

Journal of The Association of Physicians of India



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Editorial

Precision Medicine in
Diabetes: Rethinking a
Heterogeneous Disease

Original Article

Association of Asian-Specific
BMI Categories with Age
Sex and Elevated Blood
Pressure among
Opportunistically Screened
Subjects in Punjab India

Original Article

Clinical Profile Laboratory
Findings and Outcomes
in Patients with
Cleistanthus Collinus
Poisoning: A Prospective
Observational Study

Review Article

Increasingly recognized
long-term side effects of
Proton Pump Inhibitors

Review Article

Expert-Opinion Review
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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. **Nonclinical 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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Hypertension. 2018;71:e13–e115

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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 Tandon¹*, 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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Note: Additional information will be provided on request. For further information, please write to: medical@pharmed.in
Data on file. Image is for representational purpose only.
Ref.: 1. Journal of the Association of Physicians of India (JAPI) 2026;74(5):42-47.

Contents

EDITORIAL

1. Precision Medicine in Diabetes: Rethinking a Heterogeneous Disease
Thyparambil Aravindakshan Pramodkumar, Mangesh Tiwaskar, Viswanathan Mohan..... 11
2. The Sieve and the Shield: Preserving Scientific Integrity in the Era of Publication Deluge
Shrikanth N Hegde..... 14

ORIGINAL ARTICLES

3. Association of Asian-specific BMI Categories with Age, Sex, and Elevated Blood Pressure among Opportunistically Screened Subjects in Punjab, India
Manpreet Singh Brar, Meghna Gupta, Vitull Kumar Gupta, Keshav Garg, Chandni Garg, Harit Gupta, Jasan Jindal, Raghav Gupta..... 16
4. Hyperhomocysteinemia Outperforms CD4 Count and Framingham Risk Score in Detecting Subclinical Coronary Atherosclerosis Based on Agatston Scoring, and Cardiac Morbidity in Human Immunodeficiency Virus Patients on Antiretroviral Therapy: A Cross-sectional Study from Northern India
Ajeet Kumar Chaurasia, Shreya Dastidar, Poonam Gupta, Abhishek Sachdeva, Sharad Varma..... 24
5. Clinical Profile, Laboratory Findings, and Outcomes in Patients with *Cleistanthus collinus* Poisoning: A Prospective Observational Study
M Krishna Kumar, K Praveen, E Venkataramanaiah, JC Madhusudhana Rao, D Padma, M Ramadevi..... 30
6. C-reactive Protein–Albumin Ratio: New Marker in Mortality Risk and Disease Severity in Pulmonary Thromboembolism
Aysel Orulju, Ayshan Mammadova, Zeynep Yalçinkaya, Ipek Kivilcim Ouzügen..... 36
7. Perceived and Observed Side Effects of Noninvasive Mechanical Ventilation in Patients at a Tertiary Care Center: A Prospective Observational Study
Sonal Prabhakar Karpe, Vishwambar Khadekar, Sidharth K, Shivam Gurme, Snehal Ramdas Kawade, Swapnil Manaji Thorve, Siddharth Ravindranath Waghmare, Jairaj P Nair, Monica Harish Bansal..... 41
8. Beyond Rheumatoid Factor and Anticyclic Citrullinated Peptide: Role of 14-3-3 η Protein in the Diagnosis of Rheumatoid Arthritis and the Evaluation of Disease Severity
Anu Aravindh, Akanksha Gupta, Jyotsna Agarwal, Kasturi Hazarika, Jaya Garg..... 50
9. Multiple Choice Question Metamorphosis—Enhancing Question Quality through Faculty Training: A Pragmatic Study
Ankeeta Menona Jacob, Kishan Prasad Hosapatna Laxminarayana..... 55

REVIEW ARTICLES

10. Increasingly Recognized Long-term Side Effects of Proton Pump Inhibitors
CL Nawal, Govind Rankawat, Hazari Lal Saini, Radhey Shyam Chejara..... 60
11. Pycnodysostosis—A Sparsely Diagnosed Entity and an Underrecognized Cause of Growth Hormone Responsive Reversible Short Stature: An Update
Jayanta Chakraborty, Semanti Chakraborty..... 70
12. Monoclonal Gammopathy of Renal Significance: Clinical Insights and Therapeutic Advances
Archana Rajan, Himansu Sekhar Mahapatra, Muthukumar Balakrishnan, Lalit Pursnani..... 73
13. Expert Opinion Review on the Shift from Dual Antiplatelet Therapy to Single Antiplatelet Therapy in Indian Clinical Practice
J Ezhilan, PC Manoria, Ripen Gupta, George Koshy, Satish Kumar S, CK Ponde, Suvendu Chattopadhyay, Dipak Pawar, Pradip Mate, Vivek Kolapkar, Gurunath Chavan..... 80

POINT OF VIEW

14. Rising Violence against Doctors: Roots and Remedies
Rajesh Agrawal..... 86

15. Atma and Medicine: Bridging Ancient Wisdom and Modern Understanding of Life and Consciousness
HNS Bhatnagar..... 89

CORRESPONDENCE

16. Letter to Editor (Correspondence) on “Correlation of Conventional and Extended Lipid Profiles with Plaque Burden in Statin-naïve Patients with Acute Coronary Syndrome: A Prospective Observational Study from South India”
Nitin Chintaman Gawari, Sujata Prakash Shingare, Bhalchandra Tryambak Rane, AV Tilak..... 91
17. Therapeutic Wheel for Hypertension: A Squared Critique
Ankit Kumar Sahu, Arshad Nazir, Aditya Kapoor..... 92
18. Can We Have Paperless Conferences in the Era of Digitalization?
Abhijit Anil Trailokya..... 94
19. A Study on Electrocardiography, Echocardiography, and Cardiac Biomarkers in Aluminum Phosphide Poisoning and Their Prognostic Correlation
Gaurav Ashok Chaudhary, Sharveen Kumbhar, Siddharth Garge..... 95

BOOK REVIEW

20. Treatise on Heart Disease in Indians
Enas A Enas, Basil Varkey..... 96

ANNOUNCEMENT

21. Annual Conference of Association of Physicians of India (East Zone).....54
22. Election Results of API, PRF and ICP.....59
23. Medical Education & Research Trust® Association of Physicians of India (KC).....88

e-ONLY

ORIGINAL ARTICLES

24. Exploring Attitude and Practices with Family Adoption Programme: A Mixed Method Study among Undergraduate Students of Bangalore Medical College and Research Institute
Rose Treasa Mathew, Farsana Nathankodan, Hamsa L, Jai Krishna MG, Jyothi Jadhav, Selvi Thangaraj.....e1
25. How Real-time Blood Glucose Shapes Sweet Taste Sensitivity: A Comparative Study in Diabetic and Healthy Subjects
Sanjil Verghese, Sneha PM, John Michael Raj, Don J Maliyakkal, Anna Alisha Tommy, Christina George Elavanan.....e8

REVIEW ARTICLE

26. Need for Early Intensification of Therapy and Strategies to Improve Utilization of Biologic Therapies in Spondyloarthritis: Experiences and Perspectives of Indian Rheumatologists
Rohini Handa, Sundeep Upadhyaya, Sarath Chandra Mouli Veeravali, Lalit Duggal, Santosh Kumar Mandal, Shashank M Akerkar, Syamasis Bandyopadhyay, Sagar Panchal..... e13

THERAPEUTIC SPOTLIGHT

27. Four-week Symptom-score Changes After Vonoprazan Prescription in Routine Indian Outpatient Practice: A Multicenter Retrospective Complete-Case Study
BS Satyaprakash, Sandip Pal, Sudipta Ghosh, Monika Jain, Parimal Lawate, Dhiren Pipalia, Anil Kumar KR, Goutham Morupogu, Prashant Verma, Mohd Imran Chouhan, Manoj MG, Keyur A Sheth, Nitin Borse, Darshan Rana, Priyank Shah, Rajat Singal..... e22
28. Parenteral 1,000 μ g Vitamin B12 for Peripheral Neuropathy: A Narrative Review of Expert Consensus and Clinical Practice in India
Mangesh H Tiwaskar, Nikhil Balankhe, Suhas Erande, Amit Saraf, Agam Vora, Rakesh Bhadade, Milind Nadkar, Anuj Maheshwari, Ramanatha Balamurugan, Saikat Datta, Arkadip Choudhury..... e29



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Generic Name: Semaglutide Injection 0.25 mg r-DNA Origin, solution for injection in pre-filled pen, Semaglutide Injection 0.5 mg r-DNA Origin, solution for injection in pre-filled pen, Semaglutide Injection 1 mg r-DNA Origin, solution for injection in pre-filled pen **Brand Name:** Ozempic® **Presentation:** Ozempic® is available in 0.25 mg, 0.5 mg and 1 mg. **Indication:** Semaglutide injection is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus and established cardiovascular disease. To reduce the risk of sustained eGFR decline and cardiovascular death in adults with type 2 diabetes mellitus and chronic kidney disease. **Description:** Ozempic® is a clear and colourless or almost colourless solution for injection in a pre-filled pen. **Posology:** The starting dose is 0.25 mg semaglutide once weekly after 4 weeks, the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. **Method of administration:** Subcutaneous use. Ozempic® is administered once weekly at any time of the day, with or without meals. It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It should not be administered intravenously or intramuscularly. If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (72 hours). Patients should be advised to read the instructions for use included in the package leaflet carefully before administering Ozempic®. **Special Populations:** No dose adjustment is required based on age. No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited. No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. The safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** In order to improve the tolerability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function. Increased risk of retinal detachment has been observed in patients with diabetic retinopathy treated with semaglutide. An increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. **Use in special populations (fertility, pregnancy and lactation):** Women of child-bearing potential are recommended to use contraception when treated with semaglutide. To patients with diabetic retinopathy treated with insulin and semaglutide, there are limited data regarding the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant or pregnancy occurs, semaglutide should be discontinued. Semaglutide should not be used during breast-feeding. The effect of semaglutide on fertility in humans is unknown. **Drug Interactions:** Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. Paracetamol: Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardized meal test. No clinically relevant effect on paracetamol was observed with semaglutide. No dose adjustment of paracetamol is necessary when administered with semaglutide. Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptive as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.02 mg levonorgestrel) was administered with semaglutide. Alzocet: Semaglutide did not change the overall exposure of alfentanil following a single dose administration of alfentanil (5 mg). Digoxin: Semaglutide did not change the overall exposure or C_{max} of digoxin following a single dose of digoxin (0.5 mg). Metformin: Semaglutide did not change the overall exposure or C_{max} of metformin following dosing of 500 mg twice daily over 3.5 days. Warfarin: Semaglutide did not change the overall exposure or C_{max} of R₁ and S₁ warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalized ratio (INR) were not affected in a clinically relevant manner. **Effects on ability to drive and use machines:** Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable effects:** In phase 3a trials, 4792 patients were exposed to semaglutide up to 1 mg. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration. **Overdose:** Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications. There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. **Shelf life:** Before first use: 36 months. After first opening: 6 weeks. Store below 30 °C or in a refrigerator (2 °C - 8 °C). **Storage:** Store in a refrigerator (2 °C - 8 °C). Keep away from the cooling element. Do not freeze. Keep the pen up in order to protect from light. **Disclaimer:** The abbreviated package insert is updated from the CDSO approved package insert file No. B02JMR25A00001 dated 19 Sep 2025 and subsequent approved file No. 1-DNA-110113/2025-efcda dated 23 Oct 2025.

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IN26OZM00208 | Review Date: 30 July 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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Precision Medicine in Diabetes: Rethinking a Heterogeneous Disease

Thyparambil Aravindakshan Pramodkumar¹, Mangesh Tiwaskar², Viswanathan Mohan^{3*}

Keywords: Insulin Resistance, Obesity precision medicine, Type 2 Diabetes Mellitus.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1687

INTRODUCTION

Diabetes mellitus remains one of the most significant global health challenges, currently affecting more than half a billion individuals worldwide.¹ Traditionally, diabetes has been classified into type 1 (autoimmune, insulin-deficient) and type 2 diabetes (T2D) (insulin-resistant, lifestyle-associated).² However, clinical and epidemiological evidence increasingly demonstrates that this binary classification fails to reflect the true heterogeneity of the disease.^{2,3} Patients differ in their underlying pathophysiology, risk of complications, and therapeutic responses. In this context, precision medicine—tailoring diagnosis, risk prediction, and therapy to the individual—offers a transformative framework for diabetes care.^{4,5} Emerging research, including cluster-based stratification of T2D, the recognition of lean diabetes phenotypes in South Asians with predominantly insulin secretory defects and advances in genetic diagnosis of monogenic forms such as maturity-onset diabetes of the young (MODY), demonstrates how precision diabetes is gradually moving from theory into clinical practice.^{6–8} In Asian Indians, visceral fat—rather than subcutaneous fat—showed a progressive increase with worsening glucose tolerance and is strongly associated with insulin resistance.⁹ Genetic studies in the same population demonstrated that several *ADIPOQ* gene variants are significantly associated with T2D, obesity, and hypoadiponectinemia, highlighting the dual impact of both visceral adiposity and adiponectin pathway genetics on diabetes susceptibility in South Indians.¹⁰

Recent international consensus highlights that precision medicine is a natural evolution of evidence-based diabetes care, aiming to reduce errors and optimize outcomes by explicitly accounting for disease heterogeneity.¹¹ However, significant gaps persist in generating clinically translatable evidence, particularly in non-European ancestry populations which underscores the urgent need for more inclusive research.

BEYOND ONE-SIZE-FITS-ALL: SUBGROUPS OF TYPE 2 DIABETES

T2D is not a single disease but a spectrum. Data-driven cluster analyses, first developed in Scandinavian populations¹² and later validated in Asian Indian cohorts,⁶ have identified at least four reproducible subgroups in Indians:

- Severe insulin-deficient diabetes (SIDD).
- Insulin-resistant obese diabetes (IROD).
- Combined insulin-resistant and deficient diabetes (CIRDD).
- Mild age-related diabetes (MARD).

These clusters differ in glycemic progression, complication profiles, and treatment needs. For example, SIDD patients—often lean with poor beta-cell function—are at high risk for retinopathy and may require early insulin, while IROD patients have an elevated risk of nephropathy and cardiovascular disease and may benefit from insulin therapy. This approach challenges current guidelines, which rely primarily on duration of diabetes, HbA1c, and age of onset of diabetes. Instead, precision subtyping enables proactive, individualized monitoring and therapy.

LEAN DIABETES: A FEATURE OF TYPE 2 DIABETES IN INDIANS

Perhaps the most striking evidence of T2D heterogeneity comes from lean diabetes in India.^{13,14} A recent large-scale study demonstrated that lean T2D (BMI <18.5 kg/m²) accounts for ~1.5% of clinic-based T2D cases in India,⁸ but these patients carry disproportionately higher complication rates compared with overweight/obese peers.

Unlike classical T2D, lean diabetes is characterized by severe beta-cell dysfunction with relatively preserved insulin sensitivity.⁸ This phenotype overlaps partially with malnutrition-related diabetes (MRDM) described decades ago, but the lack of a specific marker for MRDM makes it difficult to diagnose.¹⁵ A recent commentary on the

epidemic of cardiometabolic disorders in South Asia has emphasized that lean diabetes is not only common but is accompanied by distinct metabolic traits such as excess ectopic fat deposition, smaller adipocytes, and adverse lipid profiles, which significantly increase cardiometabolic risk despite normal or low BMI.¹⁶ The recognition of lean diabetes raises several precision-medicine questions: Should treatment be intensified earlier with insulin? Can biomarkers of beta-cell reserve (e.g., C-peptide, proinsulin-to-insulin ratios) help refine the diagnosis? Importantly, it highlights the fact that ethnicity-specific phenotypes must be incorporated into future classification systems, particularly in low- and middle-income countries (LMICs) where lean diabetes is more common.

MONOGENIC DIABETES: A PROTOTYPE FOR PRECISION CARE

Monogenic diabetes (particularly MODY) and neonatal diabetes represent the precision medicine paradigm.^{17,18} Identification of genetic mutations in MODY has immediate therapeutic and prognostic implications:

- HNF1A-MODY and HNF4A-MODY → respond significantly to sulfonylureas
- GCK-MODY → usually requires no pharmacological therapy
- Neonatal diabetes → neonates diagnosed below 6 months of age with KCNJ11 or ABCC8 mutations respond to sulfonylureas, and insulin can often be stopped completely.

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How to cite this article: Pramodkumar TA, Tiwaskar M, Mohan V. Precision Medicine in Diabetes: Rethinking a Heterogeneous Disease. *J Assoc Physicians India* 2026;74(10):11–13.

Without genetic testing, many MODY cases are misclassified as type 1 or T2D, leading to unnecessary insulin use. The clinical overlap between MODY and T2D emphasizes the need for genetic testing in targeted subgroups (young-onset, lean, antibody-negative patients). This is particularly crucial in LMICs, where clinical heterogeneity is high and low-cost genetic panels are becoming more feasible.^{19,20} Rare monogenic forms of diabetes clearly illustrate the promise of precision medicine, as the nature of the genetic defect can be directly linked to targeted therapy.^{21–24}

INTEGRATING BIOMARKERS AND DIGITAL HEALTH

While genetics and clustering represent precision tools, other emerging domains hold promise:

- Biomarkers: Proteins such as fetuin-A, adiponectin, and inflammatory markers may stratify insulin resistance, beta-cell stress, and risk of complications. Studies have reported that fetuin-A differs across gestational diabetes phenotypes and correlates with HOMA-IR.²⁵
- Digital health and artificial intelligence (AI): Retinal imaging combined with AI-based grading not only aids complication screening but may also serve as a proxy for systemic risk stratification.^{26,27} Diabetic retinopathy (DR), a leading microvascular complication and the fifth most common cause of blindness worldwide, underscores the urgent need for scalable screening approaches.²⁸ Annual retinal assessment is recommended, but the massive volume of individuals requiring review poses a significant global challenge.^{29,30} AI-driven deep learning tools have emerged as promising solutions, capable of analyzing large numbers of retinal images and automating DR diagnosis.³¹ However, building such robust AI models requires access to large, diverse, high-quality retinal image databases with standardized annotations from trained ophthalmic professionals. Recognizing this need, recent efforts in India have initiated the creation of a large-scale multicenter Retinal Image Database, designed to support the development of cost-effective and scalable AI diagnostic tools for DR.³² This initiative exemplifies how digital health innovations can strengthen precision diabetes care by enabling both early detection of complications and system-level risk stratification, particularly in resource-constrained LMIC settings. The DIANA

(Diabetes Novel Subgroup Assessment) tool, developed in Asian Indians, uses machine learning to classify patients into four distinct T2D endotypes and predict the risk of retinopathy (78.4%) and nephropathy (89.6%) with high accuracy.³³

- Omics approaches: Transcriptomics, proteomics, and metabolomics could eventually refine subgrouping, although accessibility and affordability remain limited in LMICs.³⁴

CHALLENGES IN IMPLEMENTING PRECISION MEDICINE

Despite clear scientific rationale, several barriers remain:

- Cost and accessibility: Genetic tests, biomarker assays, and advanced imaging are not universally available and are expensive.
- Validation across ethnicities: Most clustering studies originate from Europe; applying them directly to South Asian or African populations may be misleading without validation.
- Clinical translation gap: Clinicians still lack decision-support tools to incorporate precision subtyping into routine care.
- Equity: Precision medicine must not exacerbate health disparities by allowing only those who can afford them to receive more expensive tests or medications.

