may introduce bias, as the multiple

regression model in the second stage tends to remove the shrinkage applied with the penalization parameter in the first stage (LASSO) for variable selection. However, unpenalized coefficients (from OLS) are more interpretable and hence clinically useful, while fully penalized coefficients are known to over-shrink clinically meaningful effects, reducing interpretability without improving predictive accuracy. LASSO-then-OLS, therefore, represents a pragmatic balance between regularization and interpretability. The study did not explicitly include or model the rich cytomorphological features in the peripheral blood smear relevant to the β -TT that could be extracted by the digital image analysis of the peripheral blood smear. The scatterplots comparing measured and predicted HbA2 illustrate that the model exhibits modest imprecision, with predictions deviating from the identity line, particularly at higher HbA2 values. Clinically, this level of imprecision is less likely to affect interpretation for individuals with clearly normal range values. The model has more pronounced imprecision in the β -TT range. In this range, even small prediction errors could shift a value across the cutoff, potentially leading to misclassification or unnecessary confirmatory testing. Thus, while the model may support preliminary screening or triage, definitive diagnostic decisions should continue to rely on direct HbA2 measurement. Future work with larger datasets and more comprehensive predictors may help reduce uncertainty around threshold-adjacent values.

CONCLUSION

The present study has explored the feasibility of devising a regression-based machine learning model to estimate HbA2 from various blood-derived metrics, including RBC indices and iron profile. Such a model could be developed as a mass-screening/triage tool in the context of India, where the use of a fixed cutoff value for HbA2 is untenable in the background of pervasive IDA. However, the best model was able to explain only 47% of the overall variance, and the predictive performance deteriorated at the clinically critical higher HbA2 values. Nevertheless, the model was able to identify some of the relevant variables needed to develop such a predictive model. Further development of the model, particularly through expansion of the β -TT cohort and training on a larger dataset, will be essential to improve predictive accuracy. Incorporating an expanded feature set, including quantitative digital image analysis of peripheral blood smears, may also enhance model performance. These steps are

necessary before the model can be considered sufficiently robust for clinical deployment.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Asma Niloufer, Senior Consultant, Department of Biochemistry, Apollo Hospitals, Hyderabad, for her support. The authors also thank Dr. N Balakrishna for statistical support in the design of the study.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee, Apollo Institute of Medical Sciences and Research (AIMSR), Hyderabad (approval no. EC/NEW/INST/1527/2025/12/010, dated 23 December 2025).

SOURCE OF FUNDING

None.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

None.

SUPPLEMENTARY MATERIAL

The supplementary Table S1 is available online on the journal website.

Table S1: Missing data in the study variables

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*doi: 10.2147/jaa.s10839

Clinical Profile of Patients Presenting with Scrub Typhus at a Tertiary Care Center in Eastern India: A Cross-sectional Study



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Received: 07 May 2026; Accepted: 15 July 2026

ABSTRACT

Background: Scrub typhus is a reemerging rickettsial infection in India and remains an important cause of acute febrile illness with the potential for severe multi-organ involvement if diagnosis and treatment are delayed. Data from eastern India remain limited.

Objectives: To delineate the clinical and laboratory profile of patients diagnosed with scrub typhus admitted to a tertiary care center in eastern India.

Methods: A retrospective cross-sectional study was conducted at All India Institute of Medical Sciences (AIIMS) Patna, including adult patients (>15 years) with serologically confirmed scrub typhus admitted between January and December 2023. Demographic details, clinical features, laboratory parameters, and complications were retrieved from medical records. Descriptive statistics were used for analysis.

Results: A total of 69 patients were included; 58.0% were male. Fever was the most common presenting symptom (94.2%), followed by headache (66.7%) and myalgia (53.6%). Eschar was identified in 10.1% of patients. Thrombocytopenia was present in 82.6%, hyperbilirubinemia in 65.2%, and acute kidney injury in 20.3%. Meningoencephalitis occurred in 13.0%, while hypotension/shock and acute respiratory distress syndrome (ARDS) were infrequent (4.3 and 1.4%, respectively).

Conclusion: Scrub typhus commonly presents as acute febrile illness with significant hematological and hepatic involvement. Eschar, though specific, was infrequently observed. High clinical suspicion and early recognition are crucial to prevent complications.

Keywords: Biomarker, Clinical profile, Epidemiology, Scrub typhus, Severity.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1700

INTRODUCTION

Scrub typhus is an acute febrile infection caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium transmitted to humans by the bite of larval trombiculid mites. It is endemic in the Asia-Pacific region and represents a significant cause of undifferentiated febrile illness worldwide. The disease is often under-recognized because of its heterogeneous and nonspecific clinical features, limited availability of confirmatory diagnostic tests in many regions, and inadequate clinical suspicion even in endemic areas. Despite the availability of effective antibiotic therapy, including doxycycline and azithromycin, scrub typhus remains a cause of largely preventable illness and death, largely due to underdiagnosis and delayed initiation of treatment. Hence, the true burden of scrub typhus is likely underestimated, particularly in resource-limited settings.

Scrub typhus shows a wide spectrum of clinical presentations, from mild febrile illness with constitutional symptoms to severe disease with multi-organ dysfunction involving the liver, kidneys, lungs, and central nervous system, with severe cases progressing to acute kidney injury,¹ hepatitis,

acute respiratory distress syndrome (ARDS), meningitis or meningoencephalitis, circulatory shock, and hemorrhagic manifestations. Although eschar is considered a pathognomonic feature, its absence does not exclude the diagnosis, particularly in Indian patients.^{2,3}

Clinical presentation typically follows an incubation period of approximately 6–21 days, after which patients develop acute-onset high-grade fever, often associated with headache, nausea, vomiting, cough, myalgia, conjunctival suffusion, and gastrointestinal symptoms. Although an eschar at the mite bite site, along with regional lymphadenopathy and a maculopapular rash, is considered characteristic and diagnostically helpful, these features are inconsistently observed. Several Indian studies have reported low detection rates of eschar, which limits its utility as a reliable diagnostic marker in routine clinical practice.

Scrub typhus is associated with considerable morbidity owing to its propensity to cause systemic inflammation and vascular endothelial injury, leading to multiple complications. Hepatic dysfunction and thrombocytopenia are common laboratory abnormalities. Studies

from tertiary care centers in India have demonstrated that scrub typhus-associated acute kidney injury is a frequent and clinically significant complication, contributing to increased disease severity and poorer outcomes.¹ Mortality rates increase substantially in the presence of severe complications, particularly respiratory and neurological involvement.^{3–5}

Recently, scrub typhus has reemerged in multiple parts of India.^{5–7} However, data from eastern India, especially Bihar, remain sparse. Understanding the regional clinical and laboratory profile is essential to aid early diagnosis and guide management strategies.

In this context, the present study was undertaken at a tertiary care center in eastern India to characterize the clinical features, laboratory profile, and complications of scrub typhus among adult patients. Diagnosis was established using an IgM/IgG rapid test [enzyme-linked immunosorbent assay (ELISA)], which offers relatively higher sensitivity and specificity, with the objective of improving regional understanding of scrub typhus and aiding clinicians in timely recognition and treatment of this potentially fatal yet treatable infection.

METHODS

Study Design and Setting

This was a retrospective cross-sectional study conducted at the Department of General Medicine, AIIMS Patna.

Study Period

Records from 1st January 2023 to 31st December 2023 were reviewed.

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How to cite this article: Prakash J, Kumar A, Prasad J, et al. Clinical Profile of Patients Presenting with Scrub Typhus at a Tertiary Care Center in Eastern India: A Cross-sectional Study. *J Assoc Physicians India* 2026;74(9):26–31.

Study Population

Adult patients (>15 years) admitted with a diagnosis of scrub typhus were included.

Sampling Technique

Nonprobability convenience sampling. Patients admitted to the IPD of AIIMS Patna and meeting the suitable criteria were included.

Inclusion Criteria

- Age >15 years.
- Serologically confirmed scrub typhus (IgM/IgG rapid test positive).

Exclusion Criteria

- Preexisting chronic liver disease, chronic kidney disease, heart failure, or other chronic systemic illnesses.

Data Collection

Clinical data were collected through detailed history, including symptoms, occupational and recreational exposure, travel to endemic areas, prior treatment, and thorough physical examination. Treatment outcomes were documented. Baseline investigations included complete blood count, urine routine, renal and liver function tests, coagulation profile, and blood cultures. Other causes of acute febrile illness were excluded using malaria testing, *Leptospira* IgM, Widal test, and dengue serology. Scrub typhus was confirmed by serum IgM enzyme-linked immunosorbent assay (ELISA). Chest X-ray, ultrasonography, and neuroimaging were performed when indicated. Fine-needle aspiration cytology was done for lymphadenopathy. Standard definitions from published scrub typhus studies were used to diagnose complications.^{8,9}

Sample Size Calculation

Based on the prevalence of scrub typhus reported in recent studies from the local region, the sample size was calculated using a 95% confidence level and a 5% margin of

error. The estimated minimum sample size was 65.44, and therefore a total of 69 patients were included in the study.

Statistical Analysis Plan

Data were entered into Google Forms and exported to spreadsheets.

The collected data were cleaned in Microsoft Excel and coded whenever necessary.

Normal distribution of the continuous data was tested by Q-Q plot.

The data collected were entered and analyzed using Jamovi (v2.3.28 or higher).

Descriptive Statistics

Categorical variables are expressed as proportion, percentile, and frequency and presented with pie charts or bar graphs, as appropriate.

Continuous data are expressed as mean (SD, 95% CI) or median (IQR), depending on normality of distribution.

RESULTS

A total of 69 patients confirmed to have scrub typhus by IgM/IgG serological testing, which was positive in 100% of cases.

Demographic Profile

A total of 69 subjects who fulfilled the inclusion and exclusion criteria were studied. The mean age was 36.7 years, with a standard deviation of 22.4 years, as shown in the histogram in Figure 1.

Among the study population, 40 patients (58.0%) were male and 29 (42.0%) were female, as shown in the bar graph in Figure 2.

Sex	Counts	% of total
Female	29	42.0%
Male	40	58.0%

Farmers formed the largest group (37.68%), emphasizing the link with agricultural and outdoor exposure. This was followed by unemployed individuals (26.09%) and

homemakers (11.59%). Businesspersons and students each accounted for 7.25%, teachers for 4.35%, while drivers, retired persons, and a few others formed a small minority. Overall, scrub typhus mainly affected people with rural or outdoor exposure, consistent with its known epidemiology, as shown in Figure 3.

Clinical Presentation

The most frequent presenting symptom was fever, in 65 patients (94.2%). This was followed by headache in 46 (66.7%), myalgia in 37 (53.6%), and rash in 26 (37.7%) patients, as shown in Table 1. Eschar was identified in seven patients (10.1%), with common sites being the axilla and thigh (Table 2). Lymphadenopathy was observed in 20 patients (29.0%), as shown in Table 3.

On systemic examination, the majority of patients had normal cardiovascular and respiratory findings. Respiratory abnormalities such as crepitations or wheeze were present in eight patients (11.6%). Neurological examination was largely normal, although meningeal signs were noted in a small proportion.

Laboratory Findings

Hematological abnormalities were common. Thrombocytopenia (platelet count $<150 \times 10^3/\mu\text{L}$) was seen in 57 patients (82.6%), while leukopenia ($<4 \times 10^3/\mu\text{L}$) was observed in five patients (7.2%).

Low hemoglobin (<12 gm/dL in females and <13 gm/dL in males) was noted in 79.3 and 95% of females and males, respectively.

Biochemical derangements showed a predominance of hepatic involvement. Hyperbilirubinemia was present in 44 patients (63.8%), with total bilirubin elevation in 76.8% and direct bilirubin elevation in 97.1% of cases. Alanine aminotransferase (ALT) elevation was noted in 55 patients (79.7%), whereas aspartate aminotransferase (AST) elevation was less frequent (8.7%). Raised blood urea levels were observed in 35 patients (50.7%). The biochemical abnormalities have been tabulated in Table 4.

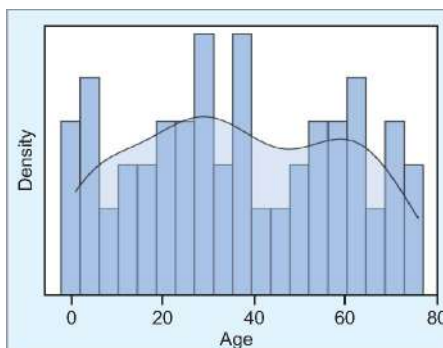


Fig. 1: Histogram showing a bimodal peak at 32 and 63 years of age

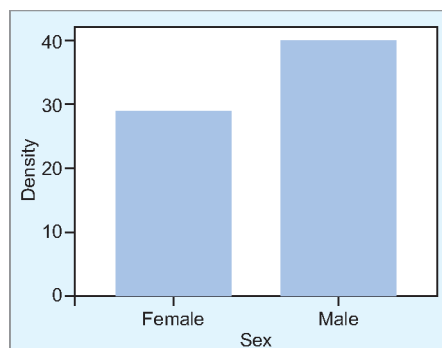


Fig. 2: Bar graph demonstrating the distribution of sex among the study population

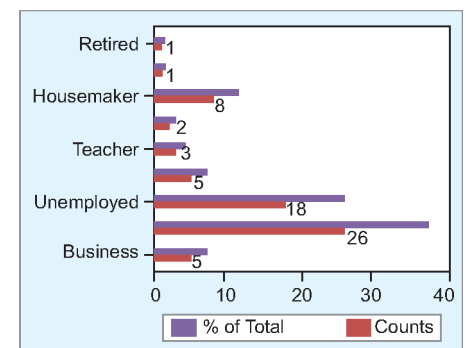


Fig. 3: Bar graph demonstrating the frequency of occupation among the study population

Thrombocytopenia was the most common laboratory abnormality (82.6%), followed by elevated total bilirubin (76.8%) and leukocytosis (49.3%).

Table 1: Frequency of clinical features among our study population

Clinical symptom	Number of patients (n)	Percentage (%)
Fever	65	94.2
Headache	46	66.7
Myalgia	37	53.6
Rash	26	37.7
Lymphadenopathy	20	29.0
Eschar	7	10.1
Meningoencephalitis	9	13.0
Hyperbilirubinemia	44	63.8%
Renal failure (AKI)	14	20.3
Hypotension/shock	3	4.3
ARDS	1	1.4

Table 2: Frequencies of lymphadenopathy

Lymphadenopathy	Counts	% of total
No	49	71.0%
Yes	20	29.0%

Table 3: Demonstrating site of eschar if present

If eschar is present, specify location and size	Counts	% of total
Back	1	14.3%
Right axilla	2	28.6%
Abdomen	1	14.3%
Left axilla	1	14.3%
Left thigh	2	28.6%

Table 4: Lab parameters in patients with scrub typhus (n = 69)

Laboratory parameter	Category	Number of patients (n)	Percentage (%)
White blood cell count	Low	5	7.2
	Normal	30	43.5
	High	34	49.3
Platelet count	Low ($<150 \times 10^3/\mu\text{L}$)	57	82.6
	Normal/high	12	17.4
Blood urea	Elevated	35	50.7
	Normal	34	49.3
Serum creatinine	Normal	40	100.0
Total bilirubin	Elevated	53	76.8
	Normal	16	23.2
Direct bilirubin	Elevated	67	97.1
	Normal	2	2.9
AST (SGOT)	Elevated	6	8.7
	Normal	63	91.3
Hemoglobin (females)	Low	23	79.3
	Normal	6	20.7
Hemoglobin (males)	Low	38	95.0
	Normal	2	5.0

Complications

It was found that 72.5% had an uncomplicated clinical course, presenting predominantly with fever and constitutional symptoms without significant organ dysfunction, owing to timely diagnosis and prompt treatment. A total of 27.5% had complications owing to later presentation or delayed diagnosis, as shown in Table 5. It is to be noted that isolated hepatic involvement was not considered a complication unless accompanied by severe disease manifestations. Hepatic dysfunction alone was excluded from the complication category, as it is a common and often self-limiting manifestation of scrub typhus.

This classification provides a more clinically meaningful assessment of disease severity and aligns with standard definitions used in scrub typhus literature.

The Chi-squared test was applied to assess the association between sex and disease complication status. The analysis showed a statistically significant association, with $\chi^2 = 4.74$, $df = 1$, and $p = 0.030$ ($N = 69$).

Complications were observed more frequently among males compared with females, indicating that male sex was significantly associated with a higher likelihood of complicated disease in the study.

Table 5: Distribution of complicated and uncomplicated scrub typhus among study population

Complicated	Counts	% of total
Uncomplicated	50	72.5%
Complicated	19	27.5%

χ^2 tests			
	Value	df	p
χ^2	4.74	1	0.030
N	69		

While uncomplicated cases were found with similar frequency among both genders, males were observed to have a higher rate of complications than females, which was statistically significant ($p < 0.05$), as shown in the bar graph (Fig. 4).

On multivariable logistic regression analysis evaluating predictors of complicated scrub typhus, as shown in Table 6, serum creatinine was identified as the only independent predictor of complicated disease, with increasing creatinine levels significantly associated with higher odds of complications ($\beta = 1.16$, $SE = 0.41$, $p = 0.005$).

Male sex showed a trend toward increased odds of complicated scrub typhus but was not

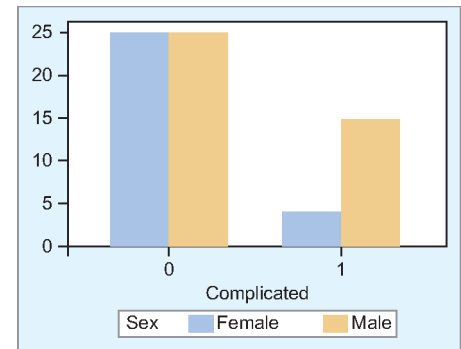


Fig. 4: Bar graph showing the distribution of complicated and uncomplicated cases among different sexes in the study population

Table 6: Logistic regression analysis demonstrating predictors of severity of complicated scrub typhus

Model coefficients—complicated				
Predictor	Estimate	SE	Z	p
Intercept	-3.70501	2.7397	-1.35234	0.176
Age	-0.00403	0.0198	-0.20372	0.839
Creatinine	1.15726	0.4143	2.79360	0.005
Total bilirubin	-0.12947	0.1829	-0.70790	0.479
Hb	-0.14097	0.1869	-0.75411	0.451
Eschar				
Yes-no	1.50639	1.2487	1.20633	0.228
Yes-no	13.16403	2399.5454	0.00549	0.996
Rash				
Yes-no	0.05840	0.8217	0.07107	0.943
Sex				
Male-female	1.78806	0.9430	1.89619	0.058
Platelet count	7.25e-7	5.13e-6	0.14125	0.888
Fever				
Yes-no	1.01839	2.1471	0.47430	0.635
Yes-no	1.47022	2.2841	0.64369	0.520

Note: Estimates represent the log odds of “complicated = 1” vs “complicated = 0”

statistically significant ($\beta = 1.79, p = 0.058$). Age did not show a significant association with complicated scrub typhus ($\beta = -0.004, p = 0.839$). Similarly, total bilirubin ($\beta = -0.13, p = 0.479$) and hemoglobin levels ($\beta = -0.14, p = 0.451$) were not significantly associated with disease complications.

In summary, renal dysfunction is the main marker of severe scrub typhus in our study, with a higher prevalence of complications noted among males. Early detection of rising creatinine and timely treatment are essential to reduce complications and improve outcomes.

DISCUSSION

Scrub typhus, being a reemerging rickettsial disease in India, manifests wide clinical heterogeneity and potential for severe multisystem involvement. The present retrospective cross-sectional study provides valuable regional data and highlights both concordance and variation with previously published Indian and international literature.

In the present study, males constituted 58.0% of cases, indicating a male preponderance. This finding is consistent with observations by Mahajan¹⁰ and Narvencar et al.⁸ in Goa, who reported male predominance (approximately 60%), and Varghese et al.² from South India, where males constituted 62–65% of cases. This male preponderance has been consistently attributed to increased occupational exposure among men engaged in farming and outdoor activities, rather than biological susceptibility.

Similar male dominance has also been documented by Takhar et al.,¹¹ where males formed the majority during a scrub typhus outbreak in Rajasthan.

Occupationally, farmers (37.68%) formed the largest working group in our cohort, supporting the classical epidemiological association of scrub typhus with agricultural activity. Park, in Park's Textbook of Preventive and Social Medicine,¹² emphasizes that scrub typhus predominantly affects individuals involved in farming and outdoor occupations due to exposure to chigger-infested vegetation. Comparable occupational patterns were noted by Pathania et al.,¹³ who reported farming as the most common occupation among scrub typhus patients. Mahajan et al. in the Himalayan region,¹⁴ Narvencar et al.,⁸ and Khan et al. in Northeast India¹⁵ also reported similar findings, where agricultural workers and outdoor workers constituted the majority of affected patients.

Fever was the most common presenting symptom in 94.2% of patients in our study, reinforcing its role as the hallmark feature of scrub typhus. This mirrors findings by Philomena et al.,¹⁶ who reported fever in nearly all patients (>95%), and by Saha et al.,¹⁷ where fever was universally present. Comparable reports were found in studies by Narvencar et al. (100%),⁸ Varghese et al. (96%),² and Mahajan (95–100%).¹⁰

Headache (66.7%) and myalgia (53.6%) were common associated symptoms in our cohort. Peesapati et al.¹⁸ from North Andhra Pradesh reported headache in approximately 60% and myalgia in nearly

half of their patients, closely aligning with our observations. The prevalence was also similar to that reported by Jim et al.¹⁹ from Taiwan and Sirisanthana et al.²⁰ from Thailand, suggesting consistency in early clinical manifestations across regions.

Rash was observed in 37.7% of patients, which is comparable to the rates reported by Pathania et al.¹³ (34–40%) but higher than those noted by Takhar et al.,¹¹ who documented rash in about one-third of cases. Eschar, though pathognomonic, was detected in only 10.1% of our patients. This low prevalence is consistent with Indian studies such as Saha et al.¹⁷ (8–12%) and Takhar et al.,¹¹ who also reported eschar in <15% of cases. Narvencar et al.⁸ reported eschar in 12%, Varghese et al.² in 9.5%, and Stephen et al.²¹ in 7–15% of cases. These findings support the observation that eschar prevalence varies significantly by geography, skin pigmentation, patient awareness, and thoroughness of physical examination. Mahajan¹⁰ emphasized that eschars are often overlooked in Indian patients due to darker skin and hidden sites, leading to low detection rates.

Among the study population, acute kidney injury was documented in 14 patients (20.3%). Meningoencephalitis was observed in nine patients (13.0%). Hypotension/shock occurred in three patients (4.3%), while ARDS was noted in one patient (1.4%). These complications were categorized in accordance with the definitions as per Harrison's Principles of Internal Medicine (21st ed), as shown in Table 7.⁹

Table 7: Glossary of terminologies for scrub typhus (definitions)

Multiple organ dysfunction syndrome (MODS)	Simultaneous dysfunction of ≥ 2 organ systems in an acutely ill patient, necessitating medical intervention to preserve physiological equilibrium
Acute kidney injury (AKI)	Acute renal dysfunction characterized by a rise in creatinine ≥ 1.6 mg/dL or decrease in urine output < 400 mL/24 hours, unresponsive to adequate volume resuscitation
ARDS	Acute hypoxemia defined by bilateral Lung infiltrates on chest imaging not attributable to cardiac causes, with a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 mm Hg
Hepatitis	Acute hepatic involvement indicated by elevation of serum aminotransferases (AST and/or ALT) > 3 times the upper limit of normal and/or serum bilirubin levels more than three times normal values
Pancreatitis	Acute inflammatory condition of the pancreas diagnosed by a threefold or greater elevation of serum amylase or lipase levels, accompanied by characteristic epigastric pain or supportive radiological findings
Meningitis	Inflammation of the meninges presenting with altered mental status and meningeal signs such as neck stiffness or positive Kernig's sign, supported by cerebrospinal fluid abnormalities including elevated protein and/or polymorphonuclear pleocytosis
Disseminated intravascular coagulation (DIC)	A systemic disorder of coagulation manifested by bleeding, thrombocytopenia, and laboratory evidence of coagulation pathway activation, including prolonged PT/INR and aPTT with elevated fibrin degradation products; operationally defined as platelet count $< 80,000/\mu\text{L}$ or a $\geq 50\%$ decline from baseline within 3 days
Myocarditis	Inflammatory myocardial disease characterized by global left ventricular systolic dysfunction on echocardiography, associated electrocardiographic abnormalities, and clinical evidence of cardiac dysfunction in patients without preexisting heart disease
Shock	A state of circulatory failure defined by sustained SBP < 90 mm Hg for at least 1 hour despite adequate fluid resuscitation, resulting in impaired tissue perfusion

Lymphadenopathy was present in 29.0% of cases, comparable to the findings of Philomena et al.¹⁶ (approximately 25–30%). Most patients had normal cardiovascular and respiratory examinations, with only 10.1% showing respiratory signs and 2.9% demonstrating abnormal central nervous system (CNS) findings, reflecting the variable systemic involvement described by Tsay and Chang.²² in severe scrub typhus.

Thrombocytopenia was a prominent laboratory abnormality, present in 82.6% of patients. This high prevalence is similar to that reported by Peesapati et al.¹⁸ (75–85%), Khan et al.¹⁵ (78%), and Rath et al.²³ (80%), highlighting platelet consumption as a consistent feature of scrub typhus. Leukocytosis was observed in 49.3%, while leukopenia occurred in 7.2% of cases. Mahajan et al.¹⁰ described leukocyte count abnormalities as variable, with both leukocytosis and leukopenia reported depending on disease severity.

Hepatic involvement was evident, with 76.8% having elevated total bilirubin and 79.7% showing elevated ALT. Chayakul et al.²⁴ and Rath et al.²³ reported transaminase elevation as one of the earliest and most consistent biochemical abnormalities in scrub typhus, often preceding overt clinical hepatitis. Tsay and Chang²² similarly noted hepatic dysfunction as a major contributor to disease severity. Mahajan et al.¹⁰ (transaminase elevation in 70–85%) and Jim et al.¹⁹ (hepatic involvement in 68%) reported similar findings. Varghese et al.² also reported elevated liver enzymes in $> 75\%$ of hospitalized

patients, confirming hepatic involvement as a consistent feature of scrub typhus.

Acute kidney injury was present in 20.3% of our patients, which aligns with findings from Vikrant et al. (35%),²⁵ Varghese et al.² (13%), and Jayaprakash et al.,¹ who reported AKI in approximately 22–30% of hospitalized scrub typhus patients. Differences in AKI prevalence across studies may be related to disease severity, referral bias, and diagnostic criteria used.

Meningoencephalitis was observed in 13.0% of cases, aligning with the findings of Tsay and Chang²² who reported CNS involvement in 10–20% of severe scrub typhus cases. Indian Council of Medical Research (ICMR) guidelines²⁶ also recognize neurological involvement as a serious but under-recognized complication. Varghese et al.²⁷ reported meningitis/meningoencephalitis in 19.2% and also showed that scrub typhus meningitis can be distinguished from bacterial meningitis using combined clinical and laboratory parameters, supporting our observations.

Shock (4.3%) and ARDS (1.4%) were relatively uncommon in our cohort, which contrasts with higher rates reported by Varghese et al.² (43.5%) and Mahajan et al.¹⁴ (30–40%). These lower rates may reflect early diagnosis and treatment, as emphasized by Varghese et al.,²⁸ who reported significantly higher complication rates in delayed presentations. Chayakul et al.²⁴ highlighted that scrub typhus pneumonitis and ARDS are often missed and contribute substantially to mortality if untreated.

The occupational and clinical patterns observed in our study are aligned with the epidemiological trends reported by Gautam et al. in Nepal²⁹ and Saha et al.¹⁷ in eastern India, reinforcing scrub typhus as a significant cause of acute fever in this region. The ICMR guidelines²⁶ emphasize the need for heightened clinical suspicion, particularly in endemic areas, even in the absence of eschar.

No mortality occurred in our study, contrasting with Indian reports showing 10–30% fatality. Narvencar et al.⁸ noted approximately 8% mortality, while Varghese et al.² and Mahajan et al.¹⁴ reported higher mortality with delayed diagnosis and multi-organ failure. Overall, our results align with existing literature, with variations attributable to population differences, diagnostic delay, and healthcare access.

Strengths

- Provides region-specific data on scrub typhus from eastern India, where published evidence is limited.
- Includes serologically confirmed cases, reducing diagnostic misclassification.
- Comprehensive assessment of clinical features, laboratory abnormalities, and complications.
- Use of standardized definitions for complications allows reliable comparison with other studies.
- Reflects real-world clinical practice in a tertiary care setting.

Limitations

- Retrospective, single-center design limits generalizability and causal inference.

- Reliance on medical records may have resulted in incomplete or missing data.
- Small sample size limits detailed subgroup and statistical analyses.
- Diagnosis based on IgM ELISA alone, without molecular confirmation or strain typing.
- Lack of long-term follow-up data and detailed outcome measures such as duration of hospitalization and seasonal variations.

CONCLUSION

Scrub typhus remains a less-recognized cause of acute febrile illness in India due to its variable presentation and severity. In view of limited regional data from eastern India, this study aimed to define the clinical and laboratory profile of scrub typhus and its complications. This retrospective cross-sectional study included serologically confirmed cases. Clinical features, laboratory parameters, and complications were systematically analyzed.

Fever was the most significant symptom, with frequent hematological and hepatic abnormalities. Eschar was infrequently detected. Significant complications included acute kidney injury and meningoencephalitis, while severe respiratory involvement was uncommon. No mortality was observed, likely reflecting timely diagnosis and appropriate antimicrobial therapy.

Overall, the findings align with international studies and underscore the need to suspect scrub typhus in cases of acute febrile illness, thrombocytopenia, and hepatic dysfunction, especially during the monsoon season. Early recognition and prompt treatment remain crucial in reducing complications and improving outcomes.

RECOMMENDATION

- Scrub typhus should be suspected in acute febrile illness in endemic areas, especially during the monsoon, and promptly evaluated in patients with thrombocytopenia or hepatic dysfunction.
- Early serological testing (IgM ELISA) should be strengthened at secondary and tertiary care levels to enable prompt diagnosis.
- Thorough physical examination, including hidden body sites, should be performed to detect eschar despite its low prevalence.
- Early initiation of appropriate antibiotics (doxycycline or azithromycin) should be emphasized to prevent complications and reduce morbidity.

- Larger multicentric prospective studies are needed to better define regional patterns.

ETHICAL APPROVAL

The ethical approval was obtained from the Institutional Ethics Committee, All India Institute of Medical Sciences, Patna.

AUTHOR CONTRIBUTIONS

Dr Jyoti Prakash (JP): Main idea of the project, research design, protocol making, and supervision.

Dr Anjani Kumar (AK): Data collection and segregation.

Dr Janmeshwar Prasad (JsP): Data collection, literature review, and logistics.

Dr Pratibha Modi (PM): Data analysis, manuscript making, editing, and submission.

ETHICAL COMPLIANCE

Ethical clearance was obtained from the Institutional Ethics Committee of AIIMS Patna. As this was a retrospective record-based study, informed consent was waived.

ACKNOWLEDGMENTS

I would like to extend my heartfelt gratitude to my fellow colleagues, students, and Department of General Medicine for their participation and help in conducting this study.

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Predicting Clinical Outcome in Dengue Fever: A Retrospective Cohort Modeling Study



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Received: 13 March 2026; Accepted: 15 July 2026

[Visual Abstract](#)

ABSTRACT

Background: Dengue fever demonstrates a broad spectrum of clinical severity, ranging from self-limiting illness to life-threatening complications. Early identification of patients at risk of progression remains a clinical challenge, particularly in high-burden settings. Although platelet count and World Health Organization (WHO) dengue classification are routinely used in clinical practice, reliance on individual parameters may not adequately capture the multifactorial nature of disease severity. Development of multivariable predictive models integrating clinical and laboratory markers available at admission may improve early risk stratification and support evidence-based triage decisions.

Methods: This retrospective predictive analysis included 667 consecutively hospitalized patients with laboratory-confirmed dengue infection. This retrospective cohort study was conducted in a tertiary care teaching hospital in Western Maharashtra over a 1.5-year period. Data were extracted from hospital records of patients evaluated during their admission period. An ordinal logistic regression model was developed to predict clinical outcome. Internal validation was performed using bootstrap resampling.

Results: Of 667 patients, 585 (87.7%) had uncomplicated recovery, 69 (10.3%) had complicated recovery, and 13 (1.9%) had adverse outcomes. WHO classification, platelet count, neutrophil-to-lymphocyte ratio (NLR), and warning sign count at admission independently predicted clinical outcome, with an optimism-corrected C-index of 0.820.

Conclusion: Admission WHO classification, platelet count, NLR, and warning signs enable accurate early prediction of dengue severity and may assist in triage and monitoring decisions.

Keywords: Clinical outcome, Dengue fever, Neutrophil-to-lymphocyte ratio, Predictive modeling, Thrombocytopenia.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1712

INTRODUCTION

Dengue fever is one of the most rapidly expanding mosquito-borne viral infections worldwide, with an estimated 100–400 million infections annually, particularly in tropical and subtropical regions.^{1,2} India remains a major endemic region, with recurrent outbreaks contributing substantially to the healthcare burden.³ The disease spectrum ranges from self-limiting febrile illness to severe dengue characterized by plasma leakage, hemorrhage, shock, and organ dysfunction.⁴

Thrombocytopenia is a hallmark feature of dengue infection and arises from bone marrow suppression, immune-mediated platelet destruction, and peripheral consumption.^{5,6} Severe thrombocytopenia has been associated with increased bleeding risk and adverse outcomes.⁷ While platelet count is widely used in disease monitoring, it represents a global measurement and does not provide insight into bone marrow response or recovery potential.

Platelet indices such as immature platelet fraction (IPF) have been explored as

markers of thrombopoietic activity, though their role in predicting clinical severity remains uncertain.^{8,9} Prior studies have demonstrated the predictive value of IPF in various thrombocytopenic conditions.^{10–12}

Markers such as neutrophil-to-lymphocyte ratio (NLR) have also been associated with disease severity in dengue infection.^{13,14} However, most studies have evaluated predictors individually rather than integrating them into validated multivariable prediction models.

Regression modelling strategies enable integration of multiple predictors to generate individualized risk estimates and improve clinical decision-making.¹⁵ The objective of this study was to develop and internally validate a multivariable predictive model for clinical outcome in hospitalized dengue patients.

METHODS

Study Design and Population

This retrospective cohort study was conducted at a tertiary care teaching

hospital in Western Maharashtra over a 1.5-year period. A total of 667 consecutive patients admitted with laboratory-confirmed dengue infection during the study period were included in the analysis. Patients were evaluated during their hospital stay, and clinical and laboratory data—including demographics, World Health Organization (WHO) dengue classification, hematological parameters, biochemical parameters, and clinical outcomes—were extracted from hospital records using a structured data abstraction form. Patients were eligible for inclusion if they were aged ≥ 18 years, had laboratory-confirmed dengue infection according to the hospital diagnostic protocol, and had complete clinical and laboratory data required to predict clinical outcome. These included baseline WHO category, platelet count, NLR, and warning sign count recorded on the first day of admission. Patients were excluded if admission laboratory records were incomplete or if an alternative confirmed diagnosis was established during hospitalization.

Outcome Definitions

Clinical outcomes were categorized into three ordered levels based on in-hospital clinical course and disease severity at discharge.

Uncomplicated recovery ($n = 585$) was defined as hospitalization without development of severe dengue, organ dysfunction, or major complications.

Complicated recovery ($n = 69$) was defined as development of warning signs, organ dysfunction (including acute kidney

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How to cite this article: Singh SK, Kumar S, V SP, et al. Predicting Clinical Outcome in Dengue Fever: A Retrospective Cohort Modeling Study. *J Assoc Physicians India* 2026;74(9):32–36.

injury), requirement of platelet transfusion, or other complications requiring intensified monitoring or therapeutic intervention during hospital stay, but with eventual recovery.

Adverse outcome ($n = 13$) was defined as progression to severe dengue with significant clinical deterioration, including shock, requirement of intensive care support, or in-hospital mortality.

Predictor Variables

Predictors were restricted to day 1 admission values to enable early prognostication. Laboratory parameters were measured using automated hematology analyzers as per hospital laboratory standard operating procedures. All measurements were obtained from admission samples. The predictors are shown in Table 1.

Statistical Analysis

Variable Selection Strategy

Variable selection followed a 5-step strategy prespecified before model fitting. It was based on domain-specific knowledge from published literature, parameter budgeting, unsupervised data reduction using variable clustering and redundancy analysis, prespecification of nonlinearity based on recommendations by Harrell,¹⁵ and internal validation using bootstrap resampling. Parameter budgeting was used as a prespecification strategy that limits model complexity to avoid overfitting. The maximum number of predictor terms (degrees of freedom) was set at $Lm/15J$, where m represents the number of events in the least frequent outcome category. This more conservative threshold, compared with the commonly cited 10 events-per-variable minimum, follows the recommendations of Harrell,¹⁵ to ensure stable coefficient estimates. Variable clustering (varclus) was performed as an unsupervised data reduction technique that groups correlated predictor variables into clusters using hierarchical clustering on Hoeffding's D or Spearman's ρ^2 similarity matrices. This identifies collinear predictors before examining any predictor-outcome associations, thereby preventing data-driven variable selection bias. Redundancy analysis (redun) was subsequently used as a complementary step to identify predictors that can be almost perfectly predicted by other predictors ($R^2 > 0.3$), flagging them for removal to avoid multicollinearity.

Model Specifications

Clinical Outcome

Eighty-two events (complicated and adverse outcomes combined) yielded a parameter budget of 5° of freedom using the more stringent 15 events-per-variable approach

recommended by Harrell.¹⁵ The final ordinal logistic regression model utilized the full 5°-of-freedom budget and included baseline WHO category (2° of freedom), platelet count day 1 (1° of freedom), NLR day 1 (1° of freedom), and warning sign count day 1 (1° of freedom). Under the more conventional 10 events-per-variable criterion, the available parameter budget would have been larger; however, the more conservative threshold was deliberately chosen to minimize overfitting risk and improve model stability. Continuous predictors were prespecified to be assessed for potential nonlinearity using restricted cubic splines with 3 knots placed at the 10th, 50th, and 90th percentiles, following the recommendations of Harrell.¹⁵ Restricted cubic splines were preferred over polynomial transformations because they remain linear in the tails, reduce instability at data extremes, and require fewer additional degrees of freedom. However, nonlinear terms were not incorporated into the final model because the available parameter budget was fully utilized by the clinically selected predictors in linear form. Internal validation using bootstrap resampling demonstrated stable model performance with minimal optimism, and the bootstrap shrinkage slope was 0.978, suggesting adequate control of overfitting.

Details of the model, including the number of events, model parameters, and number of events, are provided in Supplementary Table S1.

Missing Data

The model included WHO baseline classification, day 1 platelet count, NLR, and warning sign count; all predictors and outcome data were complete (0% missing) in the full cohort of 667 patients.

Supplementary Material

Detailed internal validation metrics, discrimination statistics, comparative model performance characteristics (Supplementary Tables S1–S2), and graphical outputs, including calibration plots and variable importance analyses (Supplementary Figures S1–S2), are presented in the online Supplementary Appendix.

RESULTS

Study Population

A total of 667 consecutive hospitalized patients met eligibility criteria during the study period and were included in the final analysis. Among 667 patients, 585 (87.7%) had uncomplicated recovery, 69 (10.3%) had complicated recovery, and 13 (1.9%) had adverse outcomes.

Baseline Characteristics

Baseline characteristics stratified by clinical outcome are presented in Table 2.

Clinical Outcome Prediction Model

In the multivariable ordinal logistic regression model, WHO dengue classification demonstrated the strongest association

Table 1: Predictor variables

Variable	Description
WHO baseline	WHO 2009 dengue classification at admission
PLT D1	Platelet count (lakh/ μ L) at admission
NLR D1	Neutrophil to lymphocyte ratio at admission
Warning signs	Number of WHO-defined warning signs present
IPF D1	IPF (%) at admission
MPV D1	Mean platelet volume (fL) at admission
HCT D1	Hematocrit (%) at admission
TLC D1	Total leucocyte count (/cumm) at admission
Albumin	Serum albumin (gm/dL)
Calcium	Serum calcium (mg/dL)
SGOT D1	Serum glutamic-oxaloacetic transaminase (AST) (IU/L) at admission
Age	Age (years)
BMI	Body mass index (kg/m^2)
DM	Diabetes mellitus (binary variable: present/absent)
HTN	Hypertension (binary variable: present/absent)
AKI	Acute kidney injury (binary variable: present/absent) Acute kidney injury was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria, including an increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours, or ≥ 1.5 times the baseline value within 7 days, or urine output < 0.5 mL/kg/hour for at least 6 hours during hospitalization. For this retrospective analysis, AKI status was ascertained based on documented clinical diagnosis in the hospital case records supported by corresponding laboratory and urine output data meeting KDIGO criteria
PLT transfusion	Platelet transfusion received during hospitalization (binary variable)
Antibiotics	Antibiotics administered during hospitalization (binary variable)

Table 2: Baseline characteristics

Variable	N	Uncomplicated (N = 585)	Complicated-recovered (N = 69)	Adverse (N = 13)
Age (years)*	667	25/31/38	20/29/33	21/21/34
Gender [#]	667			
Male (%) [#]		81% (475/585)	81% (56/69)	92% (12/13)
Body mass index (kg/m ²)*	667	21.50/23.50/25.59	20.93/24.10/27.00	22.40/22.40/24.24
WHO classification at admission [#]	667			
DWOWS		97% (567/585)	35% (24/69)	46% (6/13)
DWWS		2% (9/585)	42% (29/69)	15% (2/13)
Severe dengue		2% (9/585)	23% (16/69)	38% (5/13)
Platelet count day 1 (lakh/ μ L)*	667	0.66/1.18/1.57	0.68/0.90/1.38	0.60/1.30/2.03
NLR day 1*	667	1.28/1.90/3.52	1.93/2.84/4.75	2.30/3.63/3.63
Hematocrit day 1 (%)*	666	39.5/43.7/47.8	38.4/44.2/46.0	36.9/39.5/46.6
TLC day 1 (/cumm)*	667	2700/3480/5010	2500/3900/5590	2800/5070/5070
Diabetes mellitus (%) [#]	667	12% (72/585)	17% (12/69)	0% (0/13)
Hypertension (%) [#]	667	12% (71/585)	19% (13/69)	0% (0/13)
Acute kidney injury (%) [#]	667	3% (18/585)	23% (16/69)	0% (0/13)
Warning signs count [#]	667			
0 warning signs		72% (420/585)	46% (32/69)	38% (5/13)
1 warning sign		24% (143/585)	30% (21/69)	15% (2/13)
2 warning signs		4% (22/585)	9% (6/69)	46% (6/13)
3 warning signs		0% (0/585)	7% (5/69)	0% (0/13)
4 warning signs		0% (0/585)	7% (5/69)	0% (0/13)

*Values are expressed as median/interquartile range; [#]Values are expressed as number (%) of patients; DWOWS, dengue without warning signs; DWWS, dengue with warning signs; IPF, immature platelet fraction; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; TLC, total leukocyte count

Table 3: Adjusted odds ratios for worse clinical outcome

Variable	Upper value vs lower value	Adjusted odds ratio	95% confidence interval
Platelet count day 1 (lakh/ μ L)	1.57 vs 0.66	0.88	0.64–1.19
Neutrophil to lymphocyte ratio day 1 (ratio)	3.54 vs 1.32	1.07	1.01–1.13
Warning signs count	1 vs 0	1.48	1.07–2.05
WHO classification	DWWS vs DWOWS	27.79	12.96–59.62
WHO classification	Severe vs DWOWS	31.09	13.82–69.96

Continuous predictors (platelet count and NLR) are expressed as interquartile range (75th vs 25th percentile) contrasts. Reference category for WHO classification: dengue without warning signs (DWOWS). Odds ratios >1 indicate increased odds of worse clinical outcome

with worse clinical outcome. Compared with dengue without warning signs, patients presenting with dengue with warning signs had an adjusted odds ratio of 27.79 (95% CI 12.96–59.62), while those with severe dengue had an adjusted odds ratio of 31.09 (95% CI 13.82–69.96). Higher NLR was associated with increased odds of worse outcome (OR 1.07; 95% CI 1.01–1.13), and each additional warning sign increased the odds of progression (OR 1.48; 95% CI 1.07–2.05). Although lower platelet count showed a directional association with worse outcome (OR 0.88; 95% CI 0.64–1.19), the confidence interval included unity. Odds ratio estimates are depicted in [Table 3](#). Partial effects of predictors on log odds of worse outcome are depicted in [Figure 1](#). The nomogram for predicting clinical course is depicted in [Figure 2](#). The optimism-corrected C-index was 0.820. Detailed discrimination indices,

calibration plot, and variable importance plot are given in Supplementary Table S2, Figure S1, and Figure S2.

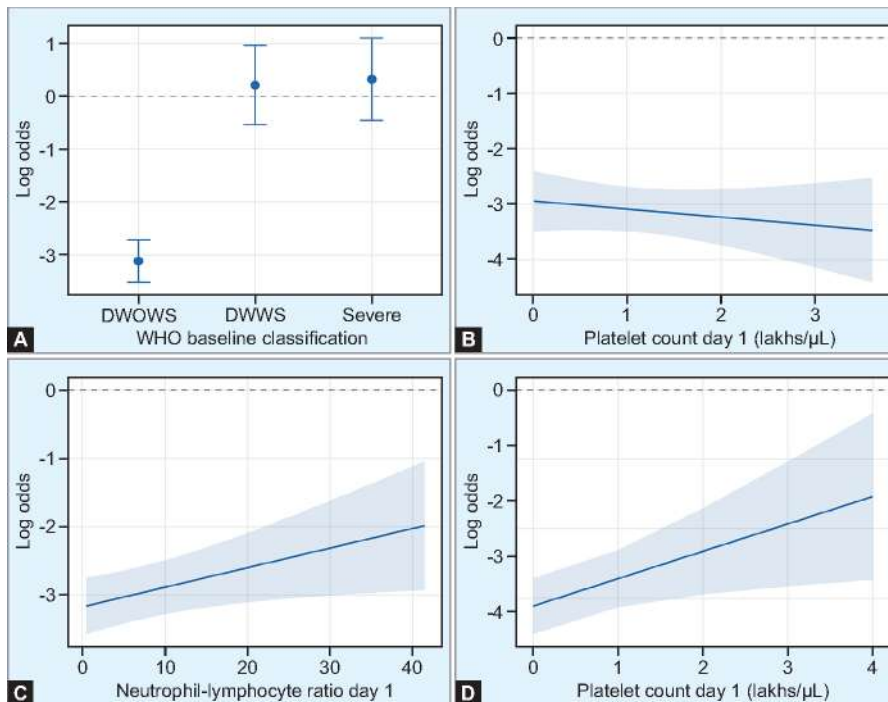
The nomogram provides an individualized estimate of the probability of developing a complicated or adverse clinical outcome based on admission variables. To use the nomogram, each predictor—WHO classification at admission, platelet count (day 1), NLR (day 1), and warning signs count—is located on its respective axis, and a vertical line is drawn upward to the “Points” scale to determine the corresponding score for that variable. The points assigned for each predictor are then summed to obtain the “Total Points.” This total is projected downward onto the “Linear Predictor” scale and subsequently onto the probability scale labeled “P (Complicated or Adverse)” to estimate the patient’s risk of worse clinical outcome. Higher total points correspond to a higher predicted

probability of developing complicated or adverse dengue. The nomogram therefore translates the multivariable ordinal logistic regression model into a clinically usable bedside tool for early risk stratification at the time of admission.

Detailed internal validation metrics and calibration statistics are provided in Supplementary Table S1, Supplementary Table S2, and Supplementary Figure S1.

DISCUSSION

This study developed and internally validated a multivariable prognostic model to predict clinical outcome in hospitalized adults with dengue using routinely available admission clinical and laboratory parameters. The magnitude of association was strongest for baseline WHO classification, followed by warning signs and inflammatory markers.



Figs 1A to 1D: Partial effects of predictors on log odds of worse outcome: (A) WHO baseline; (B) PLT D1; (C) NLR D1; (D) Warning signs count

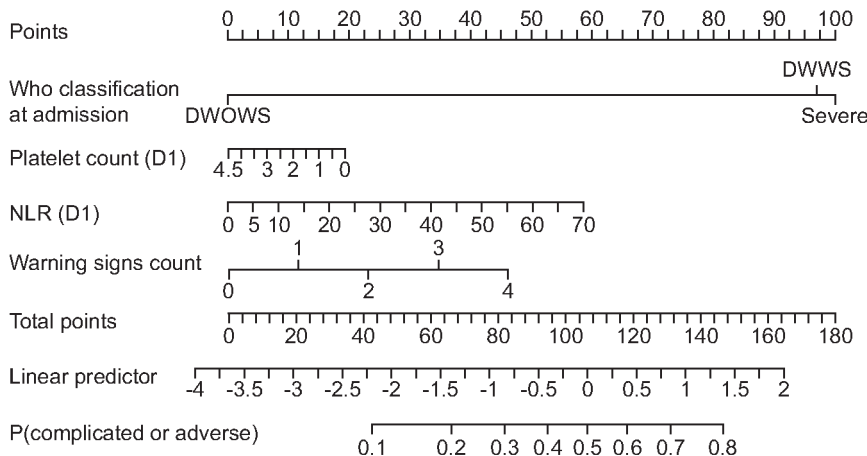


Fig. 2: Nomogram for predicting clinical outcome

These findings indicate that variables available at first presentation can be systematically integrated into an evidence-based framework to generate individualized risk estimates. Rather than relying on isolated laboratory thresholds, combining structured clinical classification with inflammatory and hematological markers offers a more comprehensive assessment of early disease trajectory.

Dengue infection is characterized by complex and dynamic hematological and inflammatory changes driven by viral replication, immune activation, cytokine release, and endothelial dysfunction.^{1–3} Thrombocytopenia remains a central laboratory feature and reflects contributions

from bone marrow suppression, immune-mediated platelet destruction, and peripheral consumption secondary to endothelial activation and systemic inflammation.^{4,5} Severe thrombocytopenia has consistently been associated with increased risk of bleeding, plasma leakage, organ dysfunction, and mortality.^{6–8} In the present multivariable analysis, the adjusted odds ratio for admission platelet count crossed unity, indicating that platelet count did not function as an independent prognostic factor after adjustment for WHO classification. This attenuation is biologically plausible because WHO classification partially captures information related to thrombocytopenia severity and evolving

clinical instability, thereby reducing the apparent independent contribution of platelet count in the multivariable model. Platelet count nevertheless retains clinical relevance as a continuous quantitative marker of disease severity and may provide incremental prognostic information when interpreted alongside structured clinical classification and inflammatory markers rather than as an isolated predictor. Its clinical utility may therefore lie more in quantifying thrombocytopenia severity within WHO categories than functioning as a stand-alone prognostic marker.

WHO dengue classification emerged as the dominant predictor of outcome, with a marked gradient in risk across severity categories. The WHO framework incorporates warning signs and evidence of plasma leakage, which reflect the underlying pathophysiology of increased vascular permeability and endothelial injury.^{4,16} Plasma leakage results from immune-mediated endothelial activation and disruption of endothelial junction integrity,¹⁷ processes central to progression from uncomplicated dengue to severe disease. The strong association between baseline WHO category and adverse outcomes in this model provides quantitative validation of its clinical utility and supports its continued application as a triage tool in hospital settings.

The very high adjusted odds ratio (aOR) for WHO classification (aOR >27) reflects near-complete separation between dengue without warning signs (DWOWS) and complicated outcomes, with 97% of uncomplicated cases classified as DWOWS at admission. This produces unstable maximum likelihood estimates with wide confidence intervals. Furthermore, a degree of definitional circularity exists: WHO classification incorporates warning signs and severity markers that overlap with the criteria defining the clinical course outcome. While the temporal separation—day 1 classification predicting subsequent course—partially mitigates this concern, the strength of the association is likely inflated by this incorporation bias and should be interpreted with caution.

The independent association between elevated NLR and worse clinical outcomes aligns with growing evidence that systemic inflammatory activation plays a critical role in dengue pathogenesis.^{13,14} NLR reflects the balance between innate immune activation and adaptive immune response, and elevated values may indicate heightened inflammatory stress and endothelial injury. Importantly, unlike specialized laboratory markers such as IPF, which require advanced hematology analyzers with optical fluorescence capability, NLR is

derived from the routine complete blood count, making it inexpensive, rapidly obtainable, and universally available even in resource-limited settings where dengue burden is highest. In the present model, inflammatory burden at admission contributed prognostic information beyond structured clinical classification, suggesting that NLR captures a dimension of dengue pathophysiology not fully reflected by platelet count or WHO classification alone. Its integration into prognostic assessment may therefore enhance early identification of patients at higher risk of deterioration while remaining practical for widespread bedside implementation and resource-constrained triage settings.

Notably, 38% of patients in our cohort presented with zero WHO warning signs at admission. That a subset of patients who subsequently developed complications lacked classical warning signs at presentation underscores a critical limitation of the current WHO triage framework: it may provide false reassurance in patients who appear uncomplicated at admission but are destined to deteriorate. This finding reinforces the value of laboratory-based predictors (platelet count, NLR) that may identify at-risk patients independently of clinical warning signs. The ordinal model's incorporation of both clinical (WHO classification, warning sign count) and laboratory (platelet count, NLR) predictors addresses this gap by enabling risk stratification even in the absence of overt warning signs. Clinically, this argues for maintaining vigilant monitoring of all dengue patients during the critical phase (days 3–5), regardless of warning sign status at presentation.

The model demonstrated good discrimination after bootstrap internal validation, suggesting stability and limited optimism in predictive performance. Importantly, the modeling strategy was prespecified, parameter budgeting was respected, and internal validation was undertaken using resampling techniques, which reduces the risk of overfitting. Multivariable modeling allows estimation of cumulative risk rather than reliance on binary thresholds, thereby enabling a more nuanced and clinically applicable assessment of severity at admission. In outbreak situations or high-burden settings, structured risk estimation may assist clinicians in prioritizing monitoring intensity, anticipating potential deterioration, and allocating high-dependency resources more efficiently.

Several limitations warrant consideration. The retrospective single-center design may limit generalizability, as practice patterns, admission thresholds, and case mix may differ across institutions and regions. Inclusion

of only hospitalized adult patients restricts extrapolation to outpatient, pediatric, or nonendemic populations. Although internal validation was performed using bootstrap resampling, external validation in independent cohorts is essential before routine clinical implementation. Additionally, residual confounding cannot be excluded, and unmeasured variables may have influenced risk estimates. Nevertheless, the large consecutive cohort and complete outcome ascertainment strengthen the internal validity of the findings.

Taken together, these results provide internally validated evidence that admission clinical classification and inflammatory markers, interpreted alongside platelet count, can be operationalized into a structured prognostic model for dengue severity, supporting more consistent and evidence-informed risk stratification in hospitalized patients.

CONCLUSION

A multivariable prognostic model incorporating WHO dengue classification, platelet count, NLR, and warning signs enables early prediction of disease severity in hospitalized adults with dengue. Integration of routinely available admission parameters into a validated risk framework may support structured triage decisions, guide monitoring intensity, and improve allocation of healthcare resources during dengue outbreaks. While internal validation demonstrates stable predictive performance, external validation across diverse healthcare settings and populations is required before widespread clinical adoption. Future prospective studies should evaluate the clinical impact of model-guided risk stratification on patient outcomes and healthcare resource utilization.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee of the participating tertiary care hospital. Given the retrospective design and use of anonymized hospital records, the requirement for informed consent was waived.

DATA AVAILABILITY

De-identified data underlying the findings are available from the corresponding author upon reasonable request, subject to institutional regulations.

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Study of Depression, Anxiety, Somatic Symptoms, and Quality of Life in Patients with Chronic Kidney Disease on Maintenance Hemodialysis in a Tertiary Hospital in Chennai



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Received: 06 October 2025; Accepted: 27 July 2026

[Visual Abstract](#)

ABSTRACT

Background: Chronic kidney disease (CKD) is associated with substantial psychological morbidity, particularly among patients receiving maintenance hemodialysis (MHD). Depression, anxiety, and somatic symptoms adversely affect health-related quality of life (HRQoL), yet these factors remain under-recognized in routine clinical practice.

Objectives: To assess the prevalence and severity of depression, anxiety, and somatic symptoms and to evaluate their association with quality of life among patients with CKD undergoing maintenance hemodialysis.

Materials and methods: This hospital-based cross-sectional observational study included 50 adult patients with CKD receiving maintenance hemodialysis at a tertiary care hospital in Chennai. Participants were assessed using the Hospital Anxiety and Depression scale (HADS), Somatic Symptom scale-8 (SSS-8), and World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire. Data were analyzed using R software. Categorical variables were compared using the Chi-square test, and a p -value < 0.05 was considered statistically significant.

Results: Psychological distress and somatic symptom burden were common among patients undergoing maintenance hemodialysis. Female participants demonstrated a higher prevalence of abnormal depression scores, whereas abnormal anxiety scores were more frequent among males; however, these differences were not statistically significant (anxiety: $p = 0.053$; depression: $p = 0.170$). No significant associations were observed between age, CKD stage, or overall quality-of-life quartiles and HADS anxiety or depression scores ($p > 0.05$). A highly significant association was observed between SSS-8 quartiles and somatic symptom severity ($p < 0.0001$), indicating that higher somatic symptom scores were associated with greater symptom burden.

Conclusion: Depression, anxiety, and somatic symptoms are common among patients with CKD receiving maintenance hemodialysis. Although most demographic and clinical variables were not significantly associated with psychological distress, greater somatic symptom burden was strongly associated with higher SSS-8 scores. Routine psychological assessment using validated screening tools may facilitate early identification and comprehensive management of psychological morbidity in patients undergoing maintenance hemodialysis.

Keywords: Anxiety, Chronic kidney disease, Depression, Hospital Anxiety and Depression Scale, Maintenance hemodialysis, Quality of life, Somatic Symptom Scale-8, Somatic symptoms.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1691

INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition characterized by the gradual decline of kidney function, leading to impaired filtration of waste and fluid, systemic complications, and significant health burdens.¹ It is a growing global health concern due to its association with cardiovascular disease and the eventual need for renal replacement therapies like dialysis or transplantation. CKD is diagnosed when kidney damage or decreased function persists for more than 3 months and is staged based on glomerular filtration rate (GFR). Common causes include diabetes, hypertension, genetic disorders, infections, and autoimmune diseases. As the disease advances, remaining nephrons compensate

for lost function, which accelerates kidney damage and results in symptoms like nausea, swelling, and fatigue. Early CKD often lacks symptoms, making diagnosis difficult without targeted testing.²

Management aims to slow progression and treat complications through lifestyle changes, dietary modifications, and medications such as ACE inhibitors.³ When kidney failure progresses to end-stage renal disease (ESRD), maintenance hemodialysis (MHD) becomes essential. MHD helps maintain electrolyte balance, removes toxins, and prevents life-threatening complications. Although not curative, it significantly improves patients' quality of life (QoL) and prolongs survival. MHD also plays a vital role in bridging patients awaiting kidney transplants.⁴

However, CKD patients on MHD frequently suffer from psychological disorders such as depression and anxiety, as well as somatic symptoms such as fatigue and muscle pain, which greatly reduce their QoL.⁵ These issues are linked to the chronic nature of the illness, treatment burden, and social and financial stress. Psychological distress affects adherence to treatment and worsens outcomes. Depression and anxiety may also accelerate disease progression through physiological mechanisms like inflammation.⁶

Effective management requires integrating mental health services with renal care. Interventions such as cognitive behavioral therapy, medications, and peer support can improve emotional well-being and compliance.⁷ This study aims to assess levels of depression, anxiety, somatic symptoms, and QoL in CKD patients on MHD using HADS, SSS-8, and WHOQOL-BREF tools, emphasizing the need for holistic and personalized care approaches.

MATERIALS AND METHODS

This hospital-based, cross-sectional observational study was conducted in the Department of General Medicine and Nephrology at Sree Balaji Medical College and Hospital, Chennai, after obtaining approval from the Institutional Ethics Committee. Adult patients (≥ 18 years) with CKD undergoing maintenance hemodialysis for at least 3 months were eligible for inclusion. Patients were recruited using purposive sampling after obtaining written informed consent.

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How to cite this article: Subramaniam SK, Rao VR. Study of Depression, Anxiety, Somatic Symptoms, and Quality of Life in Patients with Chronic Kidney Disease on Maintenance Hemodialysis in a Tertiary Hospital in Chennai. *J Assoc Physicians India* 2026;74(9):38–42.

Individuals with preexisting psychiatric illness, cognitive impairment, or acute medical complications were excluded.

Sample Size Estimation

The sample size was determined in consultation with a biostatistician based on the primary objective of evaluating the correlation between psychological distress and quality of life. Assuming an anticipated correlation coefficient (r) of 0.35, a two-sided α error of 0.05, and a study power of 80%, the minimum required sample size was calculated to be 50 participants. Accordingly, 50 eligible patients fulfilling the inclusion criteria were enrolled in the study.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using R software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as mean $\pm$ standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Associations between categorical variables were assessed using the Chi-square test. A two-tailed p -value < 0.05 was considered statistically significant.

RESULTS

A total of 50 patients with chronic kidney disease undergoing maintenance hemodialysis were included in the study. The demographic and clinical characteristics of the study population are summarized in Tables 1 and 2. Abnormal anxiety scores were highest among participants aged 18–29 years and ≥ 60 years (75% each), whereas abnormal depression scores were most frequent in the 45–59-year age group (55%). However, there was no statistically significant association between age group and anxiety ($p = 0.433$) or depression ($p = 0.249$). Male participants demonstrated a higher proportion of abnormal anxiety scores than females (72.73% vs 50.00%), whereas abnormal depression scores were more frequent among females (53.57% vs 31.82%). These differences were not statistically significant for anxiety ($p = 0.053$) or depression ($p = 0.170$). Participants in the second WHOQOL quartile exhibited the highest proportion of abnormal anxiety scores, whereas abnormal depression scores were most frequent in the third quartile. No statistically significant association was observed between overall WHOQOL quartiles and HADS anxiety ($p = 0.2450$) or HADS depression ($p = 0.1982$). Among patients with CKD stage 4, very high somatic symptom severity was observed more frequently than in other CKD stages. However, the association

between CKD stage and somatic symptom severity was not statistically significant ($p = 0.2958$). Participants in the second quartile of HADS anxiety scores demonstrated the highest frequency of very high somatic symptom severity. However, no statistically significant association was observed between HADS anxiety quartiles and somatic symptom severity ($p = 0.2321$). A statistically significant association was observed between SSS-8 quartiles and somatic symptom severity ($p < 0.0001$). Participants in the third and fourth SSS-8 quartiles exclusively demonstrated very high somatic symptom severity, whereas those in the first quartile predominantly exhibited low to medium symptom severity. Very high somatic symptom severity was most frequently observed among participants in the lowest WHOQOL quartile. However, the distribution of somatic symptom severity did not differ significantly across WHOQOL quartiles ($p = 0.8168$).

Table 1 summarizes sociodemographic data. The mean age was 45.6 years (SD 15.23), and the mean BMI was 25.59 kg/m² (SD 4.97). Most participants were female (56%) and resided in rural areas (52%). A majority were unemployed (36%), with varied educational

levels and marital statuses, notably 30% separated.

Table 2 shows that 44% of participants had abnormal anxiety levels, while 16% were borderline and 40% normal. For depression, 60% had abnormal scores, 14% were borderline, and only 26% were normal. This indicates a high prevalence of psychological distress among the study population.

Abnormal anxiety was highest among participants aged 18–29 years and ≥ 60 years (75% each), whereas abnormal depression was most frequent in the 45–59-year age group (55%). However, Chi-square analysis showed no statistically significant association between age group and anxiety ($p = 0.433$) or depression ($p = 0.249$) (Table 3).

Male participants had a higher proportion of abnormal anxiety scores than females (72.73% vs 50.00%), whereas abnormal depression scores were more common among females (53.57% vs 31.82%). However, these differences were not statistically significant for anxiety (Chi-square test, $p = 0.053$) or depression (Chi-square test, $p = 0.170$) (Table 4).

HADS score distribution by eGFR category is presented in Table 5.

Table 1: Sociodemographic summary

Variable	Mean	Standard deviation (SD)	
Age (years)	45.6	15.23	
BMI (kg/m²)	25.59	4.97	
Categorical variables			
Variable	Category	Count (n)	Percent (%)
Sex	Female (F)	28	56
	Male (M)	22	44
Residency	Rural	26	52
	Urban	24	48
Marital status	Married	11	22
	Separated	15	30
	Single	11	22
	Widowed	13	26
Education level	College	8	16
	Elementary	14	28
	Graduate	12	24
	High school	8	16
	None	8	16
Occupation	Employed	16	32
	Retired	16	32
	Unemployed	18	36

Table 2: HADS category distribution

Category	Anxiety (n)	Anxiety (%)	Depression (n)	Depression (%)
Normal	20	40	13	26
Borderline abnormal	8	16	7	14
Abnormal	22	44	30	60

Table 3: HADS categories by age group

Age group (years)	Anxiety abnormal (%)	Anxiety borderline (%)	Anxiety normal (%)	Depression abnormal (%)	Depression borderline (%)	Depression normal (%)
18–29	75.0	25.0	0.0	50.0	0.0	50.0
30–44	57.14	7.14	35.71	21.43	35.71	42.86
45–59	50.0	15.0	35.0	55.0	10.0	35.0
60+	75.0	12.5	12.5	50.0	12.5	37.5

Table 4: HADS categories by sex

Sex	Anxiety abnormal (%)	Anxiety borderline (%)	Anxiety normal (%)	Depression abnormal (%)	Depression borderline (%)	Depression normal (%)
Female	50.0	10.71	39.29	53.57	17.86	28.57
Male	72.73	18.18	9.09	31.82	13.64	54.55

Table 5: HADS by eGFR category

eGFR Category (mL/min/1.73 m ²)	Anxiety Abnormal (n)	Anxiety Borderline (n)	Anxiety Normal (n)	Depression Abnormal (n)	Depression Borderline (n)	Depression Normal (n)
<15	13	2	5	10	3	7
15–30	17	5	8	12	5	13
Chi-square <i>p</i> -value	Anxiety <i>p</i> = 0.7662		Depression <i>p</i> = 0.7781			

Table 6: HADS by overall WHOQOL score

Overall WHOQOL score (quartile)	Anxiety abnormal (n)	Anxiety borderline (n)	Anxiety normal (n)	Depression abnormal (n)	Depression borderline (n)	Depression normal (n)
Q1 (Lowest QoL)	8	4	2	6	1	7
Q2	9	0	2	3	4	4
Q3	5	2	5	8	0	4
Q4 (Highest QoL)	8	1	4	5	3	5

Table 7: Somatic symptom severity vs CKD stage

CKD stage	High (n)	Low (n)	Medium (n)	Minimal (n)	Very high (n)
Stage 3	2	4	1	0	6
Stage 4	3	1	2	0	10
Stage 5	2	3	6	2	8

Table 8: Somatic symptom severity vs HADS anxiety score

HADS Anxiety Score (Q)	High (n)	Low (n)	Medium (n)	Minimal (n)	Very high (n)
Q1	2	4	1	1	5
Q2	1	0	2	0	10
Q3	2	3	2	0	7
Q4	2	1	4	1	2

Participants in the second WHOQOL quartile had the highest frequency of abnormal anxiety (9/11), whereas abnormal depression was most frequent in the third quartile (8/12). However, no statistically significant association was observed between overall WHOQOL quartiles and HADS anxiety ($p = 0.2450$) or HADS depression ($p = 0.1982$) (Table 6).

Patients with CKD stage 4 demonstrated the highest frequency of very high somatic symptom severity (10 cases), whereas

stage 5 patients showed a broader distribution across medium and minimal severity categories. However, there was no statistically significant association between CKD stage and somatic symptom severity (Chi-square test, $p = 0.2958$) (Table 7).

Participants in the second quartile of HADS anxiety scores demonstrated the highest frequency of very high somatic symptom severity (10 cases). However, no statistically significant association was

observed between HADS anxiety quartiles and somatic symptom severity (Chi-square test, $p = 0.2321$) (Table 8).

Participants in the third and fourth quartiles of SSS-8 scores exclusively demonstrated very high somatic symptom severity, whereas those in the first quartile predominantly had low to medium symptom severity. A highly significant association was observed between SSS-8 quartiles and somatic symptom severity (Chi-square test, $p < 0.0001$) (Table 9).

Table 9: Somatic symptom severity vs SSS-8 score

SSS-8 Score (Q)	High (n)	Low (n)	Medium (n)	Minimal (n)	Very high (n)
Q1	0	8	4	2	0
Q2	7	0	5	0	0
Q3	0	0	0	0	14
Q4	0	0	0	0	10

Table 10: Somatic symptom severity vs overall WHOQOL score

Overall WHOQOL (Q)	High (n)	Low (n)	Medium (n)	Minimal (n)	Very high (n)
Q1	4	0	1	2	7
Q2	1	2	2	0	6
Q3	0	3	3	0	6
Q4	2	3	3	0	5

Very high somatic symptom severity was most frequently observed among participants in the lowest WHOQOL quartile. However, the distribution of somatic symptom severity did not differ significantly across WHOQOL quartiles (Chi-square test, $p = 0.8168$) (Table 10).

DISCUSSION

Chronic kidney disease (CKD), affecting 10–15% of adults globally, is increasingly prevalent due to rising diabetes and hypertension rates.⁸ While early CKD stages focus on slowing disease progression, stage 5—end-stage renal disease (ESRD)—requires renal replacement therapies such as dialysis or transplantation. ESRD places enormous burdens on healthcare systems and imposes substantial physical and psychological stress on patients. These individuals must adhere to strict medical routines, diet restrictions, and face the mental toll of dependency, lifestyle change, and fear of death. These challenges contribute significantly to the high prevalence of psychiatric comorbidities like depression, anxiety, somatic symptoms, and reduced quality of life (QoL) in this group.⁹

Our study aimed to evaluate these psychological factors in CKD patients undergoing maintenance hemodialysis. The population was predominantly middle-aged, female, rural, unemployed, and borderline overweight—demographics that align with previous studies by Mousa et al. and Lekskulchai et al., who noted similar risk profiles and CKD prevalence patterns. In our study, 60% of patients had abnormal depression and 44% abnormal anxiety scores, with no significant associations with age, sex, height, weight, or BMI, consistent with studies by Chilcot et al. and Qawaqzeh et al.^{10–13}

Depression and anxiety were common across all demographic and clinical subgroups, irrespective of BMI, marital status, education,

occupation, CKD stage, dialysis duration, or lifestyle factors. Bahall et al. and Dziubek et al. similarly found that psychological distress in CKD patients was mostly independent of demographic predictors. Comorbidities like diabetes and hypertension were significantly associated with depression ($p = 0.0174$), as was smoking ($p = 0.0044$), confirming prior findings by Khan et al. and Chiou et al.^{14–17}

Somatic symptoms were widespread, especially among older adults and those with high urinary albumin-to-creatinine ratios (UACR >300 mg/g, $p = 0.0001$), reinforcing UACR's role as a biomarker of symptom burden. Though QoL scores varied, somatic symptom intensity remained high, especially in widowed, unemployed, and long-term dialysis patients. This matches prior research by Senanayake et al. and Shedden-Mora et al., highlighting the complex and multifactorial nature of symptom experience in CKD.^{18,19}

Finally, while quality of life and HADS scores did not predict somatic symptom severity, SSS-8 scores did ($p < 0.0001$), affirming the tool's validity. This suggests that in CKD, psychological distress, physical symptoms, and subjective quality of life are interrelated yet distinct domains, requiring integrated, patient-centered care strategies.

LIMITATIONS

This study has several limitations. First, the cross-sectional design precludes establishing temporal or causal relationships between depression, anxiety, somatic symptoms, and quality of life among patients with chronic kidney disease undergoing maintenance hemodialysis. Second, the study was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings to other populations. Third, purposive sampling may have introduced selection bias. Fourth, psychological assessment was based on

validated self-administered questionnaires, which are subject to reporting and response bias. In addition, several potential confounding factors, including socioeconomic status, dialysis adequacy (Kt/V), inflammatory markers, nutritional status, medication adherence, and social support, were not evaluated. Future multicenter studies with larger sample sizes and longitudinal follow-up are required to better understand the temporal relationship between psychological distress, somatic symptoms, and quality of life in patients receiving maintenance hemodialysis.

CONCLUSION

This study concludes that depression, anxiety, and somatic symptoms are highly prevalent among CKD patients undergoing maintenance hemodialysis, significantly impacting their quality of life. Psychological distress was closely linked to age, comorbidities, and physical symptom burden, with a strong association between HADS and SSS-8 scores. Men experienced more anxiety, while depression was more common in women. Longer dialysis duration correlated with increased psychological morbidity. These findings emphasize the urgent need for integrated care approaches, routine mental health screening, and timely psychosocial interventions within dialysis settings to improve overall well-being and treatment outcomes in this vulnerable population.

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An Epidemiological Study to Assess the Prevalence of Anemia and Its Determinants in Women of Reproductive Age Group (15–49 Years) in an Urban Slum of a Metropolitan City

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Received: 20 September 2025; Accepted: 27 July 2026

[Visual Abstract](#)

ABSTRACT

Background: Anemia is a serious public health concern among women of reproductive age (WRA) 15–49 years in India. The prevalence of anemia in WRA in Mumbai and the Mumbai suburban district was 45%–50%, respectively, as per National Family Health Survey-5 (NFHS-5) data. This study was done to assess the prevalence of anemia and its determinants in WRA in the urban slums of Mumbai.

Materials and methods: A total of 1,500 WRA were enrolled in this community-based cross-sectional study by the convenience sampling method. A structured validated questionnaire was used to record sociodemographic variables and determinants. Hemoglobin (Hb) estimation was done with a digital hemoglobinometer. SPSS v.18, Chi-square test, and binary logistic regression were used for analysis. The study was approved by the Institutional Ethics Committee of HBT Medical College and Dr. RN Cooper Hospital (Approval No. HBTMC/IEC/025-2025/RP/0/330/07072025/26) on 07/07/2025, and written informed consent was obtained from all participants.

Results: Prevalence of anemia in WRA was 57.9%. Significant associations were found between anemia and education level ($p = 0.004$), socioeconomic class ($p < 0.001$), gravida status ($p < 0.001$), spacing between pregnancies ($p < 0.001$), iron tablet consumption in the past 1 year ($p = 0.014$), duration of menses ($p = 0.019$), and pad changes per day ($p = 0.013$).

Conclusion: Determinants such as education level, socioeconomic class, number of pregnancies, spacing between pregnancies, iron tablet consumption, duration of menses, and pad changes per day affect the Hb level of WRA.

Keywords: Anemia, Prevalence, Urban slum, Women of reproductive age.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1690

INTRODUCTION

Anemia is a significant public health problem worldwide. WHO defines anemia as a condition in which the number of red blood cells or the Hb concentration within them is lower than normal.¹ Anemia affects 30% of WRA, 37% of pregnant women, and 40% of all children aged 6 to 59 months worldwide.¹ As per NFHS-5 data (2019–2021), the prevalence of anemia in WRA in India was 57%, and in Mumbai and the Mumbai suburban district was 45% and 50%, respectively.^{2,3} WRA carry the highest burden of anemia across all age groups, with iron deficiency anemia as the most prevalent cause.^{4–6}

As per various studies, determinants such as low education levels, lower socioeconomic class, multiple pregnancies, and inadequate spacing between pregnancies were some of the major contributors to anemia in WRA.^{7–11}

The present study was conducted to estimate the prevalence of anemia and identify its sociodemographic and reproductive determinants among the WRA residing in the urban slums of Mumbai.

AIM

To assess the prevalence of anemia and its sociodemographic and reproductive determinants among women of reproductive age in an urban slum of Mumbai.

OBJECTIVES

Primary Objectives

- To estimate the prevalence of anemia in the study participants.
- To identify sociodemographic and reproductive factors associated with anemia.

Secondary objective

- To assess the sociodemographic profile of study participants.

MATERIAL AND METHODS

Study Design and Setting

This was a community-based cross-sectional study conducted over a period of 3 months in the urban slums of Mumbai.

Study Population

The study population comprised women aged 15–49 years residing in the selected urban slum area of Mumbai who attended community-based anemia screening camps and provided informed consent. A total of 1,500 eligible women were enrolled using a convenience sampling method.

As the study was conducted through screening camps, complete enumeration of the resident women of reproductive age was not undertaken. However, based on Census of India 2011 and NFHS-5 data, it is estimated that approximately 1–1.3 million women aged 15–49 years reside in urban slums of Mumbai.^{2,3,12} This estimate is provided for contextual purposes only.

Inclusion Criteria

Women aged 15–49 years residing in the study area who attended the screening camps and were willing to participate were included in the study.

Exclusion Criteria

Women who did not provide consent or were unavailable during the screening camps were excluded from the study.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee of HBT Medical College and Dr RN Cooper Hospital (Approval No. HBTMC/IEC/025-

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How to cite this article: Deshmukh KR, Chavhan SS, Tupe SD, *et al.* An Epidemiological Study to Assess the Prevalence of Anemia and Its Determinants in Women of Reproductive Age Group (15–49 Years) in an Urban Slum of a Metropolitan City. *J Assoc Physicians India* 2026;74(9):43–47.

2025/RP/0/330/07072025/26) on 07/07/2025. Written informed consent was obtained from all participants prior to enrollment in the study.