THE LOW- AND MIDDLE-INCOME COUNTRIES PERSPECTIVE

For LMICs, where the diabetes burden is greatest, scalable and affordable precision strategies are needed. Examples include:

- Using simple clinical clustering algorithms [age, BMI, homeostatic model assessment of beta-cell function (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR)] instead of omics-heavy approaches.
- Deploying portable fundus (retinal) imaging for early detection of high-risk phenotypes.
- Building local biobanks and data repositories to study population-specific diabetes subtypes.
- Developing tiered genetic testing (low-cost panels for MODY, targeted sequencing for atypical cases of diabetes).
- Such pragmatic approaches can ensure that precision medicine is not a luxury but a reality even in less-resourced settings.

CONCLUSION

Diabetes is not a single disease but a spectrum of disorders with overlapping and distinct mechanisms. Precision medicine—through cluster-based phenotyping, identification of lean diabetes, and genetic diagnosis of

MODY and neonatal diabetes—offers a roadmap to individualized care. While high-income countries can lead with omics and advanced diagnostics, LMICs must adopt scalable models of precision care that leverage clinical algorithms, digital health, and selected biomarkers.

The future of diabetes care will be defined not by a one-size-fits-all approach, but by nuanced strategies that respect biological diversity, ethnicity-specific patterns, and socioeconomic realities. Precision medicine is not a distant dream—it is already emerging, but the challenge is to integrate it equitably into everyday practice, especially in developing countries.

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The Sieve and the Shield: Preserving Scientific Integrity in the Era of Publication Deluge

Shrikanth N Hegde*



Keywords: Committee on Publication Ethics, Medical journals, Scientific writing.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1748

Publishing scientific communications is an important means of sharing the results of scientific experiments, and scientific journals are the vehicle for disseminating such information. The output of publications has been advancing rapidly, and it is estimated that >3 million articles are published in approximately 46,000 journals each year.¹ Medical journals historically gained trust by rigorously peer reviewing to meet strict moral, ethical, and scientific standards. In the last decade, there has been an exponential growth in the number of published articles. This is not matched by the growth in researchers qualified to review the articles. Editors find it difficult to get qualified reviewers, and scientists are overwhelmed by the number of new articles, described as “a strain on scientific publishing.”² This landscape is further clouded by the growth of predatory journals with poor or absent peer review processes, poor-quality articles, and a lack of transparency.³ An increasing number of fake research articles are being produced by the “paper mills,” fraudulent organizations that make money by selling fake articles to academic customers. Many such fake articles get published even in good-quality journals.⁴

Articles are being written using artificial intelligence (AI) tools and are becoming increasingly difficult to detect. With the growing trend of recognizing publications as a metric of academic progress, researchers are driven by the culture of “publish or perish” and prioritize quantity over quality, which is driving high publication output and the growth of the publication industry (both genuine and predatory).⁵ It is important for a discerning reader to sieve through the information and be aware of the nuances of critical appraisal of an article. Because individual researchers are overwhelmed by this volume, journals can no longer act as passive repositories but must actively step forward to fulfill a dual institutional responsibility: acting as a sieve to filter out compromised data and a shield to protect the collective evidence base from ideological or methodological distortion.

THE ANATOMY OF PUBLICATION DELUGE AND THE EFFECT ON TRUST

To understand how the deluge of literature affects trust, we must understand how the hyperpublishing boom works. Analyzing the strain on scientific publishing, a study of the publishing industry reveals that the most recent growth is concentrated in specific for-profit open-access publishing models that aggressively utilize “special issues” handled by temporary guest editors. Between 2016 and 2022, publishers saw exponential growth in article output due to increased article output from the special issues. Peer review requires independent, qualified experts to dedicate considerable, uncompensated time to assess the manuscripts. However, the special-issue model frequently compresses this timeline into an increasingly homogeneous, rapid-processing frame. For example, mean turnaround times from submission to acceptance at some mega-journals have dropped to as low as 37 days, with a flat distribution curve in which articles across vastly different fields are approved in identical, rapid timeframes.²

While the growth in scientific literature is welcome, especially when it comes from the global south and developing countries with improved research capabilities, a surge driven by commercial interests undermines trust. Institutional mandates for publication, a publish-or-perish culture, and the exploitation of these pressures by predatory journals and paper mills, together with shortened turnaround times, have created a publication deluge that erodes trust in the system. When peer review is compressed or manipulated, low-quality, biased, or entirely fabricated studies leak into the literature. One journal was found to publish a supplement issue containing >11,000 pages, with articles on every possible subject!⁶ Scoping reviews show that articles from presumed predatory journals or paper-mill operations are routinely cited in high-tier evidence syntheses, with

some large Cochrane reviews finding that up to 9% of included clinical trials originated from dubious sources.³ With fast-track papers lacking rigorous data checking, peer review ceases to be an independent quality check and instead becomes a vehicle for propagating disinformation under a trusted brand. These factors have also led to an increase in the number of retracted articles globally, with as many as 65,000 retractions recorded as of 6th June 2026, according to Retraction Watch, a website that maintains an online database of retracted research articles.⁷ When an article is published in a high-impact journal, it is considered a “fact.” An example is a 1998 paper linking MMR vaccines to autism, which was retracted in 2010.⁸ But the paper may have caused a decline in MMR vaccination among children for some time, at least.

THE DISCERNING READER'S SIEVE: NEED FOR CRITICAL APPRAISAL OF PUBLISHED ARTICLES

In this changing landscape, it is insufficient to read only the Abstract and Conclusion of a paper. Navigating the literature deluge requires a shift toward intentional, active skepticism. Discerning readers must systematically audit the Methodology and Results sections of a manuscript to identify subtle analytical anomalies.

Identifying Data Dredging and Statistical Manipulation: P-hacking

A famous quote by the British economist Ronald H Coase, “If you torture the data long enough, it will confess to anything,” highlights critical pitfalls in modern statistics, data analysis, and research. Readers must watch out for the common practice of data

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How to cite this article: Hegde SN. The Sieve and the Shield: Preserving Scientific Integrity in the Era of Publication Deluge. *J Assoc Physicians India* 2026;74(10):14–15.

dredging, also known as p-hacking. In the rush to have publications, investigators may collect many variables and perform endless statistical permutations behind the scenes until an association yields a statistically significant p -value ($p < 0.05$) purely by chance. When a clinical trial fails to meet its primary endpoint, authors may systematically divide their data until they find a narrow patient outcome in which a positive effect appears. Unless these specific subpopulations and analytical models were explicitly prespecified in an independent trial registry before data collection began, such findings represent random statistical noise rather than genuine biological cause and effect.⁹

Validity of the Surrogate Endpoints

A major problem in some clinical trials is substituting soft endpoints (e.g., blood pressure or biomarker reductions) for hard endpoints (e.g., stroke reduction, all-cause mortality) and treating them as proxies for the hard endpoints. In clinical practice, benefits observed on soft endpoints may not translate into a discernible reduction in hard endpoints. Systematic evaluations of oncology drug approvals reveal that up to 67% of contemporary cancer therapies are authorized by regulatory bodies based entirely on surrogate endpoints such as progression-free survival or response rates. However, long-term follow-up demonstrates that a vast majority of these drugs subsequently fail to show any true benefit in overall survival, with some causing significant subsequent toxicity.¹⁰

Citation Gaming: Impact Inflation

Citations are often used as a proxy for journal quality, but this metric is also susceptible to manipulation and attempts to inflate it through self-citation and coordinated "citation cartels." According to Goodhart's law, when a measure becomes the target, it ceases to be a good measure, a principle that applies to citation metrics as well.²

Methodological and Bibliometric Health

It is important to conduct a quick audit of the information source, including the journal's indexing status in major databases such as MEDLINE, Scopus, and Web of Science, and to review transparent policies on data availability, authors' competing interests,

funding sources, and the role of sponsors in the study to assess whether the information is unbiased and trustworthy.

THE ROLE OF THE JOURNALS IN PRESERVING SCIENTIFIC INTEGRITY

- The restoration of scientific trust cannot rely solely on the vigilance of the individual reader; it requires institutional leadership. Flagship national medical journals, such as the Journal of the Association of Physicians of India (JAPI), are uniquely positioned to serve as the premier sieve and shield for the local scientific community. As independent entities, free from the commercial imperatives of international publishing conglomerates, these journals can enforce a uniform quality benchmark that prioritizes clinical truth over sheer quantity.
- Apart from the mandatory disclosures of financial conflicts of interest from authors and reviewers, persistent digital identifiers such as ORCID, nonfinancial conflicts of interest, and disclosures of roles/positions within the organization/association would bring greater transparency.
- A regular peer review may not be sufficient to detect data anomalies; editorial workflows should integrate review by statistical experts who screen for statistical plausibility, check for data smoothing, overfitted parameters in small sample sizes, and timeline discrepancies such as immortal time bias.
- Journals must actively work to transform peer review from an invisible, voluntary task into a recognized, rewarded academic achievement. By introducing dedicated critical appraisal columns, journal clubs, and research literacy continuing medical education (CME) initiatives, journals can train the next generation of physicians to evaluate the literature.
- Adoption of technology: Use of AI for detecting data or image manipulation and AI-generated texts and figures can serve as an effective sieve for filtering out fake manuscripts at the initial stages, saving the precious time of the editorial team and the reviewers. Many major publishing houses have developed in-house AI tools, and many more will adopt them sooner or later.

They are expected to help the journals fight against paper mills.^{11,12}

Many editorials have expressed concern about the growing trend of declining scientific integrity and fraud and have described various approaches to combating it.^{6,8,13} Ultimately, science remains a self-correcting enterprise only if its practitioners actively engage in the process of correction. By serving as a meticulous sieve and an unyielding shield, trusted national medical journals ensure that the clinical literature guiding patient care remains anchored in undisputable evidence rather than in data noise.

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Association of Asian-specific BMI Categories with Age, Sex, and Elevated Blood Pressure among Opportunistically Screened Subjects in Punjab, India

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Received: 29 June 2026; Accepted: 15 July 2026

ABSTRACT

Introduction: Obesity/overweight has become an important public health issue. Obesity is a major contributor to noncommunicable diseases, especially among Indians. The present study evaluated the burden of BMI categories and their association with age, sex, and BP among adults screened during the May Measurement Month (MMM) initiative in Punjab using Asian BMI criteria.

Materials and methods: An observational study design implementing an opportunistic screening model was used to screen 24,685 adults aged 18–80 years during the MMM initiative in Punjab. Subjects were categorized according to Asian BMI criteria. Associations of BMI categories with age, sex, and elevated BP (≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic) were analyzed using Chi-square tests, multivariable logistic regression, modified Poisson regression, and multinomial logistic regression.

Results: The present study showed that 6.2% of subjects were underweight, 25.6% had normal BMI, 17.1% were overweight, and 51.1% were obese using Asian BMI criteria; 68.2% had BMI ≥ 23 kg/m². Obesity was more prevalent in the 18–60-year age group than in the 61–80-year age group (52.9% vs 44.2%, $p < 0.001$), among males compared with females (55.9% vs 45.8%, $p < 0.001$), and among subjects with elevated BP compared with normal BP (60.0% vs 46.8%, $p < 0.001$). Multivariable analyses demonstrated independent associations of obesity with male sex (adjusted OR 1.59, 95% CI 1.51–1.67) and elevated BP (adjusted OR 1.49, 95% CI 1.40–1.58), while the older age group of 61–80 years was associated with lower odds of obesity (adjusted OR 0.75, 95% CI 0.70–0.81). The low values of Nagelkerke R² analysis show that only a small part of BMI categories are influenced by variables like age, sex, and BP because obesity has a multifactorial pathophysiology influenced by several factors not included in the present study.

Conclusion: A substantial burden of excess BMI was observed among subjects screened in Punjab. Obesity was strongly associated with younger age, male sex, and elevated BP, underscoring the need for integrated obesity and hypertension prevention strategies.

Keywords: Asian BMI categories, Body mass index, Elevated BP, Obesity, Punjab.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1692

INTRODUCTION

Globally, overweight and obesity are becoming major public health issues because of increased morbidity and mortality linked to the increased prevalence of noncommunicable diseases (NCDs) such as hypertension (HTN), diabetes, dyslipidemia, and cardiovascular diseases (CVDs). South Asian populations, including India, face increased metabolic risk at lower levels of adiposity compared to Western populations; that is why Asian-specific BMI cutoffs were recommended for risk stratification in South Asian populations. The Asian-specific BMI cutoffs define a BMI of < 18.5 kg/m² as underweight, 18.5–22.9 kg/m² as normal weight, 23.0–24.9 kg/m² as overweight, and ≥ 25.0 kg/m² as obesity.^{1,2} The WHO BMI classification defines a BMI of < 18.5 kg/m² as underweight, 18.5–24.9

kg/m² as normal weight, 25–29.9 kg/m² as overweight, and ≥ 30.0 kg/m² as obesity.¹ Data from the National Family Health Survey (NFHS) show a substantial increase in excess body weight over the last decade. Data from NFHS-5 (2019–2021) among the 15–49-year age group show a 22.6% prevalence of overweight/obesity in India, including about 23.0% prevalence of overweight/obesity in women and 22.1% in men.³ NFHS used the standard WHO BMI classification. Recent data from NFHS-6 show that the burden of overweight/obesity in India has increased to about 29.0%, including 30.7% in women and 27.3% in men aged 15–49 years.⁴

Punjab has consistently shown the highest burden of overweight/obesity compared with other states. NFHS-5 data observed about 36.6% prevalence of

overweight/obesity in Punjab, including 40.8% burden of overweight/obesity among women and 32.3% among men, whereas recent NFHS-6 data showed an increase in the burden of overweight/obesity to about 41.1%, including 44.7% among women and 37.5% among men in Punjab.^{3,4} Data from Punjab show a higher burden of overweight/obesity compared with the Indian national average. The high burden of obesity is especially important for Punjab because clustering of risk factors increases the risk of CVDs and metabolic diseases. The ICMR-INDIAB national cross-sectional study, including 113,043 subjects aged 20 years and older, observed a 28.6% weighted prevalence of generalized obesity using Asian BMI cutoffs.^{5,6}

The present study was conducted to assess the burden of BMI categories and their association with age, sex, and BP among subjects screened opportunistically in Punjab during the MMM initiative. It is important to note that the present study used Asian-specific BMI cutoffs to categorize BMI, whereas NFHS-5, NFHS-6, and many other studies used conventional WHO

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How to cite this article: Brar MS, Gupta M, Gupta VK, et al. Association of Asian-specific BMI Categories with Age, Sex, and Elevated Blood Pressure among Opportunistically Screened Subjects in Punjab, India. *J Assoc Physicians India* 2026;74(10):16–22.

BMI categories for the general population. Adopting Asian BMI cutoffs for the present study is a methodological strength for estimating the actual burden of overweight/obesity as a cardiometabolic risk in Asian Indians and helps capture data on excess adiposity in Punjab.

AIMS AND OBJECTIVES

To study the association of Asian-specific BMI categories with age, sex, and elevated blood pressure among opportunistically screened subjects in Punjab, India.

MATERIALS AND METHODS

Participants and Study Design

The present study adopted an observational study design implementing an opportunistic screening model as part of the May Measurement Month (MMM) initiative, a worldwide blood pressure (BP) screening initiative by the International Society of Hypertension (ISH) and Indian Society of Hypertension (InSH). The screening initiative was conducted in 2017–2019, 2021, and 2024. The opportunistic screening model involved various screening centers and settings such as hospitals, community health care centers, general health checkups, and outreach camps, and used a walk-in recruitment method to reduce the possibility of selection bias from enrolling only health-conscious, aware, or symptomatic subjects. The MMM initiative was mainly carried out in May and sometimes extended into June or July. Institutional Ethics Committee approval was granted vide letter no. 2/2017/3.4.2017. The ethics committee approved verbal informed consent because the MMM screening initiative included an anonymous screening protocol recording only nonidentifiable variables such as age, sex, BMI, and BP, with a focus on anonymization and data security. The present study is aligned with the STROBE guidelines for observational studies. After obtaining verbal informed consent, subjects aged 18–80 years were recruited via convenience sampling. Information about other variables such as region, urban vs rural residence, socioeconomic profile, diet, salt intake, physical activity, alcohol/tobacco use, diabetes/lipid profile, and medication use was not recorded as part of the MMM initiative and therefore was not available for data analysis.

Body Mass Index

Body mass index (BMI) was calculated using the standard formula: weight (kg)/height (m)². Asian-specific BMI cutoffs were used to categorize BMI: <18.5 kg/m² as underweight, 18.5–22.9 kg/m² as

normal weight, 23.0–24.9 kg/m² as overweight, and ≥25 kg/m² as obesity.^{1,2}

For analysis, BMI was divided into two groups: BMI ≥23 kg/m² (overweight/obese) and BMI <23 kg/m² (underweight/normal).

Blood Pressure Measurement

Blood pressure (BP) was measured adopting standard protocols. Omron provided validated and calibrated automated oscillometric BP devices for the present study. Appropriate cuff sizes were used, including standard adult (mid-arm 22–32 cm) and large adult (32–42 cm) cuffs. BP was preferably recorded from the left arm after 5 minutes of rest. Subjects were seated comfortably with back support and both feet flat on the ground. Three BP readings were taken 1 minute apart, and the mean of the second and third readings was used for data analysis.

Definition of Hypertension

Hypertension (HTN) was defined according to the Indian guidelines on hypertension-IV (2019). HTN was diagnosed when BP was ≥140 mm Hg systolic and/or >90 mm Hg diastolic. Systolic HTN (SHTN) was defined as systolic BP (SBP) ≥140 mm Hg, and diastolic HTN (DHTN) as diastolic BP (DBP) ≥90 mm Hg.⁷

Since a single occasion measurement of BP and even the mean of second and third BP readings is not considered sufficient to make a clinically confirmed diagnosis of HTN. Therefore, in the present study, the categorization of recorded BP among screened subjects was labeled as elevated BP (>140 mm Hg systolic and/or >90 mm Hg diastolic), normal BP (<140/90 mm Hg), systolic HTN (>140 mm Hg), and diastolic HTN (>90 mm Hg), rather than as a confirmed diagnosis of HTN. A confirmed clinical diagnosis of HTN requires confirmation of elevated BP on repeated office BP measurements or by ambulatory/home blood pressure monitoring.⁷ Therefore, the present study presents BP data as the burden or prevalence of elevated BP rather than a confirmed diagnosis of HTN in the population.