Sample Size Calculation

Based on data from NFHS-5, the prevalence of anemia among women aged 15–49 years in India was estimated to be 57%.² Using this expected prevalence, a 95% confidence level, and an absolute precision (margin of error) of 2.51%, the required sample size was calculated using the standard formula for estimation of a single proportion:

$$n = \frac{Z^2 \times p \times (1-p)}{e^2}$$

Where:

n = required sample size.

Z = Z-score corresponding to 95% confidence level (1.96).

p = expected prevalence of anemia (0.57).

e = margin of error (0.0251).

Substituting the values:

$$n = \frac{(1.96)^2 \times 0.57 \times (1-0.57)}{(0.0251)^2}$$

$$n = \frac{0.9417}{0.000630}$$

$$n \approx 1495$$

The sample size was therefore rounded off to 1,500 participants to ensure better statistical precision.

Data Collection

Participants were screened through community-based anemia screening camps conducted at the local Anganwadi Centers (AWCs) with the help of Accredited Social Health Activists (ASHAs) and Anganwadi Workers (AWWs).

A pretested structured questionnaire was used to record sociodemographic data of all the participants. Data on potential determinants such as type of diet, iron folic acid (IFA) tablet consumption, menstrual history, and obstetric history were also recorded.

Hb estimation was done by using a digital hemoglobinometer (TRUEHb, by Wrig Nano System, with ASIN-B0C28CHXDND), and the WHO classification of anemia was used for identifying the anemia cases. All participants diagnosed with anemia were provided IFA tablets as per the standard guidelines.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS V.18. Descriptive statistics were performed for qualitative variables. Quantitative data were represented using mean $\pm$ SD. The association between the

Table 1: Distribution of women according to sociodemographic characteristics, dietary pattern, menstrual and obstetric information

Variable	Category	Total, n (%)
Age group (years)	15–24	660 (44.0)
	25–34	605 (40.3)
	35–44	203 (13.5)
	≥ 45	32 (2.1)
Education level	Illiterate	166 (11.1)
	Primary	319 (21.3)
	Secondary	525 (35.0)
	Higher secondary	313 (20.9)
	Graduate	155 (10.3)
	Postgraduate	22 (1.5)
Marital status	Married	1006 (67.1)
	Unmarried	476 (31.7)
	Separated	14 (0.9)
	Widowed	4 (0.3)
Religion	Hindu	192 (12.8)
	Muslim	1305 (87.0)
	Christian	3 (0.2)
BG Prasad SES (2025)	Class II	194 (12.9)
	Class III	490 (32.7)
	Class IV	816 (54.4)
Diet	Vegetarian	28 (1.9)
	Mixed diet	1472 (98.1)
Duration of menses (days)	1	11 (0.7)
	2	60 (4.0)
	3	346 (23.1)
	4	359 (23.9)
	5	421 (28.1)
	6	164 (10.9)
	7	131 (8.7)
	8	8 (0.5)
Sanitary pad changes per day	1	150 (10.0)
	2	623 (41.5)
	3	449 (29.9)
	4	188 (12.5)
	5	86 (5.7)
	6	4 (0.3)
Iron tablet consumption in the past 1 year	Yes	313 (20.9)
	No	1187 (79.1)
Pregnancy status	Pregnant	70 (4.7)
	Nonpregnant	1430 (95.3)
Number of pregnancies ($n = 932$)	1	170 (18.2)
	2	279 (29.9)
	3	237 (25.4)
	≥ 4	246 (26.4)
Spacing between pregnancies (years) ($n = 762$)	<1	407 (53.4)
	1–2	66 (8.7)
	2–3	115 (15.1)
	>3	174 (22.8)

SES, socioeconomic status

qualitative variables was assessed by the Chi-square test. Binary logistic regression was performed to find out the association between various determinants and a 95% confidence interval. A p -value of < 0.05 was considered significant for all statistical purposes.

RESULTS

The results are summarized in Tables 1 to 5.

DISCUSSION

This study revealed an anemia prevalence of 57.9%, which is higher than the NFHS-5 (2019–21) rates for Mumbai (45%) and Mumbai Suburban District (50%). Among the anemic participants, moderate anemia was most prevalent (31.8%), followed by mild anemia (17.5%) and severe anemia (8.5%). These findings contrast with several studies conducted in similar urban slum settings. Lilare et al. reported a lower prevalence of 49.5% among WRA in Mumbai's urban slums. Also, mild anemia was predominant (37.1%) in their study.⁷ Panigrahi

et al. found a higher prevalence of 60.8% in Bhubaneswar's urban slums, with the majority of cases of mild anemia (39.6%).⁸ Pande et al. also reported a higher prevalence of 61% among WRA in Indore's urban slums, with 33.25% having mild anemia.¹³ Sharif et al. also found that the prevalence of moderate anemia was higher than that of mild and severe anemia in the NFHS-5 data.¹⁴ These comparative findings suggest that while anemia remains a widespread public health issue among WRA in urban slums of different cities, the distribution of severity varies.^{15–19}

Anemia was more common in the age group (35–44 years), with 63.5% of its participants having anemia. However, there was no statistically significant ($p = 0.133$) association between anemia and the age groups. Panigrahi et al. also reported a higher prevalence of anemia (75%) in the 31–40 years age group.⁸ Viveki et al. also found a very high prevalence of 97.7% in participants above 26 years of age in their study.²⁰ In contrast, Lilare et al. found that anemia was more

common in the 15–25 years age group, with 76 (54.3%) participants.⁷ Sharif et al. also found a higher prevalence of anemia in the 15–24 years age group compared to the other age groups.¹⁴

The prevalence of anemia among WRA was found to be significantly correlated ($p = 0.004$) with educational status in the current study. Women with only primary (58.7%) or secondary (63%) education and those who were illiterate (59.8%) were more likely to suffer from anemia than those with graduate (46.4%) or postgraduate (42%) education. According to Panigrahi et al., the prevalence of anemia was 41.2% among women with higher secondary education and above, compared to 74.6% among illiterate women and 62.2% among those with only a primary education.⁸ Similarly, a prevalence of 69.75% was found by Lilare et al. in women with only a primary education, which is significantly higher than the 21.1% found in women with graduate-level education.⁷ According to Sharif et al., women with only primary or no formal education had a significantly higher prevalence of anemia than women with secondary or higher education.¹⁴

In this study, those in class IV of the modified BG Prasad Socioeconomic Scale (2025) had a high prevalence of anemia (51.6%). Anemia prevalence and socioeconomic status (SES) were found to be statistically significantly correlated ($p < 0.001$), suggesting that a lower SES is a major factor in anemia. Lilare et al. also found a strong correlation between socioeconomic status and anemia.⁷ Similar findings were

Table 2: Distribution of women as per WHO classification for anemia

Anemia category	Frequency	Percentage (%)	Anemic/nonanemic (%)
Normal	632	42.1	42.1
Moderate	477	31.8	57.9
Mild	263	17.5	
Severe	128	8.5	
Total	1500	100.0	100.0

WHO, World Health Organization

Table 3: Association of anemia with sociodemographic determinants in WRA

Variable	Category	Nonanemic, n (%)	Anemic, n (%)	Total, n (%)	Chi-square test
Age group (years)	15–24	273 (41.4)	387 (58.6)	660 (100.0)	$\chi^2 = 5.59$, $df = 3$, $p = 0.133$, $N = 1500$
	25–34	268 (44.3)	337 (55.7)	605 (100.0)	
	35–44	74 (36.5)	129 (63.5)	203 (100.0)	
	≥45	17 (53.1)	15 (46.9)	32 (100.0)	
Education level	Illiterate	66 (39.8)	100 (60.2)	166 (100.0)	$\chi^2 = 18.1$, $df = 5$, $p = 0.003$, $N = 1500$
	Primary	131 (41.1)	188 (58.9)	319 (100.0)	
	Secondary	194 (37.0)	331 (63.0)	525 (100.0)	
	Higher secondary	147 (47.0)	166 (53.0)	313 (100.0)	
	Graduate	82 (52.9)	73 (47.1)	155 (100.0)	
	Postgraduate	12 (54.5)	10 (45.5)	22 (100.0)	
Marital status	Married	434 (43.1)	572 (56.9)	1006 (100.0)	$\chi^2 = 4.03$, $df = 3$, $p = 0.258$, $N = 1500$
	Unmarried	191 (40.1)	285 (59.9)	476 (100.0)	
	Separated	4 (28.6)	10 (71.4)	14 (100.0)	
	Widowed	3 (75.0)	1 (25.0)	4 (100.0)	
Religion	Hindu	66 (34.4)	126 (65.6)	192 (100.0)	$\chi^2 = 6.11$, $df = 2$, $p = 0.047$, $N = 1500$
	Muslim	564 (43.2)	741 (56.8)	1305 (100.0)	
	Christian	2 (66.7)	1 (33.3)	3 (100.0)	
BG Prasad SES (2025)	Class II	114 (58.8)	80 (41.2)	194 (100.0)	$\chi^2 = 26.8$, $df = 2$, $p < 0.001$, $N = 1500$
	Class III	205 (41.8)	285 (58.2)	490 (100.0)	
	Class IV	313 (38.4)	503 (61.6)	816 (100.0)	

WRA, women of reproductive age; SES, socioeconomic status; df, degrees of freedom

Table 4: Association of anemia with other determinants in WRA

Variable	Category	Nonanemic, n (%)	Anemic, n (%)	Total, n (%)	Chi-square test
Diet	Vegetarian	10 (35.7)	18 (64.3)	28 (100.0)	$\chi^2 = 0.482$, df = 1, $p = 0.487$, $N = 1500$
	Mixed diet	622 (42.3)	850 (57.7)	1472 (100.0)	
Duration of menses (days)	1	8 (72.7)	3 (27.3)	11 (100.0)	$\chi^2 = 16.8$, df = 7, $p = 0.019$, $N = 1500$
	2	22 (36.7)	38 (63.3)	60 (100.0)	
	3	138 (39.9)	208 (60.1)	346 (100.0)	
	4	159 (44.3)	200 (55.7)	359 (100.0)	
	5	192 (45.6)	229 (54.4)	421 (100.0)	
	6	70 (42.7)	94 (57.3)	164 (100.0)	
	7	42 (32.1)	89 (67.9)	131 (100.0)	
	8	1 (12.5)	7 (87.5)	8 (100.0)	
Sanitary pad changes per day	1	63 (42.0)	87 (58.0)	150 (100.0)	$\chi^2 = 14.4$, df = 5, $p = 0.013$, $N = 1500$
	2	292 (46.9)	331 (53.1)	623 (100.0)	
	3	174 (38.8)	275 (61.2)	449 (100.0)	
	4	75 (39.9)	113 (60.1)	188 (100.0)	
	5	28 (32.6)	58 (67.4)	86 (100.0)	
	6	0 (0.0)	4 (100.0)	4 (100.0)	
Iron tablet consumption in the past 1 year	Yes	151 (48.2)	162 (51.8)	313 (100.0)	$\chi^2 = 6.06$, df = 1, $p = 0.014$, $N = 1500$
	No	481 (40.5)	706 (59.5)	1187 (100.0)	
Pregnancy status	Pregnant	32 (45.7)	38 (54.3)	70 (100.0)	$\chi^2 = 0.386$, df = 1, $p = 0.534$, $N = 1500$
	Nonpregnant	600 (42.0)	830 (58.0)	1430 (100.0)	
Number of pregnancies	1	94 (55.3)	76 (44.7)	170 (100.0)	$\chi^2 = 25.8$, df = 3, $p < 0.001$, $n = 932$
	2	124 (44.4)	155 (55.6)	279 (100.0)	
	3	95 (40.1)	142 (59.9)	237 (100.0)	
	≥ 4	76 (30.9)	170 (69.1)	246 (100.0)	
Spacing between pregnancies (years)	<1	142 (34.9)	265 (65.1)	407 (100.0)	$\chi^2 = 18.9$, df = 3, $p < 0.001$, $n = 762$
	1–2	32 (48.5)	34 (51.5)	66 (100.0)	
	2–3	49 (42.6)	66 (57.4)	115 (100.0)	
	>3	93 (53.4)	81 (46.6)	174 (100.0)	

WRA, women of reproductive age; df, degrees of freedom

Table 5: Binomial logistic regression analysis of determinants of anemia

Predictor	B	SE	Wald	df	p-value	OR	95% CI lower	95% CI upper
Primary vs graduate	0.45	0.21	4.63	1	0.031	1.57	1.04	2.38
Secondary vs graduate	0.63	0.20	9.76	1	0.002	1.87	1.25	2.80
Duration of menses: 1 vs 8 days	-3.59	1.30	7.64	1	0.006	0.03	0.00	0.29
BG Prasad SES: class II vs III	-0.63	0.18	12.14	1	<0.001	0.53	0.37	0.75
Number of pregnancies: 1 vs 3	-0.99	0.23	19.33	1	<0.001	0.37	0.24	0.56
Spacing between pregnancies: <1 year vs >3 years	0.85	0.19	19.85	1	<0.001	2.35	1.61	3.43

B, regression coefficient; SE, standard error; df, degrees of freedom; OR, odds ratio; CI, confidence interval; SES, socioeconomic status

made by Panigrahi et al., who discovered that the prevalence of anemia peaked in Class IV (71.1%) and gradually declined as SES improved, reaching its lowest in class II (51.9%) ($p < 0.05$).⁸ Sharif et al. also found that anemia was more prevalent in the poorest and poorer categories compared to the richer and richest groups.¹⁴

In the current study, anemia was more common in women who followed a vegetarian diet (64.3%) than in those who followed a mixed diet (57.7%), however, this difference was not statistically significant. Lilare et al. found no statistically significant difference in

the prevalence of anemia between vegetarian women (64.4%) and women consuming a mixed diet (47.4%).⁷ Similarly, Viveki et al. found that vegetarians had a significantly higher prevalence of anemia (86.8%), but the association was not statistically significant.²⁰ These findings were corroborated by Panigrahi et al., who found that people who consume insufficient amounts of nonvegetarian foods, pulses, green leafy vegetables, and milk and milk products are more likely to suffer from anemia.⁸ These results imply that vegetarian diets might raise the risk of anemia.

The prevalence of anemia was marginally higher among nonpregnant women (58%) in the current study than among pregnant women (54.3%), although this difference was not statistically significant. Mishra et al. found that there was no discernible difference in the prevalence of anemia between non-pregnant (96.8%) and pregnant women (96.4%).²¹ On the contrary, Lilare et al. discovered that pregnant women had a greater prevalence of anemia (54.2%) than nonpregnant women (48.7%).⁷

The prevalence of anemia and gravida status was found to be statistically

significantly correlated in the current study ($p < 0.001$). Primigravida women had the lowest prevalence (44.7%), while multigravida women (≥ 4 pregnancies) had the highest prevalence (69.1%). Lilare et al. discovered that women with parity three or more had a higher prevalence of anemia (65.9%) than women with parity one (52.2%) although the difference was not statistically significant.⁷ Panigrahi et al. also found that women who had two or more pregnancies had a higher likelihood of being anemic than those who had one or none, although the difference was not statistically significant.⁸ According to Viveki et al., the prevalence of anemia increased gradually as parity increased, but this trend was also not statistically significant.²⁰

The current study discovered a statistically significant correlation ($p < 0.001$) between the prevalence of anemia and the spacing between pregnancies. Anemia was significantly more common in women with less than a year gap between pregnancies (65.1%) than in those with more than three years (46.6%). Lilare et al. reported similar findings, showing that the prevalence of anemia was significantly higher (77.6%) among women who had ≤ 1 year gap between pregnancies than among those who had > 3 years (34.1%) gap.⁷ According to a study by Viveki et al., the prevalence of anemia was significantly higher (90.9%) in cases where the interval between the index and prior pregnancies was less than 2 years.²⁰

In the current study, the prevalence of anemia was lower in women who had taken iron and folic acid (IFA) tablets in the previous year (51.8%) than in those who had not (59.5%). This association was found to be statistically significant ($p = 0.014$). The study by Viveki et al. provides supporting evidence, revealing a significantly higher prevalence of anemia (88.15%) among women who had recently received IFA tablets for less than two months.²⁰

The length of menstruation and the prevalence of anemia were found to be statistically significantly correlated in this study ($p = 0.019$). Anemia was more common in women with longer menstrual periods (≥ 7 days) than in those with shorter ones (≤ 5 days), with a prevalence of 67.9%. Panigrahi et al. found a significant correlation ($p = 0.01$) between anemia and a history of excessive menstrual bleeding.⁸ Additionally, Pande et al. observed that 13.11% of the 244 nonpregnant anemic women had heavy periods, suggesting that menstrual blood loss may be a contributing factor to anemia in this population.¹³

The average number of sanitary pad changes per day and the prevalence of anemia were found to be statistically significantly correlated in this study ($p = 0.013$). Anemia was

more common in women who reported using ≥ 3 sanitary pads per day (61.2%) than in those who reported using ≤ 2 pads per day (53.1%).

LIMITATIONS

The study was done using convenience sampling through anemia screening camps. This might limit the generalizability of the findings of the study. Also, complete enumeration of the study population was not done. Moreover, as it is a cross-sectional study, no cause-effect relationship can be established.

CONCLUSION

This study shows a higher prevalence of anemia (57.9%), among WRA living in Mumbai's urban slums compared to the NFHS-5 data. With notable correlations found between anemia and factors like educational attainment, socioeconomic status, gravida status, spacing between pregnancies, IFA tablet use, and menstrual characteristics, the results highlight anemia as a multifactorial public health concern.

The study confirms that anemia is significantly influenced by socioeconomic status and lower levels of education. The risk is further increased by poor adherence to IFA supplementation and insufficient spacing between pregnancies.

Community-based screening, health education, nutritional support, and reproductive health services in underprivileged areas must be given priority in intensive interventions under programs like Anemia Mukh Bharat in order to lower anemia and enhance maternal health among vulnerable urban populations.

ACKNOWLEDGMENTS

The authors thank their colleagues who participated in the study.

CONFLICT OF INTEREST

None.

SOURCE OF SUPPORT

This study was supported by the Action Against Hunger (AAH) team.

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Prevalence of Gastroesophageal Reflux Disease among Postgraduate Medical Students in North India: A Cross-sectional Study



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Received: 07 January 2026; Accepted: 27 July 2026

 Visual Abstract

ABSTRACT

Background and objectives: Gastroesophageal reflux disease (GERD) is a persistent state due to the retrograde flow of acidic gastric contents, leading to symptoms such as heartburn, regurgitation, chest pain, and dysphagia. Postgraduate medical students are exposed to high stress and lifestyle factors that predispose them to gastrointestinal symptoms. Limited Indian data exist on GERD prevalence in this cohort.

Materials and methods: A questionnaire-based cross-sectional study was conducted using the GERD-Q tool. Data were collected via an online Google Form and analyzed using Microsoft Excel. The Chi-square statistical test and univariate analysis were performed to identify associations between GERD and variables.

Results: Among 324 participants (mean age, 28.1 years), 77.4% were aged 25–30 years; 52.5% were male. Most were hostellers or paying guests. GERD prevalence was 25.3%. The prevalence was higher among males (27.6%) compared with females (22.7%) and among participants with higher BMI (27.6%) compared with those with normal BMI (23.5%). GERD prevalence was highest among postgraduates in medicine and allied specialties (31.3%), followed by surgical (23.3%) and preclinical/paraclinical departments (19.2%).

Conclusion: This study highlights a significant burden of GERD among postgraduate medical students. Identifying associated risk factors may help in designing targeted interventions to improve gastrointestinal health and overall well-being of healthcare providers.

Keywords: Gastroesophageal reflux disease, GERD-Q, Lifestyle factors, Postgraduate medical students.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1701

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic digestive condition in which the retrograde flow of acidic stomach contents irritates the esophageal lining, leading to characteristic symptoms such as persistent heartburn, acid regurgitation, chest pain, and dysphagia (difficulty swallowing). Untreated GERD can lead to complications such as erosive esophagitis, strictures, and Barrett's esophagus, which increases the risk of esophageal cancer.^{1,2}

Globally, the pooled prevalence of GERD is an estimated 13.98% of the world's population,³ while in India, its prevalence is 15.6%,⁴ reflecting an increasing burden on the healthcare system.

Postgraduate medical students, who are at the forefront of healthcare delivery and medical advancements, are faced with significant academic and professional pressures beginning even before their admission, with highly competitive entrance exams such as NEET setting the stage for a challenging educational journey in medical colleges and beyond. These resident doctors

endure long working hours, intensive clinical case evaluations, and continuous academic assessments. This high-stress environment often leads to lifestyle-related risk factors such as irregular eating habits, skipping meals, excessive caffeine consumption, lack of sleep, and insufficient physical exercise, which contribute to the development and aggravation of common GI symptoms, including dyspepsia (indigestion), heartburn, acid reflux, bloating, and abdominal discomfort. Additionally, the frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) to manage various types of pain and inflammation can further worsen these symptoms.

There is a paucity of published studies specifically investigating the prevalence of GERD among postgraduate medical students in India. However, there are some studies examining GERD and other gastrointestinal symptoms among undergraduate medical students and healthcare workers. This study aims to fill this gap in the literature by investigating the prevalence of GERD in this demographic and examining the association of symptoms with lifestyle factors, which will

help in formulating targeted interventions to improve their overall well-being and clinical performance.

MATERIALS AND METHODS

This study was conducted and reported in accordance with the STROBE Guidelines. A questionnaire-based cross-sectional study was conducted on 324 postgraduate medical students from medical colleges in North India. A sample size of 320 participants was calculated using Cochran's formula, assuming a prevalence of 29%,⁵ an absolute error of 5%, and a 95% confidence interval.

Ethics clearance was obtained from the Institutional Ethics Committee before beginning the study. The approval number was MGMCH/IEC/JPR/2024/4221, dated 4th November 2024. Those who consented to participate and had completed 6 months of residency were included, and those who suffered from hiatus hernia or morbid obesity, as well as pregnant and lactating females, were excluded until the desired sample size was achieved.

The questionnaire was structured into three distinct parts related to demographic and socioeconomic characteristics, clinical history, preexisting medical conditions, particularly gastrointestinal disorders, and lifestyle factors. The last part had questions related to the GERD-Q tool.⁶ The GERD-Q tool is a validated Likert scale specifically designed to assess the frequency and severity of GERD and has been found effective in management and diagnosis without the need for a specialist doctor or invasive procedures

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How to cite this article: Chauhan D, Mangal S, Kumar A, et al. Prevalence of Gastroesophageal Reflux Disease among Postgraduate Medical Students in North India: A Cross-sectional Study. *J Assoc Physicians India* 2026;74(9):48–52.

such as endoscopy. The total score ranges from 0 to 18. A higher score, with a score of ≥ 8 , is suggested for diagnosis, allowing for assessment of GERD prevalence and severity within the study population.

The study was conducted using an online questionnaire on Google Forms among postgraduate students of various medical colleges in North India.

The data were analyzed using appropriate statistical methods in Microsoft Excel. The test of significance (Chi-squared test) and generalized linear regression analysis were used to explore the connection between GERD and possible risk factors. A value of $p \leq 0.05$ was considered statistically significant.

RESULTS

A total of 331 postgraduate medical students from multiple specialties across various medical colleges and hospitals in North India were contacted for participation in the study, out of which data from 324 participants met the inclusion criteria and were analyzed. The majority of participants (77.4%) were in the 25–30-year age-group. Among the participants, 52.5% were male, and the rest were female. Nearly two-thirds of participants were living in hostels or as paying guests. With respect to BMI, 56.5% of the participants had BMI within the normal range, while the rest had high BMI. Most participants belonged to medicine and allied specialties. These demographic variables are mentioned in Table 1. Common comorbidities

reported among participants included asthma, hypothyroidism, diabetes, PCOS, and migraine.

The prevalence of GERD, as determined by the GERD-Q score, wherein a score of 8–18 implies GERD-positive status, was 25.3% (82) as shown in Figure 1.

The mean GERD-Q score was 9.34 ± 1.40 among GERD-positive participants and 5.96 ± 0.83 among GERD-negative participants.

GERD was relatively higher among males, individuals aged 25–30 years, those residing as paying guests or hostellers, those with higher BMI, and participants from medicine and allied specialties. However, the difference observed was not statistically significant, as shown in Table 1.

The association of lifestyle factors with GERD status was obtained as mentioned in Table 2. The difference observed among variables such as frequent carbonated beverage consumption, smoking, alcohol, and NSAID use was statistically significant. A statistically significant difference was also observed among those with stress and anxiety and self-reported gastrointestinal symptoms with GERD status.

Sixty percent of GERD-positive participants reported experiencing symptoms prior to entering residency, while 34.1% had a family history of GERD. A large proportion experienced worsening of symptoms upon lying down, with more than half reporting symptoms peaking at night. Notably, 88% of GERD-positive participants reported symptomatic relief with antacid use.

Table 3 presents the results of the generalized linear regression analysis evaluating factors associated with GERD, considering the dependent variable as GERD score (positive for ≥ 8 and negative for < 8).

In the crude analysis, smoking, alcohol intake, carbonated beverage consumption, fast food consumption, painkiller consumption, and stress and anxiety worsening symptoms were significantly associated with GERD.

After adjusting for potential confounding variables, including age, gender, BMI, residence, department, family history of GERD, type of diet, tea/coffee consumption, physical exercise, and sleeping hours, only smoking and stress and anxiety worsening symptoms remained independently associated with GERD.

Participants who smoked had an 11% higher prevalence of GERD than nonsmokers after adjustment (aPR = 1.11; 95% CI: 1.00–1.23;

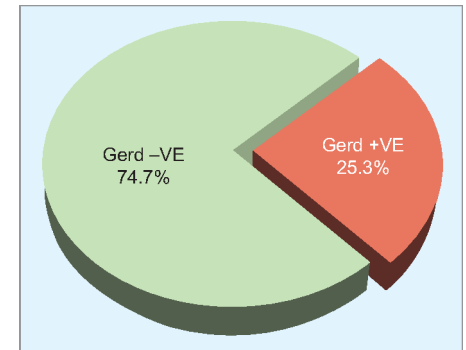


Fig. 1: Prevalence of GERD among postgraduate medical students

Table 1: Association of demographic variables with GERD status

Demographic variables	GERD +ve N = 82 n (%)	GERD -ve N = 242 n (%)	Total N = 324 n (%)	p-value
Age (in years)				
<25	3 (16.7)	15 (83.3)	18 (5.6)	$p > 0.05$
25–30	63 (25.1)	188 (74.9)	251 (77.4)	
>30	16 (29.1)	39 (70.9)	55 (17.0)	
Gender				
Male	47 (27.6)	123 (72.4)	170 (52.5)	$p > 0.05$
Female	35 (22.7)	119 (77.2)	154 (47.5)	
Residence				
Hostel	37 (25.0)	111 (75.0)	148 (45.7)	$p > 0.05$
Paying guest	16 (30.2)	37 (69.8)	53 (16.3)	
Home	29 (23.6)	94 (76.4)	123 (38.0)	
BMI				
Normal BMI	43 (23.5)	140 (76.5)	183 (56.5)	$p > 0.05$
High BMI	39 (27.7)	102 (72.3)	141 (43.5)	
Department				
Pre- and paraclinical	20 (19.2)	84 (80.8)	104 (32.1)	$p > 0.05$
Surgery and allied	20 (23.3)	66 (76.7)	86 (26.5)	
Medicine and allied	42 (31.3)	92 (68.7)	134 (41.4)	

Table 2: Association of lifestyle factors with GERD status

Lifestyle factors	GERD +ve (N = 82)	GERD -ve (N = 242)	Total (N = 324)	p-value
	n (%)	n (%)	n (%)	
Type of diet				
Vegetarian	51 (23.6)	165 (76.4)	216 (66.7)	$p > 0.05$
Nonvegetarian	29 (26.9)	77 (73.1)	108 (33.3)	
Skip breakfast				
Everyday and often	46 (27.2)	123 (72.8)	169 (52.1)	$p > 0.05$
Occasionally, rare	31 (25.4)	91 (74.6)	122 (37.7)	
Never	5 (15.2)	28 (84.8)	33 (10.2)	
No. of tea/coffee per day				
0 cups	10 (27.8)	26 (72.2)	36 (11.1)	$p > 0.05$
1–3 cups	65 (24.3)	203 (75.7)	268 (82.7)	
≥4	7 (35.0)	13 (65.0)	20 (6.2)	
Carbonated beverage consumption				
Everyday and often	23 (30.3)	53 (69.7)	76 (23.5)	$p < 0.05^*$
Occasionally and rare	54 (27.1)	145 (72.9)	199 (61.4)	
Never	5 (10.2)	44 (89.8)	49 (15.1)	
Fast food consumption				
Everyday and often	37 (31.4)	81 (68.6)	118 (36.4)	$p > 0.05$
Occasionally and rarely	44 (22.2)	154 (77.8)	198 (61.1)	
Never	1 (12.5)	7 (87.5)	8 (2.5)	
Smoking				
Yes	18 (46.2)	21 (53.8)	39 (12.0)	$p < 0.05^*$
Former smoker	6 (42.9)	8 (57.1)	14 (4.3)	
No	58 (21.4)	213 (78.6)	271 (83.7)	
Alcohol consumption				
Yes	42 (39.3)	65 (60.7)	107 (33.0)	$p < 0.05^*$
Former drinker	5 (21.7)	18 (78.3)	23 (7.1)	
No	35 (18.0)	159 (82.0)	194 (59.9)	
Pain killer—NSAIDS consumption				
Often	9 (37.5)	15 (62.5)	24 (7.4)	$p < 0.05^*$
Occasionally	31 (33.0)	63 (67.0)	94 (29.0)	
Rarely	42 (20.4)	164 (79.6)	206 (63.6)	
Physical exercise				
Frequent exercise (≥3 times weekly)	16 (18.6)	70 (81.4)	86 (26.5)	$p > 0.05$
Infrequent exercise (≤2 times weekly)	66 (27.7)	172 (72.3)	238 (73.5)	
Sleeping hours				
<6 hours	28 (28.0)	72 (72.0)	100 (30.9)	$p > 0.05$
6 or more hours	54 (24.1)	170 (75.9)	224 (69.1)	
Stress and anxiety worsen symptoms				
Yes	71 (35.1)	131 (64.9)	202 (62.3)	$p < 0.05^*$
No	11 (9.0)	111 (91.0)	122 (37.7)	
Self-reported GI symptoms				
Yes	68 (50.0)	68 (50.0)	136 (42.0)	$p < 0.05^*$
No	14 (7.4)	174 (92.6)	188 (58.0)	

*Statistically significant at $p < 0.05$ **Table 3:** Generalized linear regression analysis for factors associated with GERD

Variable	cPR (95% CI)	p-value	aPR (95% CI)	p-value
Smoking	1.61 (1.25–2.07)	<0.001	1.11 (1.00–1.23)	0.044
Alcohol intake	1.45 (1.13–1.86)	0.003	1.09 (0.98–1.20)	0.100
Carbonated beverage consumption	0.70 (0.53–0.92)	0.011	1.01 (0.92–1.10)	0.883
Fast food consumption	0.70 (0.49–0.99)	0.044	0.96 (0.86–1.08)	0.501
Painkiller consumption	0.70 (0.54–0.90)	0.005	0.94 (0.86–1.02)	0.160
Stress and anxiety worsen symptoms	3.90 (2.15–7.06)	<0.001	1.17 (1.00–1.37)	0.046

Adjusted for: Age, gender, BMI, residence, department, family history of GERD, type of diet, tea/coffee consumption, physical exercise, and sleeping hours; cPR, crude prevalence ratio; aPR, adjusted prevalence ratio; CI, confidence interval

$p=0.044$). Likewise, participants who reported that stress and anxiety worsened their symptoms had a 17% higher prevalence of GERD compared with those who did not ($aPR = 1.17$; 95% CI: 1.00–1.37; $p = 0.046$).

Although alcohol intake, carbonated beverage consumption, fast food consumption, and painkiller consumption were significantly associated with GERD in the crude analysis, these associations were no longer statistically significant after adjustment for confounding variables, indicating that their observed crude associations were likely explained by differences in demographic and lifestyle characteristics.

DISCUSSION

With lifestyle-related illnesses on the rise, GERD has become a significant concern among young medical professionals, whose routines often predispose them to gastrointestinal distress. While several Indian studies have explored GERD in undergraduate medical students, limited studies are present among postgraduate medical students—an underinvestigated cohort despite high exposure to risk factors.

In this study, the prevalence of GERD among postgraduate medical students was found to be 25.3%, based on the GERD-Q scale. This exceeds the GERD prevalence in the general Indian population⁴ as well as the global pooled prevalence.³ This could be attributed to the unique stressors of postgraduate medical training, including long working hours, irregular meals, sleep deprivation, and academic pressure—all known to contribute to reflux symptoms.⁷

The results of the present study are comparable with several recent Indian and international findings among undergraduate and postgraduate medical students.^{5,8,9}

The majority of GERD-positive participants in the 25–30-year age-group adds to the growing evidence suggesting that GERD is becoming increasingly common in younger populations, particularly in South Asia, where changing dietary patterns and increasing workload are major risk factors.¹⁰

In the current study, GERD was slightly more prevalent among males (27.6%) compared with females (22.7%), although the mean age among females was lower than that among males. This finding is consistent with earlier studies conducted on undergraduate students in North India.¹¹

Elevated BMI was a particularly important factor in this study, with more GERD-positive individuals falling into the high BMI category compared with those with normal BMI. This mirrors findings from studies conducted

in Iran and North India.^{12,13} While some community-based Indian studies have reported mixed associations with obesity, a consistent finding shows that even modest weight gain affects lower esophageal sphincter tone and increases intra-abdominal pressure, contributing to reflux.^{13–15}

Among various specialties in the present study, GERD was found to be most prevalent among postgraduates in medicine and allied specialties, followed by surgical branches, and least prevalent among preclinical and paraclinical departments. It could be due to the high-stress environment faced by medicine residents being posted in emergency departments or intensive care units, where patients require round-the-clock attention from postgraduate doctors. A study from Pakistan reported surgical specialties having the highest prevalence of GERD, followed by medicine and diagnostic specialties.⁵

Dietary and lifestyle patterns further supported these associations. A considerable proportion of GERD-positive individuals reported higher intake of fast food, carbonated beverages, midnight snacking, and a nonvegetarian diet. These findings parallel those of other studies.^{12,16}

The present research also highlighted the impact of eating quickly and skipping breakfast, as suggested by previous studies.^{17,18} GERD was also more prevalent among students who ate late at night and did not have a gap of >3 hours between dinner and sleep, which is supported by previous literature.^{18–20}

The role of stress was notable in our study, with 35.1% of GERD-positive students reporting symptom exacerbation, which can be linked to anxiety or psychological pressure and supports similar studies in the past.^{21–23} Disrupted sleep and demanding work hours might worsen this issue. These observations are consistent with another study showing the impact of circadian misalignment and night shifts on gastrointestinal health.²⁴

In this study, a statistically significant number of current smokers and alcohol and frequent NSAID consumers were GERD-positive, similar to findings from past studies.^{8,25–28}

CONCLUSION

This study highlights a higher prevalence of GERD among postgraduate medical students compared with the general population, indicating an increased occupational risk. Residency-related stressors and lifestyle factors appear to play a contributory role, with variations observed across specialties.

Early recognition of at-risk groups may enable timely, targeted interventions. Addressing modifiable factors during postgraduate training may enhance digestive health and general well-being and emphasize the need for institutional policies that encourage a healthier work–life balance for medical trainees.

This study has several strengths but limitations as well. Being a cross-sectional study, it relies on self-reported data, which can be prone to recall bias, reporting bias, and individual variation in symptom perception. The use of the GERD-Q scale, where results are calculated based on symptom frequency experienced over the preceding week, helped minimize recall bias. However, symptom assessment relied on participants' individual interpretation and reporting of their symptoms, which may have affected the accuracy and consistency of the responses. The absence of objective diagnostic tools such as endoscopy or 24-hour esophageal pH monitoring limits the ability to confirm GERD physiologically, but the GERD-Q scale is an accurate noninvasive diagnostic marker to clinically diagnose this condition. Future longitudinal studies using objective diagnostic investigations would allow a more comprehensive evaluation of disease burden and associated risk factors in this population. Medical institutions and regulatory bodies should consider implementing resident wellness initiatives, which include periodic health screening for the early identification of at-risk residents, increasing awareness about GERD symptoms so residents seek professional medical attention early rather than self-medicating, reasonable duty hours with adequate meal breaks, easy availability of healthier food options even during overnight shifts, and confidential mental health and stress-management services to facilitate timely preventive measures rather than delayed treatment after symptom progression.

As resident doctors form the backbone of healthcare delivery, the present findings reinforce the importance of prioritizing their health through preventive strategies and comprehensive resident wellness initiatives, thus encouraging a healthier work–life balance.

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Abridged Prescribing Information

Indication: It is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. Dosage and Administration: The recommended dose is one tablet daily. Each tablet contains a fixed dose of dapagliflozin, Sitagliptin and Metformin Hydrochloride. Adverse Reactions: Most common adverse reactions reported are: Dapagliflozin- Female genital mycotic infections, nasopharyngitis, and urinary tract infections. Sitagliptin- Upper respiratory tract infection, nasopharyngitis and headache. Metformin- Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Warnings and Precautions: Dapagliflozin: Volume depletion; Ketoacidosis in Patients with Diabetes Mellitus; Urosepsis and Pyelonephritis; Hypoglycaemia; Genital Mycotic Infections. Sitagliptin: General- Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Acute pancreatitis: Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal product; Renal impairment; Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions- Stevens-Johnson syndrome; Bullous pemphigoid. Metformin Hydrochloride: Lactic acidosis; In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Contraindications: Hypersensitivity to the active substance of Dapagliflozin, Sitagliptin & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma. Severe renal failure (eGFR<30mL/min). Acute conditions with the potential to alter renal function such as: Dehydration, Severe infection, Shock, Acute or chronic disease which may cause tissue hypoxia such as: Cardiac or respiratory failure, Recent myocardial Infarction, Shock, Hepatic Impairment, Acute Alcohol intoxication, alcoholism. Use in a special population: Pregnant Women: Due to lack of human data, drug should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drug has not yet been established. No data are available. Geriatric Patients: In Patients > 65 years, it should be used with caution as age increases. Additional information is available on request. Last updated: March 2020

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Safety and Effectiveness of Cyclosporine and Eltrombopag in Acquired Aplastic Anemia: Experience from a Tertiary Care Center in Eastern India



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Received: 22 April 2026; Accepted: 27 July 2026

[Visual Abstract](#)

ABSTRACT

Introduction: Acquired aplastic anemia (AAA) is an immune-mediated bone marrow failure syndrome traditionally treated with antithymocyte globulin (ATG)-based immunosuppressive therapy. However, many patients—particularly older adults and those with significant comorbidities—are unable to tolerate ATG. The combination of cyclosporine (CSA) and eltrombopag (EPAG) without ATG has emerged as a potential alternative, though real-world data from India remain limited.

Materials and methods: This single-center, retrospective observational study included consecutive adult patients ($n = 40$; ≥ 18 years) with severe or very severe AAA treated with CSA and EPAG without ATG between January 2020 and December 2025, study ends December 2025. Patients had contraindications to ATG due to age and/or comorbidities. Hematologic responses were assessed at 3–6 months. Overall response rate (ORR) was defined as complete plus partial response. Safety was evaluated using CTCAE v5.0 criteria.

Results: The median age was 56.5 years, with 72.5% having severe and 27.5% very severe AAA. At 6 months, complete response was observed in 17.5% and partial response in 45%, yielding an ORR of 62.5%. Notable improvements were observed in hemoglobin, absolute neutrophil count, and platelet count (all $p < 0.001$). Younger age (≤ 60 years), fewer comorbidities (≤ 1), higher baseline blood counts, and severe (vs very severe) disease were significantly associated with response. Treatment was well tolerated; hepatic adverse events were mild (grade ≤ 2), transient, and did not necessitate treatment discontinuation.

Conclusion: Cyclosporine combined with eltrombopag is a relatively safe and effective ATG-free therapeutic option for selected patients with acquired aplastic anemia, particularly older individuals and those with comorbidities. This regimen offers meaningful hematologic recovery with acceptable toxicity and represents a pragmatic alternative in real-world and resource-limited settings.

Keywords: Acquired aplastic anemia, Comorbidities, Cyclosporine, Eltrombopag, Overall response rate.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1689

INTRODUCTION

Acquired aplastic anemia (AAA) is a rare, heterogeneous disorder characterized by pancytopenia and a hypocellular bone marrow without abnormal infiltration or fibrosis, resulting from immune-mediated destruction of hematopoietic stem and progenitor cells. Diagnosis requires at least two of the following: hemoglobin < 100 gm/L, platelets $< 50 \times 10^9$ /L, or neutrophils $< 1.5 \times 10^9$ /L.¹ Severe aplastic anemia (SAA) is defined by bone marrow cellularity below 25% (or 25–50% with less than 30% hematopoietic cells) and at least two of the following: neutrophils $< 0.5 \times 10^9$ /L, platelets $< 20 \times 10^9$ /L, or reticulocytes $< 60 \times 10^9$ /L. Very severe AA (VSAA) meets the same criteria as SAA but with neutrophils $< 0.2 \times 10^9$ /L. Nonsevere AA (NSAA) includes cases that do not meet the thresholds for SAA or VSAA.² The incidence of AA varies widely worldwide and across

India, with limited epidemiological data from Asia. Reported incidence in Asia is two to three times higher than in Western countries, reaching up to 8.8 per million per year. While Western studies show a bimodal age distribution (15–25 years and ≥ 60 years), Indian studies report a younger median age at presentation, ranging from 25 to 36.5 years. The disease shows a biphasic age distribution (10–25 years and over 60) and occurs more frequently in East Asia than in Europe (2–3 cases per million annually).³ Cyclosporine (CSA) suppresses T-cell-mediated immune injury and improves hematopoiesis, though responses are variable and relapses frequent.⁴ Antithymocyte globulin (ATG) combined with CSA is recommended as the first-line treatment for patients with NSAA who are transfusion-dependent, have recurrent infections or bleeding, or whose daily functioning is notably affected. For those

with SAA/VSAA without a matched sibling donor (MSD), the preferred initial therapy includes ATG, CSA, and eltrombopag (EPAG). This combination is also advised for patients with an MSD who are over 40 years old. In individuals aged 40 to 50, hematopoietic stem cell transplantation (HSCT) from an MSD may still be considered, depending on their general health, functional status, and the expertise of the transplant center.⁵ In routine clinical practice, treating AAA in patients with significant comorbidities—such as advanced age, diabetes, hypertension, cardiovascular disease, infections, or organ dysfunction—poses substantial challenges due to poor tolerance to intensive immunosuppressive therapy (IST). Many such patients are unable to receive ATG because of concerns regarding infusion-related reactions, infectious complications, prolonged hospitalization, and overall treatment-related morbidity. In these settings, a less intensive immunosuppressive approach combining CSA with EPAG, without ATG, may offer a safer and more feasible therapeutic alternative, particularly in low-resource environments or when ATG is contraindicated. EPAG's oral administration, favorable safety profile, and capacity to stimulate hematopoiesis make it especially suitable for vulnerable patient populations. Emerging real-world evidence supports the use of CSA with EPAG in patients with multiple comorbidities, although prospective data remain limited.⁶ The present study evaluates the safety and effectiveness of this combination in such high-risk patients to help inform pragmatic treatment strategies.

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How to cite this article: Baul S, Sharma A, Ghosh K, et al. Safety and Effectiveness of Cyclosporine and Eltrombopag in Acquired Aplastic Anemia: Experience from a Tertiary Care Center in Eastern India. *J Assoc Physicians India* 2026;74(9):58–62.

MATERIALS AND METHODS

Study Design and Patients

This was a single-center, retrospective observational study evaluating the safety and effectiveness of CSA combined with EPAG in patients with AAA. Consecutive patients ($n = 40$) aged ≥ 18 years treated between January 2020 and December 2025, study ends December 2025 were included. The diagnosis of AAA was confirmed by bone marrow biopsy demonstrating hypocellularity without malignant infiltration or fibrosis.

Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they had a diagnosis of AAA classified as SAA or VSAA, were aged ≥ 18 years, and were treated with CSA and EPAG without ATG due to the presence of contraindications to ATG. Eligible patients had at least one significant comorbidity, including poorly controlled diabetes mellitus, hypertension, chronic infection such as tuberculosis, organ dysfunction (pulmonary, hepatic, or renal), or cardiovascular disease. Comorbidities were defined based on documented physician diagnosis and active medical treatment at the time of initiation of immunosuppressive therapy.

Patients were excluded if they had inherited bone marrow failure syndromes, had undergone prior hematopoietic stem cell transplantation, or had no contraindication to ATG and were eligible for standard ATG-based immunosuppressive therapy.

Treatment Protocol

Cyclosporine was administered orally at an initial dose of 5 mg/kg/day in two divided doses, with dose adjustments to maintain therapeutic trough levels between 150 and 250 ng/mL.⁴ Eltrombopag was initiated at 50–75 mg/day based on baseline liver function and was titrated according to platelet response and tolerability.⁶ In patients with hepatic dysfunction, reduced starting doses were used in accordance with prescribing guidelines. Transfusion support was given as per institutional guidelines.

Data Collection and Parameters Analyzed

Baseline demographic and clinical data, including age, sex, and comorbidities, were recorded. Hemoglobin concentration (Hb), absolute neutrophil count (ANC), and platelet count were assessed at baseline, 3 months, and 6 months after initiation of therapy. Treatment-related adverse events—including hepatotoxicity, renal dysfunction, thromboembolic events, gastrointestinal

symptoms, and skin hyperpigmentation—were documented and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).⁷

Outcome Definitions and Response Assessment

Treatment response at the end of 6 months was categorized as:⁵

- **Complete response (CR):** Hemoglobin >10 gm/dL, ANC $>1.5 \times 10^9/L$, and platelet count $>150 \times 10^9/L$ without transfusion support.
- **Partial response (PR):** Transfusion independence with improvement in at least one hematopoietic lineage.
- **No response (NR):** Persistent transfusion dependence and cytopenias.
- Overall response rate (ORR) was defined as the sum of CR and PR.

Ethical Considerations

The study was approved by the Institutional Ethics Committee (Nilratan Sircar Medical College and Hospital), India (IEC approval No. IEC/NMC/6673), and conducted in accordance with the Declaration of Helsinki. Patient confidentiality was maintained throughout the study.

Statistical Analysis

SPSS 20.0 statistical software (SPSS Inc., Chicago, IL) was used for statistical analysis to draw appropriate conclusions. Qualitative data (Categorical variables) were presented in numbers and percentages (%). Data distribution was assessed and found to be nonparametric. Continuous variables were expressed as median with interquartile range (IQR) and compared using the Wilcoxon signed-rank test for paired observations. Categorical variables were expressed as frequencies and percentages. Associations between baseline variables—including age, sex, baseline blood counts, and comorbidities—and treatment response were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A two-sided p -value <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

Baseline Characteristics and Outcome

The median age of the patients was 56.5 years (interquartile range/IQR 54.0–64.0). Males comprised 57.5% ($n = 23$) and females 42.5% ($n = 17$) of the cohort. None or single comorbidity was present in 72.5% ($n = 29$) of patients, while over a quarter (27.5%) of the patients presented with more than one

significant comorbidity, most commonly a combination of type 2 diabetes and hypertension. On severity assessment, 72.5% ($n = 29$) had SAA and 27.5% ($n = 11$) had VSAA. At baseline, the median hemoglobin level was 7.0 gm/dL (IQR 5.7–8.0). The median absolute neutrophil count was $0.9 \times 10^9/L$ (IQR 0.6–1.1), and the median platelet count was $15 \times 10^9/L$ (IQR 5–19). Regarding safety, hyperbilirubinemia occurred in 27.5% ($n = 11$) of patients, and elevation of aspartate aminotransferase and alanine aminotransferase was observed in 22.5% ($n = 9$). All hepatic adverse events were grade ≤ 2 according to CTCAE v5.0, were transient in nature, and did not require dose reduction or discontinuation of CSA or EPAG.

At 6 months, complete response was achieved in 17.5% ($n = 7$) of patients, partial response in 45% ($n = 18$), while 37.5% ($n = 15$) had no response. Table 1 summarizes the baseline characteristics and outcome.

Hematological Kinetics Over Time

To assess the primary efficacy of the treatment, blood counts were tracked at three critical time points: baseline, 3 months, and 6 months. Given the paired nature of the data and the non-normal distribution of blood counts in bone marrow failure states, the Wilcoxon signed-rank test was utilized to determine statistical significance. All hematologic parameters showed significant improvement over the 6-month period (Table 2). Median hemoglobin increased from 7.0 gm/dL at baseline to 9.1 gm/dL at 6 months ($p < 0.001$). ANC rose from 0.9 to $1.95 \times 10^9/L$ ($p < 0.001$), and platelet count improved from 15 to $54 \times 10^9/L$ ($p < 0.001$). Significant changes were observed at both 3 and 6 months compared to baseline, with additional incremental gains between 3 and 6 months.

Quantitative Baseline Predictors of Response

To further delineate the differences between responders and non-responders, baseline continuous variables were compared using the Mann–Whitney U test. This analysis identifies the specific hematologic thresholds that distinguish the two groups at the outset of therapy. Responders were significantly younger than non-responders (median 56 vs 66 years, $p < 0.001$). Responders had significantly higher baseline hemoglobin, ANC, and platelet counts compared to nonresponders (Hb: 7.4 vs 5.8 gm/dL; ANC: 1.0 vs $0.4 \times 10^9/L$; Plt: 17 vs $6 \times 10^9/L$; all $p < 0.001$). Younger age was also significantly associated with response (Table 3).

Table 1: Descriptive statistics of the study cohort (N = 40)

Characteristic	Value
Age (Years): median (interquartile range)	56.5 (54.0–64.0)
Sex	
Male, n (%)	23 (57.5%)
Female, n (%)	17 (42.5%)
Comorbidities	
None or single comorbidity, n (%)	29 (72.5%)
More than one comorbidity (>1), n (%)	11 (27.5%)
Type 2 diabetes mellitus	16 (40%)
Hypertension	15 (37.5%)
Ischemic heart disease	2 (5%)
Chronic obstructive lung disease	4 (10%)
Severity	
Severe aplastic anemia	29 (72.5%)
Very severe aplastic anemia	11 (27.5%)
Baseline blood counts (median, interquartile range)	
Hemoglobin (gm/dL)	7.0 (5.7–8.0)
Absolute Neutrophil Count (/10 ⁹ /L)	0.9 (0.6–1.1)
Platelets (/10 ⁹ /L)	15 (5–19)
Side effects	
Hyperbilirubinemia, n (%)	11 (27.5%)
Elevated AST/ALT, n (%)	9 (22.5%)
Clinical response at 6 months	
Complete response, n (%)	7 (17.5%)
Partial response, n (%)	18 (45%)
No response, n (%)	15 (37.5%)

Categorical Predictors of Response

Understanding which patients are likely to benefit from a CsA–eltrombopag regimen is essential for personalized treatment planning. A subgroup analysis using Fisher's exact test was performed to evaluate the association between baseline categorical variables and objective response at 6 months (Table 4). Response rates were significantly higher in patients aged ≤60 years compared with those >60 years (84.0% vs 26.7%, $p < 0.001$). Similarly, patients with ≤1 comorbidity demonstrated markedly superior responses compared with those having multiple comorbidities (75.9% vs 27.3%, $p < 0.001$). Disease severity also influenced outcome, with patients with severe aplastic anemia (SAA) showing significantly better responses than those with very severe aplastic anemia (VSAA) (79.3% vs 18.2%, $p < 0.001$). Although response rates were numerically higher in females compared with males (64.7% vs 60.9%), this difference did not reach statistical significance ($p = 0.31$).

Discussion

In this geriatric cohort of severe aplastic anemia (SAA), frontline treatment with cyclosporine (CsA) combined with

Table 2: Hematologic response over 6 months in patients of aplastic anemia

Parameter	B median (IQR)	3 m median (IQR)	6 m median (IQR)	B vs 3 m (p-value)	B vs 6 m (p-value)	3 m vs 6 m (p-value)
Hb (gm/dL)	7.0 (5.7–8.0)	8.2 (7.0–9.0)	9.1 (8.2–11.8)	<0.001	< 0.001	<0.001
ANC (×10 ⁹ /L)	0.9 (0.6–1.1)	1.6 (0.8–1.9)	1.95 (1.5–2.3)	<0.001	< 0.001	0.004
Plt (×10 ⁹ /L)	15 (5–19)	33 (10–64)	54 (15–87)	<0.001	< 0.001	0.002

Hb: hemoglobin; ANC: absolute neutrophil count; Plt: platelet count; B: baseline; 3m: 3 months; 6m: 6 months

Table 3: Comparison of baseline hematologic parameters and age between responders and non-responders

Variable	Responders (n = 29) median (IQR)	Nonresponders (n = 11) median (IQR)	z-score	p-value
Age (years)	56 (54–60)	64 (60–70)	–3.10	0.002
Baseline hemoglobin (gm/dL)	7.4 (6.5–8.5)	5.8 (5.0–6.5)	–3.85	<0.001
Baseline absolute neutrophil count (×10 ⁹ /L)	1.0 (0.7–1.4)	0.4 (0.2–0.6)	–4.20	<0.001
Baseline platelet count (×10 ⁹ /L)	17 (10–30)	6 (3–10)	–4.35	<0.001

Table 4: Subgroup analysis showing the effect of age, sex, comorbidities, and disease severity on treatment response in patients with acquired aplastic anemia

Variable	Subgroup	Responders (n)	Nonresponders (n)	Response rate	p-value
Age	> 60 Years	4	11	26.7%	<0.001
	≤ 60 Years	21	4	84 %	
Sex	Male	14	9	60.9%	0.31
	Female	11	6	64.7%	
Comorbidity	≤ 1	22	7	75.9%	<0.001
	> 1	3	8	27.3%	
Severity	SAA	23	6	79.3%	<0.001
	VSAA	2	9	18.2%	

Table 5: Comparison of the present study with other studies published in literature

	Study population	Study type/focus	Response
Present study	40 adults (≥ 18 years) patients with treatment-naïve SAA, VSAA	Retrospective cohort (older adults)	ORR 62.5% (CR 17.5%, PR 45%) at 6 months
Scheinberg et al. ⁸	54 adults (≥ 18 years) patients with treatment-naïve SAA	Phase II, single-arm (CsA + EPAG)	Overall hematological response rate by 6 months of treatment was 46%
Chen et al. ⁹	AAA patients receiving front-line ATG combined with CSA and EPAG (group A, 51 patients) or CSA plus EPAG alone (group B, 38 patients)	Retrospective, real-world multicenter analysis	The 6-month ORR/CR was 73.3%/24.4% and 60.6%/27.3% in groups A and B ($p > 0.1$). For SAA patients, the 6-month ORR was 74.1% vs 50% and 6-month CR was 25.9% vs 20% in Groups A and B ($p > 0.1$)

AAA, acquired aplastic anemia; SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; CSA, cyclosporine A; EPAG, eltrombopag; ATG, antithymocyte globulin; ORR, overall response rate; CR, complete response

eltrombopag (EPAG) resulted in a high overall response rate (ORR) of 72.5% at 6 months, with clinically meaningful trilineage hematologic recovery. Median hemoglobin increased from 7.0 to 9.0 gm/dL, absolute neutrophil count (ANC) from 0.9 to $1.95 \times 10^9/L$, and platelet count from 15 to $54 \times 10^9/L$, translating into reduced transfusion dependence and lower risks of infection and bleeding. Continued improvement between 3 and 6 months highlights the gradual kinetics of hematologic recovery in SAA and supports persistence with therapy even in the absence of early robust responses, consistent with prior eltrombopag-based frontline studies.^{8,9} These findings align with the SOAR trial by Scheinberg et al.,⁸ a multicenter phase II study of frontline CsA plus EPAG in treatment-naïve adult SAA, which reported a 46% ORR at 6 months. Despite enrolling a younger, fitter population, SOAR confirmed biological activity and acceptable safety of this ATG-free regimen, with hepatic toxicity being the most common adverse event. The higher response observed in our real-world cohort likely reflects differences in patient selection, disease severity, dosing strategies, and treatment persistence. Additional support comes from the multicenter Chinese study by Chen et al.,⁹ which compared ATG + CsA + EPAG with CsA + EPAG alone as frontline therapy. Although response rates were numerically higher with triple therapy, differences were not statistically significant, including in SAA patients. Notably, CsA + EPAG was associated with fewer adverse events and no treatment-related mortality, underscoring its favorable tolerability. Collectively, these findings suggest that CsA plus EPAG offers comparable efficacy with reduced toxicity in selected patients, particularly older individuals and those unsuitable for ATG-based therapy.

In the landmark study by Peffault de Latour et al.,⁶ the addition of EPAG to ATG and CSA resulted in higher response

rates; however, such regimens may not be feasible in older patients or those with multiple comorbidities. In this context, our findings support the growing evidence that EPAG combined with CSA alone can offer meaningful hematologic improvement in carefully selected patients. Importantly, our study specifically focuses on a clinically challenging subgroup—patients with contraindications to ATG—who are often underrepresented in clinical trials. The median age of 56.5 years and the high burden of metabolic and cardiovascular comorbidities reflect real-world practice in India and other low- and middle-income countries. In such settings, avoidance of ATG may reduce treatment-related morbidity without completely compromising efficacy.

Baseline hematopoietic reserve emerged as a dominant determinant of response. Responders were younger (median 56 vs 64 years) and had significantly higher baseline ANC and platelet counts, reinforcing prior observations that preserved marrow activity predicts responsiveness to IST augmented with EPAG.¹⁰ Age > 60 years, multiple comorbidities, and VSAA were associated with inferior outcomes, highlighting the importance of early intervention before irreversible marrow exhaustion occurs. These findings are consistent with the large international analysis by Fattizzo et al.,¹¹ involving 1,113 patients with aplastic anemia, which demonstrated significantly lower response rates and higher mortality in elderly patients irrespective of treatment modality, with age and disease severity emerging as the strongest independent predictors of adverse outcomes—even in the TPO-receptor agonist era.

Comparison of the present study with other studies published in the literature is outlined in Table 5.

This study has several limitations inherent to its retrospective, single-center design, including potential selection bias and incomplete capture of confounding

variables. The relatively small sample size limits statistical power and precludes robust subgroup analyses. Absence of a contemporaneous control group receiving ATG-based immunosuppression restricts direct comparative conclusions. Follow-up was limited to 6 months, preventing assessment of long-term outcomes such as relapse, clonal evolution, and overall survival. Additionally, treatment decisions and dosing adjustments were individualized, introducing heterogeneity.

CONCLUSION

Cyclosporine combined with eltrombopag is an effective and well-tolerated treatment option for selected patients with acquired aplastic anemia who are unsuitable for ATG-based immunosuppression. This regimen provides meaningful hematologic recovery with acceptable toxicity, particularly in older patients and those with comorbidities. Further prospective and multicentric studies are needed to validate these findings and define long-term outcomes.

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ANNOUNCEMENT

Nominations are invited from members of API for the post of “Editor-in-Chief Journal of the Association of Physicians of India (JAPI)”.

Post will be for a period of 3 years from January 2028 onwards.

The nomination should be proposed and seconded by two members along with your Biodata in a sealed envelope by post/Courier/by email - api.hdo@gmail.com and should reach by 20th September 2026 and withdrawal date 30th September 2026, to the Hon. General Secretary of API, Dr. Puneet Saxena, Unit No. 3301 Prestige Turf Tower “C”, Shakti Mill Lane, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400011, Maharashtra, India.

Dr. Puneet Saxena
Hon. General Secretary



Echocardiographic Manifestations in Chronic Obstructive Pulmonary Disease Patients with a History of Chronic Smoking: A Cross-sectional Study

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Received: 19 March 2026; Accepted: 31 July 2026

[Visual Abstract](#)

ABSTRACT

Background: This study aimed to evaluate the clinical profile and its association with spirometry and two-dimensional (2D) echocardiographic findings in patients with chronic obstructive pulmonary disease (COPD).

Methodology: A cross-sectional study was carried out at LLRM Medical College, Meerut, which included 144 COPD patients over 40 years of age, selected after informed consent and ethical approval. Patients with other respiratory or cardiac diseases, immunocompromised status, or poor echocardiographic imaging were excluded. Each participant underwent clinical evaluation, which included a history of respiratory symptoms and comorbidities, along with comprehensive investigations such as blood tests, spirometry, chest X-ray, sputum analysis, electrocardiography (ECG), arterial blood gases, and 2D echocardiography. Data analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 29. A p -value < 0.05 was considered statistically significant.

Results: The data reveal that most COPD patients fall into Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 (severe), with a significant number also in stage 2 (moderate), indicating a high prevalence of advanced disease. COPD predominantly affects individuals over 50, with peak occurrence in the 60–69 age-group. Disease duration increases with severity, ranging from 2.38 years in stage 1 to 16.74 years in stage 4, showing a clear link between duration and progression. ECG abnormalities such as P-pulmonale, right ventricular hypertrophy (RVH), arrhythmias, and low QRS voltage were more frequent in severe stages, especially stage 3, highlighting the cardiovascular burden in advanced COPD. Echocardiographic findings, including pulmonary hypertension, right atrial enlargement, right ventricular dysfunction, and tricuspid regurgitation, showed significant association with disease severity ($p < 0.05$).

Conclusion: This study demonstrates a strong link between COPD severity and cardiovascular complications, especially right heart involvement. Significant associations between GOLD stages and 2D echocardiographic findings highlight the importance of routine cardiac screening in COPD patients. Pulmonary hypertension, right ventricular dysfunction, and tricuspid regurgitation were the most common complications, underscoring the need for close monitoring and targeted treatment. Early intervention and integrated cardiac evaluation in COPD management can help prevent right heart failure and improve patient outcomes.

Keywords: Chronic obstructive pulmonary disease, Smoking, Spirometry.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1688

women (12.2%), associated with smoking and environmental risks. Smoking worsens cardiac outcomes, leading to pulmonary hypertension and right heart failure.⁸

Two-dimensional (2D) echocardiography and electrocardiography (ECG) are effective in detecting cardiac abnormalities, such as right ventricular hypertrophy and tricuspid regurgitation. These findings correlate with disease severity, highlighting the need for early cardiovascular screening and intervention in COPD patients.

MATERIALS AND METHODS

A cross-sectional study was carried out at LLRM Medical College, Meerut, among patients admitted to the Medicine Ward, following informed written consent from participants and approval from the institutional ethical committee. The total sample size for the study was 144, calculated using the formula $4pq/D^2$, where p represents the prevalence of COPD (taken as 10%), $q = 100 - p = 90$, and d is the allowable error (5%). All patients meeting the inclusion criteria were interviewed, and relevant investigations were conducted. Clinical and laboratory data were extracted from patient records and analyzed using appropriate statistical software. Smoking exposure was quantified in pack-years and categorized based on the duration and intensity of smoking to assess its association with spirometric severity and echocardiographic abnormalities.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) contributes significantly to global mortality and morbidity, responsible for over 3 million deaths annually. In 2020, 251 million individuals were affected worldwide, with a high burden in low- and middle-income countries like India.^{1,2} Prevalence in India varies regionally, ranging from 2 to 22% in men and 1.2 to 19% in women, with higher rates seen in Empowered Action Group (EAG) states and the Northeast. Risk factors include aging, smoking, biomass fuel use, poor ventilation, and past tuberculosis.^{3,4}

Pathologically, COPD is characterized by chronic inflammation, airway remodeling, and airflow obstruction.⁵ The Global

Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines classify disease severity based on spirometry.⁶ Importantly, COPD extends beyond pulmonary impairment and significantly affects cardiovascular health.

Cardiovascular problems—particularly coronary artery disease (30.2%), heart failure (15.7%), and dysarrhythmias (13%)—are major causes of morbidity and mortality among COPD patients. A 10% reduction in FEV₁ increases heart-related death by 28% and morbid coronary events by 20%. COPD is also linked to atherosclerosis, as shown by raised carotid intimal medial thickening (CMT).⁷

A study in Madurai found a 22.1% COPD prevalence, higher in men (39.2%) than

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How to cite this article: Mittal AK, Singh Y, Soni PK, et al. Echocardiographic Manifestations in Chronic Obstructive Pulmonary Disease Patients with a History of Chronic Smoking: A Cross-sectional Study. *J Assoc Physicians India* 2026;74(9):63–66.

Statistical Analysis

Data were compiled using Microsoft Excel and analyzed with Statistical Package for the Social Sciences (SPSS) version 29. Continuous variables were summarized using mean and standard deviation, and categorical variables as frequency and percentage. Associations between categorical variables were tested using the Chi-squared test/Fisher's exact test. Relationships between continuous variables were analyzed using Pearson correlation (*r*). A *p*-value < 0.05 was considered statistically significant.

The inclusion criteria comprised adult female and male COPD patients aged over 40 years. The exclusion criteria comprised patients having known respiratory diseases other than COPD, those with a history of cardiac diseases such as ischemic heart disease, rheumatic or valvular heart disorders, congenital heart conditions, or peripheral vascular disease. Additionally, immunocompromised individuals and patients with poor echogenicity, in whom diagnostic echocardiographic evaluation could not be performed, were excluded.

Each enrolled patient underwent a comprehensive evaluation, including a detailed clinical history of presenting complaints such as breathlessness, chest pain, cough with sputum, fever, weight loss, and appetite loss. Symptoms of comorbid conditions such as cardiac, hepatic, or renal failure (e.g., pedal edema, abdominal distension, and reduced urine output) were documented. Past medical history, particularly of tuberculosis, antitubercular treatment, diabetes, or other significant illnesses, as well as contact with patients with tuberculosis, was recorded. All participants underwent investigations such as complete blood count, kidney and liver function tests, serum electrolytes, virology screening, spirometry, chest X-ray (PA view), sputum analysis for CBNAAT and culture sensitivity, ELISA for HIV, arterial blood gas analysis, ECG, and a 2D echocardiogram. This comprehensive approach aimed to assess the systemic and cardiac impact of COPD in detail.

RESULTS

The distribution of COPD patients according to GOLD staging is shown in Table 1. The majority of patients fall under stage 3 (severe), followed by stage 2 (moderate). Stage 4 (very severe) and stage 1 (mild) comprise 13.19 and 9.02% of the population, respectively. Overall, the data show a higher prevalence of severe forms of COPD among the study population.

The age-wise distribution of patients is presented in Table 2. The highest number

of patients falls in the 60–69 age-group (56 cases), followed closely by the 50–59 age-group (52 cases). The 40–49 and 70–79 age-groups account for 14 and 18 patients, respectively. Very few cases are seen in the 80–89 age-group (4 patients), and none are reported in the 30–39 range. This indicates that COPD predominantly affects individuals over 50 years of age.

The mean duration of COPD across different GOLD stages is shown in Table 3. Patients in stage 1 (mild) have had the disease for an average of 2.38 years. The duration increases progressively with disease severity: 5.58 years in stage 2, 9.93 years in stage 3, and 16.74 years in stage 4. This trend suggests a strong correlation between disease progression and duration of illness. Longer disease duration is associated with more severe GOLD stages.

The distribution of ECG abnormalities across GOLD stages is summarized in Table 4. P-pulmonale and right ventricular hypertrophy (RVH) are most prevalent in stage 3 (severe), with 46 and 43 cases, respectively. Stage 2 (moderate) shows a high incidence of arrhythmias (18) and low QRS voltage (21). In stage 4 (very severe), RVH remains notable (17 cases), but arrhythmias and low QRS voltage are less frequent. ECG abnormalities become more prominent with increasing COPD severity, especially in GOLD stages 2 and 3 (*p*-value < 0.05).

Table 1: Distribution of COPD patients according to GOLD staging (*n* = 144)

GOLD stage	Number of patients	Percentage
Stage 1 (mild)	13	9.02%
Stage 2 (moderate)	52	36.11%
Stage 3 (severe)	60	41.66%
Stage 4 (very severe)	19	13.19%
Total	144	100%

GOLD, Global Initiative for Chronic Obstructive Lung Disease

Table 2: Age-wise distribution of COPD patients (*n* = 144)

Age-group (years)	Number of patients
40–49	14
50–59	52
60–69	56
70–79	18
80–89	4
Total	144

GOLD, Global Initiative for Chronic Obstructive Lung Disease

Echocardiographic findings across different GOLD stages are presented in Table 5. It shows a progressive increase in right-sided cardiac abnormalities (RAE, RVD, RVH, TR, pulmonary hypertension, and cor pulmonale) from mild to very severe COPD. Left ventricular changes (LVDD, LVH) rise in severe stages. Overall, advanced GOLD stages were strongly associated with right heart dysfunction and pulmonary hypertension (*p*-value < 0.05).

The distribution of clinical symptoms across GOLD stages is shown in Table 6. Breathlessness was the most common symptom across all GOLD stages. Raised JVP and pedal edema were more prevalent in severe and very severe stages, suggesting worsening right heart strain in advanced COPD. Symptoms progressively worsen from mild to moderate to severe stages, with a slight drop in symptoms at the very severe stage, possibly due to patient adaptation or reduced reporting.

DISCUSSION

This study classified patients based on the GOLD criteria. The highest prevalence was noted in GOLD stage 3 (severe COPD), with 60 patients, followed by stage 2 (moderate, 52 patients), stage 4 (very severe, 19 patients), and stage 1 (mild, 13 patients). These findings are consistent with global trends, where moderate to severe cases dominate clinical presentations, often due to delayed diagnosis and intervention. Comparable findings have been reported in earlier studies.¹

When symptoms were stratified across GOLD stages, breathlessness and cough were universally present, with increasing frequency and severity noted from GOLD 1 to GOLD 4. Raised JVP and pedal edema—markers of right heart strain—were most prevalent in GOLD stages 3 and 4. For instance, breathlessness was reported in all 19 GOLD 4 patients and 50 of 60 GOLD 3 patients. These findings are consistent with established clinical guidelines and prior studies,¹ underscoring that symptom burden escalates with disease severity.

Table 3: Mean duration of COPD across GOLD stages

GOLD stage	Mean duration (years)
Stage 1 (mild)	2.38
Stage 2 (moderate)	5.58
Stage 3 (severe)	9.93
Stage 4 (very severe)	16.74

GOLD, Global Initiative for Chronic Obstructive Lung Disease

Table 4: Distribution of ECG abnormalities across GOLD stages

GOLD stage	P-pulmonale	RVH	Arrhythmia	Low QRS voltage
Stage 1	12	4	3	2
Stage 2	23	11	18	21
Stage 3	46	43	21	17
Stage 4	15	17	5	2

ECG, electrocardiogram; RVH, right ventricular hypertrophy

Table 5: Echocardiographic findings across GOLD stages

Finding	Mild	Moderate	Severe	Very severe
Cor pulmonale	7	21	33	16
LVDD	2	1	4	5
LVH	6	9	44	16
Pulmonary hypertension	4	11	43	17
RAE	4	23	46	15
RVD	6	25	43	15
RVH	4	15	41	16
TR	9	20	49	14

RAE, right atrial enlargement; RVD, right ventricular dilatation; TR, tricuspid regurgitation

Table 6: Distribution of clinical symptoms across GOLD stages

GOLD stage	Breathlessness	Raised JVP	Pedal edema	Cough
Stage 1	13	7	7	9
Stage 2	50	21	21	33
Stage 3	57	33	33	45
Stage 4	19	16	16	13

JVP, jugular venous pressure

The age distribution of participants ranged from 46 to 85 years, with a mean age of 60.79 ± 8.52 years and a median of 61. These figures align with global literature indicating higher COPD prevalence in older populations, as chronic exposure to smoking and environmental pollutants accumulates over time. Previous studies have also highlighted a strong association between age and COPD severity¹⁰ and onset, reinforcing the need for early screening in individuals over 50 years. In terms of gender distribution, a significant male predominance was observed—122 males compared to 22 females. Similar gender-based trends have been observed in earlier studies,^{10,11} which attribute higher male prevalence to greater exposure to smoking and occupational hazards. However, increasing COPD incidence among women in recent years due to biomass fuel exposure and rising smoking trends underlines the necessity of gender-sensitive public health strategies.

A significant correlation was found between clinical symptoms and 2D echocardiographic findings. Raised JVP and pedal edema showed perfect positive correlations ($r = 1.0$) with cor pulmonale, reflecting their reliability as clinical markers for right heart dysfunction. Additionally, mild

positive correlations were noted between breathlessness and echocardiographic signs like right atrial enlargement (RAE) and right ventricular hypertrophy (RVH), reinforcing their diagnostic value.

Analyzing the duration of COPD revealed a strong link with disease severity. The average disease duration in GOLD 4 patients was 16.74 years, compared to just 2.38 years in GOLD 1. A correlation coefficient of 0.92 indicated a very strong positive association, suggesting that the longer the disease persists, the more likely patients are to develop severe airflow obstruction. This observation is supported by findings from previous studies,¹⁰ where disease duration and exposure were key predictors of progression.

ECG findings also showed clear stratification with disease severity and duration. ECG signs like P-pulmonale and RVH were more common in GOLD stages 3 and 4, with P-pulmonale observed in 46 GOLD 3 patients and 15 GOLD 4 patients. These changes are hallmarks of chronic right heart strain due to pulmonary hypertension. RVH prevalence also rose with disease duration, reaching over 90% in patients with disease duration beyond 12 years. These

results reinforce ECG's utility^{12,13} as a simple yet effective screening tool, especially in resource-constrained settings.

A strong correlation was also seen between ECG findings and 2D echocardiography. For example, RAE was 100% consistent with ECG P-pulmonale, and pulmonary hypertension was strongly associated with ECG RVH. Tricuspid regurgitation (TR), another marker of right heart pressure overload, was noted in 65.28% of patients, further reinforcing the interdependence, as reported in earlier studies,^{13,14} of echocardiographic and ECG indicators.

By GOLD stage, echocardiographic abnormalities became progressively common. RVH increased from 21.6% in GOLD 1 to 84.21% in GOLD 4. Similarly, pulmonary hypertension rose from 30.77% in GOLD 1 to nearly 90% in GOLD 4. Other cardiac manifestations, such as RVD, cor pulmonale, TR, and RAE, followed similar patterns. These findings are in agreement with previous studies¹³ that persistent hypoxia and pulmonary vascular remodeling in advanced COPD lead to progressive right heart involvement (Chi-square p -value < 0.05).

Interestingly, left-sided cardiac abnormalities like LVH and LVDD, though not primary manifestations of COPD, were more frequent in advanced stages, suggesting coexisting systemic hypertension or aging-related changes. LVDD was highest in GOLD 4 (26.32%), with similar observations reported in previous studies,¹⁵ where LV diastolic dysfunction was linked to poor exercise capacity and comorbid cardiovascular disease in COPD patients.

The correlation coefficient between FEV1 and pulmonary hypertension was -0.48 , indicating a moderate negative association—lower FEV1 values were linked with a higher likelihood of pulmonary hypertension, as associated in previous studies.¹⁵ This supports well-established pathophysiology that airflow obstruction and hypoxia elevate pulmonary artery pressure. Similarly, the correlation of cor pulmonale with raised JVP and pedal edema (Pearson correlation $r = 1.0$) validates these signs as important noninvasive diagnostic tools.

In conclusion, the study underscores the intertwined nature of pulmonary and cardiac complications in COPD. With increasing GOLD stage and longer disease duration, both the prevalence and severity of right heart dysfunction escalate significantly. Clinical signs like raised JVP and pedal edema, alongside ECG and echocardiographic findings, provide valuable insight into disease progression and should be routinely evaluated in COPD management. Early detection

of cardiac involvement through simple clinical and diagnostic tools can guide timely interventions and improve patient outcomes.

CONCLUSION

In conclusion, this cross-sectional study of 144 COPD patients found that echocardiographic abnormalities were highly prevalent and increased significantly with disease severity. Cor pulmonale was present in 53.5% and showed a significant association with advanced GOLD stages (Chi-square $p = 0.03$). Tricuspid regurgitation increased significantly with GOLD severity ($p < 0.001$), while right atrial enlargement (66.7%, $p = 0.0008$) and right ventricular dysfunction (65.3%, $p = 0.008$) were significantly more common in severe and very severe COPD.

The statistically significant associations observed between GOLD staging and various 2D echocardiographic parameters underscore the necessity of incorporating echocardiographic screening into routine COPD evaluation. Pulmonary hypertension, right ventricular dysfunction, and tricuspid regurgitation emerged as the most prominent cardiovascular complications, necessitating close monitoring and targeted management. The correlation analysis further elucidated the interlinked nature of these abnormalities, providing valuable insights into disease progression. Most

importantly, the findings reinforce the need for early intervention strategies to impede or alleviate right heart failure in COPD patients. By integrating comprehensive cardiac assessments into COPD management protocols, healthcare providers can enhance patient care and improve long-term outcomes.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study received prior approval from the Institutional Ethics Committee of LLRM Medical College, Meerut, and informed consent was obtained from all participants.

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Perspectives on Newer Antiobesity Drugs (Semaglutide and Tirzepatide) among Healthcare Professionals Treating Obesity in South Asia: A Cross-sectional Survey

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Received: 27 April 2026; Accepted: 31 July 2026

[Visual Abstract](#)

ABSTRACT

Introduction: Obesity has reached epidemic proportions in South Asia, contributing significantly to metabolic diseases and economic burdens. Newer antiobesity medications (AOMs), such as semaglutide and tirzepatide, show promising efficacy but face barriers such as high costs and limited familiarity among healthcare professionals (HCPs) in low- and middle-income countries (LMICs). This study explored perceptions, prescribing practices, efficacy, safety concerns, and barriers to AOM use among HCPs managing obesity in South Asia.