Statistical Analysis

Data were analyzed using standard statistical methods. BMI was categorized according to Asian BMI cutoffs, and associations with variables such as age group, sex, and BP group were assessed using the Chi-square test. Multivariable logistic regression was used to estimate crude odds ratios (ORs), adjusted ORs, and adjusted prevalence ratios (APRs) with 95% confidence intervals, with BMI categories as the dependent

variables. Model performance was assessed using the Nagelkerke R² statistic, and multicollinearity among predictor variables was evaluated.

RESULTS

Table 1 shows the baseline characteristics of 24,685 subjects: 79.5% (19,628) were aged 18–60 years, and 20.5% (5,057) were aged 61–80 years; 52.6% (12,996) were males and 47.4% (11,689) were females. According to BP status, 21.5% (5,307) had normal BP (<140/90 mm Hg), whereas 32.5% (8,029) had elevated BP (≥140 mm Hg systolic and/or ≥90 mm Hg diastolic), 24.9% (6,158) had SHTN (>140 mm Hg), and 22.2% (5,483) had DHTN (>90 mm Hg). According to BMI categories, 31.8% (7,840) had underweight/normal BMI of <23 kg/m² and 68.2% (16,845) had overweight/obese BMI of ≥23 kg/m², including 6.2% (1,516) who were underweight (<18.5 kg/m²), 25.6% (6,324) who had normal BMI (18.5–22.9 kg/m²), 17.1% (4,229) who were overweight (23–24.9 kg/m²), and 51.1% (12,616) who were obese (≥25 kg/m²).

Table 2 shows the burden of BMI across categories and their association with age, sex, and BP. Among the total study population, 6.2% (1,516) were underweight, 25.6% (6,324) were normal weight, 17.1% (4,229) were overweight, and 51.1% (12,616) were obese. In the 18–60-year age group, 5.3% (1,048)

Table 1: Baseline characteristics of the study population according to blood pressure, age group, sex, and body mass index

Characteristic	% (n)
Study population (N = 24,685)	
Blood pressure	
BP <140/90	67.5 (16,656)
BP >140 and/or >90	32.5 (8,029)
SBP >140	24.9 (6,158)
DBP >90	22.2 (5,483)
Age group	
18–60 years	79.5 (19,628)
61–80 years	20.5 (5,057)
Sex	
Male	52.6 (12,996)
Female	47.4 (11,689)
BMI	
<23 kg/m ²	31.8 (7,840)
<18.5 kg/m ²	6.1 (1,516)
18.5–22.9 kg/m ²	25.6 (6,324)
≥23 kg/m ²	68.2 (16,845)
23–24.9 kg/m ²	17.1 (4,229)
≥25 kg/m ²	51.1 (12,616)

BP, blood pressure; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 2: Distribution of BMI categories and their association with age group, sex, and blood pressure

Characteristic variables	BMI <18.5 kg/m ² , % (n)	BMI 18.5–22.9 kg/m ² , % (n)	BMI 23–24.9 kg/m ² , % (n)	BMI ≥25 kg/m ² , % (n)
Total burden (N = 24,685)	6.1 (1,516)	25.6 (6,324)	17.1 (4,229)	51.1 (12,616)
Age groups				
18–60 years (n = 19,628)	5.3 (1,048)	24.1 (4,734)	17.7 (3,465)	52.9 (10,381)
61–80 years (n = 5,057)	9.3 (468)	31.4 (1,590)	15.1 (764)	44.2 (2,235)
p-value	p < 0.001 (S)	p < 0.001 (S)	p < 0.001 (S)	p < 0.001 (S)
95% CI	5.8–6.4	25.1–26.2	16.7–17.6	50.5–51.7
Sex				
Male (n = 12,996)	4.8 (630)	21.1 (2,736)	18.2 (2,368)	55.9 (7,262)
Female (n = 11,689)	7.6 (886)	30.7 (3,588)	15.9 (1,861)	45.8 (5,354)
p-value	p < 0.001 (S)	p < 0.001 (S)	p < 0.001 (S)	p < 0.001 (S)
95% CI	5.8–6.4	25.1–26.2	16.7–17.6	50.0–51.7
Blood pressure				
BP <140/90 (n = 16,656)	7.2 (1,191)	28.6 (4,764)	17.4 (2,905)	46.8 (7,796)
BP >140 and/or >90 (n = 8,029)	4.0 (325)	19.4 (1,560)	16.5 (1,324)	60.0 (4,820)
p-value	p < 0.001 (S)	p < 0.001 (S)	p < 0.001 (S)	p < 0.001 (S)
95% CI	3.62–4.48	18.56–20.30	15.68–17.30	58.96–61.10

BMI, body mass index; BP, blood pressure; CI, confidence interval; S, statistically significant

Table 3: Distribution of subjects with BMI <23 kg/m² and ≥23 kg/m² according to age group, sex, and blood pressure

Characteristic variables	BMI <23 kg/m ² (underweight/normal BMI), % (n)	BMI ≥23 kg/m ² (overweight/obese BMI), % (n)
Total burden (N = 24,685)	31.8 (7,840)	68.2 (16,845)
Age groups		
18–60 years (n = 19,628)	29.5 (5,783)	70.5 (13,845)
61–80 years (n = 5,057)	40.7 (2,057)	59.3 (3,000)
p-value	p < 0.001 (S)	p < 0.001 (S)
95% CI	31.2–32.3	67.7–68.8
Sex		
Male (n = 12,996)	25.9 (3,366)	74.1 (9,630)
Female (n = 11,689)	38.3 (4,474)	61.7 (7,215)
p-value	p < 0.001 (S)	p < 0.001 (S)
95% CI	25.1–26.7	73.3–74.9
Blood pressure		
BP <140/90 (n = 16,656)	35.8 (5,955)	64.2 (10,701)
BP >140 and/or >90 (n = 8,029)	23.5 (1,885)	76.5 (6,144)
p-value	p < 0.001 (S)	p < 0.001 (S)
95% CI	22.6–24.4	75.6–77.4
Systolic blood pressure		
BP <140 (n = 18,527)	34.3 (6,354)	65.7 (12,173)
BP >140 (n = 6,158)	24.1 (1,486)	75.9 (4,672)
p-value	p < 0.001 (S)	p < 0.001 (S)
95% CI	23.1–25.2	74.8–76.9
Diastolic blood pressure		
BP <90 (n = 19,202)	33.5 (6,437)	66.5 (12,765)
BP >90 (n = 5,483)	25.6 (1,403)	74.4 (4,080)
p-value	p < 0.001 (S)	p < 0.001 (S)
95% CI	24.4–26.7	73.3–75.6

BMI, body mass index; BP, blood pressure; CI, confidence interval; S, statistically significant

were underweight, 24.1% (4,734) were normal weight, 17.7% (3,465) were overweight, and 52.9% (10,381) were obese. In the 61–80-year age group, 9.3% (468) were underweight, 31.4% (1,590) were normal weight, 15.1% (764) were overweight, and 44.2% (2,235) were

obese. The table shows a higher burden of underweight and a lower burden of obesity in the older age group, whereas overweight and obesity were more common in the younger age group; this difference was statistically significant ($p < 0.001$).

Results show that 4.9% (630) of males were underweight, 21.1% (2,736) were normal weight, 18.2% (2,368) were overweight, and 55.9% (7,262) were obese. Among females, 7.6% (886) were underweight, 30.7% (3,588) were normal weight, 15.9% (1,861) were overweight, and 45.8% (5,354) were obese. Overweight and obesity were more frequent among men, whereas underweight and normal weight were more common among women; this difference was statistically significant ($p < 0.001$).

Among subjects with normal BP, 7.2% (1,191) were underweight, 28.6% (4,764) were normal weight, 17.4% (2,905) were overweight, and 46.8% (7,796) were obese. Among subjects with elevated BP, 4.1% (325) were underweight, 19.4% (1,560) were normal weight, 16.5% (1,324) were overweight, and 60.0% (4,820) were obese. Obesity was more common in the elevated BP group than in the normal BP group, and the distribution of BMI categories differed significantly by BP status ($p < 0.001$).

Table 3 shows the association of two BMI groups—underweight/normal weight (<23 kg/m²) and overweight/obese (≥23 kg/m²)—with age, sex, and BP groups. Among all subjects, 31.8% (7,840) were underweight/normal weight, whereas 68.2% (16,845) were overweight/obese. In the 18–60-year age group, 29.5% (5,783) were underweight/normal weight and

Table 4: Distribution of BMI categories according to age groups

Age group	BMI <18.5 kg/m ² (underweight), % (n)	BMI 18.5–22.9 kg/m ² (normal), % (n)	BMI 23–24.9 kg/m ² (overweight), % (n)	BMI ≥25 kg/m ² (obese), % (n)
18–30 years	8.4 (509)	26.1 (1,579)	17.5 (1,055)	48.0 (2,905)
31–40 years	4.1 (228)	20.0 (1,112)	18.1 (1,006)	57.8 (3,208)
41–50 years	3.8 (200)	22.4 (1,175)	18.0 (943)	55.8 (2,916)
51–60 years	6.1 (270)	29.1 (1,308)	16.1 (725)	48.7 (2,189)
61–70 years	8.2 (199)	30.2 (730)	15.5 (376)	46.1 (1,117)
71–80 years	11.9 (111)	34.8 (325)	14.1 (131)	39.2 (368)

BMI, body mass index

Table 5: Multivariable logistic regression and modified Poisson regression analyses of age, sex, and blood pressure associated with BMI categories

Variable	Comparison	Crude OR (CI)	Adjusted OR (CI)	APR (CI)	p-value (OR)	p-value (APR)
BMI ≥25 kg/m ² (obesity)						
Age group	61–80 vs 18–60	0.71 (0.66–0.76)	0.75 (0.70–0.81)	0.85 (0.80–0.90)	p < 0.001 (S)	p < 0.001 (S)
Sex	Male vs female	1.50 (1.42–1.58)	1.59 (1.51–1.67)	1.23 (1.19–1.28)	p < 0.001 (S)	p < 0.001 (S)
BP	>140 and/or >90 vs <140/90	1.71 (1.62–1.81)	1.49 (1.40–1.58)	1.20 (1.15–1.25)	p < 0.001 (S)	p < 0.001 (S)
BMI 23–24.9 kg/m ² (overweight)						
Age group	61–80 vs 18–60	0.83 (0.76–0.90)	0.89 (0.81–0.97)	0.92 (0.86–0.98)	p = 0.009 (S)	p = 0.012 (S)
Sex	Male vs female	1.18 (1.10–1.26)	1.14 (1.06–1.22)	1.08 (1.02–1.14)	p < 0.001 (S)	p = 0.003 (S)
BP	>140 and/or >90 vs <140/90	0.93 (0.87–1.00)	0.98 (0.91–1.06)	0.99 (0.93–1.05)	p = 0.612 (N)	p = 0.720 (N)
BMI 18.5–22.9 kg/m ² (normal weight)						
Age group	61–80 vs 18–60	1.45 (1.35–1.55)	1.38 (1.29–1.48)	1.21 (1.15–1.27)	p < 0.001 (S)	p < 0.001 (S)
Sex	Male vs female	0.60 (0.57–0.64)	0.56 (0.53–0.60)	0.69 (0.65–0.72)	p < 0.001 (S)	p < 0.001 (S)
BP	>140 and/or >90 vs <140/90	0.60 (0.57–0.64)	0.66 (0.62–0.71)	0.75 (0.71–0.79)	p < 0.001 (S)	p < 0.001 (S)
BMI <18.5 kg/m ² (underweight)						
Age group	61–80 vs 18–60	1.82 (1.62–2.04)	1.67 (1.48–1.88)	1.41 (1.27–1.56)	p < 0.001 (S)	p < 0.001 (S)
Sex	Male vs female	0.62 (0.56–0.69)	0.58 (0.52–0.65)	0.64 (0.58–0.71)	p < 0.001 (S)	p < 0.001 (S)
BP	>140 and/or >90 vs <140/90	0.55 (0.49–0.62)	0.61 (0.54–0.69)	0.69 (0.61–0.77)	p < 0.001 (S)	p < 0.001 (S)

APR, adjusted prevalence ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; N, statistically nonsignificant; OR, odds ratio; S, statistically significant

70.5% (13,845) were overweight/obese. In the 61–80-year age group, 40.7% (2,057) were underweight/normal weight and 59.3% (3,000) were overweight/obese. Overweight/obesity was more common in the younger age group, whereas underweight/normal weight was relatively more common among older subjects; this difference was statistically significant ($p < 0.001$). Association of BMI categories with males and females shows that 25.9% (3,366) of males were underweight/normal weight and 74.1% (9,630) were overweight/obese. Whereas 38.3% (4,474) of females were underweight/normal weight and 61.7% (7,215) were overweight/obese. Males had a higher burden of overweight/obesity than females; this difference was statistically significant ($p < 0.001$). In the normal BP group, 35.8% (5,955) were underweight/normal weight and 64.2% (10,701) were overweight/obese,

whereas in the elevated BP group, 23.5% (1,885) were underweight/normal weight and 76.5% (6,144) were overweight/obese. Similarly, in the normal systolic BP group, 34.3% (6,354) were underweight/normal weight and 65.7% (12,173) were overweight/obese, whereas in the systolic HTN group, 24.1% (1,486) were underweight/normal weight and 75.9% (4,672) were overweight/obese. In the normal diastolic BP group, 33.5% (6,437) were underweight/normal weight and 66.5% (12,765) were overweight/obese, whereas in the diastolic HTN group, 25.6% (1,403) were underweight/normal weight and 74.4% (4,080) were overweight/obese. Results show a positive association between higher BMI and elevated BP, including systolic and diastolic BP; these differences were statistically significant ($p < 0.001$).

Table 4 shows the burden of BMI categories across age groups. Among

subjects in the 18–30-year age group, 8.4% (509) were underweight, 26.1% (1,579) were normal weight, 17.5% (1,055) were overweight, and 48.0% (2,905) were obese. In the 31–40-year age group, 4.1% (228) were underweight, 20.0% (1,112) were normal weight, 18.1% (1,006) were overweight, and 57.8% (3,208) were obese. In the 41–50-year age group, 3.8% (200) were underweight, 22.4% (1,175) were normal weight, 18.0% (943) were overweight, and 55.8% (2,916) were obese. In the 51–60-year age group, 6.1% (270) were underweight, 29.1% (1,308) were normal weight, 16.1% (725) were overweight, and 48.7% (2,189) were obese. In the 61–70-year age group, 8.2% (199) were underweight, 30.2% (730) were normal weight, 15.5% (376) were overweight, and 46.1% (1,117) were obese. In the 71–80-year age group, 11.9% (111) were underweight, 34.8% (325) were normal weight, 14.1% (131) were overweight, and 39.2% (368) were

Table 6: Multinomial logistic regression analysis for obesity and overweight among characteristic variables using normal BMI as the reference category

Variable	Overweight RRR (95% CI)	Obesity RRR (95% CI)	p-value
Age 61–80 years	0.65 (0.58–0.72)	0.54 (0.49–0.60)	$p < 0.001$ (S)
Male sex	2.03 (1.87–2.21)	2.84 (2.64–3.06)	$p < 0.001$ (S)
Elevated BP	1.41 (1.29–1.54)	2.25 (2.09–2.42)	$p < 0.001$ (S)

Normal BMI, <23 kg/m²; overweight BMI, 23–24.9 kg/m²; obesity, ≥ 25 kg/m²; BMI, body mass index; BP, blood pressure; CI, confidence interval; RRR, relative risk ratio; S, statistically significant

Table 7: Nagelkerke R² values for the logistic regression models across BMI categories

Model	Nagelkerke R ²
BMI ≥ 25 kg/m ² (obese)	0.055–0.065
BMI 23–24.9 kg/m ² (overweight)	0.012–0.020
BMI 18.5–22.9 kg/m ² (normal)	0.045–0.055
BMI <18.5 kg/m ² (underweight)	0.018–0.030

obese. Results show a progressive rise in BMI within the age groups with a modest decline in the overweight BMI group. On the other hand, the burden of obesity was higher among younger age groups as compared to older age groups.

Table 5 shows multivariable logistic regression and modified Poisson regression analyses of age, sex, and BP groups associated with BMI categories.

In the obese group, subjects aged 61–80 years had a crude OR of 0.71 (95% CI: 0.66–0.76), an adjusted OR of 0.75 (95% CI: 0.70–0.81), and an APR of 0.85 (95% CI: 0.80–0.90) compared with those aged 18–60 years. Males had a crude OR of 1.50 (95% CI: 1.42–1.58), an adjusted OR of 1.59 (95% CI: 1.51–1.67), and an APR of 1.23 (95% CI: 1.19–1.28) compared with females. The elevated BP group had a crude OR of 1.71 (95% CI: 1.62–1.81), an adjusted OR of 1.49 (95% CI: 1.40–1.58), and an APR of 1.20 (95% CI: 1.15–1.25) compared with the normal BP group. These results suggest that obesity was significantly associated with male sex, elevated BP, and younger age.

In the overweight group, subjects aged 61–80 years had a crude OR of 0.83 (95% CI: 0.76–0.90), an adjusted OR of 0.89 (95% CI: 0.81–0.97), and an APR of 0.92 (95% CI: 0.86–0.98) compared with those aged 18–60 years. Males had a crude OR of 1.18 (95% CI: 1.10–1.26), an adjusted OR of 1.14 (95% CI: 1.06–1.22), and an APR of 1.08 (95% CI: 1.02–1.14) compared with females. The elevated BP group had a crude OR of 0.93 (95% CI: 0.87–1.00), an adjusted OR of 0.98 (95% CI: 0.91–1.06), and an APR of 0.99 (95% CI: 0.93–1.05) compared with the normal BP group. Results suggest no strong independent association

Table 8: Variance inflation factor (VIF) values for age group, sex, and blood pressure

Variable	VIF
Age group	1.08
Sex	1.03
Blood pressure	1.09

between elevated BP and the overweight BMI category after adjustment.

In the normal-weight group, subjects aged 61–80 years had a crude OR of 1.45 (95% CI: 1.35–1.55), an adjusted OR of 1.38 (95% CI: 1.29–1.48), and an APR of 1.21 (95% CI: 1.15–1.27) compared with those aged 18–60 years. Males had a crude OR of 0.60 (95% CI: 0.57–0.64), an adjusted OR of 0.56 (95% CI: 0.53–0.60), and an APR of 0.69 (95% CI: 0.65–0.72) compared with females. The elevated BP group had a crude OR of 0.60 (95% CI: 0.57–0.64), an adjusted OR of 0.66 (95% CI: 0.62–0.71), and an APR of 0.75 (95% CI: 0.71–0.79) compared with the normal BP group. Results suggest that older age was associated with this BMI category, while males and the elevated BP group were less likely to be in the normal-weight range.