Methods: A cross-sectional online survey was conducted from May to September 2025 among 552 HCPs (physicians, endocrinologists, bariatric surgeons, nephrologists, gastroenterologists, and dietitians) specializing in obesity care, recruited via social media groups using convenience sampling. The questionnaire, developed from prior surveys and pilot-tested, assessed knowledge, attitudes, and practices regarding AOMs. Descriptive analysis was performed using SPSS version 21.

Results: Of 552 responses, 86.4% were from India. Endocrinologists (62.9%) and internists (21.6%) dominated, with varied experience levels. Key factors influencing prescriptions included efficacy (83%), affordability (75.9%), and safety (58.9%). Reported efficacy was high with 51.7% of the patients achieving > 10% weight loss. Barriers encompassed high costs (93.8%), side effect fears (46.2%), and poor adherence (41.3%). Biosimilars were available to 52.7%, with 78.6% of HCPs open to them if efficacy/safety matched originators.

Conclusions: South Asian HCPs recognize AOMs' transformative potential but are hindered by costs, safety, and access. Biosimilars could enhance equity, but require robust data and regulation. Targeted education, reimbursement policies, and region-specific evidence are essential to optimize AOM integration in obesity management.

Keywords: Antiobesity medications, Biosimilars, Healthcare professionals, South Asia.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1709

INTRODUCTION

Obesity rates have surged globally to epidemic levels, with South Asia being a primary contributor. Obesity rates range from 3.5% in rural Bangladesh to 36.2% in India to over 65% in the Maldives.^{1,2} Early intervention is essential not only to manage metabolic diseases but also to alleviate the economic burden of workplace absences, reduced work capacity, and premature mortality, among many obesity-linked consequences. A 2017 report from the World Obesity Federation forecasted that India could face annual costs of US\$13 billion for addressing obesity-linked conditions by 2025.³

A systematic review reported that supervised exercise and diet incur costs similar to those of pharmaceuticals such as orlistat.⁴ Previously, due to safety issues and lesser efficacy, antiobesity medications (AOMs) were used in less than 1% of individuals with obesity.⁵ Better understanding of obesity's underlying mechanisms, coupled with the

proven efficacy of newer AOMs, is paving the way for a new phase in obesity treatment.⁶ The cost of newer AOMs like tirzepatide and semaglutide remains high, limiting their use and availability, especially in low- and middle-income countries (LMICs) of South Asia.⁷

Given the economic burden on the person and healthcare system, management of obesity needs to be patient-centric, culturally appropriate and cost-effective. Previously, biosimilar liraglutide was shown to be noninferior to reference liraglutide.⁸ Given the rapid emergence of newer AOMs and their potential role in obesity management, this study aimed to investigate perceptions, prescribing practices, perceived efficacy, safety concerns, and barriers to the use of AOMs among HCPs managing obesity in South Asia.

MATERIALS AND METHODS

The study involved HCPs who filled out an online questionnaire on knowledge, attitudes,

and practices related to AOMs. Data were collected between May and September 2025. The HCPs included doctors with postgraduate or higher degrees practicing as physicians, endocrinologists, bariatric surgeons, nephrologists, gastroenterologists, and dietitians specializing in obesity management with a significant practice centered around obesity and complications related to obesity.

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How to cite this article: Agarwal K, Nagendra L, Bhattacharya S, et al. Perspectives on Newer Antiobesity Drugs (Semaglutide and Tirzepatide) among Healthcare Professionals Treating Obesity in South Asia: A Cross-sectional Survey. *J Assoc Physicians India* 2026;74(9):67–70.

The questionnaire was developed based on prior published surveys and expert consensus and was pilot-tested with 20 clinicians to assess clarity and relevance.

The participants were contacted through social media groups to obtain their views about the efficacy and side-effect profile of newer AOMs, and hindrances to their use. They were asked about the strategies for addressing obesity and perceptions about it, alongside patient interactions centered on weight and obesity oversight. Their outlooks on AOMs, along with hands-on involvement in prescribing AOMs, were also assessed. It was convenience sampling based on voluntary participation and anonymity. HCPs not directly involved in obesity care were not included. Since the data required filling out an online questionnaire, no ethical approval was needed.

Descriptive analysis was performed using SPSS (version 21; SPSS, Inc., Chicago, IL).

RESULTS

Baseline Characteristics

A total of 552 responses were received, of which 477 (86.4%) were from India. Other countries included Bangladesh: 40 (7.2%), Nepal: 27 (4.9%), and Pakistan: 4 (0.7%). Most respondents were endocrinologists (62.9%), followed by internists with special interest in diabetes (21.6%). Other specialties represented included bariatric surgeons (3.4%) and nephrologists (2.7%). The group included HCPs with a wide range of experience in managing obesity. 194 (35.3%) had less than 5 years, 135 (24.4%) had 5–10 years, 68 (12.3%) had 11–15 years, 49 (8.9%) had 16–20 years, while 106 (19.2%) had more than 20 years of experience. The HCPs came from varied professional backgrounds, including government and private teaching institutes (25.9% and 23.1%), government and private nonteaching institutes (2.7% and 21.9%), private clinics (19.5%), or private clinics with additional institutional practice (11.6%). The frequency of AOM prescriptions varied from 2–9 per month in 43% of respondents, 10–49 per month in 22.6%, and > 50 in 6.3% of the respondents, while 21.9% of them recommended <1 AOM prescription/month. The availability of GLP-1 analogs varied according to country, and the summary of availability is shown in Figure 1. The most common GLP-1 analogs available include oral (87.9%) and injectable semaglutide (76.1%), tirzepatide (80.6%), and dulaglutide (66.1%). Other less common GLP-1 analogs include exenatide (15.6%) and lixisenatide (22.6%).

Factors influencing AOM Prescription

The factors influencing the decision of GLP-1 analogs are shown in Table 1. The most

significant factors that HCPs considered were efficacy in weight reduction (83%) and affordability (75.9%). Other factors included care-seeker preference (46.7%), the safety profile (58.9%), and availability (45.9%). Most HCPs reported high efficacy with the use of these drugs, with 51.7% reporting > 10% weight loss in their patients and another 44.3% reporting 5–10% weight loss in their patients. Most users reported gastrointestinal side effects (97.8%), including nausea, vomiting, and diarrhea. Other side effects reported included psychiatric (5.2%), ophthalmological (4.7%), and neurological (3.4%). The challenges faced while prescribing AOMs include high cost (93.8%), fear of side effects (46.2%), limited availability (26.6%), lack of insurance coverage (39.1%), and poor patient adherence (41.3%).

Perception of care-seekers using AOMs

Antiobesity medication users had several concerns regarding these drugs, which are summarized in Figure 2. The most common apprehensions included rebound weight gain after discontinuation (68.5%), long-term safety (47.5%), and weight loss efficacy of the AOM (38.9%). Misconceptions related to AOMs included the belief that they work without lifestyle changes (74.6%), that they should be used only in extreme obesity

(23.5%), or that their use causes dependency (21%).

Perceptions regarding Biosimilar AOMs

Biosimilars were available to 52.7% of the doctors. 78.6% of the HCPs opined they would prefer biosimilars once efficacy and safety data are comparable. Major concerns regarding the use of biosimilars are shown in Figure 3. These included a lack of long-term safety data (64.7%), differences in efficacy compared to the original molecule (56.9%), and regulations around their approval and quality (48.7%).

Future Developments

Despite these limitations, the HCPs were hopeful about the future of antiobesity therapy. 58% of them believed that new AOMs will revolutionize obesity management, while 15.9% of the respondents thought that the impact will be limited by cost and accessibility. When asked about the possible improvements in the current AOM landscape, better affordability (87.2%), fewer side effects (49.7%), and longer duration of action (48%) were possible areas of improvement. 61.2% of HCPs wanted real-world data from South Asia to make better-informed decisions.

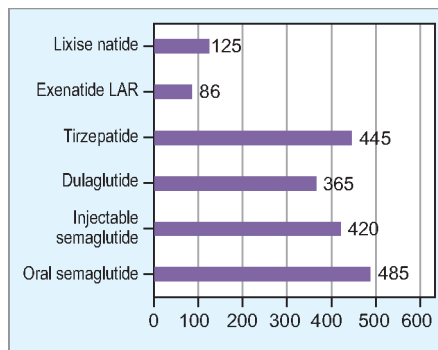


Fig. 1: Availability of GLP-1 analogs to doctors

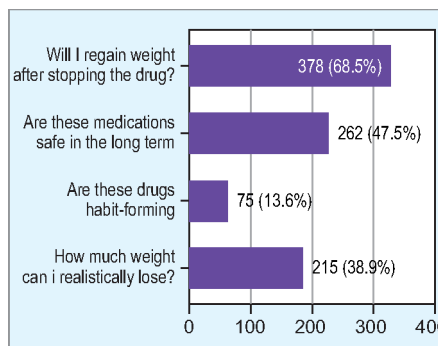


Fig. 2: Patients' concerns regarding GLP-1 analogs

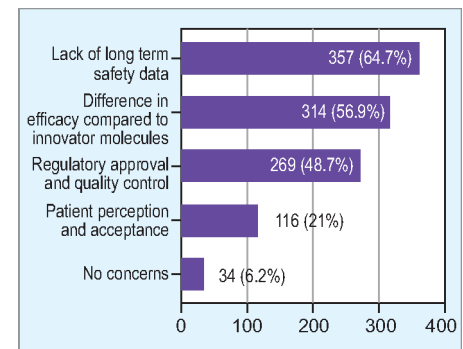


Fig. 3: Concerns regarding biosimilars of GLP-1 agonists

Table 1: Factors influencing use of GLP-1

Factor	Count	Percentage (%)
Efficacy in weight reduction	458	83
Cost and affordability	419	75.9
Insurance/ reimbursement availability	89	16.1
Safety profile and side effects	325	58.9
Patient adherence in your country	254	46.1
Patient preference/ request	258	46.7

DISCUSSION

This was a survey across multiple countries in South Asia regarding the use of newer AOMs by HCPs. The rising obesity rates have driven the global obesity drug market, projected to cross 100 billion dollars by 2030, while battling shortages due to increased demand. LMICs face an unusual double burden of malnutrition and obesity, with most of the healthcare expenditure borne by care-seekers. Given this situation, lower cost of AOMs will ensure equitable distribution of these drugs.

The HCPs most likely to prescribe AOMs were endocrinologists (62.9%) and internists (21.6%). While they had considerable experience in managing obesity, the frequency of AOM use remained around 2–9 per month in 43% of respondents. A study involving 197 physicians revealed that even when HCPs consider weight loss to be important for the management of a particular disease, such as osteoarthritis, polycystic ovary syndrome, and obstructive sleep apnea, they are likely to advise lifestyle measures, placing the burden of weight loss solely on the individual.⁹ HCPs usually initiate AOM use after failure or noncompliance with diet and exercise.¹⁰ The overestimation of standalone lifestyle approaches may trace back to longstanding paradigms in prior clinical directives, which prioritized such methods amid fewer alternatives available previously.¹¹

The important factors that the doctors considered were efficacy in weight reduction (83%), affordability (75.9%), patient preference (46.7%), the safety profile (58.9%), and availability (45.9%). This was similar to another large survey where expense and insurance coverage were the biggest concerns regarding AOM use.¹² Similarly, Rubino et al. reported that 71–93% of HCPs were willing to prescribe AOMs if reimbursed.⁹ For better insurance coverage, we need to evaluate the costs and indirect gains from averting obesity-linked secondary conditions. A small study has shown that incremental cost-effectiveness exceeded the threshold for semaglutide.¹³

Most respondents reported high efficacy with the use of AOMs, with 51.7% reporting > 10% weight loss. The most common side effects reported were gastrointestinal (97.8%). High cost (93.8%) and fear of side effects (46.2%) remain the biggest challenges for HCPs prescribing AOMs. In a study by Fadel et al.,¹⁴ 65% of the gastroenterologists felt that the risks and side effects of AOMs precluded their widespread use despite being effective. Kaplan et al.¹² reported that side effects (26.1%) and high cost and lack of insurance coverage (11.2%) were the most common reasons for discontinuing AOMs.

For AOM users, the biggest concerns were weight gain after stopping the drug (68.5%) and long-term safety (47.5%). In a similar study from Saudi Arabia,¹⁵ the most common concern was potential side effects (68.5%), but more than half (53.5%) were open to AOM use if their HCP prescribed it. Kaplan et al.¹² reported long-term side effects (57.5%), negative impact on health (56.3%), and interactions with other medicines (54.4%) as the biggest concern among the patients.

While biosimilars were available to 52.7% of the HCPs, most (78.6%) were open to the idea of biosimilars once long-term safety data (64.7%) and quality (48.7%) were ensured. It has been shown that the newer AOMs can be manufactured at a cost lower than the currently marketed one, and that the prices vary between countries.⁷ Previously, biosimilar liraglutide was shown to be noninferior to reference liraglutide.⁸ Factors influencing the choice of a particular biosimilar include pedigree of the manufacturers, their policies regarding the cold chain maintenance, shelf-life, precision and comfort of the delivery device, studies regarding safety, cost, physicians' and peer experience with the brand.¹⁶

For the future, better affordability (87.2%), fewer side effects (49.7%), and longer duration of action (48%) remained the real goals for AOMs and their biosimilars. In a survey by Lin et al.¹⁰ in China, the future perspectives included better efficacy (26%) and safer long-term use (26%). In another survey, HCPs flagged tolerance to AOMs (46.6%), dependence on AOMs for weight management (36.3%) as potential concerns.¹²

The strengths of the study are the wide category of HCPs who have been covered, including endocrinologists, internists, dietitians, nephrologists, and bariatric surgeons. However, the study has various limitations. The one-time snapshot risks temporal bias, and self-reports invite memory errors. HCPs were approached in common groups on social media and may not be representative of all doctors. While every effort was made to ensure representation from all parts of South Asia, most responders are from India. Patient-level outcomes were not analyzed. While the results may not be generalizable, the data represent the views of the doctors at the forefront of obesity management and show the shifts in obesity treatment paradigms. Future research should focus on how socioeconomic position, racial and ethnic backgrounds, and geographic locations influence health and prescription of AOMs.

This study highlights many policy implications. It is high time we recognize obesity as a chronic noncommunicable disease that demands long-term supervised medical treatment. High costs and lack of insurance coverage prioritize the need for simplified reimbursement policies and inclusion of AOMs in various public health initiatives. There is a need to establish regulatory guidelines and post-marketing surveillance for successful adoption of biosimilar AOMs. Nevertheless, continued medical education of healthcare providers and culturally relevant public education are essential to addressing misconceptions and promoting the ethical use of AOMs.

CONCLUSION

The survey highlights that HCPs from South Asia recognize that obesity treatment has entered a new era with the availability of newer AOMs with improved efficacy. Despite this recognition, the study identifies several barriers to the use of AOMs, including limited acceptance of obesity as a chronic disease. Cost and safety concerns remain the most important deterrents among HCPs to the use of AOMs. Biosimilar GLP-1 receptor agonists are likely to feature prominently in the AOM landscape in South Asia, pending efficacy and safety data. Bridging the gap between access and efficacy through improved affordability, targeted education of HCPs and the public, appropriate biosimilar regulation, and generation of real-world evidence will be pivotal to realize the full potential of AOMs in South Asia.

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Smartphone Usage Sleep Quality and Behavioral Health in Adolescents: A Cross-sectional Study from Eastern India



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Received: 27 June 2025; Accepted: 20 June 2026

[Visual Abstract](#)

ABSTRACT

Background: Widespread smartphone use has raised concerns regarding its effects on adolescent health, particularly sleep quality and behavioral outcomes. The associations between smartphone usage patterns, sleep disturbances, and markers of obesity and vision health have yet to be systematically evaluated in India.

Objectives: To assess the prevalence of smartphone usage, bedtime usage patterns, and their association with sleep quality, overweight status, and visual acuity among adolescents in Eastern India.

Methods: A cross-sectional study was conducted among 140 adolescents aged 13–19 years attending urban and rural schools in Eastern India. Participants completed a structured questionnaire covering demographics, daily and bedtime smartphone use, and sleep quality. Sleep quality was assessed using a modified Pittsburgh Sleep Quality Index (PSQI), and smartphone addiction was estimated using behavioral proxies. Chi-square tests were employed to assess associations, and logistic regression was used to identify predictors of poor sleep quality.

Results: The mean age of participants was 16.8 ± 1.9 years, with 55% male participants and 70% from urban areas. Smartphone usage at bedtime was reported by 89.3% of participants, and 42.1% reported poor sleep quality. Longer bedtime smartphone use (>30 minutes) was significantly associated with poor sleep quality ($\chi^2 = 42.5$, $p < 0.001$). Daily usage exceeding 2 hours was significantly associated with overweight status ($\chi^2 = 21.9$, $p = 0.001$).

Conclusion: A high prevalence of bedtime smartphone use among adolescents in Eastern India is significantly associated with poor sleep quality. Excessive daily smartphone use is also linked with overweight status. Public health strategies should include digital hygiene awareness and school-based interventions.

Keywords: Adolescents, Digital health, Overweight, India, Sleep quality, Smartphone use.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1618

INTRODUCTION

The exponential rise in smartphone penetration among Indian adolescents has reshaped their communication, entertainment, and study habits.¹ However, this technological boon has been accompanied by rising concerns over digital overexposure, particularly its impact on sleep, emotional regulation, and physical health. Sleep is an essential component of adolescent well-being, and multiple international studies have associated excessive screen exposure—especially at bedtime—with reduced sleep duration and quality.²

Smartphones have become an indispensable part of modern adolescence, facilitating social connectivity, academic support, gaming, and entertainment. While they enhance access to information and interpersonal relationships, they also demand constant attention, encouraging compulsive behaviors.³ Adolescents, characterized by developmental vulnerabilities and

evolving cognitive control, are particularly susceptible to behavioral dependencies such as problematic smartphone use (PSU) and smartphone addiction. These behaviors are increasingly linked to negative outcomes such as reduced academic performance, mood disorders, and physical health disturbances.⁴

The intersection of digital habits and sleep is especially critical. Adolescents need approximately 8–10 hours of sleep per night for optimal health and cognitive functioning.⁵ Yet, studies from the United States, Japan, and Europe consistently report a decline in adolescent sleep duration correlated with increased electronic media use, particularly before bedtime.⁶ Smartphones, unlike traditional media, are interactive, portable, and equipped with blue-light-emitting screens—factors that can delay sleep onset, reduce melatonin secretion, and impair sleep architecture. Consequently, smartphone usage close to bedtime has been linked to delayed circadian rhythms, shortened sleep duration, poorer sleep efficiency, and increased daytime dysfunction.⁷

In the Indian context, digital access has expanded across socioeconomic strata due to low-cost mobile services and government digitization efforts.⁸ Consequently, Indian adolescents have experienced a similar rise in digital engagement, with increasing trends in social media consumption, mobile gaming, and digital streaming. However, empirical studies investigating how these behaviors affect physiological outcomes such as sleep, weight, and vision are still sparse. Unlike Western countries, where longitudinal data sets and national sleep surveillance systems are more robust, India lacks population-level behavioral health tracking systems for adolescents.

Moreover, cultural factors such as parental control, joint family systems, and academic pressure may differentially influence screen behaviors among Indian adolescents. Many adolescents attend tuition classes or engage in schoolwork until late in the evening, pushing leisure screen time into the night. This overlap between academic use and leisure browsing complicates the estimation of problematic use. In urban Indian households, where parental monitoring of device usage may be minimal or absent because of dual-working parents, unrestricted access to smartphones is common. This results in late-night screen exposure, further deteriorating sleep quality.⁹

While sleep is a well-established determinant of physical and mental health, it is also intricately linked to broader behavioral markers such as obesity and a sedentary lifestyle. Sleep restriction alters appetite-regulating

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How to cite this article: Chatterjee R, Sarkar SD, Mukherjee S, *et al.* Smartphone Usage Sleep Quality and Behavioral Health in Adolescents: A Cross-sectional Study from Eastern India. *J Assoc Physicians India* 2026;74(9):72–76.

hormones such as ghrelin and leptin, promotes late-night snacking, and reduces energy expenditure.¹⁰ These physiological changes have been implicated in rising adolescent overweight and obesity. Furthermore, prolonged smartphone use often replaces outdoor physical activities, thereby promoting a sedentary lifestyle. Thus, screen addiction not only disrupts sleep but also contributes to a broader risk of noncommunicable diseases.

Visual health is another domain of concern. Prolonged near-work activities, especially under poor lighting or on small screens, may cause visual fatigue, dry eye syndrome, and refractive errors such as myopia. The increasing incidence of school-based myopia in India and other Asian countries is suspected to be partially linked to digital overuse.^{11,12} However, few Indian studies have rigorously examined the relationship between screen duration and vision status in adolescents.¹³

Given the complexity and relevance of these associations, it is imperative to generate localized evidence. In India, empirical data on how bedtime smartphone use and screen exposure relate to sleep health and physical markers such as body weight and vision among adolescents are sparse. This study aims to explore these relationships in a school-based population in Eastern India.

METHODS

Study Design and Setting

This was a school-based, observational, analytical, cross-sectional study conducted over a 3-month period from January to March 2025. The study was carried out in both urban and rural areas of Eastern India, specifically targeting secondary and higher secondary school students. Schools included a mix of government, government-aided, and private institutions to ensure heterogeneity and better generalizability of the results. The institutional ethics committee approved the study protocol, and written informed consent was obtained from parents/guardians, while assent was obtained from each adolescent participant. Anonymity was ensured using coded identifiers, and the confidentiality of all responses was maintained.

Participants

Adolescents aged between 13 and 18 years enrolled in classes 8 through 12 were eligible to participate. The inclusion criteria were: (A) current smartphone usage for any duration, (B) ability to understand and complete the questionnaire in English or

the local language, and (C) provision of written informed consent from guardians and assent from students. The exclusion criteria included: (A) known history of chronic neurological, endocrine, or sleep disorders; (B) use of sleep-modifying medications, including sedatives or stimulants; and (C) diagnosed psychiatric illness or developmental disorders.

Sample Size and Sampling Technique

A minimum required sample size of 134 was calculated using the formula for cross-sectional studies (Z^2pq/d^2), assuming a 40% prevalence of poor sleep quality from prior literature,¹⁴ a 95% confidence level, and 8% absolute precision. Accounting for potential nonresponses and incomplete data, the final target sample was set at 150, with 140 complete responses included in the final analysis. A stratified random sampling technique was employed. Schools were first stratified by location (urban/rural) and type (government/private). Within each stratum, classes were chosen randomly. From the selected classes, students were then selected using systematic sampling based on the class register. Stratification also considered academic stream (science/general) for higher secondary students to capture variability in academic demands.

Data Collection Instruments

Data were collected using a pretested, structured, self-administered questionnaire, made available in both English and a validated vernacular translation. The questionnaire was divided into the following sections:

Sociodemographic details: Age, gender, place of residence, type of school, parental education, and monthly household income.

Smartphone usage patterns: Duration of use per day (<1 hour, 1–2 hours, >2 hours), bedtime smartphone use (yes/no), frequency of use at bedtime (1–3 times/month, weekly, daily), and types of activities (social media, study, gaming, video streaming).

Sleep quality: Evaluated using a modified version of the Pittsburgh Sleep Quality Index (PSQI), adapted for adolescent self-report.¹⁵ A global PSQI score >5 indicated poor sleep quality.

Body weight perception: Participants self-classified into weight categories based on a reference image scale validated in adolescent health surveys (normal, overweight, obese).

Vision status: The most recent school vision screening results (6/6 or subnormal <6/6) were recorded where available or were self-reported.

The questionnaire was reviewed by two public health experts and piloted among

15 students in a nonparticipating school to ensure clarity and cultural appropriateness.

Statistical Analysis

Data were entered and cleaned in Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY). Descriptive statistics were computed for all variables. Continuous variables (e.g., age) were summarized as means and standard deviations, whereas categorical variables (e.g., gender, residence, and smartphone usage categories) were presented as frequencies and percentages. Bivariate analyses using Chi-squared tests were performed to assess associations between sleep quality and categorical independent variables such as bedtime smartphone use, duration of use, and body weight category. Logistic regression analysis was conducted to identify predictors of poor sleep quality, with independent variables including bedtime smartphone use, daily screen time, and urban residence. A p -value < 0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 140 adolescents were included in the analysis. The mean age of the participants was 16.8 years [standard deviation (SD) $\pm$ 1.9], with an age distribution ranging from 13 to 19 years. There was a slight male predominance ($n = 77$, 55%), and the majority ($n = 98$, 70%) resided in urban settings. Regarding parental education, 91 participants (65%) reported that either parent had completed higher secondary education or above.

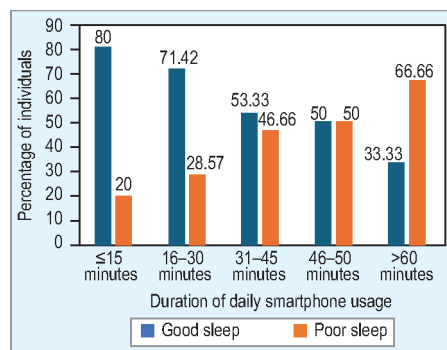
Concerning socioeconomic status, the majority of families reported a monthly income between ₹30,000 and ₹40,000, with urban participants predominantly clustered in the higher income brackets. Use of hands-free devices while using smartphones was reported by only 25% of participants.

Smartphone Usage Patterns

Among the 140 participants, 125 (89.3%) reported using their smartphones at bedtime. The frequency of bedtime smartphone use was as follows: 73.5% ($n = 103$) used them every day, 17% ($n = 24$) several times a week, 6.5% ($n = 9$) once a week, and 3% ($n = 4$) only 1–3 times per month. Regarding the duration of bedtime use, 43% of participants ($n = 60$) reported using their smartphones for >30 minutes before sleep, including 12.5% who used them for >60 minutes (Table 1). The most commonly reported purpose of use was

Table 1: Smartphone usage pattern

Variables	N (%)
Smartphone use at bedtime	125 (89.3%)
Smartphone usage frequency	
Everyday	103 (73.57%)
Several times a week	24 (17.14%)
Once a week	9 (6.42%)
3 times/month	4 (2.85%)
Smartphone usage duration	
Duration >30 minutes	60 (42.86%)
Duration >60 minutes	50 (35.71%)
Daily use >2 hours	30 (21.42%)
Reasons for use	
Social networking	113 (80.5%)
Watching videos	68 (48.57%)
Gaming	39 (27.85%)
Educational purposes	5 (3.57%)

**Fig. 1:** Relationship between daily smartphone usage and sleep quality

social networking (80.5%), followed by watching videos, messaging, gaming, and educational purposes. More than 40% ($n = 56$) reported daily smartphone use exceeding 2 hours (Table 1).

Sleep Quality

Based on the modified PSQI scores, 59 participants (42.1%) were classified as having poor sleep quality (PSQI >5). The average reported sleep duration was approximately 6 hours per night, with a substantial proportion reporting difficulty initiating sleep or frequent awakenings. Notably, poor sleep quality was more prevalent among participants using smartphones at bedtime (47.2%) than among those who did not (10.7%), a statistically significant difference ($\chi^2 = 6.42, p = 0.011$).

A strong relationship was found between the time spent using smartphones at bedtime and sleep quality. Participants using smartphones for 31–45 minutes and 46–60 minutes showed significantly higher rates of poor sleep, and those using them for >60 minutes had several-fold increased odds of poor sleep ($\chi^2 = 42.5, p < 0.001$)

Table 2: Logistic regression

Variable	Coefficient	Standard error	z	$p > z $	0.025	0.975
Constant	-1.91	0.95	-2	0.05	-3.78	-0.04
Gender	-0.94	0.82	-1.15	0.25	-2.55	0.66
Residence	3.76	1.45	2.59	0.01	0.92	6.61
Daily smartphone usage	1.27	0.46	2.78	0.01	0.37	2.16
Bedtime usage of smartphone	-0.54	0.34	-1.58	0.11	-1.21	0.13

(Fig. 1). Participants using smartphones for ≤15 minutes at bedtime had the lowest prevalence of poor sleep (20%).

Other Health Associations

Among the total participants, 33 (23.6%) self-identified as overweight or obese. There was a significant association between daily smartphone usage exceeding 2 hours and overweight status ($\chi^2 = 21.9, p = 0.001$). Of those who used smartphones for >2 hours per day, 70% were overweight, compared with 20% among those with ≤1 hour of usage.

Regarding blood pressure, only six participants were classified as hypertensive based on school health records or self-report, and no significant association was found between hypertension and smartphone usage patterns ($p > 0.05$).

Visual acuity (defined as 6/6 or subnormal) was reported to be subnormal in 18% of participants. However, no statistically significant association was found between visual status and bedtime smartphone use ($p > 0.05$), although trends suggested marginally higher rates of subnormal vision among heavy users.

Multiple logistic regression analysis revealed that both place of residence and daily smartphone use duration were significant predictors of poor sleep quality among adolescents (Table 2). Specifically, residing in urban areas was strongly associated with increased odds of poor sleep, with a regression coefficient of 3.76 ($p = 0.009$), indicating that urban adolescents were significantly more likely to experience disturbed sleep than their rural counterparts. Additionally, daily smartphone use duration showed a significant positive association with poor sleep quality ($\beta = 1.27, p = 0.005$), suggesting that higher screen exposure throughout the day independently contributed to adverse sleep outcomes. In contrast, gender and the frequency of bedtime smartphone use did not show statistically significant associations in the model ($p > 0.05$), implying that these factors may not independently influence sleep quality when other variables were controlled for. These findings underscore the multifactorial

nature of sleep disturbances in adolescents, particularly emphasizing environmental and behavioral contributors.

DISCUSSION

This study comprehensively examined the relationship between smartphone usage—particularly bedtime exposure—and sleep quality among adolescents in Eastern India. It further explored the impact of daily smartphone usage patterns on indicators such as overweight status and visual acuity. The findings establish a robust association between longer durations of smartphone use at bedtime and a higher prevalence of poor sleep quality, underlining the growing concern of digital overexposure in this vulnerable age-group.

The prevalence of poor sleep quality among the study participants was found to be 42.1%, which aligns closely with several international reports. For instance, Alosaimi et al.¹⁶ reported similar figures among Saudi university students, noting that excessive smartphone use contributed to reduced sleep duration in 43% of the cohort. A comparable pattern was also described by Exelmans and Van den Bulck, who found that frequent bedtime phone usage among Flemish adults correlated with increased insomnia symptoms and shorter sleep durations.¹⁷ Extending this evidence to an adolescent Indian population, our study demonstrates that such associations are not geographically restricted and likely reflect universal neurobehavioral responses to screen exposure.

Our results notably confirm a gradient association between the duration of bedtime smartphone use and sleep disturbances. Adolescents who used their phones for >60 minutes before sleeping had >7.5-fold higher odds of reporting poor sleep than those who used them for <15 minutes. This reinforces the physiological hypothesis proposed by Cajochen et al.¹⁸ that exposure to blue light from light-emitting diode (LED) screens inhibits melatonin secretion and delays the circadian phase. Similarly, Wood et al.¹⁹ demonstrated that electromagnetic radiation from mobile phones might delay

the onset of melatonin production, thereby impairing sleep onset and maintenance. The consistency of our findings with such mechanistic studies suggests that physiological processes play a critical role in the observed behavioral outcomes.

In our cohort, bedtime smartphone use was reported by 89.3% of adolescents. This high figure likely reflects the rapid digitization of Indian society, increasing access to affordable internet services, and the pervasive role of social media in adolescent life. These findings parallel the outcomes of the nationwide survey by Davey and Davey,²⁰ which reported that over 44% of Indian adolescents demonstrated characteristics of smartphone addiction, reinforcing the notion that digital dependency is a pressing public health concern in India.

Importantly, the observed sleep disruption appears to escalate with increased smartphone engagement. Adolescents who used their phones for >30 minutes at bedtime exhibited significantly poorer sleep quality than those with minimal usage. This response pattern is both statistically and clinically meaningful, suggesting the potential utility of digital cutoff recommendations or curfews as part of school- or family-level interventions.²¹

Additionally, 23.6% of the adolescents in our study self-identified as overweight or obese, with a clear and significant association observed between daily smartphone use exceeding 2 hours and elevated body weight. These results are in agreement with the findings of Okoli et al., who postulated that prolonged screen time contributes to weight gain by decreasing physical activity, altering appetite regulation, and negatively impacting sleep duration.²² In our urban subgroup, the clustering of high screen use and overweight status also raises important questions about the influence of the built environment, sedentary recreation, and access to outdoor activity spaces.

Contrary to expectations, no statistically significant relationship was found between smartphone usage and visual acuity, although a nonsignificant trend toward subnormal vision among heavy users was observed. These findings echo those of Chu et al.,²³ who reported only a weak correlation between visual strain and screen time among Hong Kong adolescents. It is plausible that self-reported vision measures and the lack of objective ophthalmic testing limited our ability to detect small but meaningful visual effects. Future studies incorporating standardized clinical eye examinations would help clarify this relationship.

Similarly, no significant association was found between smartphone use and

hypertension status. Only six participants reported elevated blood pressure, and the lack of statistical significance aligns with the current literature, which suggests that although screen time may indirectly affect cardiovascular health through sedentary behavior and poor sleep, direct hypertensive effects in adolescents remain unsubstantiated.

In the current analysis, we were able to build a multivariable logistic regression model that identified urban residence and daily smartphone usage (in hours) as statistically significant predictors of poor sleep quality. The significance of urban residence as an independent risk factor highlights possible environmental contributors, such as noise pollution, lower physical activity levels, or higher academic stress. Interestingly, the frequency of bedtime smartphone use and gender were not statistically significant, suggesting that overall exposure duration may outweigh these categorical variables in determining sleep quality outcomes. Although model convergence was achieved, future studies may benefit from even larger sample sizes and additional covariate adjustments to better understand these multifactorial dynamics.

This study contributes to the expanding body of evidence advocating better digital hygiene practices among adolescents. The strong associations with sleep and overweight risk markers suggest that targeted interventions—such as sleep education, restricted screen time policies, and the promotion of physical activity—could mitigate some of the negative health impacts of excessive smartphone use. Parental monitoring, school health awareness programs, and digital detox initiatives could serve as practical community-level solutions.²⁴

At the policy level, these findings underscore the need to integrate digital behavior monitoring into school health programs and public health frameworks. The Rashtriya Kishor Swasthya Karyakram (RKSK) could be enhanced to include modules on sleep health, screen use guidelines, and circadian education.²⁵ Incorporating questions on digital usage into routine school health screenings may also help in the early identification of at-risk adolescents.

This study is not without limitations. Being cross-sectional in design, it cannot establish causal relationships. Additionally, reliance on self-reported data for sleep quality, vision, and smartphone use introduces potential recall and reporting biases. The absence of objective assessments such as actigraphy, digital use logs, or standardized body mass index (BMI) calculations limits the clinical accuracy of the health outcomes. Furthermore, despite the

adequate sample size of 140 participants, broader generalizability remains constrained to similar school-going populations in Eastern India.

Future research directions include longitudinal cohort studies to establish temporal associations, incorporation of wearable technology and digital monitoring apps to capture objective screen and sleep metrics, and qualitative studies exploring adolescent perspectives on smartphone use and sleep. Randomized controlled trials evaluating the effectiveness of digital hygiene curricula or behavioral interventions would also provide policy-relevant evidence.

CONCLUSION

This study highlights a strong association between bedtime smartphone usage and poor sleep quality among adolescents, with extended use beyond 30 minutes posing a greater risk. Additionally, excessive daily smartphone use correlates significantly with overweight status, reflecting its impact on both behavioral and physical health. Although associations with vision and blood pressure were not statistically significant, the observed trends warrant further evaluation. These findings emphasize the importance of integrating digital hygiene into adolescent health education and school-based interventions. Larger, longitudinal studies using objective tools are needed to establish causality and refine targeted public health strategies.

ACKNOWLEDGMENT

We thank the participating schools and students for their cooperation.

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Common Cold—An Update

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Received: 07 August 2025; Accepted: 12 December 2025

ABSTRACT

The common cold, a mild yet highly prevalent upper respiratory tract infection (URTI), imposes a substantial societal and economic burden through healthcare costs, lost productivity, and widespread morbidity. Primarily caused by diverse respiratory viruses (e.g., rhinoviruses, coronaviruses), it encompasses a spectrum of acute infections affecting the nasal passages, throat, larynx, and bronchi, manifesting as rhinitis, pharyngitis, or bronchitis. Framed by the “iceberg concept” of disease, most cases are mild or asymptomatic, yet severe outcomes (e.g., exacerbations of chronic conditions) contribute to rare mortality. Management focuses on symptom relief: decongestants and antihistamines alleviate nasal congestion and cough in adults, though cough suppressants are discouraged in children. Despite its self-limiting nature, the common cold underscores challenges in primary care due to viral diversity and a lack of targeted therapies. Annual influenza vaccination, while not preventing colds, mitigates flu-related complications, indirectly reducing overlapping URTI burdens. Public health strategies emphasizing prevention, symptom management, and judicious antibiotic use remain critical to curbing its widespread impact.

Keywords: Acute respiratory infections, ARI, Common cold, COVID-19, Influenza, Respiratory syncytial virus, Respiratory viral infections.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1613

INTRODUCTION

The common cold is caused by various viruses, typically characterized by a range of symptoms, including cough, rhinorrhea (runny nose), nasal congestion, and throat discomfort, and may also present with additional symptoms such as fever, myalgia (muscle ache), fatigue, headache, and diminished appetite.¹

The common cold has a significant economic impact on healthcare expenditures and productivity losses. It is noteworthy that upper respiratory tract infections contribute significantly to temporary disability, resulting in absenteeism from work and educational institutions, along with symptoms that may be bothersome and fatigue that is often pronounced.

Its complex viral etiology, caused by multiple pathogens such as rhinoviruses, influenza, and other viruses presents challenges in developing effective treatments and vaccines. This is often inappropriately treated with antibiotics, contributing to the growing problem of antimicrobial resistance and underscoring the need for improved management strategies. Additionally, the common cold can exacerbate underlying conditions such as asthma and chronic obstructive pulmonary disease (COPD), and may increase the risk of more severe infections. It can predispose individuals to more severe lower respiratory illnesses, such as bronchiolitis or pneumonia, and, though uncommon, may even lead to fatal outcomes, represented metaphorically by the tip of the iceberg (Fig. 1).

The iceberg model pertinent to viral infections suggests that a substantial proportion of such infections manifest either asymptotically or with mild clinical manifestations, insufficient in severity to elicit self-diagnosis as a common cold. These instances remain obscured, analogous to the submerged portion of an iceberg. In contrast, more severe clinical presentations may achieve a severity threshold justifying the classification of “influenza-like illness.” Furthermore, lower respiratory tract infections, including but not limited to bronchiolitis and pneumonia, may frequently be misidentified due to their initial presentation resembling a common cold, thus complicating clinical recognition and management.

The discussion situates the common cold within the framework of the “iceberg concept” (Fig. 1) of disease to serve as an umbrella term (Fig. 2) with comprehensive designation for acute infections affecting the nasal passages, throat, larynx, and bronchi, causing rhinitis, rhinosinusitis, pharyngitis, laryngitis, and bronchitis.

The common cold plays a critical role in the exacerbation of bronchial asthma,² and other chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD),³ and interstitial lung disease like idiopathic pulmonary fibrosis (IPF).⁴

EPIDEMIOLOGY

The manifestation of the common cold exhibits a distinct seasonal pattern. The temporal

patterns of viral pathogens traditionally associated with respiratory infections, specifically respiratory viruses and SARS-CoV-2, in the Northern Hemisphere during the post-COVID-19 epoch exhibit notable seasonality. While adenoviruses and human rhinoviruses exhibit persistent circulation and are etiological agents of respiratory infections throughout the calendar year, the temporal interval delineated between late autumn and early spring (specifically, from November to April) is posited to constitute

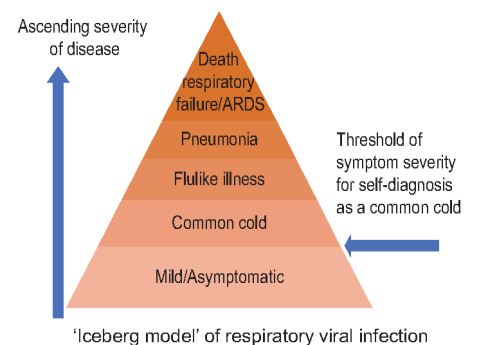


Fig. 1: The iceberg model pertinent to viral infections

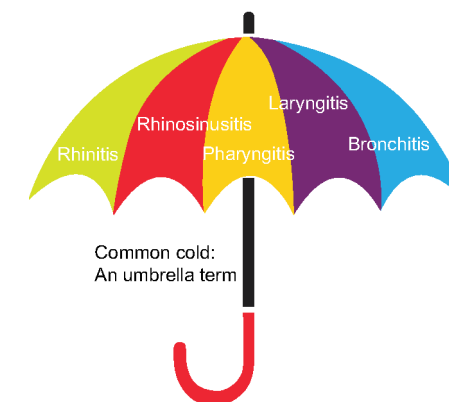


Fig. 2: The common cold serves as an umbrella term

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How to cite this article: Mohapatra PR, Mishra B. Common Cold—An Update. *J Assoc Physicians India* 2026;74(9):77–82.

the winter respiratory season in the Northern Hemisphere. During this defined period, there is a marked augmentation in the activity levels of influenza viruses, respiratory syncytial virus (RSV), and human metapneumovirus (hMPV). Moreover, enteroviruses are observed to reach their peak of activity in late autumn. Although seasonal human coronaviruses (HCoV) can induce mild upper respiratory tract infections throughout the year, their activity is significantly heightened during the aforementioned winter respiratory season.⁵ Adults typically experience a common cold approximately two to three times annually, while pediatric populations may encounter up to eight instances within the same year.^{6,7} Additionally, during the early stages of life, males tend to present a higher respiratory infection frequency than females. Research indicates that women engaged in external employment tend to have a lower incidence of infections compared to their counterparts who primarily remain at home. The attendance of children at daycare facilities represents a significant risk factor for respiratory illnesses. This observation may be attributed to a higher level of exposure to children among those who do not participate in the workforce.⁵

Due to the significant involvement of rhinoviruses in the etiology of the common cold, its epidemiological patterns are closely aligned with those of rhinovirus infections. While rhinoviruses can be identified year-round, the frequency is highest in autumn, followed by a more moderate resurgence in the spring.⁸ Influenza epidemics generally arise during the winter months in the Northern Hemisphere, frequently coinciding with RSV.⁹

Respiratory viruses, particularly rhinovirus, spread indoors via two pathways: (1) indirect transmission through fomites (contaminated surfaces) or contact; (2) direct transmission via large respiratory droplets or airborne aerosols.¹⁰

Influenza viruses and other respiratory viruses are believed to be predominantly transmitted via small-particle aerosols (Fig. 3). In contrast, transmission of rhinoviruses is predominantly achieved through hand contact followed by self-inoculation into the nasal passages or eyes. Other determinants affecting the incidence of common cold infections are population overcrowding, increased stress levels, tobacco and alcohol consumption, age demographics, sleep quality, seasonal variations, exposure to cold temperatures, and low physical activity.¹¹ The pandemic resulting from SARS-CoV-2 has ushered in a transformative era in the research of respiratory viruses. It is noteworthy that, with the global increase in exposure to and immunity against SARS-CoV-2, there is a possibility that COVID-19 may evolve into a viral

symptom that resembles those responsible for the common cold.¹²

ETIOLOGY

The designation “common cold” has been utilized for numerous centuries and is frequently linked to the notion that exposure to lower temperatures induces the manifestation of disease symptoms. It was not until the groundbreaking research conducted around 1950 that respiratory viruses, including rhinoviruses, were identified as a causative factor.¹³ The pathogens implicated in the common cold’s etiology encompass various viruses, including: (1) rhinovirus, (2) respiratory syncytial virus, (3) parainfluenza virus, (4) adenovirus, (5) enterovirus, and (6) coronavirus. It is important to highlight that Rhinovirus, which is categorized within the *Enterovirus* genus of the Picornaviridae family, is recognized as the primary etiological factor in the manifestation of the common cold.¹⁴ Among

humans worldwide, accounting for up to 80% of respiratory infections observed during peak incidence periods.¹⁵ The rhinovirus accounts for approximately 50% of cases of upper respiratory tract infections (URTI) and also in an otherwise. Even after 75 years of the discovery of Rhinovirus, the search for a definitive treatment for rhinovirus remains a topic of active research and exploration.¹⁴ Additionally, various viral infections have the potential to produce similar symptoms and their characteristics, which are summarized in Table 1.

CLINICAL MANIFESTATIONS

The common cold is characterized as “a mild, self-limiting upper respiratory tract infection” in a healthy person. The incubation period can significantly differ among various viral pathogens. In controlled experimental settings involving rhinovirus infections, it has been observed that symptoms may commence

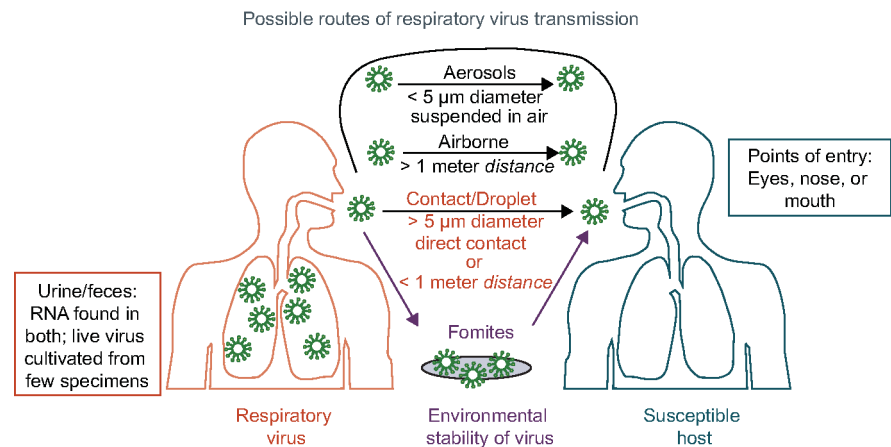


Fig. 3: Transmission of respiratory viruses via small-particle aerosols

Table 1: Respiratory viruses and their basic characteristics

Virus	Abbreviation	Nucleic acid	Classification	Structure
Rhinovirus	HRV	RNA	Species A, B, C, with 100 serotypes	Nonenveloped icosahedral capsid
Seasonal coronavirus	HCoV	RNA	Types OC43, 229E, NL63, HKU1	Enveloped
Pandemic coronavirus	SARS, MERS, SARS-CoV-2	RNA	Variants such as Alpha, Delta, Omicron	Enveloped
Respiratory syncytial virus	HRSV	RNA	Groups A and B	Enveloped
Parainfluenza virus	HPIV	RNA	Types 1, 2, 3, 4	Enveloped
Influenza virus	Inf	RNA	Types A, B, C, D	Enveloped
Adenovirus	ADV	DNA	51 serotypes	Nonenveloped icosahedral capsid
Human metapneumovirus	HMPV	RNA	Groups A and B	Enveloped
Human bocavirus	HBoV	DNA	2 lineages	Nonenveloped icosahedral capsid

as early as 10–12 hours after the intranasal administration of the virus. The incubation period for influenza viruses is usually 1–7 days, with early symptoms observed to increase rapidly, typically peaking in the subsequent 2–3 days following the onset of infection, and thereafter tends to diminish promptly. The average duration of the common cold symptoms is approximately 7–10 days; however, occasionally, individuals may continue to experience lingering symptoms for up to 3 weeks.¹⁶

Rhinovirus infections typically initiate with the presentation of a sore throat, which is shortly followed by symptoms such as nasal congestion, nasal discharge, sneezing, and coughing. Rhinitis caused by respiratory viral infections (e.g., the common cold) shares clinical features with allergic rhinitis, such as nasal congestion and rhinorrhea. However, their underlying mechanisms differ: allergic rhinitis symptoms (e.g., itching, sneezing) are primarily mediated by histamine,¹⁷ prostaglandins, and bradykinin; viral rhinitis symptoms (e.g., pain, congestion).¹⁸

The discomfort associated with the sore throat generally resolves rapidly, while the initial watery nasal discharge may progress to a thicker and more purulent form. Notably, the increase in nasal purulence does not correlate with alterations in the nasopharyngeal bacterial flora nor indicate a concurrent bacterial infection of the nasal mucosa. Fever during rhinovirus infections in adults is relatively uncommon; however, it is a more frequent symptom in children experiencing upper respiratory infections from various etiologies. Additional symptoms of common cold syndrome may include headaches, general malaise, and lethargy. Although myalgia may be observed during colds, it is more characteristically associated with influenza infections.

The presence of numerous rhinovirus serotypes, coupled with their frequent antigenic variability, presents considerable challenges for identification, characterization, and potential eradication efforts. Following exposure to the anterior nasal mucosa, rhinovirus replication and subsequent infection are believed to initiate due to mucociliary transport to the posterior nasopharynx and adenoidal tissues. Symptoms may manifest as early as 12 hours postinoculation. The microbial invasion of the nasal epithelium, in conjunction with the host's innate immune-mediated inflammatory response, initiates a cascade of physiological phenomena characterized by the induction of vasodilation and an elevation in endothelial permeability within the vascular microenvironment, leading to nasal obstruction and rhinorrhea. Additionally, cholinergic stimulation contributes to increased mucus production and the occurrence of sneezing.

Influenza is frequently considered a distinct clinical entity, separate from the common cold. Nevertheless, the clinical manifestations of influenza can vary widely, ranging from asymptomatic cases to more severe illness, resulting in an overlap with the common cold. The underlying mechanisms of symptom manifestation related to the innate immune response are elucidated, and a summary of symptomatic treatment options is provided. Preferred symptomatic treatments should address the comprehensive resolution of all potential symptoms rather than focusing solely on treating an isolated symptom, such as mucus hypersecretion, in relation to the anticipated anatomical site, such as acute bronchitis.

A particular study involving adult asthma patients revealed that symptoms associated with the common cold were documented as wheezing or dyspnea in nearly 80% of cases, with rhinoviruses being identified as the causative agent in approximately 60% of these asthma exacerbations.¹⁹

In individuals exhibiting immunocompromised states, RSV is conventionally identified as the predominant etiological agent responsible for the manifestation of severe viral respiratory pathologies. Notwithstanding, pathologies associated

with infections caused by rhinoviruses have been quantitatively correlated with severe lower respiratory tract diseases. Moreover, in infrequent circumstances, these pathological conditions may result in mortality. There are no officially recognized antiviral therapies available for human rhinoviruses (HRVs), and the approach to treatment continues to be primarily supportive in nature. Symptoms of the common cold are shown in Figure 4.

The common risk factors for the common cold are described in Figure 5.

EVALUATION AND DIAGNOSIS

The identification of classical indicators associated with rhinovirus infection, in conjunction with the lack of evidence for bacterial infection or severe respiratory conditions, provides a foundation for diagnosing the common cold, primarily a clinical diagnosis, thus eliminating the necessity for diagnostic testing. In the context of influenza testing, it is advisable to collect specimens as soon as symptoms begin to manifest. For infants and young children, it is advisable to collect nasal aspirates or swabs as the most suitable specimens. In contrast, nasopharyngeal swabs and aspirates are recommended for older children and adults. Furthermore, the use of rapid streptococcal swabs may be beneficial in ruling out bacterial pharyngitis, which can help decrease the number of antibiotic prescriptions associated with these infections.

LABORATORY DIAGNOSIS

Reverse transcription polymerase chain reaction (RT-PCR) serves as a cornerstone for respiratory virus detection, offering high sensitivity and specificity. The emergence of multiplex PCR panels has further expanded diagnostic capabilities

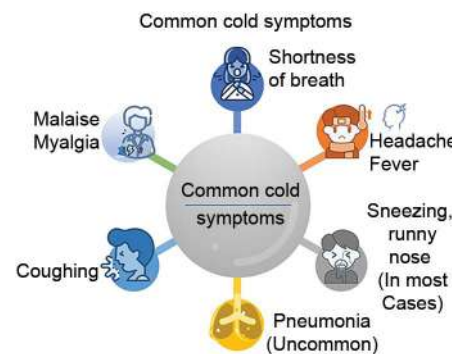


Fig. 4: Symptoms of the common cold

Risk factors for the common cold:
Age (children, elderly); Seasonality (cold weather); Weakened immune system;
Environmental exposure (crowded place); Lifestyle factors (smoking, poor hand hygiene)

Close contact with children and elderly
• Day care
• School
• Office
• Crowded place
• Public transport

People with medical disorders
• Asthma
• COPD
• Parenchymal lung disease

Immunocompromised individuals
• Cystic fibrosis
• Transplantation
• Corticosteroid use
• Post splenectomy

Anatomical anomalies
• Decreased airway defence
• nasal polyposis
• Facial dysmorphic changes
• Low mucosal defence of airway

Fig. 5: The common risk factors for the common cold

by enabling simultaneous testing for a broad range of respiratory viral pathogens, including influenza A and B, RSV A and B, parainfluenza viruses 1–4, adenovirus, rhinovirus/enterovirus (RV/EV), human metapneumovirus (HMPV), coronaviruses (including seasonal variants and SARS-CoV-2), and others.²⁰

DIFFERENTIAL DIAGNOSIS OF THE COMMON COLD

Distinguishing the common cold from other conditions with overlapping symptoms is essential to avoid misdiagnosis and ensure appropriate treatment. Influenza (flu) is marked by sudden onset, high fever, severe body aches, and exhaustion, contrasting with the cold's mild, localized symptoms. Allergic rhinitis mimics cold symptoms but includes itching (eyes/nose), clear nasal discharge, and seasonal triggers, with no fever or mild fever. COVID-19 may present with varying symptoms, including anosmia (loss of smell), dyspnea, gastrointestinal symptoms, severe respiratory infection, and bilateral pneumonia, necessitating PCR/antigen testing for confirmation. Bacterial sinusitis is suspected if symptoms persist beyond 10 days and are accompanied by purulent nasal discharge and facial pain. Streptococcal sore throat features severe sore throat, fever, and tonsillar exudate but lacks cough or nasal congestion. RSV in children often causes wheezing and respiratory distress, while pertussis (whooping cough) is distinguished by paroxysmal coughing fits and post-tussive vomiting. GERD/laryngopharyngeal reflux can mimic colds with chronic cough and hoarseness, but lacks nasal symptoms and improves with antacid therapy. Clinicians should assess symptom duration, exposure history, and red flags (e.g., high fever, dyspnea) and use targeted testing (e.g., rapid strep, imaging) when needed. Accurate differentiation ensures timely intervention, preventing complications from overlooked conditions such as the flu or COVID-19.

COMPLICATIONS

Complications from URTIs are rare except in influenza, which can lead to viral pneumonia, secondary bacterial pneumonia, sinusitis, acute otitis media, opportunistic infections, and exacerbations of asthma/COPD. Pneumonia is a common complication of the flu in children.¹¹

While the common cold is typically self-limiting, bacterial complications such as acute otitis media occur in nearly 20% of pediatric cases, peaking 3–4 days postsymptom onset. Risk factors for colds include population

density, stress, smoking, immune status, age, and environmental factors.

Bacterial sequelae such as sinusitis (0.5–2% of viral rhinitis cases) and pneumonia may follow viral URTIs. However, sinus abnormalities observed during infections might reflect the viral course rather than bacterial complications. Post-viral pneumonia often stems from bacterial coinfections or direct viral spread, with viral-bacterial coinfections notably prevalent in children.

MANAGEMENT

The primary objective of managing the common cold is to alleviate symptoms. In adults, decongestants, combined with antihistamine and decongestant medications, have been demonstrated to alleviate cough, nasal congestion, and various other manifestations associated with the common cold. However, it is strongly advised to avoid cough formulations for children.²¹ H1-receptor antagonists may slightly reduce rhinorrhea and sneezing during the initial days of a cold, particularly in adults.²² Furthermore, it is important to inform patients that first-generation antihistamines may have sedative effects, warranting caution with their use. Current evidence does not support antihistamines to treat non-allergic common cold symptoms. While they may only mildly reduce overall symptom severity within the first 48 hours, their routine use is not advised.²³

Both locally administered and systemically administered nasal decongestants, exemplified by topical oxymetazoline and orally ingested pseudoephedrine, have exhibited a statistically significant reduction in nasal airway resistance in the adult and adolescent populations, as quantified through controlled clinical trials and pharmacodynamic assessments.²² However, current evidence does not strongly support repeated nasal decongestant use, though single doses may offer mild short-term relief of nasal congestion in adults with colds.²⁴ Except in allergic rhinitis, intranasal corticosteroids (like Fluticasone Furoate), current evidence does not endorse the utilization of intranasal corticosteroids to alleviate symptoms associated with the common cold.²⁵

Additionally, evidence-based research indicates that the administration of antibacterial agents is against the therapeutic management of the prevalent URI in the common cold, as such pharmacological interventions fail to provide statistically significant amelioration of symptomatology or to abbreviate the temporal course of the ailment. Evidence confirms that antibiotics

provide no therapeutic benefit for treating the common cold or persistent acute purulent rhinitis in any age group and pose risks of adverse effects.²⁶ Routine use is not recommended.²⁶ Furthermore, their inappropriate use may contribute to the emergence and proliferation of antimicrobial resistance.²²

Several cough formulations show potential effectiveness, including dextromethorphan, bisolvon, and guaifenesin for cough relief and antihistamine-decongestant combinations that address a broad spectrum of symptoms.²⁷ A single dose of syrup comprising dextromethorphan hydrobromide, paracetamol, doxylamine succinate, and ephedrine sulfate effectively illustrates its utility as a convenient therapeutic option for alleviating symptoms such as nasal congestion, rhinorrhea, cough, and body aches commonly associated with the common cold. Furthermore, it also contributes positively to enhancing sleep quality, which may be impaired due to the presence of cold symptoms.²⁸

Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit some efficacy in alleviating discomfort such as myalgia and fever associated with the common cold; however, there is no evidence of their effectiveness in reducing respiratory symptoms.²⁹

A Cochrane Review³⁰ indicates that the prophylactic use of vitamin C at doses of 0.2 grams or more daily yields a “modest but consistent effect” on the period extent and intensity of rhinological manifestations. Nevertheless, therapeutic administration post-manifestation of clinical symptoms, higher-dose ascorbic acid, failed to exhibit statistically significant advantages in controlled clinical trials.³⁰ Zinc supplementation may exhibit minimal to no impact on the prevention of colds; however, it has the potential to decrease the duration of existing colds, albeit with a corresponding rise in the incidence of non-serious adverse events.³¹ There is no evidence of benefits or harms associated with administering heated, humidified air delivered through a humidification system in treating the common cold.³²

Timely antiviral tablets specific for influenza significantly reduce the duration and severity of symptoms, shorten hospital stays, and mitigate the risk of complications. The antiviral treatments should be administered as early as 48 hours after symptom onset for influenza, but may still be beneficial even shortly after 48 hours in pregnant individuals or in patients at high risk.³³

Antiviral chemoprophylaxis presents an additional preventive measure, demonstrating efficacy rates between 70% and 90%, and

should be considered along with vaccination. In general, the administration of antiviral chemoprophylaxis is recommended during the initial manifestation of elevated influenza activity indicators for the following categories: (1) individuals classified as high-risk who are ineligible for vaccination on account of medical contraindications or for whom the recent immunization may not elicit an adequate serological response; (2) the mitigation of influenza outbreaks within populations of high-risk individuals located in institutional environments; and (3) individuals identified as high-risk who have exposure to the influenza virus.³⁴

Patients should be advised to ensure sufficient fluid intake to achieve optimal hydration levels, prioritize periods of rest and recuperation, completely refrain from the inhalation of tobacco products, and rigorously comply with the established therapeutic protocols as delineated in their prescribed treatment regimens.^{11,35}

VACCINE

Annual influenza vaccination (updated quadrivalent) is a critical preventive measure to reduce infection risk, severity, and complications of the flu. It is especially recommended for high-risk groups, including the elderly, young children, pregnant individuals, and those with chronic conditions (e.g., asthma, COPD). The vaccine is updated yearly to match circulating viral strains, enhancing efficacy. Vaccination lowers hospitalization rates, mitigates viral spread through herd immunity, and prevents secondary bacterial infections like pneumonia.

The SARS-CoV-2 pandemic has significantly heightened interest in vaccine research. The RNA vaccines developed in response to COVID-19 may serve as a valuable technological foundation for the advancement of vaccines targeting other RNA respiratory viruses, including rhinoviruses.¹¹ Despite significant epidemiological implications of human rhinovirus, a licensed vaccine is yet to be available.³⁶ The RSV virion is enveloped by a lipid membrane containing glycoproteins G and F, which mediate viral attachment and fusion to respiratory epithelial cells. These glycoproteins, particularly the highly conserved antigenic sites on the F-glycoprotein, are critical targets for therapeutic development. Monoclonal antibodies (mAbs) against RSV, such as nirsevimab, exploit these conserved regions to neutralize the virus.

Recent advancements have led to the approval of three novel RSV vaccines: two recombinant protein subunit vaccines (e.g.,

Arexvy, Abrysvo) and one mRNA-based vaccine (e.g., mRNA-1345). All are licensed for older adults (≥ 60 years), with one subunit vaccine (Abrysvo) additionally approved for maternal immunization to protect infants through passive antibody transfer.³⁷ Population-based evaluations of newly implemented vaccination programs yield substantial real-world evidence for the assessment of vaccines following their licensure. A comprehensive analysis conducted in the years 2023 to 2024 on vaccine effectiveness among immunocompetent adults aged 60 years and above in the United States demonstrated an 80% efficacy (95% CI: 71–85) in reducing hospital admissions related to RSV.³⁸ Barring occasional scenarios, SARS-CoV-2 is expected to evolve toward milder forms—though the pace of this transition remains unclear. Historical patterns from influenza pandemics suggest COVID-19 may take approximately 20 years to attenuate to the level of the common cold.³⁹

OPTIMIZING COLLABORATIVE RESULTS WITHIN HEALTHCARE TEAMS

A primary objective is to mitigate the overprescription of antibiotics while ensuring that serious infections are not overlooked. Primary care physicians and nurses assessing these patients are encouraged to engage in open communication with infectious disease specialists when uncertainty regarding the infection's severity arises. Additionally, pharmacists should educate patients regarding upper respiratory infections and advise against the excessive use of unproven remedies.¹¹

Finally, clinicians should advocate for patients to receive the latest strains of vaccinations prior to the onset of the flu season. Notwithstanding the potential lack of efficacy in reducing the temporal extent of infectious episodes, the administration of the vaccine in the future is likely to bring a significant decline in symptom severity. In summary, the prognosis for most patients is favorable, particularly when approached through a collaborative interprofessional model.

SUMMARY POINTS ON THE COMMON COLD

The common cold is primarily caused by rhinoviruses, though other viruses such as coronaviruses, influenza virus and RSV can also contribute. Many viral strains are linked to colds. The virus spreads through respiratory droplets (sneezing/coughing), direct contact

with infected individuals, or touching contaminated surfaces (fomites). Symptoms include runny/stuffy nose, sneezing, sore throat, cough, mild fatigue, and occasional low-grade fever. Typically resolves within 7–10 days, though some symptoms (e.g., cough) may linger longer. The treatment focuses on symptom relief. Rest, hydration, over-the-counter medications (decongestants, pain relievers), and saline nasal sprays are commonly used. Antibiotics are ineffective as colds are viral. Emphasize hand hygiene, avoiding touching the face, disinfecting surfaces, and steering clear of close contact with infected individuals. No vaccine (except for annual influenza vaccination) exists due to the vast number of causative viruses.

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A Consensus Statement on the Role of Bisoprolol across the CV Continuum

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Received: 30 October 2025; Accepted: 25 November 2025

ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of death globally, affecting populations in both developed and low- and middle-income countries. Although age-adjusted mortality rates from coronary artery disease (CAD) have declined in regions such as the United States and Europe, sudden cardiac death continues to account for a significant proportion of CVD-related fatalities. The concept of the “cardiovascular continuum,” introduced more than a decade ago, describes the progressive nature of CVD—beginning with modifiable risk factors such as hypertension, diabetes, and smoking, which collectively drive oxidative stress, endothelial dysfunction, and inflammation. Over time, these pathophysiological changes lead to atherosclerosis and end-organ damage, often well before clinical symptoms become apparent.

In India, the burden of CVD has risen sharply in recent decades, particularly due to increasing rates of coronary heart disease and cerebrovascular events. Emerging evidence identifies an elevated resting heart rate as an independent predictor of adverse cardiovascular outcomes, particularly in individuals with hypertension, myocardial infarction (MI), and heart failure (HF). Among available pharmacological options, beta-blockers—particularly bisoprolol—have demonstrated strong efficacy in managing angina, atrial fibrillation (AF), and heart failure with reduced ejection fraction (HFrEF). By acting at multiple stages of the cardiovascular continuum, bisoprolol provides both symptomatic relief and disease-modifying effects, underscoring its importance in contemporary cardiovascular management.

Keywords: Beta-blockers, Bisoprolol, Cardiovascular disease, Heart failure.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1694

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, exerting a major burden on developed nations and increasingly affecting developing countries as well. Although age-specific mortality rates from CAD have significantly declined in the United States and Europe over the past four decades, sudden cardiac deaths still account for nearly one-fourth of all fatalities.

About 15 years ago, a multidisciplinary panel of experts from various research fields convened to reassess the existing understanding of CVD. They proposed a unifying concept—the cardiovascular continuum—which explains CVD as a progressive sequence of interrelated events driven by the interaction of multiple internal and external risk factors. These factors initiate a cascade of pathophysiological changes that gradually evolve into overt heart disease.

The cardiovascular continuum describes the underlying pathophysiological process of CVD as a continuum of molecular and cellular alterations (Fig. 1). Major contributors to heart disease, including hypercholesterolemia, high blood pressure, elevated blood sugar, and smoking, lead to oxidative stress and

endothelial dysfunction. This dysfunction sets off a chain of events in the coronary arteries involving alterations in vasoactive mediators, activation of inflammatory pathways, and vascular remodeling. Over time, these processes culminate in atherosclerosis and organ damage. Importantly, evidence indicates that these changes begin early in life—long before clinical symptoms appear—underscoring that CVD results from a slow, progressive pathophysiological process.¹

Cardiovascular disease remains a leading cause of premature death and disability; however, its progression is not inevitable. Over the past few decades, significant progress in understanding the pathophysiological mechanisms of heart disease has coincided with remarkable therapeutic innovations. These developments now enable effective interventions across the entire spectrum—from individuals with silent atherosclerotic risk factors to those suffering from advanced, end-stage heart failure.²

Heart rate (HR) serves as a powerful predictor of cardiovascular as well as all-cause morbidity and mortality, both in the general population and among individuals with established CVD. For the purpose of

this Consensus Statement, the cardiovascular (CV) continuum is defined as a sequence of interlinked events that illustrate the progressive nature of CVD. This progression typically begins with hypertension (HTN) and extends through angina, MI, and AF, ultimately culminating in HF.

As depicted in Figure 1, the CV continuum emphasizes the dynamic and interconnected stages of cardiovascular disease—from early, modifiable risk factors such as hypertension to severe, life-threatening outcomes like HF. This framework underscores the critical importance of early detection,

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How to cite this article: Kapoor A, Rao VD, Shetty SR, et al. A Consensus Statement on the Role of Bisoprolol across the CV Continuum. *J Assoc Physicians India* 2026;74(9):83–92.

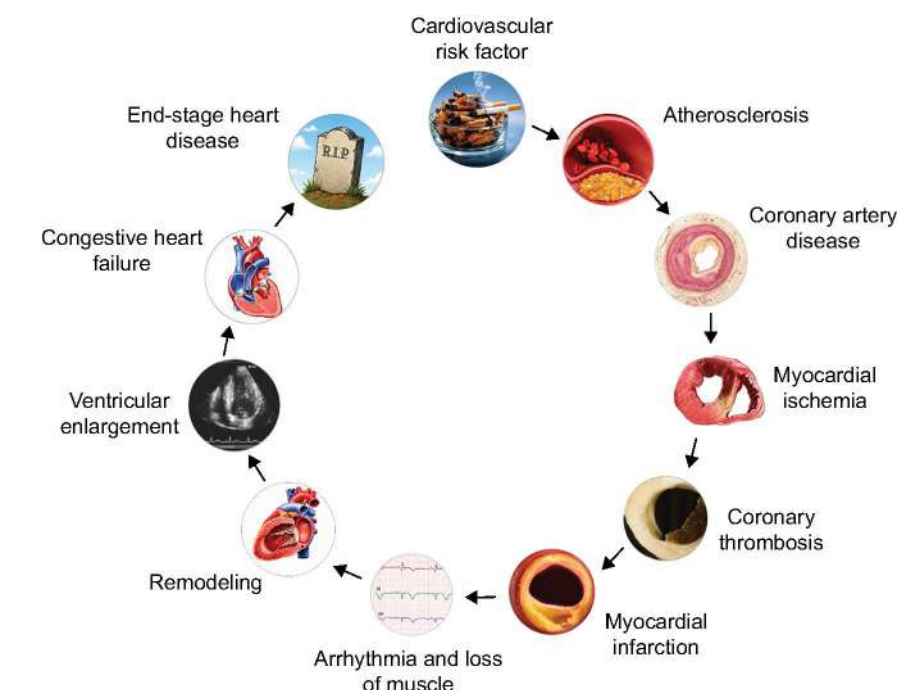


Fig. 1: Cardiovascular continuum. Schematic representation of all processes involved in cardiovascular disease from cardiovascular risk factors to end-stage heart failure

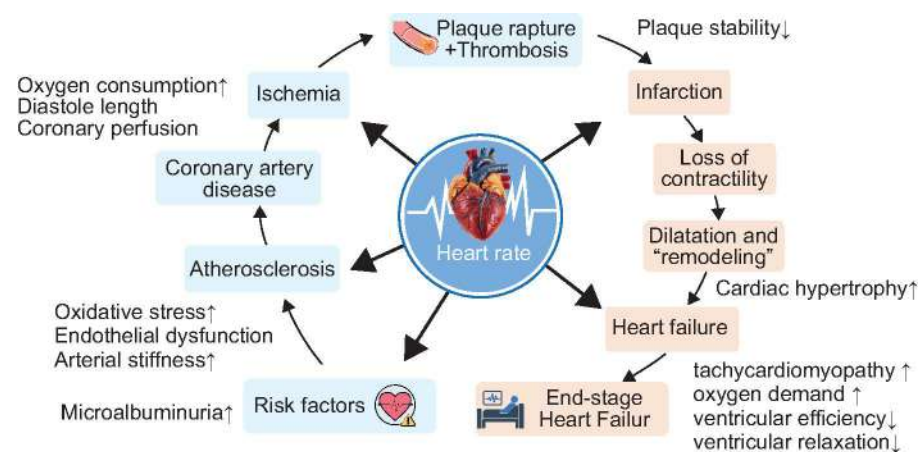


Fig. 2: Pathophysiological effects of heart rate on the cardiovascular disease continuum

timely intervention, and comprehensive management strategies to interrupt or slow the progression of disease at each stage.²⁻⁴

CARDIOVASCULAR DISEASE IN INDIANS

According to the Global Burden of Disease (GBD) study, the India State-level Disease Burden report indicates that between 1990 and 2016, the prevalence of ischemic heart disease (IHD) and stroke in India increased by 2.3 times. During this period, the number of CVD cases more than doubled—from 25.7 million (95% CI 25.1–26.0) in 1990 to 54.5 million (53.7–55.3) in 2016. However, these figures are likely conservative, given the country's substantial burden of risk factors.²

Cardiovascular diseases (CVD), including heart attacks and strokes, remain the leading cause of death and disability worldwide, accounting for one-third of all deaths in India. Uncontrolled blood pressure is a major contributor to CVD risk. Among the estimated 220 million people in India living with hypertension, only 12% have their blood pressure adequately controlled. Hypertension—the leading cause of adult mortality—is both preventable and treatable.⁵ The first national-level NCD survey (2018–2019) reported that 28.5% of individuals aged 18–49 years had hypertension. Among them, 27.9% were aware of their condition, 14.5% were receiving treatment, and only 12.6% had their blood pressure under control.⁶

BASELINE PULSE RATE: A PREDICTOR OF CARDIAC OUTCOMES

Baseline pulse rate (PR) is a well-established prognostic marker in CVD, strongly associated with adverse outcomes across conditions such as hypertension, MI, and HF. Numerous clinical studies have demonstrated that an elevated resting HR correlates with increased morbidity and mortality in these populations. Evidence from the ONTARGET/TRANSCEND trials shows that every 10 beats per minute (bpm) rise in resting HR among patients with stable CVD is associated with a 22–26% higher risk of major cardiovascular events, a 33–41% greater risk of cardiovascular death, and a 33–39% increase in all-cause mortality.⁷

Elevated HR is consistently linked to all stages of the cardiovascular continuum, demonstrating a close relationship with blood pressure in both normotensive and hypertensive individuals.⁸ As illustrated in Figure 2, heart rate influences each phase of the continuum—from early vascular risk factors to overt cardiovascular events and the development of HF. This influence stems from its impact on key pathophysiological mechanisms, including increased myocardial oxygen consumption, reduced coronary perfusion time, and enhanced arterial wall stress, all of which accelerate disease progression.⁹

Accordingly, heart rate serves not only as a risk marker but also as a focus for therapy aimed at preventing and managing heart-related disorders. Lowering HR in patients with chronic stable angina improves myocardial perfusion and reduces oxygen demand, thereby enhancing cardiac efficiency. Notably, HR-lowering agents exhibit a use-dependent effect, wherein their therapeutic efficacy strengthens with continued use, providing sustained cardiovascular protection (Fig. 2).⁹

MANAGEMENT OF ARTERIAL HYPERTENSION—INSIGHTS FROM THE 2023 ESH GUIDELINES

Preferred Pharmacologic Categories for Initial Therapy

Major clinical practice guidelines (CPGs) consistently recommend agents acting on the renin–angiotensin system (RAS blockers), thiazide and thiazide-type diuretics, and calcium antagonists as initial treatment options for hypertension management (Fig. 3). The European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines additionally include beta-blockers as first-line agents, whereas most other international guidelines reserve their use

Current Practice Guidelines	Indian CPGs	
	2016 MoHFW	2019 IGH-IV
BP threshold (mmHg) for adding pharmacological therapy	≥140/90	>140/90 >130/80 if CVD
BP Target (mmHg)	<80 years: <140/90 ≥80 years: <150/90	<60 years: 120–130/70–80 ≥60 years: 130–140/80–90
BP measurement for initial evaluation and monitoring control	Office measurement preferred.	ABPM or HBPM preferred. Alternative is repeated office measurements.
First-line BPLDs	Three classes: 1. RASI 2. CCBs 3. Thiazide	Four classes 1. RASI 2. CCB 3. Diuretics 4. Newer Beta-blockers
Stepwise approach with specific classes/drugs, dose (mg)	1. Enal 5/Los 50 or Amlol 5 or Hctz/Chlo 12.5 2. Add a second drug Enal./Amlol 2.5–5/Hctz 12.5 3. Enal 5 + Amlol 2.5 + Hctz 12.5 4. Enal 10 + Amlol 10 + Hctz 25 5. Refer to specialist	1. RASI or CCB or Diuretic 2. RASI + CCB/Diuretic 3. RASI + CCB + Diuretic 4. RASI + CCB + Diuretic + MRA 5. Add MRA or α-B; in special cases: centrally acting drugs or direct vasodilators 6. Refer to specialist
Combination therapy/SPC	Initiate with combination only if BP > 180/110. SPCs only after BP is stabilized with two drugs given separately	Initiate with combination if BP > 160/100, preferably a SPC.
Frequency of follow-up	1–2 weeks: after initiation of therapy 2–4 weeks: after change of BPLDs	Monthly: after initiation or change of BPLDs until target BP achieved 3 monthly (high risk) or 5 monthly (low–moderate risk): if target BP achieved
Target time for BP control	6–8 weeks	–

Fig. 3: Summary of guideline recommendations for pharmacological management of hypertension

for patients with established CVD or specific clinical indications. The Indian Guidelines on Hypertension-IV (IGH-IV) present a somewhat conflicting stance—stating that beta-blockers are “no longer first-line” for general use, yet still recommending the “newer” beta-blockers as first-line options in younger hypertensive patients.¹⁰

There are also notable differences among CPGs concerning the preference for thiazide vs thiazide-like diuretics. The ACC/AHA guidelines suggest these two classes can be used interchangeably, while the International Society of Hypertension (ISH) favors thiazide-like diuretics, recommending thiazide diuretics only as alternatives when necessary. Both the ESC/ESH and WHO guidelines mention the use of either class but do not indicate a clear prioritization. Within Indian recommendations, the IGH-IV document broadly refers to diuretics, omitting subclass differentiation, whereas the Ministry of Health and Family Welfare (MoHFW) guideline specifies both but gives priority to thiazide diuretics.¹⁰

Clinical Conditions Favoring Beta-blocker Use in Hypertensive Patients

Clinical trials and meta-analyses have demonstrated that both first- and second-generation beta-blockers (BBs)—including agents such as propranolol, atenolol, and metoprolol—reduce the risk of cerebrovascular accidents, heart failure, and other significant cardiac events among individuals with hypertension. In relation to alternative classes of antihypertensive drugs, BBs offer comparable protection against major cardiovascular outcomes, though their effectiveness in preventing cerebrovascular events appears slightly lower. This difference may be attributed to subtle variations in blood pressure control, particularly in central systolic blood pressure.¹¹