In the underweight group, subjects aged 61–80 years had a crude OR of 1.82 (95% CI: 1.62–2.04), an adjusted OR of 1.67 (95% CI: 1.48–1.88), and an APR of 1.41 (95% CI: 1.27–1.56) compared with those aged 18–60 years. Males had a crude OR of 0.62 (95% CI: 0.56–0.69), an adjusted OR of 0.58 (95% CI: 0.52–0.65), and an APR of 0.64 (95% CI: 0.58–0.71) compared with females. The elevated BP group had a crude OR of 0.55 (95% CI: 0.49–0.62), an adjusted OR of 0.61 (95% CI: 0.54–0.69), and an APR of 0.69 (95% CI: 0.61–0.77) compared with the normal BP group. Results suggest that underweight BMI was more likely in the older age group but less likely among males and subjects with elevated BP.

Table 6 shows multinomial logistic regression for the obesity and overweight groups using normal BMI as the reference category. Subjects aged 61–80 years had a lower relative risk ratio (RRR) for overweight (RRR 0.65, 95% CI: 0.58–0.72) and obesity (RRR 0.54, 95% CI: 0.49–0.60). Males had substantially

higher relative risks of overweight (RRR 2.03, 95% CI: 1.87–2.21) and obesity (RRR 2.84, 95% CI: 2.64–3.06). The elevated BP group also had higher relative risks of overweight (RRR 1.41, 95% CI: 1.29–1.54) and obesity (RRR 2.25, 95% CI: 2.09–2.42). Results suggest a clear graded relationship between male sex, elevated BP, and higher BMI categories, with the strongest association observed in the obesity group.

Overall, the results of the present study suggest a high burden of obesity in the study population, with strong associations with male sex, elevated BP, and younger age groups (18–60 years), whereas the older age group (61–80 years) showed a higher burden of underweight BMI. The adjusted models show that higher BMI and elevated BP cluster together, suggesting a strong cardiometabolic association in the study population.

Table 7 shows Nagelkerke R² values for the logistic regression models across BMI categories. The low values across all models indicate that only a modest proportion of the variation in BMI category was explained by the included variables of age, sex, and BP. The model for the obese group showed the highest explanatory power, with Nagelkerke R² values of 0.055–0.065, indicating that age, sex, and BP together explained about 5.5%–6.5% of the variation in the obese group. The model for the normal-weight group showed slightly lower R² values of 0.045–0.055, indicating that the variables explained about 4.5%–5.5% of the variation in this group. The model for the underweight group showed low explanatory power, with R² values of 0.018–0.030, suggesting that this group was largely determined by variables not included in the study. The model for the overweight group showed the weakest fit, with R² values of only 0.012–0.020, indicating that the model explained 1.2%–2.0% of the variation in this group. Analysis of the Nagelkerke R² values indicates that although age, sex, and BP were predictors in the models, they had limited ability to explain variation across BMI groups. Other unmeasured variables such as region, socioeconomic status, diet, physical activity, comorbidities, and lifestyle factors may play an important role in determining BMI category.

Table 8 shows the variance inflation factor (VIF) values for the variables included in the model. All values were close to 1, including 1.08 for age group, 1.03 for sex, and 1.09 for BP, indicating negligible multicollinearity. Generally, VIF values below five are considered acceptable, and values near one indicate almost no overlap among variables. These results suggest that the independent variables are not strongly correlated with one another, supporting

the stability and reliability of the regression coefficients. The low VIF values support the inclusion of age, sex, and blood pressure together in the analysis.

DISCUSSION

The results of the present study showed that, by Asian BMI criteria, 31.8% were underweight/normal weight and 68.2% were overweight/obese. Overall, 6.2% were underweight, 25.6% were normal weight, 17.1% were overweight, and 51.1% were obese, suggesting a very high burden of overweight/obesity among subjects screened in Punjab. This burden was substantially higher than the 22.6% reported in NFHS-5 and 29.0% reported in NFHS-6 data.^{4,5} Even the Punjab-specific NFHS-5 and NFHS-6 data showed overweight/obesity burdens of 36.6% and 41.1%, respectively, which were substantially lower than those documented in the present study.^{4,5} The higher burden in the present study may be explained by the use of Asian-specific BMI criteria, whereas NFHS used WHO criteria.

The results of the present study showed a noteworthy relationship between BMI and age. Obesity was observed in 52.9% of subjects aged 18–60 years compared with 44.2% of those aged 61–80 years, and the difference was statistically significant. The proportion of underweight subjects increased from 5.3% in the 18–60-year group to 9.3% in the 61–80-year group. Among subjects aged 18–60 years, 29.5% were in the underweight/normal BMI category, and 70.5% were in the overweight/obesity category; among those aged 61–80 years, 40.7% were in the underweight/normal BMI category, and 59.3% were in the overweight/obesity category. The difference was statistically significant in both BMI categories. Obesity was more common in younger age groups than in older age groups, whereas underweight became more common with age. Multivariable analysis suggested that the older age group, compared with the younger age group, had lower odds of obesity (adjusted OR 0.75, 95% CI: 0.70–0.81) and overweight (adjusted OR 0.89, 95% CI: 0.81–0.97), but higher odds of underweight (adjusted OR 1.67, 95% CI: 1.48–1.88) and normal BMI (adjusted OR 1.38, 95% CI: 1.29–1.48). Multinomial logistic regression analysis suggested that the 61–80-year age group had a lower RRR for overweight (0.65, 95% CI: 0.58–0.72, $p < 0.001$) and obesity (0.54, 95% CI: 0.49–0.60, $p < 0.001$), with normal BMI as the reference category. The higher burden of overweight/obesity in the younger age group and underweight/normal weight in the older age group may be explained by reduced

appetite, comorbidities, chronic illness, and sarcopenia in older subjects.⁸ NFHS-5 and NFHS-6 data generally show a rising burden of obesity from younger to middle-aged adults, possibly because these surveys included only subjects aged 15–49 years, whereas the present study included subjects aged 18–80 years; this difference may help explain the decline in overweight/obesity in the older age group.^{4,5}

The present study observed a significantly higher burden of overweight/obesity among males than females (74.1% vs 61.7%), in contrast to nationally representative data from NFHS-5 (22.1% vs 23.0%) and NFHS-6 (27.3% vs 30.7%), which^{4,5} consistently showed a lower prevalence of overweight/obesity among males as compared to females. Similarly, a lower prevalence of overweight/obesity among males as compared to females was observed in Punjab-specific data from NFHS-5 (32.3% vs 40.8%) and NFHS-6 (37.5% vs 44.7%).^{4,5} The observation in the present study aligns with observations from the ICMR-INDIAB-23 study reporting a higher prevalence of the metabolically obese non-obese (MONO) phenotype in males as compared to females (44.7% vs 43.1%), whereas the ICMR-INDIAB-23 study reported a lower prevalence of overall BMI-based obesity among males.^{5,6} Multivariable logistic regression analysis showed that males had 1.14 times higher odds of being overweight (adjusted OR: 1.14; 95% CI: 1.06–1.22; $p < 0.001$) and 1.59 times higher odds of being obese (adjusted OR: 1.59; 95% CI: 1.51–1.67; $p < 0.001$) compared with females. The analysis also showed lower odds of normal weight (adjusted OR 0.56) and underweight (adjusted OR 0.58) among males compared with females. Multinomial logistic regression analysis suggested that males had a higher RRR for overweight (RRR: 2.03, 95% CI: 1.87–2.21, $p < 0.001$) and obesity (RRR: 2.84, 95% CI: 2.64–3.06, $p < 0.001$), with normal BMI as the reference category. The male predominance of overweight/obesity in the present study may be influenced by several factors not considered in the study, such as dietary habits, alcohol intake, sedentary lifestyle, occupational factors, urban/rural patterns, and other health-risk behaviors.^{8,9} Moreover, the present study included subjects aged 18–80 years and used Asian BMI criteria, whereas NFHS data included subjects aged 15–49 years and used WHO BMI criteria; these differences may have influenced the male predominance in the overweight/obesity groups in Punjab. The present observations underscore the importance of regional sex-specific data on BMI categories.

Among subjects with elevated BP, 60.0% were obese, 4.1% were underweight, 19.4% were normal weight, and 16.5%

were overweight. Among subjects with normal BP, 46.8% were obese, 7.2% were underweight, 28.6% were normal weight, and 17.4% were overweight; the distribution differed significantly by BP status ($p < 0.001$). Results showed a strong and independent association between the obesity BMI category and elevated BP, whereas the overweight BMI category did not show a significant association. In the multivariable logistic regression analysis, subjects with elevated BP had 1.49 times higher odds of being obese than those with normal BP (adjusted OR: 1.49, 95% CI: 1.40–1.58, $p < 0.001$). For the overweight BMI category, the adjusted OR was 0.98 (95% CI: 0.91–1.06, $p = 0.612$); for normal BMI, it was 0.66 (95% CI: 0.62–0.71, $p < 0.001$); and for underweight BMI, it was 0.61 (95% CI: 0.54–0.69, $p < 0.001$), each compared with the normal BP group. The overweight BMI category did not show a significant association with elevated BP across the reported models: crude OR 0.93 (95% CI: 0.87–1.00; $p = 0.612$), adjusted OR 0.98 (95% CI: 0.91–1.06; $p = 0.720$), and APR 0.99 (95% CI: 0.93–1.05). Multinomial logistic regression showed an RRR of 1.41 (95% CI: 1.29–1.54) for overweight and 2.25 (95% CI: 2.09–2.42) for obesity among subjects with elevated BP. These observations are consistent with NFHS-5 and NFHS-6 data showing that overweight/obesity and HTN were closely linked.^{3,4} The ICMR-INDIAB study reported a 51.8% prevalence of HTN in Punjab, coinciding with the 41.1% burden of overweight/obesity in NFHS-6 data.^{4,6} Pathophysiological mechanisms that may explain the association between elevated BP and obesity include insulin resistance, increased sympathetic nervous system activity, the renin–angiotensin–aldosterone system, endothelial dysfunction, and adverse effects of visceral adiposity.¹⁰

Results of the present study showed a higher burden of SHTN (75.9%) and DHTN (74.4%) among the overweight/obese BMI group compared with SHTN (24.1%) and DHTN (25.6%) among the normal/underweight BMI group; the difference was statistically significant for both SHTN and DHTN. These results indicate that elevated BP was more common in the higher-BMI group. This observation is clinically important because Indian populations may develop cardiometabolic risk at lower BMI than WHO BMI cutoffs. A study showed that BMI is significantly associated with all subtypes of HTN but is more strongly associated with DHTN than with HTN and SHTN in US and nonobese Indian adults. The study also observed that the association between HTN and BMI is more complex in obese Indians,

with a higher risk of SHTN until the sixth decade and HTN thereafter.¹¹ The multinomial regression analysis in the present study showed that the association of elevated BP was strongest with the obesity BMI category rather than the overweight BMI category. Younger age (18–60 years), male sex, and elevated BP were associated with a higher relative risk of obesity. This observation is important from a public health perspective because subjects crossing the Asian obesity BMI threshold of 25 kg/m² may already represent a high-risk group, especially in Punjab, where the prevalence of obesity is high. The low Nagelkerke R² values show that only a small proportion of the variation in BMI categories was explained by age, sex, and BP because obesity has a multifactorial pathophysiology influenced by several factors such as socioeconomic status, region, diet, physical activity, education, genetic predisposition, and comorbidities.^{8,9} The very low VIF values showed negligible multicollinearity, supporting the stability of the regression estimates. Thus, while the observed associations are statistically strong and epidemiologically relevant, the analysis reflects only part of the complex determinants of body weight in the studied population. The differences in the burden of BMI categories and their associations with age, sex, and BP in the present study should be interpreted cautiously alongside NFHS-5 and NFHS-6 data because NFHS used WHO BMI criteria and a younger age group (15–49 years), whereas the present study used Asian BMI cutoffs and included subjects aged 18–80 years.^{3,4}

STRENGTHS

The main strength of the present study is the use of Asian BMI criteria, which are appropriate for Indian populations compared with conventional WHO BMI cutoffs. Asian BMI criteria improve risk stratification in a population with a high burden of obesity and elevated BP in Punjab. A large opportunistic screening sample is another strength of the study, providing real-world data and contributing to regional evidence.

LIMITATIONS

The present study has several limitations. Overweight/obesity may not be a novel issue to study, but large-scale, Punjab-specific screening data add to regional data on the burden of overweight/obesity. The present study adopted convenience and opportunistic sampling involving different screening settings, including community health centers, hospitals, health checkups, and outreach camps, which may not be fully representative of the entire

adult population of Punjab. Walk-in screening was adopted to reduce selection bias from recruiting only symptomatic or health-aware subjects. A randomized, population-based probability sampling method could have better represented the true epidemiological prevalence in the entire population of Punjab. For evaluation of HTN, the present study used a single-occasion BP assessment: three readings were recorded, and the mean of the second and third readings was used for analysis. However, a confirmed diagnosis of HTN requires confirmation of elevated BP on repeated visits or by ambulatory/home blood pressure monitoring; therefore, the present study reports elevated BP among screened subjects rather than a confirmed clinical diagnosis of HTN. Data on several determinants of overweight/obesity were not available within the dataset, including educational status, socioeconomic position, urban–rural residence, dietary patterns, physical activity, alcohol consumption, diabetes, dyslipidemia, and other metabolic or behavioral risk factors, limiting analysis of the associations between overweight/obesity, age, sex, and BP. Despite these limitations, the large sample size, standardized measurement protocol, and inclusion of participants from diverse screening settings provide valuable contemporary data regarding the burden of BMI categories and their demographic correlates in Punjab.

CONCLUSION

The results of the present study show a substantial burden of obesity/overweight among subjects opportunistically screened in Punjab during the MMM initiative using Asian BMI criteria. More than two-thirds of subjects (68.2%) were overweight/obese. These observations highlight the burden of adiposity and obesity-related health risks in Punjab; this is particularly important because Indians are known to develop noncommunicable diseases (NCDs) such as HTN, diabetes, and CVDs at lower BMI cutoffs than Western populations. The present study documents significant associations between BMI categories, age, sex, and BP. Obesity was more common among the younger age group (18–60 years) and among males, whereas underweight was increasingly common with advancing age. Elevated BP showed a strong and independent association with obesity. Coexistence of a high burden of obesity and elevated BP among younger subjects and males in Punjab represents a major challenge for the prevention and control of NCDs, especially through promotion of healthy diets, increased physical activity, and implementation of routine screening protocols for NCDs, including obesity and HTN, targeting high-risk groups such as younger adults and

males. Although the present study is based on opportunistic screening, the results should not be interpreted as population prevalence for Punjab; however, they provide valuable contemporary regional data on the burden of BMI categories and their associations with age, sex, and BP. Future population-based studies should include behavioral, socioeconomic, dietary, and metabolic determinants to document the prevalence of obesity and its association with various variables in Punjab.

AUTHORS' CONTRIBUTIONS

MSB, MG, VKG, KG, CG, HG, JJ, and RG contributed to the study concept, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. MSB, MG, VKG, KG, and CG additionally contributed to the study design and definition of intellectual content. All authors acted as guarantors.

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Hyperhomocysteinemia Outperforms CD4 Count and Framingham Risk Score in Detecting Subclinical Coronary Atherosclerosis Based on Agatston Scoring, and Cardiac Morbidity in Human Immunodeficiency Virus Patients on Antiretroviral Therapy: A Cross-sectional Study from Northern India

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Received: 09 June 2026; Accepted: 15 July 2026

ABSTRACT

Background: People living with HIV have increased cardiovascular risk despite antiretroviral therapy, and conventional risk tools like the Framingham Risk Score may underestimate subclinical coronary disease. Coronary artery calcium (CAC) scoring is a validated marker of subclinical atherosclerosis, while prior HIV imaging studies show appreciable plaque burden even among patients categorized as low risk by traditional models. Alongside, hyperhomocysteinemia is increasingly recognized as a potentially modifiable cardiovascular risk factor in HIV patients as a consequence of chronic inflammation, micronutrient deficiencies, and long-term antiretroviral therapies.

Objectives: To evaluate whether serum homocysteine outperforms current CD4 count and Framingham Risk Score in identifying subclinical coronary atherosclerosis and cardiac morbidity in treated people living with HIV.

Materials and methods: This cross-sectional analytical study enrolled 211 adults with HIV on antiretroviral therapy at a tertiary care hospital in Prayagraj, India, from March 2025 to March 2026 and assessed coronary artery calcification by noncontrast cardiac CT using Agatston scoring, along with electrocardiography, treadmill testing (TMT), and echocardiography. Serum homocysteine, CD4 count, fasting lipid profile, vitamin B12, and folate were measured. Data were analyzed using advanced software (SPSS v25.0), and associations were examined using correlation analysis, Chi-square testing, ANOVA, and regression methods.

Results: The mean age of the cohort was 41.7 years, and 81% of participants remained in the low Framingham risk category despite a substantial burden of coronary artery calcification (31% had a positive CAC score) and cardiovascular dysfunction (28.4% had detectable echocardiographic abnormalities). Serum homocysteine showed a moderate positive correlation with CAC score ($r=0.403$, $p<0.001$), whereas CD4 count had neither a significant correlation with CAC score ($r=-0.039$, $p=0.575$) nor with echocardiographic cardiovascular dysfunction ($r=-0.003$, $p=0.969$). Hyperhomocysteinemia independently predicted CAC positivity after adjustment for confounders, with an odds ratio of 7.26, while vitamin B12 deficiency showed a weaker association, with an odds ratio of 2.36; age, sex, and ART duration were not significantly associated in the model. Framingham Risk Score did not meaningfully track with homocysteine, coronary calcium burden, or immune status in this study.

Conclusion: Serum homocysteine appears to be a stronger marker of subclinical coronary atherosclerosis than current CD4 count or Framingham Risk Score in treated people living with HIV. Incorporating homocysteine, vitamin B12 status, and selective coronary calcium assessment may improve cardiovascular risk stratification in HIV care, particularly in populations where conventional risk scores may underestimate disease burden.