Historically, BBs were listed as one of the five primary categories of blood pressure-lowering medications in earlier guidelines. However, they are now primarily recommended for patients with specific comorbid conditions—including heart failure (HF), post-MI, angina, AF, or for younger women planning pregnancy.¹¹

Table 1: Selected diseases and conditions for the use of BBs in patients with hypertension

<i>Selected indications with guideline-directed medical therapy for BBs</i>
Chronic coronary syndromes, anti-ischemic therapy
Post-myocardial infarction: arrhythmias, angina, known incomplete revascularization, HF
Acute coronary syndrome
HFrEF and HFpEF if coronary disease (ischemia), arrhythmias and tachycardia
Atrial fibrillation: prevention, rhythm control, heart rate control
Women with child-bearing potential/ planning pregnancy
Hypertension disorders in pregnancy
<i>Selected other conditions in which therapy with BBs can be favorable</i>
Hypertension with elevated resting heart rate >80 bpm
Emergency, urgency and parenteral administration
Perioperative hypertension
Major noncardiac surgery
Excessive pressor response to exercise and stress
Hyperkinetic heart syndrome
Postural orthostatic tachycardia syndrome
Orthostatic hypertension
Obstructive sleep apnea (OSA)
Peripheral arterial disease with claudication
Chronic obstructive pulmonary disease (COPD)
Portal hypertension, cirrhosis-related esophageal varices and recurrent variceal bleeding
Glaucoma
Thyrotoxicosis, hyperthyroidism
Hyperparathyroidism in uremia
Migraine headache
Essential tremor
Performance anxiety and anxiety disorders
Psychiatric disorders (post-traumatic stress)

Third-generation beta-blockers, such as nebivolol and carvedilol, possess additional vasodilatory properties and a more favorable safety profile, including fewer adverse effects on sexual function. Clinical trials involving BBs such as carvedilol, bisoprolol, and nebivolol have demonstrated clear benefits in patients with HFrEF. However, evidence from hypertension-specific outcome trials remains limited, and findings from real-world studies have been inconsistent regarding their degree of cardiovascular protection (Table 1).¹¹

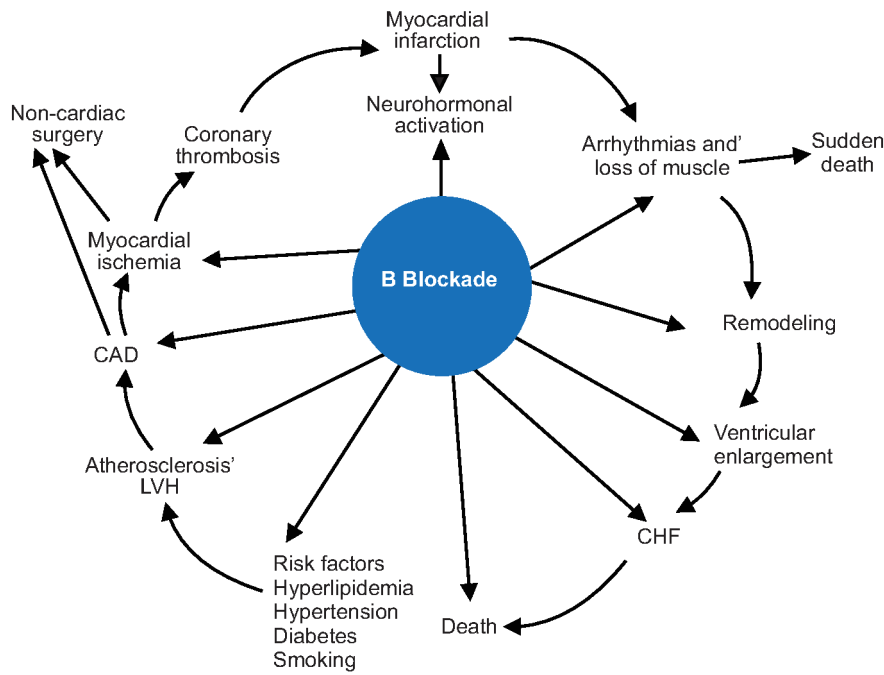


Fig. 4: Beta-blockers can intervene at many points in the cardiovascular continuum

Table 2: Summary of indications, recommendations and considerations

Indication	Recommendation	Comorbidities and considerations
Angina	All beta-blockers are considered equally effective, although bisoprolol or metoprolol may be preferred. Celiprolol and pindolol tend not to be used.	Cardioselective beta-blockers, e.g. bisoprolol or metoprolol, are less likely to cause adverse effects, e.g. cold extremities or fatigue
Arrhythmias	Metoprolol or bisoprolol	Celiprolol and pindolol have intrinsic sympathomimetic activity (ISA) which may reduce bradycardia or peripheral vasoconstriction
Heart failure	Bisoprolol, carvedilol or metoprolol	Water-soluble beta-blockers, e.g. atenolol, celiprolol or nadolol, are less likely to cause central nervous system (CNS) adverse effects, such as sleep disturbance
Hypertension	All beta-blockers are considered to be equally effective (as fourth-line treatment)	Polypharmacy: bisoprolol is less likely to interact with other medicines
Postmyocardial infarction	Bisoprolol or metoprolol; consider withdrawal after 6–12 months if revascularized and no other indications	Renal dysfunction: consider dose adjustments for water-soluble beta-blockers, e.g. atenolol, celiprolol and nadolol; bisoprolol may be preferred Respiratory disease: cardioselective beta-blockers, e.g. bisoprolol and metoprolol, are preferred

Contribution of β -Blockers (Bisoprolol) to Cardiovascular Disease Management

Beta-blockers (BBs) play a pivotal role in slowing or halting the progression of the cardiovascular continuum. Over the past two decades, extensive research has expanded their therapeutic potential beyond their traditional indications in hypertension and post-MI prevention, to include significant benefits in chronic heart failure (CHF) and in reducing cardiovascular events during surgeries unrelated to the heart. One of the most remarkable paradigm shifts in cardiology has been the repositioning of beta-blockers in

CHF, from being previously contraindicated to now serving as a cornerstone of therapy. Their ability to reduce both morbidity and mortality in CHF is well established, and ongoing studies continue to refine their optimal application. The CIBIS III trial demonstrated that initiating treatment with the beta-blocker bisoprolol prior to adding an ACE inhibitor is equally safe and effective as starting therapy in the reverse sequence (Fig. 4).¹²

Beta-blockers exert their cardiovascular benefits primarily through selective blockade of β_1 -adrenergic receptors, which constitute approximately 80% of the heart's adrenergic receptors. This mechanism helps

counteract the proarrhythmic effects of excessive sympathetic stimulation. Their antiarrhythmic properties are mediated through multiple pathways: they lower heart rate, suppress ectopic pacemaker activity, slow atrioventricular (AV) nodal conduction, and prolong the AV nodal refractory period. Additionally, by reducing sympathetic drive, myocardial ischemia, and mechanical stress, and by enhancing baroreflex sensitivity, beta-blockers effectively prevent arrhythmias and stabilize cardiac rhythm. Unlike many other antiarrhythmic agents that act directly on ion channels, beta-blockers have minimal proarrhythmic potential, offering an excellent balance of safety and efficacy across a broad spectrum of cardiovascular disorders.¹³

Cardiovascular Indications

The clinical role of beta-blockers has evolved considerably over time. Initially introduced as first-line agents for hypertension and considered contraindicated in heart failure, their therapeutic positioning has since changed. Currently, their use in hypertension is more selective, whereas they are well established as a cornerstone therapy in heart failure management. Moreover, the long-term benefits of beta-blockers following myocardial infarction are now viewed with greater uncertainty than in the past. Table 2 summarizes the contemporary indications, recommendations, and clinical considerations for beta-blocker use across cardiovascular conditions.¹⁴

Main Pharmacokinetic and Pharmacodynamic Properties of β -Blockers

While all beta-blockers act as competitive antagonists at β_1 -adrenoceptors, they differ markedly in their pharmacokinetic (PK) and pharmacodynamic (PD) characteristics (Table 3). Key PK variations include gastrointestinal absorption, hepatic first-pass metabolism, lipid solubility, plasma protein binding, penetration into the central nervous system, myocardial tissue distribution, and rates of hepatic metabolism and renal excretion. PD distinctions involve differences in β_1 -selectivity, intrinsic sympathomimetic activity, membrane-stabilizing effects, α -receptor blockade, and the presence of direct vasodilatory properties (Table 3).^{15–27}

CONSENSUS 1: ELEVATED HEART RATE IN INDIAN CLINICAL PRACTICE

In Indian patients, blood pressure often shows evening surges accompanied by elevated

Table 3: Clinical outcomes at follow-up of 3.8 median years

Drug	Extent of absorption (% of dose)	Bioavailability (% of dose)	Major first-pass hepatic metabolism	Lipid solubility	Elimination	β_1 selectivity	Dialyzability	Effect on sexual function	Effect on insulin resistance
Bisoprolol	≈90	≈88	No	Low	Renal/hepatic	++++	Low dialyzability	Improves aspects of sexual function, including erection firmness and satisfaction with sexual performance	Neutral effects on the insulin sensitivity index
Atenolol	≈50	≈40	No	Low	Renal	++	High dialyzability	Chronic worsening of sexual activity	Worsens insulin sensitivity, potentially leading to increased fasting blood glucose levels
Carvedilol	>90	≈30	Yes	Moderate	Hepatic	0	Nondialyzable	Chronic worsening of sexual activity	Lowers insulin resistance
Metoprolol	>90	≈50	Yes	Moderate	Hepatic	+	High dialyzability	Metoprolol decreases erectile function	Reduces insulin sensitivity
Nebivolol	>90	12–96	Yes	Low	Hepatic	++++ (increases NO availability)	Nondialyzable	Preserves sexual function	Improve of insulin resistance

++++, More β_1 selectivity; +, less β_1 selectivity

heart rate and heightened sympathetic activity. The therapeutic objectives are to achieve a 20% decrease from baseline pressure levels and maintain the pulse between 60 and 70 beats per minute. For patients who are hemodynamically stable, therapy can be initiated with bisoprolol 5 mg or metoprolol 50 mg daily. In individuals requiring a more gradual approach, treatment may begin with bisoprolol 1.25 mg, followed by dose escalation every 2 weeks to 2.5 mg, 5 mg, and eventually 10 mg, if target heart rate goals are not achieved. Continuous monitoring for bradycardia is essential, and further dose increases should be avoided if it occurs. Patients with bronchial hyperreactivity or chronic obstructive pulmonary disease (COPD) should be closely observed for worsening respiratory symptoms during titration, and dose escalation should be stopped if any concerning symptoms arise. Regular follow-up visits are recommended to ensure good tolerance, achievement of therapeutic heart rate targets, and absence of adverse effects.

Coronary artery disease, presenting as angina or myocardial infarction, is a leading cause of cardiac failure having preserved or moderately reduced ejection fraction in India. Data obtained through the Indian Heart Failure Registry indicate that 70–80% of cardiac failure patients also have CAD. Clinicians have noted that individuals over

35 years of age and those with hypertension, tremors, hyperhidrosis, tachycardia, or mid-range ejection fraction often respond favorably to beta-blocker therapy. Indian patients frequently exhibit resting tachycardia (80–100 bpm), necessitating vigilant monitoring of blood pressure and pulse in those with hypertension, heart failure, angina, myocardial infarction, or arrhythmias to optimize outcomes and ensure safety.

Bisoprolol in the Management of Hypertension

Recent national hypertension guidelines in India have suggested positioning beta-blockers as a later-line therapy, following diuretics, ACE inhibitors/ARBs, and calcium channel blockers. In contrast, the current ESH and ESC recommendations still recognize beta-blockers as a primary treatment option, advocating their role in both the initiation and continuation of antihypertensive therapy, either alone or in combination with other agents.¹²

Bisoprolol, a highly cardioselective β_1 -blocker, offers potential advantages over other selective beta-blockers due to its potency, tolerability, and predictable pharmacokinetics. Although head-to-head trials among selective beta-blockers are generally limited in size, meta-analyses provide useful insights into bisoprolol's role in hypertension management.²⁸

The BRIGHT study evaluated bisoprolol as an initial treatment option among Indian adults diagnosed with stage I primary hypertension. The study demonstrated that bisoprolol was both effective and well tolerated, with an average daily dose of 5 mg, achieving target blood pressure in 96.44% of patients, supporting its suitability as a first-line antihypertensive in this population.²⁹

The CREATIVE study compared bisoprolol with long-acting metoprolol CR/ZOK in patients with mild-to-moderate primary hypertension, focusing on dynamic HR and blood pressure (BP) control. Bisoprolol showed superior reduction in dynamic HR and was noninferior in controlling dynamic BP, without any new safety concerns.³⁰

A pooled analysis comparing bisoprolol against several selective beta-blockers such as atenolol, betaxolol, esmolol, acebutolol, metoprolol, and nebivolol revealed that bisoprolol was more effective in reducing BP and HR, while also showing a beneficial impact on lipid profiles, particularly by elevating HDL cholesterol levels. These findings support bisoprolol's clinical efficacy and role in therapeutic decision-making for hypertension.³¹

The AMCOR study assessed the combination of bisoprolol 5 mg and amlodipine 5 mg in patients whose BP was inadequately controlled by amlodipine monotherapy. Adding bisoprolol significantly enhanced BP management,

producing an additional decrease of 7.2 mm Hg in systolic levels and 3.95 mm Hg in diastolic values, underscoring the effectiveness of this combination in resistant hypertension.³²

A 30-center, randomized, double-blind study evaluated the antihypertensive efficacy and safety of bisoprolol 5 mg combined with hydrochlorothiazide 6.25 mg (B5/H6.25) vs monotherapy with either agent in stage I–II hypertension. The combination demonstrated sustained 24-hour BP control, a similar safety profile to placebo, and fewer adverse events compared with hydrochlorothiazide (HCTZ) 25 mg, including a lower incidence of hypokalemia.³³

The HEART study, a cross-sectional survey of hypertension specialists across India (June–December 2022), assessed real-world use of the bisoprolol + telmisartan combination. Findings included:

- 47% of physicians followed American Hypertension Guidelines.
- Telmisartan was preferred by 95% as the ARB.
- 73% favored bisoprolol for newly diagnosed hypertension, with 57% choosing a 5 mg dose for patients at cardiovascular risk.
- 44% estimated that 20–40% of patients required dual therapy.
- 70% reported improved organ function with the bisoprolol + telmisartan combination, confirming its effectiveness in blood pressure control and cardiovascular risk reduction.³⁴

Overall, these studies highlight bisoprolol's efficacy, safety, and utility in both monotherapy and combination therapy, reinforcing its role in modern hypertension management, particularly in the Indian population.

CONSENSUS 2: BISOPROLOL IN THE MANAGEMENT OF HYPERTENSION IN INDIA

In an Indian context, cardiologists tend to use beta-blockers, with bisoprolol being the most commonly used, followed by nebivolol. These beta-blockers are commonly prescribed alongside ARBs, ACEIs, or diuretics in individuals presenting with elevated BP ($\geq 150/100$ mm Hg) as well as an increased heart rate (>90 bpm). Some newer combinations are bisoprolol with amlodipine or telmisartan.

Patients with renal or liver issues can take bisoprolol as it prevents surges in hypertension during dialysis. Additionally, it is more sympathetic and more common

in younger Indian patients suffering from obesity, which makes beta-blockers such as bisoprolol, which is a cardioselective beta-blocker, more appropriate. Bisoprolol is helpful since it is a selective beta-blocker that has a heart rate-counteracting side effect, which helps with many patients' systemic issues.

Bisoprolol's selectivity makes it easier to treat hypertensive patients with comorbid illnesses like COPD. Treatment during early stages of COPD might enhance the patient's overall health; additionally, use of bisoprolol may lower inflammation, mucus and cytokine secretion, neutrophil activity and bronchoconstrictive endothelin-1 release, thus slowing COPD progression later on.

Antihypertensive medications have an impact on sexual dysfunction, which is a concern for men with hypertension, particularly induced by an increase in blood pressure.

Bisoprolol in the Management of Angina

For many patients, angina is the initial manifestation of CAD, highlighting the need for symptom control and reduction of acute cardiovascular events. Both European and US guidelines recommend beta-blockers as first-line therapy for angina. In the UK, the National Institute for Health and Care Excellence (NICE) advises treating stable angina with either a beta-blocker or a calcium channel blocker (CCB), reserving nitrates for patients who cannot tolerate these agents.³⁵

Clinical evidence demonstrates that beta-blockers reduce ischemic and anginal episodes more effectively than placebo, and often outperform CCBs. Meta-analyses also indicate that beta-blockers lower mortality risk and are associated with fewer adverse events compared to CCBs. Bisoprolol, a highly β_1 -selective blocker, has been shown to reduce angina attacks, improve exercise tolerance, and decrease ischemic burden, surpassing drugs such as nifedipine and isosorbide dinitrate.³⁵

In a study by Terol et al., patients with chronic stable angina were initiated on bisoprolol 10 mg once daily, with subsequent dose adjustments to 5, 15, or 20 mg based on clinical response. Most patients (88%) remained on the 10 mg dose. The study reported that 89% of patients experienced fewer angina attacks, with 56% becoming angina-free. Responses were consistent across age groups and smoking status. Bisoprolol was well tolerated, with only 5.1% reporting side effects, confirming its efficacy and safety in angina management.³⁶

A cohort analysis by Sabidó et al., using the UK Clinical Practice Research Datalink (CPRD), compared long-term outcomes of bisoprolol with other beta-blockers and nonbeta-blocker medications in angina patients. The study found that bisoprolol significantly reduced mortality and the risk of cardiovascular events, supporting guideline recommendations for its role as an initial treatment option in routine clinical practice.³⁵

The TIBBS study evaluated bisoprolol versus nifedipine in patients with chronic stable angina, focusing on transient myocardial ischemia. Both drugs decreased the frequency and duration of ischemic episodes, but bisoprolol demonstrated superior efficacy, particularly in reducing the morning peak of ischemic activity, highlighting its advantage in controlling ischemia.³⁷

CONSENSUS 3: BISOPROLOL IN THE MANAGEMENT OF ANGINA IN INDIA

Indian research indicates that beta-blockers (BBs) treat arrhythmias associated with angina. Cardiologists emphasize achieving a target heart rate of 60 bpm in ischemic patients, which can be facilitated by bisoprolol taken once daily.

Cardiologists check heart rate, blood pressure, COPD, diabetes, and other relevant comorbidities prior to starting pharmacological treatment for angina. For patients with borderline readings, they often start with and monitor response to bisoprolol 1.25 mg. Combination therapy with calcium channel blockers and BBs is commonly employed.

When prescribing beta-blockers, some practitioners do not use them even with heart rates at 75–80 bpm—in favor of trimetazidine or coenzyme Q—and this is a common mistake when managing CAD. Given the clear advantages that beta-blockers provide, this approach needs to be adjusted.

Cardiologists prefer bisoprolol due to its selective beta-1 activity, lack of adversely affecting pulmonary function, lipid and glucose metabolism, high bioavailability, rapid absorption, long half-life, and bisoprolol's anticipated fixed-dose combinations with telmisartan, chlorthalidone, and amlodipine to enable comprehensive management. It is documented that beta-blockers are more effective than calcium channel blockers in reducing ischemic episodes since the effect

of BBs is mostly through decreased heart rate and blood pressure.

Bisoprolol in the Management of Myocardial Infarction

Myocardial infarction is defined by acute ischemia and necrosis of the myocardium, usually resulting from prolonged or severe reductions in coronary blood flow. In China, the incidence of acute MI is rising, with rural populations experiencing higher rates than urban areas, and MI-related mortality is increasing. Cardiac insufficiency occurs when myocardial contractility declines, reducing forward blood flow and leading to congestion within the systemic or pulmonary circulation.³¹

Evidence suggests that many patients develop or worsen cardiac insufficiency after MI, primarily due to adverse myocardial remodeling, which compromises cardiac contractility. The coexistence of MI and cardiac insufficiency complicates management and significantly affects prognosis.³⁸

Conventional therapies alone are often inadequate for patients with MI complicated by cardiac insufficiency. Bisoprolol, a selective β_1 -adrenoceptor blocker, is widely used for moderate to advanced heart failure, ischemic heart conditions, and elevated blood pressure. By selectively blocking β_1 receptors, bisoprolol reduces the effects of adrenaline on the heart, exhibiting greater β_1 selectivity than metoprolol and atenolol. While its efficacy in chronic heart failure is well established, its specific role in MI with cardiac insufficiency has been further investigated.³⁸

A meta-analysis evaluating bisoprolol in MI patients with cardiac insufficiency found that, when added to conventional therapy, bisoprolol significantly improved cardiac function and reduced serum homocysteine (Hcy) and C-reactive protein (CRP) levels, without significant adverse effects.³⁹

In a randomized study by Poldermans et al., bisoprolol demonstrated long-term cardioprotective effects in high-risk patients following major vascular surgery, significantly lowering the rates of cardiac death and recurrent MI.⁴⁰

Maclean et al. studied early oral beta-blocker therapy in patients with acute non-ST elevation myocardial infarction (NSTEMI). Patients receiving bisoprolol within 4 hours of admission experienced fewer ventricular arrhythmias, cardiac deaths, and major adverse cardiovascular events (MACE) compared to those with delayed treatment, suggesting early low-dose bisoprolol confers protective benefits.⁴¹

The Tenacity study evaluated postacute coronary syndrome (ACS) patients with left ventricular systolic dysfunction (LVSD) over

one year. Bisoprolol, combined with guideline-directed medical therapy (GDMT), significantly reduced heart rate, improved left ventricular ejection fraction (LVEF), and decreased ST segment deviation at the J point, without adversely affecting HbA1C or lipid profiles.⁴²

Overall, these studies underscore bisoprolol's role in improving cardiac function, reducing inflammatory markers, preventing arrhythmias, and enhancing long-term outcomes in patients with MI and cardiac insufficiency.

CONSENSUS 4: BISOPROLOL IN THE MANAGEMENT OF MI IN INDIA

In India, beta-blockers (BBs) are useful in the treatment of STEMI, particularly in the presence of left ventricular (LV) dysfunction. Cardiologists often start with short-acting BBs for hemodynamic monitoring and transition to long-acting BBs such as bisoprolol, metoprolol ER, or carvedilol. These BBs are used in conjunction with ACEi, ARBs, ARNIs, or even SGLT2 inhibitors.

For non-STEMI myocardial infarctions and bronchospasm patients, bisoprolol is better due to its profile. Even in the setting of acute heart failure BBs are usually continued as part of multidrug therapy with ARNIs, ARBs, ACE inhibitors, MRAs, or SGLT2 inhibitors, aiming to reach target doses as quickly as safe. Often, bisoprolol is the first drug of choice for arrhythmias. Should this be ineffective, metoprolol or carvedilol can also be added. Following myocardial infarction, there is a rationale to increase or start bisoprolol since it reduces myocardial oxygen demand and heart rate while decreasing the likelihood of recurrent cardiovascular events. It is protective against post-MI arrhythmias and provides cardioprotection that improves prognosis after MI.

Additionally, as a beta-blocker, bisoprolol aids in stabilizing heart function, making it a valuable option in post-MI management for long-term outcome improvement. In Indian patients, bisoprolol is typically initiated at 2.5 mg, with dose adjustments based on heart rate and clinical response.

Role of Bisoprolol in Atrial Fibrillation Management

Bisoprolol, a highly selective β -blocker, has demonstrated strong efficacy in the management of AF by reducing heart rate, thereby decreasing cardiac workload and enhancing the efficiency of cardiac output. In patients with supraventricular arrhythmias, current evidence supports bisoprolol as a preferred agent, particularly for rate control

in AF. It also plays a preventive role in rhythm control strategies, helping to reduce the incidence of postoperative AF in patients undergoing both cardiac and noncardiac surgeries.⁴³

In the management of ventricular arrhythmias, bisoprolol contributes significantly to reducing death rates and rehospitalizations, especially among individuals with clinically stable cardiac failure who experience severe arrhythmias such as sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Early administration—within 4 hours of myocardial infarction—has been associated with lower mortality, a reduced frequency of ventricular arrhythmias, and fewer major adverse cardiac events (MACE) in patients with non-ST elevation myocardial infarction (NSTEMI). Furthermore, bisoprolol effectively decreases the burden of ventricular ectopy in patients with premature ventricular contractions (PVCs).⁴³

A comprehensive review by Muresan et al. analyzed the available evidence regarding bisoprolol's efficacy in supraventricular and ventricular arrhythmias. Of 325 studies initially screened, 28 met inclusion criteria—19 focused on supraventricular arrhythmias, 8 on ventricular arrhythmias, and 1 addressed both. The review concluded that bisoprolol is well supported by current evidence for rate control in AF and for prevention and management of ventricular arrhythmias.⁴³

A study by Mahrose et al. explored how bisoprolol could help prevent AF after on-pump coronary artery bypass graft (CABG) surgery. Patients were split into two groups: one received bisoprolol alone (Group A), while the other received bisoprolol combined with hydrocortisone (group B). The results were striking—those in group B had a significantly lower rate of postoperative AF and experienced shorter hospital stays. These findings highlight that adding hydrocortisone may enhance bisoprolol's protective effect and support faster recovery following CABG.⁴⁴

The MAIN-AF study further investigated the dose-dependent effects of bisoprolol in patients with chronic (persistent or permanent) AF. All participants initially received 2.5 mg/day of bisoprolol for two weeks; thereafter, 48 patients requiring further rate control were randomized to continue 2.5 mg/day or escalate to 5 mg/day for another two weeks. The results demonstrated a more pronounced reduction in heart rate during daytime compared to nighttime. Although the 5 mg/day group exhibited a greater decrease in systolic blood pressure, the difference was not statistically significant. Importantly, no serious adverse

Drugs	Guideline	Recommendation	COR	LOE
ARNi	ESC 2023	HFrEF	I	A
		HFmrEF	II	B
	ACC/AHA/HFSA 2022	HFpEF	II	B
Beta-blocker	ESC 2023	HFrEF	I	A
		HFmrEF	II	B
	ACC/AHA/HFSA 2022	HFpEF	II	B
MRAs	ESC 2023	HFrEF	I	A
		HFmrEF	II	B
	ACC/AHA/HFSA 2022	HFpEF	II	B
SGLT2i	ESC 2023	HFrEF	I	A
		HFmrEF	I	A
		HFpEF	I	A
	ACC/AHA/HFSA 2022	HFmrEF	II	A

Fig. 5: Management of Heart Failure in a Resource-Limited Setting: Expert Opinion from India [ACC/AHA/HFSA, American College of Cardiology/American Heart Association/Heart Failure Society of America; ARNi, angiotensin receptor–neprilysin inhibitor; COR, class of recommendation; ESC, European Society of Cardiology; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LOE, level of evidence; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium–glucose cotransporter 2 inhibitors]

events were observed. This study provided the first quantitative assessment of β -blocker monotherapy in AF, confirming that bisoprolol induces a safe, dose-dependent reduction in heart rate at 2.5 mg and 5 mg daily.⁴⁵

Collectively, these findings underscore bisoprolol's clinical versatility and safety in arrhythmia management—providing effective rate control in atrial fibrillation, reducing the risk of postoperative AF, and mitigating ventricular arrhythmias while maintaining a favorable safety profile.

CONSENSUS 5: BISOPROLOL IN THE MANAGEMENT OF ATRIAL FIBRILLATION IN INDIA

In India, metoprolol and carvedilol are the go-to options for managing heart rate, controlling rhythm, and preventing heart failure, while bisoprolol is infrequently used for AF. Due to longstanding medical traditions, metoprolol is often used first for AF.

The panel recommends that BBs should predominantly focus on the management of ventricular tachycardia (VT) and only use AF as a secondary focus. Beta-blockers have been proven to improve focal ventricular rate by increasing sympathetic outflow, which is the main driver of ventricular tachycardia. It is true that beta-blockers are routinely prescribed for AF to control the rate; however, their effectiveness for rhythm control in AF is not great. Rather, they are quite effective for rate control in tachycardia as they stabilize ventricular function, thus lowering the probability of rapid heart rate-induced sudden cardiac arrest.

Beta-blockers are not employed for prevention in AF but are used to manage

active episodes, especially in patients after cardiac surgeries. The benefit of bisoprolol is its capacity to inhibit excessively fast ventricular rates during episodes of AF. For patients with AF, regulating heart rate during physical activity can be quite difficult, and beta-blockers (BBs) like bisoprolol, occasionally used in conjunction with digoxin, are utilized to control heart rate surges induced by exercise.

Beta-blockers are crucial in the management of various arrhythmias, encompassing both supraventricular and ventricular types. They are also vital during perioperative phases, nonsurgical interventions, and following open-heart surgeries, where their membrane-stabilizing characteristics assist in maintaining rhythm control.

Bisoprolol in the Management of Heart Failure

Management Protocols for HFrEF

Heart failure with reduced ejection fraction requires a personalized treatment approach—one that carefully considers each patient's clinical profile, coexisting conditions, and individual preferences. Tailoring therapy in this way helps optimize outcomes and supports more patient-centered care. Pharmacological therapy remains the cornerstone of treatment, and clinical guidelines continue to evolve as new evidence emerges (Fig. 5).⁴⁶

Beta-Blockers

- Demonstrated to significantly reduce both mortality and morbidity in patients with HFrEF.
- Should be initiated once the patient is clinically stable and euvoletic.

- Effective in patients with either sinus rhythm or AF.
- Require gradual dose titration under close monitoring of heart rate, blood pressure, and symptoms.
- Potential adverse effects include bradycardia, hypotension, and bronchospasm.
- Abrupt discontinuation should be avoided, as it can precipitate clinical deterioration.³⁹

Since the early 2000s, BBs have become a fundamental component of HFrEF therapy, typically used alongside angiotensin-converting enzyme inhibitors (ACEi). Among the three beta-blockers recommended for chronic heart failure—bisoprolol, metoprolol succinate, and carvedilol—bisoprolol is distinguished by its high selectivity for β_1 -adrenergic receptors. This receptor specificity contributes to its strong clinical efficacy and favorable safety profile in chronic heart failure management.^{47–50}

The CIBIS-II trial provided pivotal evidence supporting bisoprolol's role in heart failure therapy. The study demonstrated a 34% reduction in overall mortality and a 44% decrease in sudden cardiac death among patients treated with bisoprolol. In addition to its survival benefits, bisoprolol was shown to improve cardiac performance, enhance physical endurance, and elevate overall well-being in individuals with chronic cardiac failure—establishing it as a cornerstone therapy in CHF management.^{47–50}

The CIBIS-II trial provided strong evidence that bisoprolol—a selective β_1 -blocker—can significantly reduce the risk of death in patients with stable CHF (chronic heart failure). Compared to a placebo, bisoprolol showed a clear survival benefit, reinforcing its role as a cornerstone in heart failure management. Importantly, the study also reported a marked reduction in the incidence of sudden cardiac death, reinforcing the survival advantage conferred by bisoprolol in this patient population.⁵¹

The BISOCOR Observational Study evaluated the real-world application of bisoprolol in stable heart failure patients, assessing the alignment between target doses recommended by the CIBIS-II trial and those achieved in clinical practice. The study also analyzed functional outcomes, adverse events, and reasons for treatment discontinuation. Conducted in Spain, it was the first study to confirm that bisoprolol can be safely titrated to its maximum recommended doses in the outpatient management of heart failure, demonstrating both its effectiveness and tolerability in routine care.⁵²

CONSENSUS 6: BISOPROLOL FOR THE TREATMENT OF HEART FAILURE AMONG PATIENTS IN INDIA

Within the Indian context, bisoprolol is recognized as the primary beta-blocker for heart failure, preferred over carvedilol. Its cardioselective characteristics lead to a less significant hypotensive effect when compared to nonselective beta-blockers. Bisoprolol is deemed more effective than other beta-blockers such as metoprolol, carvedilol, and nebivolol in the treatment of heart failure. It is especially preferred for managing patients with stable HF. Research indicates that bisoprolol should be initiated at a dose of 1.25 mg for HF, with weekly increases to 5 mg daily, targeting a final dose of 10 mg. For effective management of HF, bisoprolol is taken once daily. In patients with heart failure with preserved ejection fraction (HFpEF), beta-blockers are prescribed with caution, while sodium-glucose cotransporter 2 (SGLT2) inhibitors and diuretics are considered the first-line therapies, followed by angiotensin receptor-neprilysin inhibitors (ARNIs). Beta-blockers, including bisoprolol, are now advised alongside ACE inhibitors in the management of heart failure. The usual initiation strength for bisoprolol begins at 1.25 mg and is gradually titrated to 2.5 mg, 5 mg, or higher, depending on patient tolerance, with 5 mg being the most commonly tolerated dose. Bisoprolol has shown effectiveness in lowering mortality and preventing sudden death in patients with heart failure.

CONCLUSION

The concept of the cardiovascular continuum offers a comprehensive framework for understanding the progressive nature of CVD—from the initial development of risk factors to the eventual onset of heart failure. This continuum underscores the critical importance of early, targeted interventions aimed at preventing or slowing disease progression.

Bisoprolol, a highly selective β_1 -adrenoceptor blocker, has demonstrated consistent clinical efficacy across multiple stages of this continuum. By effectively reducing heart rate, improving left ventricular function, and lowering the incidence of major cardiovascular events, bisoprolol serves as a key therapeutic agent in a range of cardiovascular conditions, including hypertension, angina, myocardial infarction, atrial fibrillation, and HFrEF.

In the Indian clinical context, bisoprolol is especially advantageous due to its excellent

tolerability, convenient once-daily dosing, and suitability for a wide spectrum of patients—including those with diabetes, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and older adults. Expert consensus supports its use in real-world practice, emphasizing its effectiveness as part of individualized, combination-based cardiovascular therapy.

With the growing burden of cardiovascular morbidity in India, a comprehensive strategy that integrates optimal heart rate control within guideline-directed medical therapy is increasingly vital. By acting at multiple stages of the cardiovascular disease pathway, bisoprolol not only provides symptomatic improvement but also delivers sustained cardioprotection—reaffirming its pivotal role in modern cardiovascular management.

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Antibiotics in Heart Failure: A Narrative Review

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Received: 18 September 2025; Accepted: 21 July 2026

ABSTRACT

Infections commonly cause acute decompensation and poor outcomes in heart failure (HF), a major global health burden. Patients with heart failure are particularly vulnerable to infections related to the respiratory, urinary, skin, and devices because of systemic inflammation, immune dysfunction, changes in the gut barrier, and repeated exposure to healthcare facilities. The use of empirical antibiotics without confirmation due to overlapping symptoms between infection and heart failure is frequently associated with extended hospital stays, drug toxicity, and antibiotic resistance. While early targeted therapy improves outcomes in confirmed infections, evidence points to limited benefit and possible harm from unnecessary antibiotics. To maximize management in this susceptible population, careful diagnostic evaluation, stewardship, and customized prescribing are crucial.

Keywords: Acute decompensated heart failure, Acute heart failure, Acute respiratory infections, Lower respiratory tract infections, Nonresolving pneumonia.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1702

INTRODUCTION

Heart failure (HF) is becoming a bigger problem for public health around the world. It affects more than 26 million people and is a major cause of hospitalizations and deaths, especially among older people.^{1,2} Even though drug- and device-based treatments have come a long way, heart failure (HF) still causes a lot of illness and death, mostly because of recurrent decompensations and other health problems that come with them.

One of the biggest problems for people with HF is that they are more likely to get infections. These infections generally cause acute decompensation, which means longer hospital stays, higher healthcare expenses, and worse clinical outcomes.^{3,4} Patients with HF are more likely to have infections because they have a systemic inflammatory state, their important organs do not get enough blood flow, their intestines swell, and their gut permeability changes.^{3,5}

Respiratory tract infections, urinary tract infections, and sepsis are frequently observed in HF patients and are commonly treated with empirical or broad-spectrum antibiotics.⁴ While antibiotics are essential in managing infections, their widespread and sometimes inappropriate use in HF patients—often without robust diagnostic confirmation—raises several concerns. These include increased risk of antibiotic-associated complications such as *C. difficile* infection, drug interactions with heart failure medications, and the broader public health threat of antimicrobial resistance.^{6,7}

Recent clinical guidelines emphasize a careful and evidence-based approach to the

management of HF, highlighting the need to differentiate between cardiac and infectious causes of symptoms such as fever, dyspnea, and elevated biomarkers.^{1,4} Simultaneously, the global threat of antimicrobial resistance necessitates judicious antibiotic prescribing practices, particularly in vulnerable populations like those with HF.⁷

Given the clinical complexity and overlapping symptomatology in HF, this review aims to explore the use of antibiotics in patients with heart failure, the common infections encountered, diagnostic challenges, and stewardship strategies to optimize care while minimizing harm.

METHODS (FOR STRUCTURED NARRATIVE REVIEWS)

We did a detailed literature review of the existing information on treatment of heart failure, pneumonia, and protocols on management of patients with presentation of clinical features resembling both these conditions but diagnosis yet not confirmed from multiple sources, including research articles and narrative reviews from PubMed, Cochrane, NCBI, NEJM, EJCM, and textbooks (Harrison, Braunwald, etc.). We found the available data based on search keywords such as heart failure, pneumonia, LRTI, ADHF, and based on the collected data, we did a systematic interpretation and tabulated and summarized all the data with the intent to draw a draft that summarizes the available information on the topic. Based on this data, we summarized a working impression on the best management protocol for management of this clinical scenario.

ASSOCIATION BETWEEN HEART FAILURE, INFECTION AND ANTIBIOTICS

Pathophysiological Link between Heart Failure and Infection

Heart failure is a complex clinical syndrome characterized by impaired cardiac output and systemic congestion, which contributes to a cascade of physiological disturbances that increase susceptibility to infections. Several interrelated mechanisms underlie this heightened vulnerability in HF patients, including immune dysfunction, altered gut permeability, systemic inflammation, and neurohormonal activation.

Chronic heart failure induces a persistent pro-inflammatory state, marked by elevated levels of tumor necrosis factor- α (TNF- α), interleukins (e.g., IL-1, IL-6), and other cytokines that compromise immune surveillance and cellular immunity.^{3,6} This immune dysregulation impairs the host's ability to respond adequately to bacterial and viral pathogens, increasing the risk and severity of infections.

A particularly critical mechanism is gut translocation. In HF, mesenteric hypoperfusion and intestinal congestion lead to ischemia of the intestinal mucosa and disruption of tight junctions. This results in increased intestinal permeability and translocation of bacteria and endotoxins into systemic circulation—a phenomenon referred to as the "gut hypothesis" of heart failure.³ Niebauer et al. first demonstrated elevated circulating endotoxins and monocyte activation markers in patients

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How to cite this article: Kaur T, Ritu, Kohli P, et al. Antibiotics in Heart Failure: A Narrative Review. *J Assoc Physicians India* 2026;74(9):93–97.

with advanced HF, highlighting the role of gut-derived inflammation in disease progression.⁸

Systemic inflammation is also worse when the liver and kidneys are congested and cannot eliminate inflammatory mediators as well. Neurohormonal activation, which happens when the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system are turned up, further lowers immune function, making it easier for infections to spread.^{5,6}

Another thing that is often missed is how many times HF patients must go to the hospital, have invasive procedures, and be in healthcare environments, all of which raise their risk of getting infections while they are getting care. These places often have indwelling catheters, IV lines, and a lot of exposure to antibiotics, which makes people more likely to get infections and makes antibiotics less effective.