Keywords: Agatston score, CD4 count, Coronary artery calcium, Framingham Risk Score, Human immunodeficiency virus, Hyperhomocysteinemia, Subclinical atherosclerosis.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1708

INTRODUCTION

As survival improves with antiretroviral therapy, cardiovascular disease has emerged as an important contributor to long-term morbidity in people living with HIV (PLHIV).¹ Imaging studies have shown that subclinical atherosclerosis and coronary plaque are common in HIV, even in those patients who appear to be at low risk according

to conventional cardiovascular morbidity prediction tools.² This environment is marked by ongoing inflammation, damage to blood vessels, and accelerated atherosclerosis. These factors then lead to both ischemic and nonischemic heart disease.³

Coronary artery calcium measured by noncontrast CT is an established marker of cumulative coronary atherosclerotic burden and future cardiovascular events, quantified

based on Agatston scoring. A score of zero indicates an extremely low short-term risk of cardiovascular events, whereas higher scores are associated with progressively increasing risk. Interpretation: 0: No detectable coronary calcification; 1–99: Mild calcification; 100–399: Moderate calcification; ≥ 400 : Severe calcification.⁴

Traditional models such as the Framingham Risk Score (FRS), used for prediction of 10-year risk of CVD (low = $<10\%$ risk, moderate = $10\text{--}20\%$ risk, and high = $>20\%$ risk), do not account for persistent immune activation, chronic inflammation, ART-related metabolic effects, or HIV-specific biology, which may limit their performance in this population.⁵

Homocysteine is biologically plausible as a vascular risk marker because it is linked to oxidative stress, endothelial dysfunction, inflammation, and thrombosis.⁶ In treated HIV populations, hyperhomocysteinemia may additionally reflect nutritional deficits, antiretroviral-related metabolic disturbance, and chronic inflammatory activation, making it a potentially useful integrative biomarker of vascular risk.⁷

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How to cite this article: Chaurasia AK, Dastidar S, Gupta P, et al. Hyperhomocysteinemia Outperforms CD4 Count and Framingham Risk Score in Detecting Subclinical Coronary Atherosclerosis Based on Agatston Scoring, and Cardiac Morbidity in Human Immunodeficiency Virus Patients on Antiretroviral Therapy: A Cross-sectional Study from Northern India. *J Assoc Physicians India* 2026;74(10):24–29.

AIMS AND OBJECTIVES

Aims

To evaluate whether serum homocysteine outperforms current CD4 count and Framingham Risk Score in identifying subclinical coronary atherosclerosis and cardiac morbidity in treated people living with HIV in Northern India.

Objectives

To estimate the prevalence of subclinical coronary atherosclerosis based on coronary artery calcification by Agatston scoring in PLHIV patients on ART.

To estimate the prevalence of cardiovascular dysfunction based on echocardiography and TMT abnormalities in PLHIV patients on ART.

To assess the correlation of CAC scoring and cardiovascular dysfunction with hyperhomocysteinemia, current CD4 counts, and Framingham Risk Score in PLHIV patients on ART.

MATERIALS AND METHODS

This was a hospital-based cross-sectional analytical study conducted at Swaroop Rani Nehru Hospital, Prayagraj, a tertiary care center in Northern India. In this study, 500 adults, as shown in Figure 1, with HIV infection receiving antiretroviral therapy who were willing to participate were included after informed consent. Following the application of exclusion criteria, 197 adults were excluded who were critically ill or had preexisting diabetes or other comorbidities like malignancies, chronic kidney disease, and chronic liver disease. A total of 303 patients filled out the questionnaire, of whom 211 patients were willing to undergo the required diagnostic procedures. The study was largely based on clinically stable patients and was representative of PLHIV on ART attending

the hospital during the study period. Proper Institutional Ethics Committee approval was obtained from the institute, Moti Lal Nehru Medical College, Prayagraj (Ethics Committee Registration No. ECR/922/inst/UP/RR-22 issued under New Drugs and Clinical Trial Rules, 2019), dated 21st March 2025.

Inclusion Criteria

All PLHIV patients above 18 years of age who were on ART, attending the hospital during the study period, and willing to participate in the study.

Exclusion Criteria

Those patients who were critically ill, had preexisting diabetes mellitus, malignancies, chronic kidney disease, chronic liver disease, were pregnant or lactating, had newly diagnosed HIV and were not on ART, or were unwilling to undergo the required diagnostic procedures were excluded.

Data Collection Tools and Procedure

All participants underwent structured clinical evaluation, electrocardiography, treadmill testing (TMT), two-dimensional echocardiography, and noncontrast cardiac CT for CAC assessment using the Agatston method. Serum homocysteine, CD4 count, fasting lipid profile, vitamin B12, folate, and other metabolic variables were measured by standard laboratory methods used at the institution. Coronary artery calcification was categorized by Agatston score, with CAC >0 considered calcification positive. Hyperhomocysteinemia was defined in this study using a cutoff above 22 $\mu\text{mol/L}$, vitamin B12 deficiency as <180 pg/mL, and folate deficiency as 2 ng/mL or lower.

Statistical Analysis

The study used SPSS version 25 for data analysis. Associations were examined using

Chi-squared tests, Pearson and Spearman correlation coefficients, ANOVA or Kruskal–Wallis tests where appropriate, and multivariable regression methods. A two-sided *p*-value below 0.05 was considered statistically significant in the thesis analysis.

RESULTS

Baseline Profile

The mean age of the study population was 41.7 years. CD4 distribution suggested that only 6.6% of participants had severe immunosuppression, with CD4 below 200 cells/ μL , while 51.7% had CD4 200 to 500 cells/ μL and 41.7% had CD4 above 500 cells/ μL .

Metabolic Profile

A high metabolic burden was present in this study. Lipid abnormalities were documented in 78.7% of participants, with low HDL in 61.6% and high triglycerides of at least 150 mg/dL in 54.5%, yet no statistically significant CAC/CVD association ($p > 0.05$) was observed. Vitamin B12 deficiency was present in 30.8% and folate deficiency in 16.6%, as shown in Table 1.

Patients with B12 deficiency combined with hyperhomocysteinemia showed the highest burden of CAC: 51.9% had elevated CAC (38.5% mild + 13.5% moderate), whereas patients with B12 deficiency alone (without hyperhomocysteinemia) had a lower CAC burden: only 15.4% had mild CAC. This further emphasizes that B12 deficiency synergized with hyperhomocysteinemia for CAC ($\chi^2 = 18.74$, $p = 0.001$), as shown in Table 2 and Figure 2, although its association with CAC alone was not significant.

Coronary Calcium and Biomarker Associations

Among all the study subjects, as shown in Table 3, 31% had detectable coronary

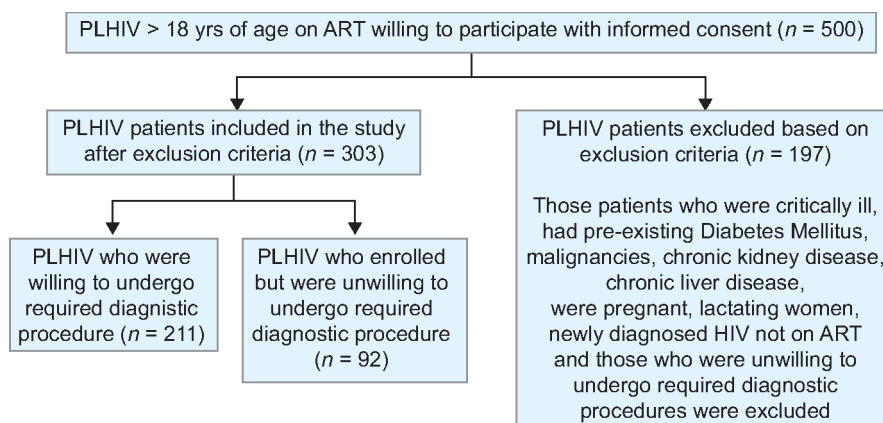


Fig. 1: A flowchart detailing recruitment of participants

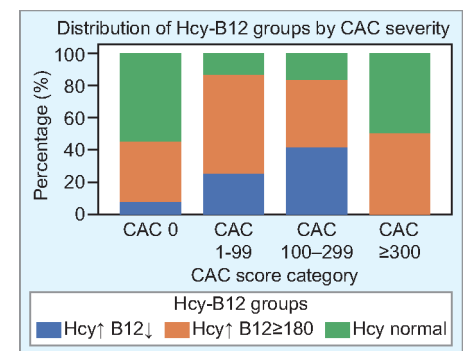


Fig. 2: Distribution of homocysteine groups across CAC severity categories, showing enrichment of hyperhomocysteinemia with increasing coronary calcium burden

Table 1: Baseline study parameters

Variable	Mean $\pm$ SD	Median (IQR)	Range
Age (years)	41.7 $\pm$ 11.4	42 (34–50)	20–59
CD4 count (cells/ μ L)	476.5 $\pm$ 213.4	456 (321–615)	185–898
Homocysteine (μ mol/L)	27.3 $\pm$ 13.5	24.6 (19.3–32.6)	7.4–82.2
CAC score	31.2 $\pm$ 66.2	0 (0–20)	0–319
FRS10-year (%)	6.12 $\pm$ 5.28	4.50 (1.50–9.40)	0.50–29.40
HbA1c (%)	4.84 $\pm$ 0.81	4.80 (4.40–5.20)	3.00–12.70
Vitamin B12 (pg/mL)	310.2 $\pm$ 242.9	267 (168–392)	83–1492
Folate (ng/mL)	5.5 $\pm$ 4.5	4.2 (2.9–6.1)	0.1–20.0
Total cholesterol (mg/dL)	155.8 $\pm$ 37.5	154 (132–178)	78–260
LDL (mg/dL)	83.9 $\pm$ 38.3	78 (56–105)	1–206
HDL (mg/dL)	42.2 $\pm$ 17.1	39 (29–53)	14–86
Triglycerides (mg/dL)	167.4 $\pm$ 55.7	164 (123–203)	69–432

Table 2: Association of homocysteine with CAC scoring

Homocysteine group	CAC = 0, n (%)	CAC > 0, n (%)	Total	χ^2	p-value
Hyper-Hcy + low B12	10 (37.0%)	17 (63.0%)	27	34.27	<0.001*
Hyper-Hcy + normal B12	55 (59.1%)	38 (40.9%)	93		
Normal Hcy	81 (89.0%)	10 (11.0%)	91		

*Highly statistically significant association ($\chi^2 = 34.27$, $p < 0.001$)

Table 3: CAC scoring distribution indicating subclinical atherosclerosis

CAC category (Agatston)	Number of patients	Percentage
0 (no calcification)	146	69%
1–99 (mild)	51	24.2%
100–299 (moderate)	12	5.7%
≥ 300 (severe)	2	1%

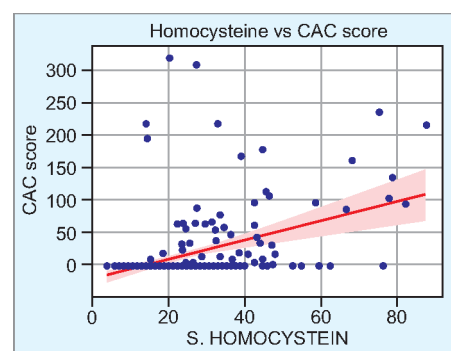


Fig. 3: Scatter plot showing a moderate positive correlation between serum homocysteine and CAC score ($r = 0.403$, $p < 0.001$). Higher homocysteine levels are associated with progressively higher coronary calcium burden

calcification (CAC > 0), indicating subclinical atherosclerosis.

Serum homocysteine demonstrated a moderate positive correlation with CAC score ($r = 0.403$, $p < 0.001$), as shown in Table 2 and Figure 3, indicating a clinically relevant relationship between rising homocysteine levels and increasing coronary calcium burden.

In contrast, CD4 count, as shown in Table 4 and Figure 4, showed no correlation with CAC

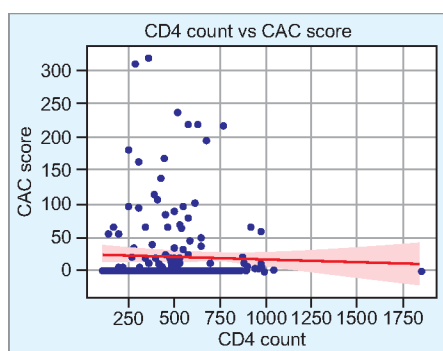


Fig. 4: Lack of association between CD4 and CAC: Distribution of CAC according to CD4 categories, showing no significant association between current CD4 count and CAC positivity

score ($r = -0.039$, $p = 0.575$). Across CD4 strata, CAC positivity was strikingly similar: 28.6% in those with CD4 below 200 cells/ μ L, 31.2% in those with CD4 200 to 500 cells/ μ L, and 30.7% in those with CD4 above 500 cells/ μ L, with no statistically significant association (Chi-square = 0.04, $p = 0.980$). These data suggest that current immune status does not discriminate calcific coronary plaque burden in treated HIV patients.

In multivariable analysis, hyperhomocysteinemia independently predicted CAC positivity, with an odds ratio

of 7.26 and a 95% confidence interval of 3.34–15.80, and the association was highly significant ($p < 0.001$), whereas vitamin B12 deficiency had a smaller association, with an odds ratio of 2.36. Age, sex, and ART duration were not significant, as shown in Table 5 and Figure 5. This pattern supports homocysteine as the most informative biomarker among the variables examined for calcific subclinical atherosclerosis in this study.

Cardiac Morbidity and Echocardiographic Findings

Prevalence of CVD was determined based on different investigative modalities. Abnormalities, as shown in Table 6 were led by echocardiography (28.4%), with LV diastolic dysfunction (9.5%) and hypertrophy (10.9%) predominant. Other abnormalities included valvular heart disease (MR/TR) (8.6%), dilated cardiomyopathy (0.9%), and heart failure with reduced ejection fraction (4.7%); TMT changes were rarer (2.36%). These findings suggest that subclinical cardiac remodeling is prevalent even in asymptomatic patients on stable ART.

Homocysteine did not show a significant relationship with echocardiographic cardiovascular dysfunction, with a correlation coefficient of -0.036 and $p = 0.606$. Likewise, the association between homocysteine category and cardiovascular dysfunction was not significant, with Chi-square = 1.25 and $p = 0.264$, as shown in Table 7.

CD4 count also did not predict echocardiographic cardiovascular

Table 4: Showing association between CD4 categories and CAC score

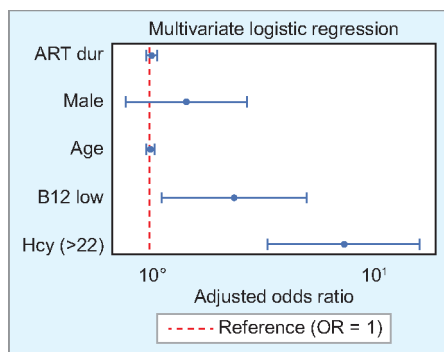
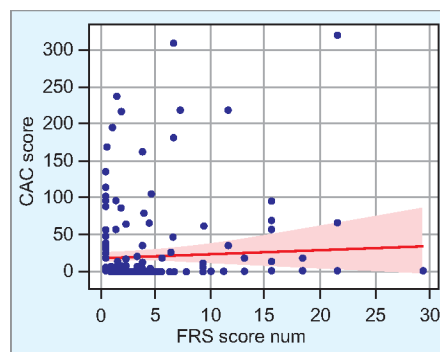
CD4 category	CAC = 0	CAC >0	Total	χ^2	p-value
<200	10 (71.4%)	4 (28.6%)	14	0.04	0.980
200–500	75 (68.8%)	34 (31.2%)	109		(not significant)
>500	61 (69.3%)	27 (30.7%)	88		

Table 5: Multivariate logistic regression model

Variable	OR	95% CI lower	95% CI upper	p-value
Homocysteine (>22 $\mu\text{mol/L}$)	7.26	3.34	15.80	<0.001
Vitamin B12 (<180 pg/mL)	2.36	1.12	4.98	0.023
Age (year)	1.02	0.99	1.05	0.248
Male vs female	1.45	0.78	2.71	0.243
ART duration (per year)	1.01	0.96	1.07	0.684

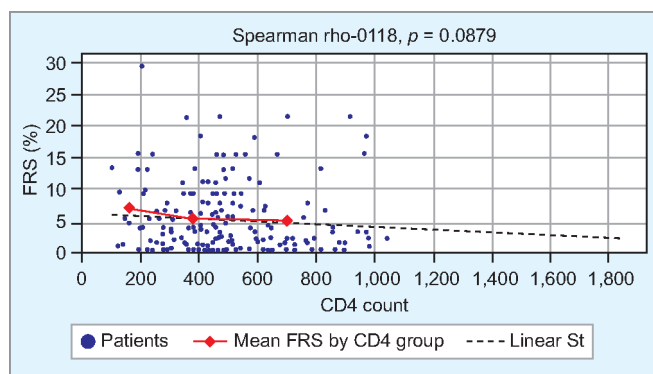
Table 6: Distribution of different 2D echocardiographic findings

Echo abnormality	Count	Percentage
Left ventricular hypertrophy	23	10.9%
LV diastolic dysfunction	20	9.5%
Reduced ejection fraction (EF <55%)	10	4.7%
Mild mitral regurgitation	9	4.3%
Mild tricuspid regurgitation	9	4.3%
LV systolic dysfunction	4	1.9%
Dilated cardiomyopathy	2	0.9%

**Fig. 5:** Multivariate logistic regression: Hyperhomocysteinemia independently predicts CAC positivity after adjustment for confounders. (OR = 7.26) Vitamin B12 deficiency: OR = 2.36 (weaker effect). Age, sex, and antiretroviral therapy (ART) duration: nonsignificant (ORs cluster near 1.0)**Fig. 6:** Scatter plot showing no linear correlation of CAC scores with Framingham Risk Score (FRS). Low FRS (<10) dominates all CAC groups (83–92%), with only scattered intermediate/high FRS cases**Fig. 7:** Scatter plot showing no linear correlation of serum homocysteine with FRS ($p = 1.21$)

dysfunction. The correlation between CD4 count and echo abnormalities was -0.003 with $p = 0.969$, and the categorical association between CD4 groups and echo abnormalities was not significant, with Chi-square = 1.89 and $p = 0.390$, as shown in Table 8.

These findings indicate that the strongest signal in the dataset relates specifically to calcific coronary atherosclerosis rather than to the broader composite of cardiac structural or functional abnormalities on echocardiography.

**Fig. 8:** Scatter plot showing an association between CD4 count and FRS, showing a weak negative trend with no significant correlation ($n = 211$). Spearman $\rho = -0.118$ ($p = 0.0879$) indicates that higher CD4 counts are associated with slightly lower FRS, but this falls short of statistical significance ($p > 0.05$)

Framingham Risk Score Performance

The study analyzed that most participants (81% of patients) remained in the low Framingham risk category despite detectable coronary calcium in a substantial subset. Visual and tabulated analyses in the study also showed no meaningful relationship between Framingham Risk Score and CAC burden, homocysteine levels, or CD4 count, as shown in Figures 6 to 8.

This discordance is consistent with prior HIV literature suggesting that conventional risk equations can miss clinically relevant subclinical vascular disease in PLHIV on ART.

Table 7: Association between homocysteine groups and Echo abnormalities

Hcy (>22)	Normal Echo	Abnormal Echo	p-value
≤22	61	30	$\chi^2 = 1.25$ $p = 0.264$
>22	90	30	(not statistically significant)

Table 8: Association of Echo abnormalities with CD4 count

CD4 category	CVD absent	CVD present	Total	χ^2	p-value
<200	3 (21.4%)	11 (78.6%)	14	1.89	0.390
200–500	44 (40.4%)	65 (59.6%)	109		(not significant)
>500	34 (38.6%)	54 (61.4%)	88		

DISCUSSION

The present cross-sectional analytical study systematically examined the correlations between CD4 count, serum homocysteine levels, and markers of cardiovascular disease—specifically, echocardiographic cardiovascular dysfunction and coronary artery calcification (CAC) quantified by Agatston scoring—in 211 PLWHA receiving a fixed-dose combination antiretroviral therapy (ART) regimen of TLD (tenofovir, lamivudine, dolutegravir).

Hyperhomocysteinemia ($\geq 22 \mu\text{mol/L}$) was strikingly prevalent in this study of PLHIV on ART, with a mean serum level of $27.3 \pm 13.5 \mu\text{mol/L}$ (median, $24.6 \mu\text{mol/L}$). This high burden underscores hyperhomocysteinemia as a major, potentially modifiable cardiovascular risk factor in this population, far exceeding general Indian population mean values (typically $11.46 \pm 2.56 \mu\text{mol/L}$ in males and $11.41 \pm 2.48 \mu\text{mol/L}$ in females)⁸ and aligning with HIV-specific metabolic disruptions.^{6,7}

Pearson correlation between hyperhomocysteinemia and CAC scoring confirmed a highly statistically significant moderate positive linear relationship ($r = 0.403$, $p = 0.001$), indicating a dose–response effect: higher hyperhomocysteinemia levels corresponded to progressively elevated CAC scores, suggesting causality. Multivariate logistic regression further established independence (OR = 7.26, 95% CI, 3.34–15.80, $p = 0.001$), with minimal B12 confounding (3.7% coefficient change; Hosmer-Lemeshow $p = 0.45$, c-statistic = 0.78). Kullo et al.⁹ demonstrated an Hcy-CAC association ($p = 0.01$) independent of age, sex, and smoking in 1,071 hypertensives, particularly at intermediate Framingham risk ($p = 0.003$), mirroring our study's low FRS (mean, 6.12). Sun et al. confirmed Hcy as an independent predictor of calcified plaques (OR = 1.668, $p = 0.037$) in asymptomatic CTA patients.¹⁰

The lack of association of current CD4 count with cardiovascular dysfunction and coronary atherosclerosis is important.

These null results challenge early HIV-CVD paradigms but align with ART-era shifts. Literature shows discordance: Mishra et al. linked CD4 <200/ μL to echo abnormalities (52% prevalence) in untreated/advanced HIV, but our suppressed study population (mean ART duration, 7.4 years) decouples immunity from outcomes.¹¹ Gupta et al.¹² found low CD4 predicted cIMT (mean, 332 cells/ μL) in younger PLWHA, yet post-ART recovery negated this. Mangili et al. (2010)¹³ tied nadir/low CD4 to mortality (HR *via* cIMT), but current CD4 failed, echoing our findings. Jachymek et al.¹⁴ found plaques in 26.5% of suppressed PLWHA despite high CD4. Mechanistically, pre-ART HIV depletes CD4 *via* gp120-mediated apoptosis/inflammation, driving monocyte activation, macrophage foam cells, and plaque. ART restores counts (>500 signals viral control), but residual risks persist *via* immune senescence (T-cell exhaustion), microbial translocation (sCD14), and ART dyslipidemia— independent of current CD4.¹⁵

The poor performance of Framingham Risk Score in this study, with null correlation, also has practical implications. Because traditional scores were developed outside HIV populations, they may underweight the contribution of chronic inflammation, ART-related dysmetabolism, and HIV-specific vascular risk, thereby classifying many patients as low risk despite imaging evidence of coronary atherosclerosis. Literature echoes this: Korten et al.¹⁶ found poor agreement across FRS/D:A:D/ASCVD in 527 PLWHA ($\kappa = 0.55$ –0.80), with 20–36% statin-eligible despite low FRS. Pereira et al.¹⁷ reclassified 43% *via* CAC (23.5% low-FRS had CAC >0). Raggi and Corwin¹⁸ critiqued FRS for ignoring HIV inflammation. Our low FRS yet 31% CAC/28.4% CVD prevalence matches: traditional factors (age/smoking/lipids) underperform versus HIV-specific factors (Hcy OR = 7.26).

The synergistic effect of hyperhomocysteinemia and vitamin B12 deficiency on subclinical coronary

atherosclerosis further suggests that nutritional and metabolic pathways influencing homocysteine may be clinically relevant in ART-treated HIV care, as mirrored in literature on B12-homocysteine interplay (Dinavahi and Falkner).¹⁹

An important nuance is that homocysteine was linked to CAC rather than to echocardiographic cardiovascular dysfunction. This may indicate that homocysteine is more useful as a marker of subclinical coronary plaque burden than of the broader spectrum of myocardial, valvular, or functional abnormalities encountered in HIV.

Limitations

Our study, being a cross-sectional study, failed to establish causality and temporal association of hyperhomocysteinemia with coronary atherosclerosis with certainty and could not assess progression and regression with interventions. The sample size being 211 and the study population being limited to a particular city reduced the generalizability to a wider population, especially different ethnic or regional groups within India. Third, a noninvasive cardiac CT imaging method was used for detecting coronary atherosclerosis instead of invasive coronary angiography, which only enabled identification of calcific plaques, while noncalcific plaque burden remained undiagnosed. Fourth, comparison with matched HIV-negative controls would have given a clearer picture of enhanced atherosclerosis in PLHIV.

CONCLUSION

Among treated adults with HIV in this tertiary-care cohort, serum homocysteine showed the clearest association with Agatston-based CAC burden, whereas current CD4 count and Framingham Risk Score performed poorly as markers of subclinical coronary atherosclerosis. These findings support

consideration of homocysteine, together with vitamin B12 assessment and selective CAC imaging, for more refined cardiovascular risk stratification in treated HIV populations.

RECOMMENDATIONS

Based on the study findings, hyperhomocysteinemia emerged as the principal modifiable predictor of coronary artery calcification in PLHIV receiving long-term antiretroviral therapy, whereas current CD4 count and FRS did not appear useful for cardiovascular risk stratification. Therefore, we recommend routine screening of serum homocysteine and vitamin B12 levels in all people living with HIV, irrespective of immunological status or conventional cardiovascular risk profile. Individuals with abnormal results should receive targeted B-vitamin supplementation, and statin therapy should be considered based on CAC scoring rather than CD4-based stratification. Cardiovascular assessment with 2D echocardiography should be used alongside metabolic evaluation to identify subclinical left ventricular hypertrophy and diastolic dysfunction at an early stage. In resource-limited settings such as India, this cost-effective approach, which prioritizes homocysteine assessment for initial triage, may support precision intervention and reduce cardiovascular morbidity by focusing on metabolic risk pathways rather than immunologic monitoring alone. Updated national HIV guidelines should incorporate HIV-specific metabolic biomarkers to improve cardiovascular prevention in the antiretroviral therapy era.

ETHICS APPROVAL

Proper Institutional Ethics Committee approval was obtained from Moti Lal Nehru Medical College, Prayagraj (Ethics Committee Registration No. ECR/922/inst/UP/RR-22 issued under New Drugs and Clinical Trial Rules, 2019), dated 21 March 2025.

CONSENT TO PARTICIPATE

All patients were informed about the study, and proper consent was obtained after explaining the advantages and risks to the patient.

DATA AVAILABILITY

Data transparency is maintained.

CODE AVAILABILITY (SOFTWARE APPLICATION OR CUSTOM CODE)

Microsoft Word.

AUTHOR CONTRIBUTIONS

AKC and SD chose the topic and planned the execution. All authors conducted the investigative part and collected data. AKC, SD, and PG wrote the main manuscript. AKC, SD, PG, AS, and SV prepared tables and figures and contributed to the discussion. All authors reviewed the manuscript. All authors contributed equally.

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Clinical Profile, Laboratory Findings, and Outcomes in Patients with *Cleistanthus collinus* Poisoning: A Prospective Observational Study



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Received: 05 May 2026; Accepted: 27 July 2026

ABSTRACT

Background: *Cleistanthus collinus* is a commonly encountered plant toxin used for deliberate self-harm in South India, leading to significant morbidity. Clinical manifestations can vary widely, with outcomes depending on early identification and aggressive supportive management.

Objectives: To evaluate the clinical profile, laboratory abnormalities, and outcomes in patients with *C. collinus* poisoning.

Materials and methods: This prospective observational study was conducted at Sri Venkateswara Medical College and its affiliated tertiary care teaching hospital in Tirupati, Andhra Pradesh, India. Sixty adult patients with confirmed *C. collinus* ingestion were included. Demographic data, clinical features, laboratory parameters, management, and outcomes were recorded and analyzed using standard statistical methods.

Results: The mean age of patients who consumed *C. collinus* poison was 29.6 ± 10.2 years, with a male predominance (65%). All the cases were due to intentional ingestion. Common clinical features included vomiting (20.0%), fatigue (15.0%), and giddiness (13.3%), while 33.3% were asymptomatic at presentation. Bradycardia (25.0%) was the most frequent cardiovascular abnormality. Laboratory findings revealed hypokalemia, metabolic acidosis, elevated transaminases, and renal impairment (serum creatinine >1.5 mg/dL in 20.0%). Intensive care was required in 13.3% of patients; 11.7% needed mechanical ventilation, and hemodialysis was done in 8.3% of patients. The mean hospital duration of stay was 4.2 ± 2.8 days. Overall survival was 98.3% with one mortality (1.7%). The nonsurvivor had older, comorbid illness, severe renal dysfunction, and required multiorgan support.

Conclusion: *C. collinus* poisoning demonstrates a variable clinical spectrum ranging from asymptomatic cases to severe multisystem organ dysfunction. Early presentation and prompt supportive management are associated with favorable outcomes. Older age, comorbidities, renal impairment, and requirement for intensive care may predict poor prognosis.

Keywords: *Cleistanthus collinus*, Hypokalemia, Metabolic acidosis, Outcomes, Plant poisoning, Renal dysfunction.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1699

INTRODUCTION

Burden of Poisoning (Global and Regional Trends)

Acute poisoning poses a public health challenge worldwide and particularly in low- and middle-income countries, causing significant morbidity and mortality.¹ Deliberate self-poisoning accounts for a large proportion of emergency department visits and is often associated with underlying socioeconomic and psychological stressors.² In South Asia, pesticide and plant-based toxins are commonly used for self-harm because of their easy availability.³ In India, poisoning continues to be a major cause of suicide-related mortality, especially in rural populations.^{4,5} Plant-derived toxins constitute a significant proportion of poisoning cases in various hospital-based studies across the country.^{5,6}

Cleistanthus collinus as a Regional Toxicological Entity

Cleistanthus collinus is a member of the Euphorbiaceae family, which is widely distributed in South India and is a well-recognized plant used for deliberate self-poisoning.^{7,8} It is known locally by vernacular names such as "Oduvanthalai" and "Vadisaaku," reflecting its easy accessibility and familiarity in rural communities (Fig. 1).⁸

The leaves of the *C. collinus* plant are typically consumed either as a ground paste or as an aqueous extract. Ingestion in the form of a decoction has been associated with more severe toxicity due to enhanced extraction and absorption of active toxic constituents.^{9,10}

Toxic Constituents and their Mechanism of Action

Cleistanthus collinus toxicity primarily stems from its lignan compounds such as

cleistanthin A, cleistanthin B, and diphyllin.¹¹ These compounds disrupt cellular metabolism by inhibiting thiol-dependent enzymes, decreasing intracellular glutathione, and impairing oxidative phosphorylation.^{12,13} Besides, they also inhibit renal tubular proton pumps (V-type H⁺ ATPase), leading to distal renal tubular acidosis and related electrolyte abnormalities, particularly hypokalemia.^{14,15} These metabolic alterations are the basis for many of the clinical features observed following ingestion.

Clinical Spectrum of *Cleistanthus collinus* Poisoning

Clinical manifestations of *C. collinus* poisoning are variable and can evolve over time. Early symptoms are usually nonspecific, with mostly gastrointestinal symptoms such as nausea, vomiting, and abdominal discomfort.^{8,16} With progression of toxicity, patients may develop metabolic acidosis, hypokalemia, neuromuscular weakness, cardiac arrhythmias, and respiratory failure.^{17,18}

In severe poisoning, complications such as acute kidney injury, acute respiratory distress syndrome, and multiorgan dysfunction may occur.^{19,20} Neurological manifestations such as altered sensorium and seizures have also been reported.²¹ Mortality rates ranging from 20% to 40% in patients with late presentation and severe complications were seen in previous studies on *C. collinus* poisoning.^{8,22}

Predictors of Outcome

Poor outcomes in *C. collinus* poisoning are associated with delayed presentation, severe metabolic acidosis, hypokalemia,

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How to cite this article: Kumar MK, Praveen K, Venkataramanaiah E, et al. Clinical Profile, Laboratory Findings, and Outcomes in Patients with *Cleistanthus collinus* Poisoning: A Prospective Observational Study. J Assoc Physicians India 2026;74(10):30–34.



Figure 1: *Cleistanthus collinus* plant (photograph taken by the authors)

respiratory failure, and circulatory shock.^{17,23,24} Early recognition and timely supportive care with correction of electrolyte and acid-base disturbances are critical in improving outcomes.^{25,26}

Variability in Clinical Outcomes

There is considerable variation in the clinical profile and outcomes reported across studies. While earlier reports describe severe toxicity with higher mortality, recent studies indicate improving survival rates reflecting advances in supportive and critical care.^{7,17}

However, much of the available literature is retrospective or focused predominantly on critically ill patients and therefore may not adequately represent the full spectrum of disease.²⁷

Rationale and Objectives

In view of the variability in reported outcomes and limitations of existing data, there is a need for contemporary prospective studies covering the full spectrum of disease severity. Most previous studies have focused on intensive care populations, which may lead to an overestimation of mortality.

In this study, patients admitted to both general wards and intensive care units are included providing a more comprehensive clinical perspective. This approach allows evaluation of the clinical profile, laboratory findings, and outcomes in patients with *C. collinus* poisoning at a tertiary care teaching hospital in South India with the aim of identifying patterns that may reflect evolving trends in disease severity and prognosis.

MATERIALS AND METHODS

Study Design and Institutional Setting

This study was designed as a prospective observational study conducted from the year

2025 to 2026 at Sri Venkateswara Medical College and its affiliated tertiary care teaching hospital in Tirupati, Andhra Pradesh, India. The institution serves as a major referral center catering to urban and rural populations, providing an appropriate setting to study poisoning cases with varied clinical presentations.

Study Population

All patients presenting with a history of *C. collinus* poisoning during the study period were screened for eligibility.

Inclusion Criteria

- Patients aged ≥ 18 years.
- Confirmed history of *C. collinus* ingestion based on:

- Patient or attendant history.
- Identification of plant material.
- Patients who provided informed consent.

Exclusion Criteria

- Patients with co-ingestion of other toxic substances.
- Patients discharged against medical advice before adequate evaluation.
- Sample Size

This was a prospective observational study. All patients with *C. collinus* poisoning who met inclusion criteria during the study period were enrolled. No formal sample size calculation was performed, as the study was exploratory and descriptive. The final sample of 60 patients reflects all eligible cases presenting to our center during the study duration. The modest sample size from a single center limits the precision of estimates for rare outcomes and may restrict generalizability. Larger multicenter studies are needed.

Data Collection

Data were collected prospectively using a structured proforma.

Demographic Data

- Age.
- Gender.
- Place of residence (rural or urban).

Poisoning Details

- Time interval between ingestion and hospital presentation.
- Mode of ingestion (raw leaves or decoction).
- Estimated quantity consumed.

Clinical Parameters

- Vital signs at presentation (heart rate, blood pressure, respiratory rate, and oxygen saturation).
- Presenting symptoms (vomiting, breathlessness, weakness, altered sensorium).

- Clinical signs (hypotension, respiratory distress, and neurological status).

Laboratory Investigations

The following laboratory tests were performed as per standard hospital protocols using calibrated equipment:

- Complete blood count (CBC).
- Liver function tests (LFT).
- Renal function tests (RFT).
- Serum electrolytes (sodium and potassium).
- Arterial blood gas (ABG) analysis.
- Serum lactate.

Outcomes

Primary Outcome

In-hospital mortality.

Secondary Outcomes

- Duration of hospital stay.
- Need for ICU admission.
- Need for mechanical ventilation.
- Occurrence of complications, including metabolic acidosis, hypokalemia, acute kidney injury, and respiratory failure.

Management Protocol

All patients received standard supportive care according to institutional protocols, which included gastric lavage, intravenous fluids, electrolyte correction, acid-base correction, and ventilatory support as required. APACHE II score was used to assess the severity of illness. No specific antidote was used, as none is currently available for *C. collinus* poisoning.

Data Analysis

Data were entered into a Microsoft Excel spreadsheet and analyzed using descriptive statistics only. Continuous variables are presented as mean $\pm$ standard deviation (SD), while categorical variables are expressed as frequencies and percentages. Since there was only one death in the study, no inferential statistical tests or *p*-values were applied. All tables were generated after double-checking the raw data for accuracy. The analyses were also cross-verified using Python (pandas library) for additional precision.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of Sri Venkateswara Medical College, Tirupati (Approval No: 315/SRC/2024, dated 09-12-2024). Written informed consent was obtained from all participants or their legally authorized representatives. Patient confidentiality was strictly maintained by anonymizing the collected data.

Table 1: Demographic profile of patients with *Cleistanthus collinus* poisoning (N = 60)

Characteristic	Value
Age (years), mean $\pm$ SD	29.6 $\pm$ 10.2
Age range (years)	17–60
Gender, n (%)	
Male	39 (65.0)
Female	21 (35.0)
Occupation, n (%)	
Laborer	28 (46.7)
Others	32 (53.3)
Past medical history, n (%)	
No comorbidities	52 (86.7)
Hypertension	4 (6.7)
Type 2 diabetes mellitus	3 (5.0)
Alcohol use, n (%)	42 (70.0)
Smoking, n (%)	8 (13.3)

SD, standard deviation

Table 2: Clinical features and severity markers (N = 60)

Parameter	n (%)
Mode of poisoning	
Ingestion	60 (100.0)
Presenting complaints	
Fatigue/weakness	9 (15.0)
Vomiting/nausea	12 (20.0)
Giddiness/palpitations	8 (13.3)
Asymptomatic (nil complaints)	20 (33.3)
Cardiovascular findings	
Normal	39 (65.0)
Bradycardia	15 (25.0)
Tachycardia/arrhythmia	7 (11.7)
Altered sensorium	12 (20.0)
ICU admission	8 (13.3)
Requirement for mechanical ventilation	7 (11.7)
Requirement for hemodialysis	5 (8.3)
Requirement for vasopressor support	4 (6.7)
Seizures	2 (3.3)

ICU, intensive care unit

RESULTS

Demographic and Baseline Characteristics

Sixty patients with *C. collinus* poisoning were enrolled. The mean age was 29.6 $\pm$ 10.2 years (range: 17–60 years), and 39 (65.0%) were male. Twenty-eight patients (46.7%) were laborers. The majority (52, 86.7%) had no comorbidities. A history of alcohol consumption was present in 42 patients (70.0%), and smoking in 8 (13.3%) (Table 1).