Patients with heart failure are at a uniquely high risk of getting infections because of the combination of systemic inflammation, immune suppression, mucosal barrier dysfunction, and healthcare exposures. To come up with focused preventative and treatment plans, it is important to understand these pathophysiological linkages.

Common Infections in Heart Failure Patients

People with heart failure are more likely to get several infections because their immune systems are weak, they are often in the hospital, they have invasive operations, and they have other health problems such as diabetes, chronic renal disease, and chronic obstructive pulmonary disease (COPD). These infections generally cause severe decompensation and are linked to more illness, longer hospital admissions, and death.

Respiratory Tract Infections

Respiratory infections, including community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), are among the most frequently encountered infections in patients with HF. The clinical overlap between symptoms of pneumonia and HF—such as dyspnea, fatigue, and crackles—often complicates the diagnosis and may lead to either delayed antibiotic therapy or unnecessary antibiotic use.⁹ Pneumonia is a major precipitating factor for acute decompensated heart failure and is associated with worse short- and long-term outcomes.¹⁰

Urinary Tract Infections

Urinary tract infections (UTIs) are also common in HF patients, especially among the elderly, those with indwelling catheters, and patients with diabetes or fluid overload. They often

present with nonspecific symptoms such as confusion or malaise, which may be mistaken for worsening heart failure. Empirical antibiotic therapy is frequently initiated based on urinalysis findings, though asymptomatic bacteriuria remains a diagnostic challenge in this group.¹⁰

Skin and Soft Tissue Infections

Patients with chronic edema, venous insufficiency, and reduced mobility are predisposed to cellulitis and other skin infections. Diuretics used in HF management can lead to electrolyte imbalances and dehydration, which further impair skin integrity. These infections may also be complicated by resistant organisms, especially in those with repeated antibiotic exposure.⁶

Sepsis and Bloodstream Infections

Sepsis is a serious consequence of HF that is often not identified. It may show low blood pressure and high lactate levels, which are also signs of cardiogenic shock, making it hard to tell what is wrong. Once sepsis is diagnosed, it is very important to start the right antibiotics right once. However, HF patients may need to have their doses changed if their organs are not working properly.⁵

Device-associated Infections

People who have pacemakers or implantable cardioverter-defibrillators (ICDs) are at risk for infections that can happen with these devices. These infections can be as mild as a pocket infection or as serious as infective endocarditis. These infections are hard to treat and may need the removal of the device along with long-term antibiotic therapy.¹¹

In all of these situations, infection not only makes the clinical picture more complicated, but it also strongly triggers decompensated heart failure. So, it is important to recognize the problem early and give the right antibiotics, but this should be done in a way that avoids overuse and resistance.

Challenges in Diagnosing Infections in Heart Failure

It might be hard to tell if a patient with heart failure (HF) has an infection because the symptoms and lab results for both illnesses are quite similar. Misunderstanding can cause a diagnosis to be delayed, antibiotics to be used incorrectly, and bad results. Older people, people with several comorbidities, and people with acute decompensated heart failure (ADHF) make things even more complicated.

Overlapping Clinical Features

Fever, shortness of breath, exhaustion, and a fast heart rate are all common indications

of infection. These are also common signs of HF exacerbation. For example, chest X-rays of people with HF may show lung congestion that looks like pneumonia, and peripheral edema may hide indications of a soft tissue infection. Also, symptoms like changes in mental state or general malaise, especially in older people, can be vague and misleading.¹²

Biomarker Limitations

Commonly used biomarkers, such as white blood cell count and C-reactive protein (CRP), may be elevated in HF even in the absence of infection due to chronic systemic inflammation. Although procalcitonin (PCT) has emerged as a potentially more specific marker for bacterial infection, its interpretation in HF is still evolving. Maisel et al. suggest that low PCT levels can safely exclude bacterial infection in patients with ADHF, but Scolletta et al. highlighted in their study that even modest elevations may be associated with increased mortality, independent of infection status.^{12,13}

Imaging and Diagnostic Tools

Radiological imaging can be inconclusive in HF patients. Pulmonary edema can mask or mimic infiltrates, and the interpretation of chest X-rays or CT scans is often complicated by volume overload. Similarly, findings on urinalysis or blood cultures may reflect colonization or contamination rather than true infection, especially in patients with indwelling devices or frequent hospitalizations.⁹

Diagnostic Stewardship in Heart Failure

The risk of diagnostic inertia—relying on suggestive but non-definitive signs—may result in the overuse of empiric antibiotics. This is particularly relevant in emergency and intensive care settings, where time pressures often drive early antibiotic initiation. Studies have shown that up to 30%–40% of patients hospitalized with ADHF receive antibiotics without a confirmed infection, which contributes to increased healthcare costs and adverse events, including antimicrobial resistance and *C. difficile* infection.⁹

Role of Clinical Judgment and Serial Assessment

Given these diagnostic ambiguities, clinical judgment remains critical. Serial evaluation of symptoms, biomarker trends, imaging findings, and therapeutic response can help refine diagnosis. Multidisciplinary collaboration—especially involving infectious disease specialists and heart failure teams—can enhance diagnostic accuracy and prevent unnecessary antibiotic use.

Patterns and Indications for Antibiotic Use in Heart Failure

Doctors commonly provide antibiotics to people with heart failure (HF) as a first line of defense against infections that could make their condition worse. When a person has a confirmed or highly suspected infection, they should get antibiotics right away. However, new evidence suggests that many HF patients get antibiotics when they do not need them or when they should not, which raises concerns about antimicrobial resistance, bad drug reactions, and costs.

Empirical Antibiotic Use in Decompensated HF

In HF patients, respiratory tract infections are still the most common reason for getting antibiotics. Because pneumonia and acute decompensated heart failure (ADHF) have similar clinical signs, antibiotics are routinely prescribed before a definitive diagnosis is made. Studies have revealed that more than 30% of hospitalized HF patients start taking antibiotics, especially beta-lactams and macrolides, without any proof that they have an infection.⁹ People do this because they think it is better to be safe than sorry, especially for elderly patients and those with high inflammatory markers.

Urinary Tract Infections and Overdiagnosis

Asymptomatic bacteriuria is frequently misinterpreted as urinary tract infection (UTI) in hospitalized HF patients. Positive urine cultures, in the absence of clinical signs of infection, often lead to unnecessary antibiotic initiation. This is especially prevalent in older adults and patients with indwelling catheters or urinary retention—common scenarios in advanced HF.⁶

Skin and Device-related Infections

In patients with chronic edema or implanted cardiac devices (e.g., pacemakers, ICDs), antibiotics are appropriately used for documented cellulitis, pocket infections, or endocarditis. These typically require longer durations of therapy and careful antimicrobial selection to cover resistant pathogens such as *Staphylococcus aureus*.¹⁷ However, the threshold for suspecting and treating these infections varies widely across institutions.

Commonly Used Antibiotic Classes

The most frequently used antibiotic classes in HF patients include:

- *Beta-lactams* (e.g., amoxicillin-clavulanate, ceftriaxone)—used for pneumonia and urinary infections.

- *Macrolides* (e.g., azithromycin)—often added empirically for atypical respiratory coverage.
- *Fluoroquinolones* (e.g., levofloxacin, ciprofloxacin)—used for broad-spectrum coverage, though associated with increased cardiovascular risk in HF.
- *Vancomycin* and *Linezolid*—reserved for MRSA or device-related infections.

These agents must be used with caution, especially in the context of altered pharmacokinetics, potential QT prolongation, and renal dysfunction common in HF patients.¹⁴

Risks Associated with Inappropriate Use

When antibiotics are prescribed incorrectly, they can cause drug-related toxicity, longer hospital stays, the growth of multidrug-resistant organisms, and a higher risk of *C. difficile* infection. Also, antibiotics such as fluoroquinolones and macrolides have been linked to arrhythmias and worsening heart failure in people who are already at risk, which makes it even more important to carefully weigh the risks and benefits.¹⁵ Antibiotics are an important part of treating infections in HF, but they should only be used when there are clear clinical reasons, diagnostic proof, and a grasp of the patient's individual situation to avoid harm and keep the antibiotics effective.

Antibiotic Pharmacokinetics and Pharmacodynamics in Heart Failure

Heart failure (HF), particularly in its acute decompensated form, significantly alters the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics, affecting their efficacy and safety (Fig. 1).

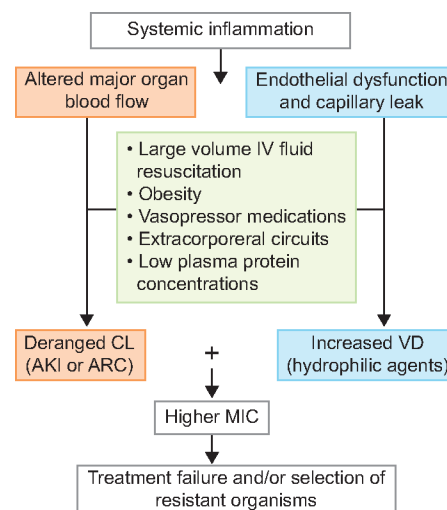


Fig. 1: Proposed pathway linking systemic inflammation to altered antibiotic pharmacokinetics and treatment outcomes

Pharmacokinetic Changes in HF

The state of systemic arterial hypoperfusion, venous congestion, and neurohormonal activation occurring in HF negatively affects the integrity and the function of key organs, particularly the gastrointestinal tract, the liver, and the kidney. Pathophysiological changes of heart failure in systemic organs can potentially affect drug absorption, first-pass metabolism, protein binding, volume of distribution, and clearance; there is significant inter-individual variability in the presence and severity of hepatic and renal dysfunction, singly or in combination, in the HF population.¹⁶ The presence of significant fluid overload can lead to modifications of specific compartments, such as the pleural space (pleural effusion) and the peritoneal cavity (ascites), and/or a systemic expansion of the interstitial fluid volume (anasarca), with significant effects on the distribution of water-soluble drugs.¹⁷

REVIEW OF LITERATURE AND DISCUSSION

Studies

Here is a tabulated representation of available studies from various resources addressing the above-discussed clinical dilemma of managing the clinical scenario of using empirical antibiotics in patients of heart failure with presentation resembling both ADHF and pneumonia, and the diagnosis of pneumonia has not yet been confirmed (Table 1).

Discussion

We noted that most studies done in the past indicate that irrational use of empirical antibiotics in unconfirmed infections leads to poor outcomes, including prolonged hospital stay and higher intermediate mortality. The benefit of empirical antibiotics in heart failure with unconfirmed pneumonia is limited to a high likelihood of infections with biomarker correlates. Irrational or aggressive antibiotic use is not supported by any of the existing literature. However, the benefit of early antibiotics is noted as the clinical evidence of infection becomes stronger in favor of infection even before final confirmation.

Gaps in Knowledge

Most of the studies done on antibiotic use in empirical therapy in heart failure are based on very small data sets, with limited inclusion of various ethnic and regional groups. Very limited data is available on tropical region protocols where the burden of infection is very high, and the potential of antibiotic use in patient benefit is possible. Studies in the Indian scenario, where the burden on Heart

Table 1: Summary of recent studies evaluating antibiotic use in heart failure

Study	Design and population	Antibiotic use	Primary outcome(s)	Key results	Conclusions
Katherine Schojan et al. (2023) ¹⁸	Retrospective cohort (2018–2022), 161 patients with ADHF without confirmed infections	≥48 hours of IV antibiotics vs no antibiotics	Hospital length of stay (LOS)	LOS significantly longer in antibiotic group (matched: 5 vs 4 days, $p < 0.01$); increased sodium/fluid exposure	Avoid empiric antibiotics unless infection is confirmed; risk of fluid overload and prolonged hospitalization
Loosen et al. (2023) ¹⁹	Retrospective case-control study, 162,188 outpatients (Germany)	Analyzed total dose and class over 5 years	Incidence of HF	Low antibiotic use (≤ 6000 mg) associated with lower HF risk (OR = 0.87); high cephalosporin use increased risk (OR = 1.16)	Antibiotic use linked to HF risk in a dose- and class-dependent manner; may involve gut microbiome alterations
Rohini Pawar et al. (2025) ²⁰	Prospective observational study, 100 patients with AHF (India)	All received antibiotics on admission	Duration and rationality of use	Mean duration, 5.37 ± 2.62 days; only 10% had antibiotics stopped at 48 hours	Highlights overuse of antibiotics; calls for rational use and de-escalation in suspected cardiac dyspnea
PAPRICA-3 study	Multicenter observational study, 6,727 patients with AHF (Spain)	Early antibiotic administration in infection-triggered AHF	13-week mortality and readmission	Higher early mortality in infection-triggered AHF (unadjusted); lower postdischarge mortality after adjustment	Infection-triggered AHF not linked to worse midterm outcomes; early antibiotic use and hospitalization may help
Frisbee et al. (2024) ²¹	Retrospective review, 144 patients with ADHF with low pneumonia risk	IV antibiotics vs no antibiotics	LOS, diuretic use, readmission, mortality	IV antibiotic group had longer LOS (6.6 vs 3.0 days), more diuretic use (930 vs 320 mg), and higher readmission (OR = 2.51)	IV antibiotics without infection worsen ADHF outcomes; reinforce stewardship to avoid fluid/sodium overload

failure patients is on an exponential rise, but the infection prevalence in the population is still high, are very few. The various antibiotic combinations, use of alternative antibiotics, and interantibiotic comparison in this scenario have also not been studied extensively. Therefore, the exact verdict on the scenario can only be drafted after more comparative studies in the future, giving us potential research topics which need to be answered and may be considered in future analysis.

CONCLUSION

Heart failure (HF) is a major global health issue marked by high morbidity and mortality, with frequent infections acting as common precipitants of acute decompensation. Patients with HF are particularly susceptible to infections due to systemic inflammation, impaired organ perfusion, gut barrier dysfunction, and immune dysregulation. Common infections in HF include respiratory tract infections, urinary tract infections, skin infections, sepsis, and device-related infections, many of which overlap symptomatically with HF itself—making diagnosis and treatment particularly challenging. Empirical antibiotic use is common but often unjustified, driven by diagnostic uncertainty, leading to potential harm such as prolonged hospitalization, drug toxicity, and increased antimicrobial resistance. Studies show that inappropriate antibiotic administration in patients with unconfirmed infections correlates with worse

outcomes, highlighting the urgent need for diagnostic stewardship, individualized clinical assessment, and careful antibiotic selection. This review underscores the pathophysiological links between HF and infection, common infectious patterns, diagnostic dilemmas, pharmacological considerations, and evidence-based approaches for judicious antibiotic use in this vulnerable population.

SOURCE OF FUNDING

Nil.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

TK and R contributed to conception, study design, supervision, funding, material collection, data collection and/or processing, analysis and/or interpretation, literature review, writing, and critical review. PK and SA contributed to material collection, data collection and/or processing, and critical review. BDM and KK contributed to material collection, data collection and/or processing, and analysis and/or interpretation.

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Efflux Pump Inhibitors: Revisiting an Old Strategy in the Era of Antimicrobial Resistance

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Received: 12 January 2026; Accepted: 24 March 2026



ABSTRACT

Antimicrobial resistance (AMR) is a growing global threat that undermines the effectiveness of existing antibiotics and complicates the treatment of infectious diseases. Among the multiple mechanisms driving resistance, bacterial efflux pumps play a critical but often underappreciated role by actively expelling antibiotics from the cell and reducing intracellular drug concentrations. These pumps are widely distributed across gram-positive and gram-negative bacteria and contribute to multidrug resistance against several major antibiotic classes. Importantly, efflux-mediated resistance is frequently an early and reversible step, allowing bacteria to survive initial antimicrobial exposure and acquire additional resistance mechanisms. Efflux pump inhibitors (EPIs) have therefore long been explored as adjuncts to antibiotic therapy. Experimental studies, particularly with natural compounds, have shown that EPIs can restore antibiotic susceptibility and enhance drug efficacy despite having little intrinsic antibacterial activity. However, clinical translation has been limited by issues related to toxicity, selectivity, pharmacokinetics, and redundancy of efflux systems. Recent advances in molecular and structural biology have renewed interest in this strategy by enabling more rational, mechanism-based EPI design. In the context of a shrinking antibiotic pipeline, revisiting efflux pump inhibition offers a promising complementary approach to prolong the usefulness of existing antibiotics and combat multidrug-resistant infections.

Keywords: Antimicrobial therapy, Drug resistance, Efflux pump inhibitors.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1643

Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges, threatening to reverse decades of progress in infectious disease management. Among the various mechanisms contributing to resistance, bacterial efflux pumps play a pivotal yet often under-recognized role. These transport systems actively expel structurally diverse antimicrobial agents from bacterial cells, thereby reducing intracellular drug concentrations below therapeutic levels and facilitating multidrug resistance.¹

Efflux pumps are widely distributed among gram-positive and gram-negative bacteria and may be either chromosomally encoded or acquired. Their overexpression has been linked to resistance against multiple antibiotic classes, including fluoroquinolones, tetracyclines, macrolides, and β -lactams, as well as to reduced susceptibility to antiseptics and disinfectants.² Importantly, efflux-mediated resistance often represents an early and reversible step in the evolution of high-level resistance, allowing bacteria to persist long enough to accumulate additional resistance mechanisms such as target-site mutations.^{1,3}

Interest in efflux pump inhibitors (EPIs) as adjuncts to antimicrobial therapy is therefore not new. Early experimental studies demonstrated that inhibition of efflux systems could restore antibiotic susceptibility

in resistant strains. Natural products have been identified as a particularly rich source of potential EPIs. Plant-derived alkaloids, flavonoids, terpenoids, and phenolic compounds have shown inhibitory activity against major efflux systems such as NorA in *Staphylococcus aureus* and AcrAB-TolC in Enterobacterales.¹ These agents often possess little intrinsic antibacterial activity but significantly enhance the efficacy of conventional antibiotics, highlighting their role as resistance-modifying agents rather than independent antimicrobials.^{1,2}

Despite promising *in vitro* findings, successful translation of EPIs into clinical practice has remained limited. Major challenges include lack of selectivity, host toxicity, unfavorable pharmacokinetics, and the functional redundancy of efflux systems within bacterial cells.⁴ Recent advances in molecular biology, structural analysis, and biophysical studies have, however, improved understanding of efflux pump architecture, substrate recognition, and energy coupling mechanisms.³ These insights have facilitated the rational design of EPIs targeting specific pump components or transport pathways, moving the field beyond empirical screening toward mechanism-based drug development.³

From a clinical standpoint, reevaluation of EPIs is particularly relevant in the current era,

where antibiotic development remains limited. Rather than relying solely on the discovery of new antimicrobial agents, combining existing antibiotics with effective EPIs may extend the therapeutic lifespan of available drugs, reduce dosage requirements, and potentially slow the emergence of further resistance.⁴ While no EPI has yet achieved routine clinical use, available evidence suggests that their most feasible role may be as adjunctive agents in the management of infections caused by multidrug-resistant organisms.^{2,4}

In conclusion, efflux pump inhibition represents a rational and complementary strategy for addressing AMR. Continued translational research focusing on safety, specificity, and clinical applicability is essential to determine whether EPIs can successfully bridge the gap between laboratory promise and bedside utility.

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How to cite this article: Naik T, Gawari NC, Kumar A, et al. Efflux Pump Inhibitors: Revisiting an Old Strategy in the Era of Antimicrobial Resistance. *J Assoc Physicians India* 2026;74(9):98.

Incidence and Pattern of Transfusion Reactions in a Tertiary Care Hospital



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Keywords: Blood safety, Blood transfusion, Febrile nonhemolytic transfusion reaction, Hemovigilance, Transfusion reaction.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1649

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Dear Sir,

We read with interest the article by Gupta et al. on “Incidence and pattern of transfusion reactions (TRs) in a tertiary care hospital.” The study provides useful institutional data; however, certain observations warrant critical appraisal.

This study has reported an overall incidence of transfusion reactions (TR) as 0.18%, which predominantly consists of febrile nonhemolytic transfusion reactions (FNHTRs) with 51%.¹ Incidences appears notably lower in comparison with similar contemporary data in Indian literature, as observed in a 2025 multiple-center analysis as 0.71%² and in a tertiary center in Central India as 0.27%,³ highlighting potential underreporting biases inherent in retrospective designs reliant on incident forms.

Methodological limitations undermine the findings’ robustness. Classification by a single blood transfusion officer as per “national blood transfusion guidelines,” invites misclassification, because FNHTRs and allergic reactions share common presentation (febrile 31.8%, chills 28.7%, rashes 27.4%),¹ in contrast with more focused classification practices as in ISBT (International Society of Blood Transfusion) guidelines, giving prime importance to laboratory-confirmed events in hemovigilance.³

Exclusion of delayed hemolytic TRs (DHTR) from acute totals, despite 100% thalassemia association ($p = 0.001$), inflates the “acute” focus while ignoring chronic risks.¹

Statistical inferences merit careful evaluation; as whole blood’s highest risk (3.84/1000 units, $p = 0.038$) differs significantly from that of packed RBCs (2.85, $p = 0.001$), yet SDP’s (single donor platelets) nonsignificance ($p = 0.571$) may reflect low power, due to uneven unit distribution rates, unadjusted for potential variables of certain demographic characteristics (median age 45–60 years, male-to-female ratio 1.3:1).^{1,4}

Global benchmarks estimate 0.2–10% TRs, often underreported due to awareness gaps, as expressed here.^{3,5}

Prospective hemovigilance with mandatory reporting could enhance accuracy, aligning with WHO recommendations for transfusion safety audits.⁶ Overall, while this study adds valuable data, it also highlights the need for strengthened hemovigilance, wider adoption of leukoreduction and standardized transfusion protocols to improve patient safety and accurately capture transfusion-related adverse events. This commentary underscores the need for rigorous validation in future TR surveillance for effective clinical practice.

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How to cite this article: Shelar SS, Pawar VU, Bhalerao SV. Incidence and Pattern of Transfusion Reactions in a Tertiary Care Hospital. *J Assoc Physicians India* 2026;74(9):100.

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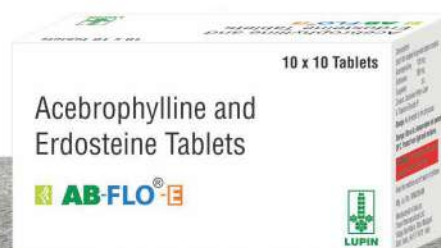


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An Uncommon Cause of Refractory Pleural Effusion

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Received: 28 September 2025; Accepted: 07 July 2026



Keywords: Bronchoalveolar lavage fluid, Pleural aspergillosis, Pleural effusion, Pulmonary aspergillosis, Refractory pleural effusion.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1704

Dear Editor,

Pleural effusion is a frequently encountered clinical problem with a broad differential diagnosis encompassing infectious, malignant, cardiac, hepatic, and inflammatory etiologies. In countries such as India, tuberculosis remains a leading cause of exudative pleural effusion, while malignancy is another major consideration in elderly patients.¹ However, fungal infections involving the pleural space are exceedingly uncommon and often remain unrecognized because of their nonspecific clinical presentation and the low diagnostic yield of routine pleural fluid investigations. We report a rare case of pulmonary aspergillosis presenting as recurrent hemorrhagic pleural effusion, highlighting the importance of considering fungal etiologies when common causes have been excluded.

A 70-year-old male with multiple comorbidities, including chronic liver disease, type 2 diabetes mellitus, hypertension, hypothyroidism, and a history of right nephroureterectomy for renal transitional cell carcinoma 4 years earlier, presented with progressive dyspnea and left-sided chest discomfort. He also had a recent history of recurrent hematuria secondary to left nephrolithiasis requiring percutaneous nephrolithotomy and double-J stent placement. Clinical examination revealed reduced breath sounds and dullness to percussion over the left hemithorax. Chest radiography and computed tomography demonstrated a moderate-to-large left-sided pleural effusion with underlying lung collapse. An intercostal drainage tube was inserted, yielding hemorrhagic pleural fluid (Fig. 1).

Initial pleural fluid analysis was inconclusive. The fluid was hemorrhagic with elevated protein levels and mixed cellularity. Importantly, microbiological investigations, including acid-fast bacilli staining and GeneXpert MTB/RIF testing, were negative. Cytological examination did not reveal malignant cells, and aerobic cultures were sterile. Despite adequate drainage, the pleural effusion persisted, prompting further evaluation.

Given the absence of a definitive diagnosis, bronchoscopy with bronchoalveolar lavage (BAL) was performed. Although routine stains, bacterial cultures, and GeneXpert testing of BAL samples were negative, the BAL galactomannan index was markedly elevated at 4.5. Furthermore, fungal culture subsequently grew *Aspergillus* species after 1 week of incubation (Fig. 2). These findings established the diagnosis of pulmonary aspergillosis with pleural involvement. The patient was treated with intravenous amphotericin B followed by oral voriconazole. Clinical symptoms gradually improved, and follow-up imaging demonstrated near-complete resolution of the pleural effusion after completion of antifungal therapy.

Pleural aspergillosis is a rare manifestation of *Aspergillus* infection.^{1,2} Unlike invasive pulmonary aspergillosis, which primarily affects severely immunocompromised hosts, pleural involvement generally occurs secondary to thoracic surgery, bronchopleural fistula, empyema, or contiguous spread from underlying pulmonary disease. The largest contemporary review by Zhang et al.³ evaluated 13 cases of pleural aspergillosis and found that most patients had a history of thoracic intervention or bronchopleural fistula, with mortality remaining substantial despite treatment. Our patient had no previous thoracic surgery or fistula, making the presentation particularly unusual.

Several isolated case reports have described atypical manifestations of pleural aspergillosis. Chang et al.⁴ reported a case of *Aspergillus* pleural empyema in a patient with bronchiectasis, while Kant et al.⁵ described pyopneumothorax caused by *Aspergillus* infection. Other reports have documented pleural-based aspergillosis mimicking malignant disease (Table 1). In contrast, our patient presented primarily with recurrent hemorrhagic pleural effusion, a clinical picture that strongly suggested tuberculosis or malignancy rather than fungal infection. Consequently, the diagnosis was considerably delayed.

The diagnostic challenge in pleural aspergillosis arises largely because pleural

fluid studies are frequently nondiagnostic. Isolation of *Aspergillus* species from pleural fluid is uncommon, and culture sensitivity is generally poor. As demonstrated in the present case, BAL galactomannan testing combined with fungal culture can provide critical diagnostic information when pleural investigations fail to identify an etiology. Galactomannan, a polysaccharide component of the *Aspergillus* cell wall, has become an important biomarker for invasive aspergillosis and may be particularly useful in patients with unexplained pleural disease and radiological evidence of pulmonary involvement. The elevated BAL galactomannan index and positive fungal culture in our patient were instrumental in establishing the diagnosis.

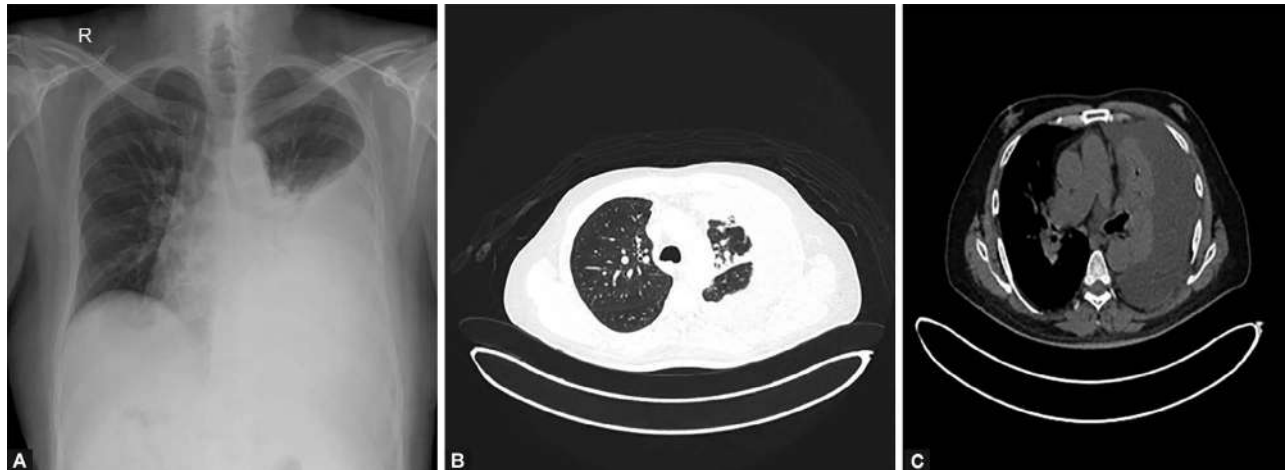
Management of pleural aspergillosis remains challenging because of the rarity of the condition and the absence of standardized treatment protocols. Current therapeutic strategies generally involve a combination of pleural drainage, systemic antifungal therapy, and, in selected cases, surgical intervention. Voriconazole is widely regarded as the first-line treatment for invasive aspergillosis owing to its favorable efficacy profile, while amphotericin B remains an important option in severe disease. In our patient, a combination of initial amphotericin B followed by prolonged voriconazole therapy resulted in complete symptomatic improvement and radiological resolution, thereby avoiding the need for surgical management.

This case underscores several important clinical lessons. First, fungal infections should be considered in patients with persistent or recurrent pleural effusion when conventional investigations fail to establish a diagnosis. Second, the absence

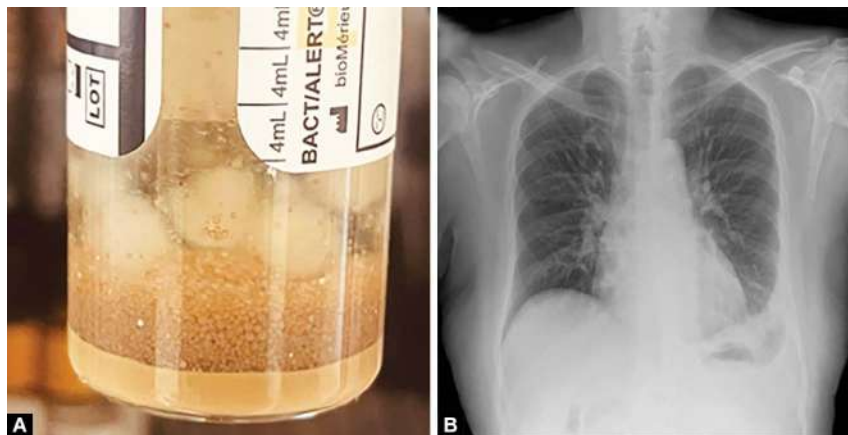
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How to cite this article: Sharma P, Bhatti RS, Gupta D. An Uncommon Cause of Refractory Pleural Effusion. *J Assoc Physicians India* 2026;74(9):102–104.

Table 1: Summary of cases of pleural aspergillosis in literature and their Outcomes

Study	Age/sex	Site	Complaints at presentation	Presentation	Diagnosis Method	Treatment	Outcome
Zhang et al. ³ (Case series)	Median age—65 years with 90% male patients	Not mentioned	Not mentioned	Mainly postsurgical, pleural <i>Aspergillus</i>	Pleural culture/biopsy	Systemic ± topical antifungals	9 recovered; poor with fistula
Chang et al. ⁴	70/male	Right	Shortness of breath, fatigue, and generalized weakness for 10 days.	Smoker with bronchiectatic changes, empyema	Pleural culture/GaM	VATS + IV voriconazole	Mortality
Zhang et al. ⁹	31/ Male	Right	Not mentioned	Recurrent Pneumothorax	Biopsy/culture	Lobectomy and loop ligation of the blebs and Itraconazole for 9 months	Recovery
Kant et al. ⁵	32/male	Right	Fever, dry cough, right-sided chest pain and progressive breathlessness (2 months)	Pyopneumothorax, tube thoracostomy	Thoracoscopic pleural biopsy & culture	Voriconazole for 6 months and thoracotomy	Recovery
O'Connor et al. ⁶	27/male	Bilateral	Not mentioned	Pleural effusion in ABPA	Clinical + labs	Steroids	Resolved
Goel et al. ⁷	57/male	Right	Fever, dry cough and chest pain	Pleural-based homogeneous shadow with Pleural effusion	Thoracoscopic pleural biopsy and culture	Thoracotomy and voriconazole	Recovered
Jing et al. ⁸ (Case series)	Mean age 58.5 years/50% male	Bilateral/left	Chest pain, cough, yellow pus sputum, dyspnea, fever, chest congestion, hemoptysis	Pleural effusion with thickening	Pleural fluid Biochemistry, cytology, culture, NGS, and BALF	Antifungals and thoracoscopic surgery	75% recovered



Figs 1A to C: (A) Chest radiograph showing a large left-sided pleural effusion with mass effect causing a slight midline shift of the mediastinal structures; (B and C) axial CT images of the thorax in parenchymal and mediastinal windows showing moderate-to-large left-sided pleural effusion with underlying lung collapse



Figs 2A and B: (A) Macroscopic appearance of pleural fluid culture showing extensive growth of *Aspergillus fumigatus* with fluffy whitish-gray colonies; (B) follow-up chest radiograph 3 months after catheter removal and continuation of antifungal therapy showing near-complete resolution of the effusion with minimal residual pleural effusion and thickening at the left costophrenic angle

of classic risk factors such as thoracic surgery or bronchopleural fistula does not exclude pleural aspergillosis. Finally, BAL galactomannan testing and fungal cultures can significantly enhance diagnostic yield and should be considered early in the evaluation of unexplained pleural effusions, particularly in individuals with underlying immunocompromising conditions or chronic systemic illnesses.

In conclusion, pulmonary aspergillosis may rarely present as refractory pleural effusion and mimic more common conditions such as tuberculosis or malignancy. A high index of suspicion, combined with appropriate fungal investigations, is essential for timely diagnosis and initiation of antifungal therapy. Recognition of this uncommon presentation can facilitate

earlier treatment and improve clinical outcomes.

SOURCE OF FUNDING

Nil.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTION

PS, RSB, and DG contributed equally to the study concept, drafting, and writing of the manuscript.

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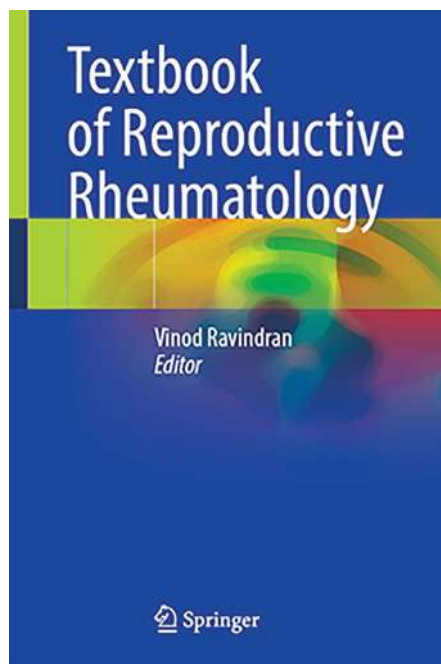
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Textbook of Reproductive Rheumatology

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Keywords: Contraception, Counselling, Fertility, Lactation, Obstetricians, Postpartum period, Reproductive health, Rheumatic diseases.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1713



Reproductive rheumatology has emerged as a vital subspecialty that bridges rheumatology, obstetrics and gynecology, reproductive medicine, and neonatology. A majority of autoimmune rheumatic diseases are more common in women, and cultural and societal pressure to plan for a family further underscores the importance of this topic. With advances in understanding and treating autoimmune rheumatic diseases, an increasing number of women and men with these conditions can pursue parenthood successfully. However, optimizing reproductive outcomes requires careful preconception counseling, appropriate disease control, judicious medication selection, and coordinated multidisciplinary care throughout pregnancy, delivery, and the postpartum period. Hence, all relevant specialists must be aware of the essentials and ensure consistent management to counsel patients appropriately.

A textbook on reproductive rheumatology has been a long-felt

need. This textbook provides detailed 360° coverage of this subject, making it collectible for all clinicians managing autoimmune rheumatic diseases. This textbook has 21 well-thought-out chapters written by relevant experts from around the world. These chapters stand out for their take-home messages for readers.

The chapters have been arranged in a narrative order, covering various aspects of reproductive rheumatology. The first four chapters set the tone for the book by addressing the basics and common topics such as immunological changes during pregnancy, fertility and sexual dysfunction, contraception, and assisted reproductive techniques. The next chapter focuses on prepregnancy counseling, one of the most important topics in clinical practice, covering everything from A to Z, including diseases and medications, vaccinations, and mental health. The next five chapters address pregnancy and individual rheumatic diseases, examining the impact of disease on pregnancy and vice versa, and touching on other relevant aspects such as postnatal care and the differentiation of disease-specific features from pregnancy-related complications. The next two chapters cover two clinically relevant and must-know topics: anti-Ro and La antibodies in pregnancy and the safety of antirheumatic drugs in pregnancy and lactation.

This is followed by obstetric topics such as maternal and obstetric complications, fetal surveillance, and postpartum management. The next three topics are less discussed but no less important: reproductive health in men, long-term outcomes of offspring born to mothers with autoimmune rheumatic diseases (AIRDs), and menopause and hormone replacement therapy. The textbook ends with current developments and challenges in this area, including barriers to providing appropriate care, maintaining registries, and a peek into digital health relevant to reproductive rheumatology, with a focus on core digital tools and artificial intelligence.

The textbook makes for very engaging reading and, particularly, the chapters on contraception, assisted reproduction techniques, and anti-Ro and anti-La antibodies in pregnancy stand out. The textbook is tightly edited, with chapters presenting only relevant and up-to-date text for all practicing clinicians. The 69 tables and 47 colorful, well-thought-out pictorial representations make the content more impactful and help in appreciating the key information quickly. The content is based on current evidence, which has been properly referenced, and strikes a balance between depth and accessibility, making it suitable for all stakeholders. Overall, one can breeze through this masterpiece while gaining the necessary knowledge for daily practice.

Future editions of this textbook could perhaps include a chapter on recurrent pregnancy loss, as its evaluation and treatment options are highly relevant to clinical practice. Another challenging clinical aspect is the transmission of queries related to rheumatic diseases to the next generation; hence, a separate chapter on genetic counseling would be very welcome.

This comprehensive textbook of reproductive rheumatology is invaluable for clinicians navigating these complex yet rewarding aspects of patient care. This book provides a timely, evidence-based, and practical guide that integrates current scientific knowledge with real-world clinical experience, making it an essential reference for rheumatologists, obstetricians, physicians, trainees, and all healthcare professionals involved in caring for patients with rheumatic diseases throughout their reproductive journey.

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How to cite this article: Santhanam S. Textbook of Reproductive Rheumatology. *J Assoc Physicians India* 2026;74(9):105.



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