Table 3: Detailed laboratory parameters

Parameter	Mean $\pm$ SD	Abnormal values/remarks
Hemoglobin (gm/dL)	12.4 $\pm$ 1.8	—
WBC count ($\times 10^3/\mu\text{L}$)	8.5 $\pm$ 3.2	Leukocytosis noted in severe cases
Serum creatinine (mg/dL)	1.45 $\pm$ 1.12	>1.5 mg/dL in 12 patients (20.0%)
AST (U/L)	94 $\pm$ 140	Marked elevation (>300 U/L) in severe cases
ALT (U/L)	92 $\pm$ 128	—
ALP (U/L)	78 $\pm$ 52	Mild elevation in some patients
Serum potassium (mEq/L)	3.69 $\pm$ 0.68	Hypokalemia was common
Arterial pH	7.32 $\pm$ 0.12	Metabolic acidosis frequent
Serum lactate (mmol/L)	1.8 $\pm$ 1.4	Elevated in critically ill patients
Anion gap	12.5 $\pm$ 8.5	Elevated in some cases

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation; WBC, white blood cell

Table 4: Management, interventions, and outcomes (N = 60)

Parameter	Value
ICU admission	8 (13.3%)
Mechanical ventilation	7 (11.7%)
Hemodialysis	5 (8.3%)
Vasopressor support	4 (6.7%)
Hospital stay (days), mean $\pm$ SD	4.2 $\pm$ 2.8
Outcome	
Survived	59 (98.3%)
Died	1 (1.7%)

ICU, intensive care unit; SD, standard deviation

Clinical Presentation

The estimated quantity consumed ranged from 3–4 to 15–20 leaves. Most patients presented to the hospital within 8–12 hours of ingestion. The most common presenting complaints were fatigue or weakness, vomiting, nausea, giddiness, and palpitations. One-third of the patients (33.3%) remained asymptomatic at the time of admission. Cardiovascular abnormalities were prominent. Bradycardia was the most common finding, while respiratory involvement and altered sensorium were noted mainly in severe cases (Table 2).

Laboratory Findings

Detailed laboratory parameters on admission are presented in Table 3.

Laboratory abnormalities were consistent with the known toxic effects of *C. collinus* on the cardiac, renal and metabolic systems. Common findings included mild to moderate elevations in hepatic transaminases, varying degrees of renal impairment, hypokalemia and metabolic acidosis with elevated lactate in severe cases.

Management and Outcomes

Patients were managed with supportive care as the mainstay of treatment. This included close

monitoring, intravenous fluids, correction of electrolyte imbalances and acidosis, and organ systems support whenever necessary. Only a minority required intensive care interventions such as mechanical ventilation or vasopressors.

The overall outcome was favorable. The mean hospital stay was 4.2 $\pm$ 2.8 days. Fifty-nine patients (98.3%) recovered completely and were discharged. There was only one death (1.7%) which occurred in an elderly female patient with multiple comorbidities who had ingested a large quantity of leaves and developed severe acute kidney injury along with respiratory failure (Table 4).

Comparison of Survivor and Nonsurvivor

Comparison between the single nonsurvivor and the survivors revealed some notable differences. The nonsurvivor was an older patient (49 years) with comorbidities (type 2 diabetes mellitus) with significantly higher serum creatinine (4.6 mg/dL) and required intensive care with multiorgan support. In contrast, survivors had a mean age of approximately 29 years, fewer comorbidities, lower creatinine levels, and only 11–13% needed ICU or organ support.

These findings suggest that older age, presence of comorbidities, severe renal impairment, and need for multiorgan support were associated with poor outcome in this study.

DISCUSSION

Cleistanthus collinus poisoning is an important cause of plant-based toxic exposure in South India, particularly among young adults with intentional self-harm.⁷⁸ The present prospective observational study provides a contemporary clinical and laboratory profile of affected patients and offers insights into factors associated with disease severity and outcomes.

In this study, the majority of patients were young, with a mean age of 29.6 years, and there was a clear male predominance (65%). This demographic pattern is consistent with prior Indian studies where poisoning is more frequently observed in economically productive age groups and is often linked to psychosocial stressors.^{5,6} The high proportion of laborers in our cohort further supports the association between socioeconomic vulnerability and the risk of toxic ingestion. A notable finding was the high prevalence of alcohol use (70%), which may act as a facilitating factor for impulsive self-harm, as also suggested in population-based studies on poisoning and suicide in India.⁵

All cases in the present study were due to intentional ingestion, with most patients presenting within 8–12 hours. Early presentation likely contributed to the favorable outcomes observed. Similar observations have been reported in recent studies highlighting improved outcomes with early hospital presentation and timely supportive care.²⁸ Notably, one-third of patients were asymptomatic at admission, underscoring the unpredictable clinical course and the importance of close monitoring even in apparently stable individuals.

The clinical spectrum observed was broad, ranging from mild gastrointestinal symptoms to significant cardiovascular and neurological involvement. Bradycardia was the most common cardiovascular abnormality, while tachyarrhythmias were less frequent. These findings are consistent with the known cardiotoxic effects of *C. collinus*, particularly its impact on cardiac conduction.⁸ Neurological manifestations such as altered sensorium and seizures, as well as respiratory compromise, were predominantly seen in patients with severe poisoning, indicating progression to systemic toxicity.^{11,18}

Laboratory abnormalities reflected multiorgan involvement. Hypokalemia and metabolic acidosis were common, with distal renal tubular dysfunction described in both experimental and clinical studies.^{14,17} Elevated transaminases suggested hepatic involvement, although this was generally mild to moderate. Renal impairment was observed in 20% of patients, emerging as an important marker of severity, in line with previous studies on poisoning-related acute kidney injury.²⁰ Elevated lactate levels in critically ill patients further indicated underlying tissue hypoxia and metabolic derangement.

Management in this study was predominantly supportive, as no specific antidote exists for *C. collinus* poisoning.²² The proportion of patients requiring intensive care (13.3%), mechanical ventilation (11.7%) and

hemodialysis (8.3%) was relatively low compared to earlier reports. The overall mortality rate was 1.7%, which is substantially lower than the 5–20% reported in previous studies.^{7,11,29} This difference may be attributed to earlier presentation, improved referral patterns, and advances in supportive and critical care.

Although limited by the low number of adverse outcomes, comparison between survivors and the single nonsurvivor provides clinically relevant insights. The nonsurvivor was older, had comorbid illness, and demonstrated significant renal dysfunction requiring multiorgan support. These findings are consistent with existing literature identifying older age, comorbidities, delayed presentation, and severity of organ dysfunction as predictors of poor outcome in acute poisoning.^{18,23}

Importantly, this study demonstrates lower mortality compared to earlier reports, likely reflecting improvements in early recognition and supportive care. Unlike previous studies that predominantly included critically ill patients, the present study encompasses the full clinical spectrum, including mild and asymptomatic cases, thereby providing a more representative assessment of disease burden and outcomes in current clinical practice.²⁹

The findings of this study reinforce the importance of early recognition and close monitoring in all cases of *C. collinus* poisoning, including those who are initially asymptomatic. Particular attention should be directed toward renal function, electrolyte disturbances, and acid–base status as these parameters correlate with disease severity.^{24,25}

This study has certain limitations. Quantification of ingested toxin was based on patient history and may be subject to recall bias. The sample size was modest, and being a single-center study, the findings may limit generalizability. Additionally, inferential statistical analysis was not feasible due to the low number of adverse outcomes. Despite these limitations, the prospective design and inclusion of consecutive patients strengthen the validity of the findings and provide a realistic representation of current clinical practice.

DECLARATIONS

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Sri Venkateswara Medical College, Tirupati (Approval No: 315/SRC/2024, dated 09 December 2024).

Informed Consent

Written informed consent was obtained from all participants or their legally authorized representatives prior to inclusion in the study.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Source of Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's Contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by the authors. The first draft of the manuscript was written by Dr K Praveen, and all authors reviewed, revised, and approved the final manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

Image Statement

The image used in Figure 1 is an original photograph taken by the authors and has not been previously published.

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C-reactive Protein–Albumin Ratio: New Marker in Mortality Risk and Disease Severity in Pulmonary Thromboembolism



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Received: 24 April 2026; Accepted: 31 July 2026

ABSTRACT

Background: Pulmonary thromboembolism (PTE), with increasing incidence and decreasing mortality rate, is still a common cause of cardiovascular mortality today. The aim of this study was to evaluate the clinical relationship between disease severity and mortality risk and C-reactive protein (CRP)–albumin ratio (CAR) in patients admitted to the hospital with acute PTE.

Materials and methods: In this single-center, retrospective study, 215 patients diagnosed with PTE between 2012 and 2022 were included. All patients were divided into four groups according to mortality risk.

Results: A total of 47 patients were in the low-risk group, 91 patients were in the intermediate-low-risk group, 59 patients were in the intermediate-high-risk group, and 18 patients were in the high-risk group. There was a statistically significant difference between mortality risk groups in terms of CAR and other biochemical parameters ($p < 0.001$). A positive correlation between CAR and mortality risk, troponin, D-dimer, pro-brain natriuretic peptide (pro-BNP), simplified Pulmonary Embolism Severity Index (sPESI), and systolic pulmonary artery blood pressure (sPAB) parameters ($r_s = 0.440, p < 0.001$; $r_s = 0.277, p < 0.001$; $r_s = 0.215, p = 0.001$; $r_s = 0.236, p = 0.001$; $r_s = 0.318, p < 0.001$; $r_s = 0.201, p = 0.005$, respectively), and a negative correlation with tricuspid annular plane systolic excursion (TAPSE) ($r_s = -0.167, p < 0.001$) were found. In the receiver operating characteristic (ROC) analysis, CAR demonstrated a high discriminative ability in predicting high mortality risk, with an area under the curve (AUC) of 0.928.

Conclusion: This study shows that CAR may have clinical importance in PTE patients, helping to predict prognosis and guide treatment strategies. Its simplicity and cost-effectiveness may offer advantages in practice. However, further studies are needed to validate CAR in larger populations.

Keywords: C-reactive protein–albumin ratio, Inflammatory markers, Mortality risk, Prognostic biomarker, Pulmonary thromboembolism.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1707

INTRODUCTION

Pulmonary thromboembolism (PTE) is still a common cause of cardiovascular mortality today, with increasing incidence and decreasing mortality.¹ It usually occurs as a complication of deep vein thrombosis (DVT) and is one of the most common acute cardiovascular diseases, accounting for approximately 5–10% of mortality in hospitalized patients.² The diagnosis of PTE begins with clinical suspicion; its symptoms are nonspecific and can be detected in a wide range of clinical presentations. Diagnosis can be made with a detailed evaluation that includes a combination of clinical symptoms, plasma D-dimer measurements, and imaging tests. Determining the mortality risk is very important for predicting the course of the disease and making treatment decisions. It is evaluated by combining the data on the hemodynamic status of the patient, the Pulmonary Embolism Severity Index (PESI) or Simplified PESI (sPESI) score, the involvement of the right heart, and the cardiac biomarker troponin value. Mortality risk is classified as high (massive), moderate (submassive), and

low (nonmassive). Intermediate-high-risk patients have right ventricular dysfunction and elevated troponin levels but intact hemodynamics and require close monitoring as their clinical condition may deteriorate at any time. In low-mortality-risk PTE, systemic blood pressure and right ventricular function are normal.¹

Serum biomarkers may also help determine the prognosis of the disease because inflammation accompanies thrombi. For this reason, as well as the algorithms mentioned above, simple and easily accessible laboratory methods are also practical. It is considered that acute-phase reactants may provide information about the severity of the disease in the early stages of embolism.

As a new parameter, C-reactive protein (CRP)–albumin ratio (CAR) provides better results compared with the use of these markers alone and is considered a marker associated with poor prognosis and mortality in various diseases.³ A retrospective study showed that CAR is an independent prognostic factor of PTE ($p = 0.03$).⁴ In the present study, our purpose was to

evaluate the clinical relationship between CAR and disease severity and mortality risk in patients with acute PTE. Also, we aimed to investigate whether CAR has prognostic value in determining the indication for escalation therapy (thrombolytic therapy) when hemodynamic deterioration occurs in some intermediate-high-risk patients. Furthermore, we investigated the relationship between CAR and troponin, D-dimer, pro-BNP, systolic pulmonary artery pressure (sPAP), and tricuspid annular plane systolic excursion (TAPSE).

PARTICIPANTS AND METHODS

This single-center, retrospective study was conducted in line with the principles of the Declaration of Helsinki after approval by the Gazi University Ethics Committee, numbered 2022-1465, and received on 30th December 2022. The study included 215 PTE patients who were followed up in our clinic between 1st December 2012, and 30th December 2022. The flowchart of the study is summarized in Figure 1. Patients who had inaccessible or missing data, concurrent acute coronary syndrome, hematological diseases that may lead to deterioration in laboratory parameters, terminal cancer, symptoms of acute infection, and pregnant women were excluded from the study. Demographic data of the patients (age, sex), smoking history (never smoked/quit/active smoker), concomitant diseases [diabetes, hypertension, heart diseases, chronic obstructive pulmonary disease (COPD), cancer, chronic renal failure, etc.], and PTE risk factors (immobilization, cancer, surgical history, etc.) were recorded. The

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How to cite this article: Orujlu A, Mammadova A, Yalçinkaya Z, et al. C-reactive Protein–Albumin Ratio: New Marker in Mortality Risk and Disease Severity in Pulmonary Thromboembolism. *J Assoc Physicians India* 2026;74(10):36–40.

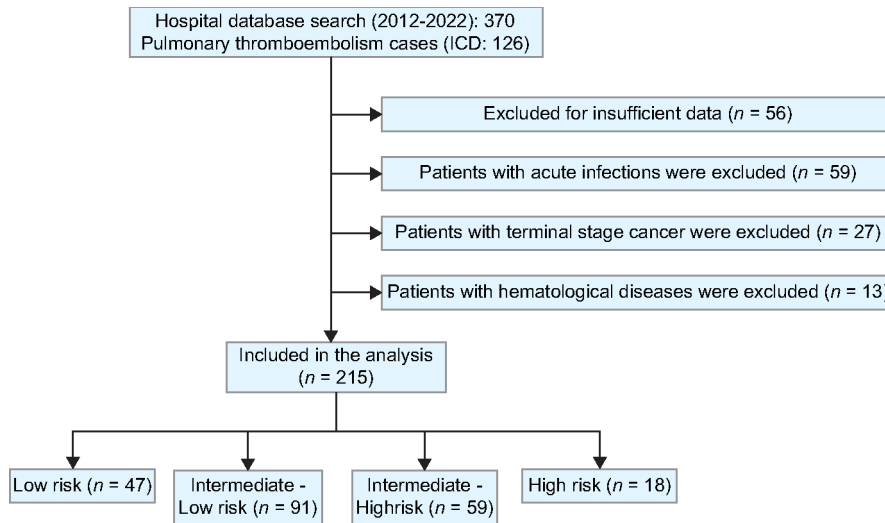


Fig. 1: Flowchart

sPESI score for PTE, hemogram, CRP, albumin, D-dimer, troponin, pro-BNP, CAR, pulmonary computed tomography angiography results, treatment status [thrombolytic therapy, heparin, direct oral anticoagulant (DOAC), warfarin], and echocardiography results (pulmonary artery pressure, right heart enlargement, TAPSE) were also recorded in the forms. All patients were divided into four groups based on mortality risk as low risk, intermediate-low risk, intermediate-high risk, and high risk. Mortality risk was calculated based on the hemodynamic status of the patients, sPESI score, cardiac troponin values, and echocardiography results, as recommended by current guidelines.¹ The sPESI was calculated based on the clinical parameters of the patients at the time of admission. If the patient had multiple records, the first laboratory parameter at the time of admission or suspicion of PTE was recorded. The CAR was obtained by calculating the ratio between these two biomarkers.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 23. Descriptive statistics were given as median (minimum and maximum values) and mean $\pm$ standard deviation for quantitative variables. Qualitative variables were expressed as frequency and percentage. To determine the normality of continuous variables, the Shapiro-Wilk test, histogram, and box plot results were evaluated. Since the normal distribution assumption was not met, the difference between the distributions of the two independent groups was compared with the Mann-Whitney *U* test. The Kruskal-Wallis analysis of variance was used because the normal distribution and variance homogeneity assumptions were not met for more than two independent groups.

In case of differences between the groups, pairwise comparisons were examined with the Dunn-Bonferroni test. For categorical variables, the difference between the groups was examined with the Chi-squared test or Fisher's exact test (or the extended version of this test, the Fisher-Freeman-Halton test). The relationship between two quantitative variables was examined with the Spearman correlation coefficient because the normal distribution assumption was not met. Receiver operating characteristic (ROC) analysis was used to examine the discrimination of the CAR between patients with acute PTE diagnosed with intermediate-high and high mortality risk, and the area under the curve (AUC) was evaluated. Also, the cutoff point to distinguish these two groups was determined by the Youden index. The significance level was set at 0.05 in all tests.

RESULTS

A total of 215 patients [124 (57.7%) female] were included in the study. The mean age of the patients was 62.9 ± 15.5 years. Demographic data and laboratory parameters of the patients are given in Table 1. A total of 47 patients (21.8%) had an sPESI score of 0. When the mortality risk group was examined, 18 (8.4%) patients were in the high-risk group, 59 (27.4%) were in the intermediate-high-risk group, 91 (42.3%) were in the intermediate-low-risk group, and 47 (21.9%) were in the low-risk group. No significant difference was detected between the mortality risk groups in terms of sex and age distribution ($p > 0.05$) (Table 2). The median CRP and CAR values of the whole group were 36 (2.68–198) and 11.0 (0.57–83.7), respectively. For mortality risk, statistically significant differences were found in CRP values between the low- and

Table 1: Demographic and laboratory characteristics of acute PTE patients

	Total number of patients (n = 215) n (%), med (min–max)
Comorbidities	
Hypertension	81 (41.1%)
Diabetes mellitus	43 (20.0%)
Coronary artery disease	19 (8.8%)
Congestive heart failure	27 (12.6%)
Chronic obstructive pulmonary disease	26 (12.1%)
Cerebrovascular accident	11 (5.1%)
Chronic renal failure	12 (5.6%)
Risk factors for PTE	
Deep vein thrombosis	44 (20.5%)
Malignancy	65 (30.2%)
Long term travel (>6 hours)	22 (10.2%)
Immobilization	58 (27.0%)
Presence of thrombophilia	10 (4.7%)
Bed rest (>3 days in the last 4 weeks)	51 (23.7%)
Estrogen use	11 (5.1%)
Operation (last 12 weeks)	45 (20.9%)
Trauma (last 12 weeks)	11 (5.1%)
Biochemical parameters of PTE patients	
CRP (mg/L)	36 (2.68–198)
Albumin (gm/dL)	3.67 (1.38–4.85)
Troponin T (ng/L)	16 (1–428)
D-dimer (ng/mL)	2.43 (0.47–35.2)
Pro-BNP (pg/mL)	385 (4.52–12500)
CAR	11.0 (0.57–83.7)

CAR, CRP-albumin ratio; PTE, pulmonary thromboembolism

intermediate-low-risk ($p < 0.001$), low- and intermediate-high-risk ($p < 0.001$), low- and high-risk ($p < 0.001$), and intermediate-low- and high-risk ($p = 0.018$) groups, but no significant difference was observed between the intermediate-high- and high-risk groups ($p > 0.05$). Similarly, for CAR, significant differences were found between the low-risk and intermediate-low-risk ($p < 0.001$), low-risk and intermediate-high-risk ($p < 0.001$), low-risk and high-risk ($p = 0.001$), intermediate-low-risk and intermediate-high-risk ($p < 0.001$), and intermediate-low-risk and high-risk ($p = 0.008$) groups, but no significant difference was detected between the intermediate-high- and high-risk groups ($p > 0.05$) (Table 3 and Fig. 2).

The Spearman correlation analysis revealed a moderate, positive, and significant association between CAR and mortality risk ($r_s = 0.440$, $p < 0.001$). A low-level, positive,

significant association was detected between CAR and troponin ($r_s = 0.277, p < 0.001$), pro-BNP ($r_s = 0.236, p = 0.001$), D-dimer ($r_s = 0.215, p = 0.001$), sPESI ($r_s = 0.318, p < 0.001$), and sPAB ($r_s = 0.201, p = 0.005$). A negative, significant correlation was detected between CAR and TAPSE ($r_s = -0.167, p < 0.001$).

When the patients' CTPAs were reviewed, 85 (39.5%) patients were found to have a pulmonary infarction area. The median CRP and CAR values of patients who had infarction were found to be significantly higher than

those of patients who did not have infarction (CRP: 57.14 vs 28.1, $p = 0.004$; CAR: 16.8 vs 7.21, $p = 0.003$).

ROC analysis was performed to examine the role of CAR in distinguishing low- and high-mortality-risk patients. The threshold value was found to be 8.7, and according to this value, sensitivity was 89.2% and specificity was 83.6%. The area under the ROC curve was calculated as 0.928 (0.880–0.977), and this value was statistically significant ($p = 0.001$) (Fig. 3).

Among the 59 patients who had intermediate-high mortality risk, the mean CAR value in patients requiring escalation therapy (thrombolytic therapy) ($n = 6$) was 12.1 ± 9.01 . The rest of the intermediate-high-risk mortality patients (who did not require escalation therapy) had a mean CAR value of 20.4 ± 13.6 . It was detected that CAR did not have a distinctive role in predicting the need for thrombolytic therapy in intermediate-high-risk mortality patients ($p > 0.05$).

DISCUSSION

Acute PTE is the third most common cause of cardiovascular mortality due to its increasing incidence.⁵ In cases with high mortality and morbidity, it is important to make a rapid diagnosis and start treatment at an early stage due to the possibility of early reembolemism. For this reason, risk stratification in patients diagnosed with PTE is essential both to predict the prognosis of the disease and to guide treatment decisions. Despite current mortality risk assessments, simple and easily accessible methods are still needed to predict the prognosis of the disease.⁶ In the present study, the role of CAR was investigated in

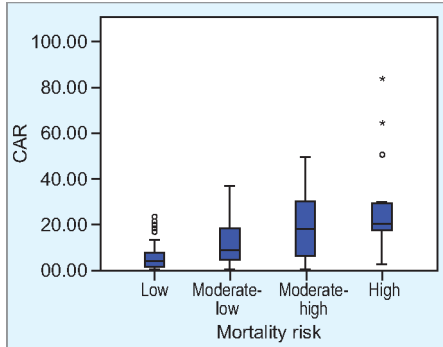


Fig. 2: Distribution of CAR values in different mortality risk groups

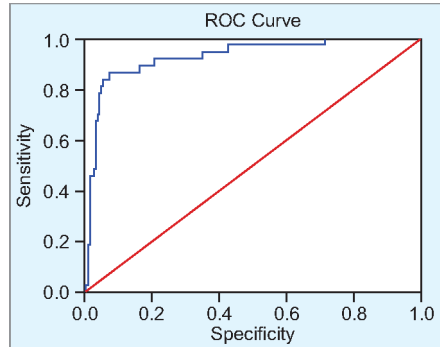


Fig. 3: ROC curve of CAR to distinguish low- and high-risk patients

Table 2: Demographic and disease-related characteristics of patients who had acute PTE according to mortality groups

	Low risk <i>n</i> = 47	Moderate-low risk <i>n</i> = 91	Moderate-high risk <i>n</i> = 59	High risk <i>n</i> = 18
Age (mean $\pm$ SD)	54.8 $\pm$ 19.1	63.6 $\pm$ 13.7	69.4 $\pm$ 12.3	59.3 $\pm$ 12.9
Sex (<i>n</i>) (%)				
Male	24 (51.1%)	37 (40.7%)	23 (39%)	7 (38.9%)
Female	23 (48.9%)	54 (59.3%)	36 (61%)	11 (61.1%)
Smoking status				
Active smoker	25 (53.2%)	37 (40.7%)	15 (25.4%)	4 (22.2%)
Never smoked	22 (46.8%)	54 (59.3%)	44 (74.6%)	14 (77.8%)
Hospitalization status				
Inpatient treatment	40 (85.1%)	86 (94.5%)	59 (100%)	18 (100%)
Outpatient treatment	7 (14.9%)	5 (5.5%)	0	0
History of PTE	4 (8.5%)	9 (9.9%)	10 (16.9%)	0

PTE, pulmonary thromboembolism

Table 3: Laboratory and echocardiographic values among mortality risk groups

	Low risk Med (min–max)	Moderate risk Med (min–max)		High risk Med (min–max)	<i>p</i> -value
		Low risk	High risk		
CRP	18 (3–106)	34 (2.68–114)	60 (3–134)	68.9 (22–198)	$p < 0.001$
Albumin	3.9 (1.38–4.85)	3.7 (2.4–4.7)	3.5 (2.8–4.5)	3.08 (1.85–4)	$p < 0.001$
CAR	4.44 (0.57–23.8)	11.5 (0.6–36.8)	16.47 (0.91–49.44)	21.6 (10.33–83.78)	$p < 0.001$
D-dimer	1.26 (0.6–9.12)	2.43 (0.47–13.9)	4.41 (0.55–20)	3.51 (1.2–35.2)	$p < 0.001$
Pro-BNP	142 (9–2481)	242 (4.52–7877)	1752 (10–12500)	2490 (66–10000)	$p < 0.001$
Troponin	8.0 (1.0–54)	11 (1.0–262)	45 (1.0–428)	147 (34–288)	$p < 0.001$
PAP (mm Hg)	25 (20–29)	28 (20–58)	54 (30–79)	60 (45–91)	$p < 0.001$
TAPSE (mm)	22 (20–34)	22 (14–27)	17 (10–23)	17 (9–24)	$p < 0.001$

CAR, CRP–albumin ratio; CRP, C-reactive protein; ECHO, echocardiography; PAP, pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion

predicting mortality risk and determining disease severity in PTE patients.

We found the infarction frequency to be 39.5%, and this result is parallel to the results in the literature. In another study in the literature, the pulmonary infarction rate was reported as 29.2% in 154 patients diagnosed with PTE.⁷ In a previous review, it was reported that pulmonary infarction was seen in 9–36% of patients in various studies performed with the CTPA method.⁸ In a single-center, retrospective study conducted by Yuan et al. in China, it was found that 16.58% of 386 PTE patients had infarction, and CRP >10 mg/L was detected in 65% of patients who had infarction. This result was significantly higher than that in patients who did not have infarction ($p < 0.001$).⁹ Also, in a different study, CRP levels of PTE patients who had infarction were found to be significantly higher compared with those of patients who did not have infarction ($p < 0.0003$).¹⁰ Although the relationship between CRP and pulmonary infarction was evaluated in detail in the studies mentioned above, to the best of our knowledge, the relationship between CAR and infarction has not yet been examined in the literature. In our study, we observed that CRP and CAR values of patients who had infarction were significantly higher compared with those of patients who did not have infarction ($p = 0.004$, $p = 0.003$).

The acute-phase response includes a series of inflammatory processes that occur in the body as a response to infection, tissue damage, and immunological disorders. CRP is a positive acute-phase reactant synthesized by the liver, and its blood level is elevated within hours as a response to inflammation and infection. In particular, elevated levels of CRP were associated with a series of diseases such as infections, tissue damage, inflammatory conditions such as psoriatic arthritis, VTE, and cardiovascular events.^{11,12} CRP increases tissue factor synthesis, activates homeostasis, and can affect fibrinolysis, which is considered to be one of the mechanisms in the development of VTE.¹³ Studies were conducted for many years showing the relationships between CRP and VTE, and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort showed that there was a positive relationship between CRP and VTE and that the risk of VTE increased with high CRP.¹⁴ In the study conducted by Elshahaat et al., patients were divided into low-, moderate-, and high-mortality-risk groups, and a statistically significant increase was observed among all groups in terms of CRP.⁶ Similarly, another study found significant differences in CRP levels in the same risk groups.¹⁵ We found that there was

a statistically significant difference between mortality risk groups in terms of CRP, similar to the literature. When mortality subgroups were evaluated, only the CRP values of the intermediate-high- and high-risk groups were similar. This can be interpreted as indicating that patients in the intermediate-high-risk group must be closely monitored and that these patients may develop a high mortality risk at any time.

As a negative acute-phase reactant, serum albumin decreases as a response to inflammation.¹⁶ The REGARDS cohort also showed that low albumin levels increase the risk of VTE.¹⁴ In the study conducted by Sağcan et al., serum albumin levels in patients who had high-mortality risk were found to be significantly lower than those in patients who had low-mortality risk ($p = 0.031$).¹⁵ Here, we showed that there was a significant difference between the high- and intermediate-high-risk groups and the low-risk group in terms of albumin, similar to the literature.

In a retrospective study that examined the prognostic value of CAR in acute PTE, 186 patients were examined, and it was reported that although it had lower sensitivity than the PESI score in predicting mortality risk, it had similar specificity.¹⁷ In a retrospective study by Hocalı and Tanrıverdi, CAR was an independent predictor in PTE patients with high-mortality risk,¹⁸ and in another study, CAR was shown to serve as a prognostic marker in predicting all-cause mortality in PTE patients both at 30 days and in the late period.¹⁹ It is a strong biomarker in determining prognosis in different types of cancer, such as esophageal cancer and upper gastrointestinal (GI) cancers, and a high CAR value is associated with poor prognosis in gastric cancer patients and can predict complications after gastrectomy.^{20,21}

The results of the present study showed that CAR is significantly different among mortality risk groups and that there was a moderate positive relationship between CAR and mortality risk in the correlation analysis. In line with the literature, it was shown that as CAR increases, the mortality risk increases; for this reason, CAR is a prognostic marker that can be obtained easily and quickly in determining mortality risk and does not require any additional cost.

In the study conducted by Özcan et al., it was reported that CAR, troponin, and PESI scores showed a moderate positive correlation.¹⁷ They reported that a threshold value of 5.33 for CAR predicted 6-month mortality with 65.3% sensitivity and 65.6% specificity,¹⁷ while another study showed that CAR was an independent predictor of late-term mortality and was more effective than both albumin and CRP.²² Since our study

was a retrospective screening and mortality information of all patients could not be obtained, we could not examine the role of CAR in determining mortality. However, when a threshold value of 8.7 was used for CAR, sensitivity and specificity were found to be 89.2 and 83.6%, respectively, in predicting the high-risk group. In the correlation analysis of the present study, a positive correlation was detected between CAR and troponin, pro-BNP, D-dimer, sPESI, and sPAB.

CONCLUSION

The results of the present study show that patients who have high CAR have a significantly increased mortality risk and a more severe disease course. Also, the positive correlation of this ratio with biomarkers such as troponin, sPESI, and pro-BNP emphasizes the clinical importance of using it as a prognostic indicator in determining the course of the disease in PTE patients.

In particular, the CAR may be a valuable tool in emergency departments where access to advanced diagnostic modalities is limited. In centers where echocardiography and cardiac biomarkers such as troponin are not readily available, CAR, based on simple, inexpensive, and rapidly obtainable laboratory tests, could serve as a surrogate marker to assist in early risk stratification of patients with suspected pulmonary embolism. Integrating CAR into the initial clinical evaluation may aid clinicians in identifying patients at higher risk who require urgent referral or closer monitoring, especially in resource-constrained settings. While it is not a replacement for a comprehensive assessment, CAR may support decision-making when key parameters of established prognostic models are not accessible during presentation.

The fact that CAR is simple, economical, and widely available may increase the clinical applicability of this parameter. However, the results of the present study showed that it has no significant role in determining escalation therapy in patients who have intermediate-high mortality risk when clinical deterioration occurs.

In conclusion, the present study highlights the potential role of CAR in determining mortality risk and disease severity in patients who had PTE, indicating that it may be a valuable prognostic indicator that can be used in clinical practice.

Limitations

The present study had several limitations. First, it had a retrospective design and

relied on archival data. The lack of a prospective controlled study may prevent us from understanding the cause-and-effect relationships more clearly. Second, the small number of patients who had high-risk and intermediate-high-risk disease and who had worsening hemodynamics during follow-up may not have fully represented these groups. With these limitations in mind, the results must be carefully evaluated and interpreted, emphasizing the need for larger and more comprehensive studies to understand the prognostic value of CAR in PTE patients.

ETHICAL DECLARATIONS

The study was approved by the Gazi University Clinical Research Ethics Committee (Date: 30th December 2022; Decision No.: 1465).

DECLARATION OF AUTHORSHIP

All authors conceived and designed the study; AO and AM acquired the data; AO, AM, and ZY analyzed and interpreted the data; AO and IKO drafted the manuscript; AM and IKO critically reviewed the manuscript for important intellectual content; all authors gave approval of the version to be submitted; and all authors agreed to be accountable for all aspects of the work.

HIGHLIGHTS

The CAR is a significant prognostic marker for mortality risk and disease severity in patients with acute PTE.

Elevated CAR levels are positively correlated with increased mortality risk and worse clinical outcomes.

CAR shows significant positive correlations with established cardiac and clinical biomarkers such as troponin, pro-BNP, and the simplified Pulmonary Embolism Severity Index.

Both CRP and CAR levels are significantly higher in patients presenting with pulmonary infarction compared with those without infarction.

CAR, as a simple, cost-effective, and rapidly obtainable laboratory test, may serve as a valuable tool for early risk stratification in emergency settings with limited access to advanced diagnostic modalities.

AUTHOR CONTRIBUTIONS

AO, AM, and IKO designed and coordinated the study, participated in data acquisition and interpretation, and drafted the article. AO and AM participated in data collection. Statistical analyses were performed by ZY and reviewed in detail by IKO. All authors participated in the review and revision of the manuscript. All authors have approved and take responsibility for the final version of the manuscript.

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Perceived and Observed Side Effects of Noninvasive Mechanical Ventilation in Patients at a Tertiary Care Center: A Prospective Observational Study

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Received: 20 September 2025; Accepted: 05 August 2026

ABSTRACT

Objectives: To evaluate the perceived and observed side effects of noninvasive ventilation (NIV) in patients at a tertiary care hospital and to assess their correlation with inspiratory positive airway pressure (IPAP) levels and duration of NIV.

Materials and methods: This prospective observational study was conducted in the Department of Respiratory Medicine, LTMMC and GH, Sion, Mumbai, over a 1-year period. A total of 300 patients receiving NIV were screened; 241 with complete datasets were included. Demographic and clinical details were recorded. Patient-reported (subjective) and clinician-observed (objective) side effects were documented. Fear and pain were assessed using a 10-point scale. Correlations between average IPAP, NIV duration, and side effects were analyzed using logistic regression and Pearson's correlation, with $p < 0.05$ considered significant.

Results: Among 241 patients (mean age 52.4 ± 13.9 years; 47.3% male), oral dryness (79.7%), fear (74.7%), disturbed sleep (74.3%), and pain (74.3%) were the most common side effects, while abdominal distension was the least frequent (15.3%). Overall, mean IPAP showed no significant association with side effects; however, in chronic obstructive pulmonary disease (COPD) patients, higher IPAP correlated significantly with oral dryness ($p = 0.003$) and skin irritation ($p = 0.029$). Longer NIV duration was significantly associated with abdominal distension, skin irritation, nasal bridge injury, and pain ($p < 0.05$). Subgroup analysis revealed distinct patterns between COPD and post-tuberculosis obstructive airway disease (post-TB OAD) groups.

Conclusion: NIV is associated with frequent subjective and objective side effects, predominantly oral dryness, fear, disturbed sleep, and pain. While IPAP influenced certain complications in COPD, duration of use emerged as the key determinant of adverse events. Routine monitoring, preventive measures, and patient education are essential to improve tolerance and adherence to NIV therapy.

Keywords: Duration, Noninvasive ventilation, Side effects.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1741

INTRODUCTION

The invention of noninvasive ventilation (NIV) dates back to the eighteenth century where the "iron lung" was the first prototype ever used with dramatic results. Over the past century, NIV usage has become a standard of care across the world for both respiratory and cardiac patients. It alleviates the need for invasive ventilation, especially in patients with type 2 respiratory failure, and thus provides protection from ventilator-associated complications whilst providing robust ventilatory support. However, over time, it has been recognized that this "wonder device" is also associated with a spectrum of adverse effects. Many of these complications may contribute to NIV intolerance, treatment failure, or reduced adherence. Careful recognition and monitoring of these side effects may improve patient comfort, compliance, and overall treatment outcomes. A better understanding of these side effects may help improve

patient compliance, minimize discomfort, and ultimately enhance treatment outcomes. We observed and studied the side effects of NIV both subjectively perceived by the patients and also observed if we could clinically come across any side effects. We further tried to analyze whether there was any correlation between the pressures received and the duration of NIV and any of the side effects.

MATERIALS AND METHODS

The study was a prospective single-center observational study conducted after approval from the Institutional Ethics Committee [IEC Number: IEC/15/24] at the Department of Respiratory Medicine, LTMMC and GH, Sion, Mumbai, over a period of 1 year. A total of 300 patients admitted and receiving NIV in the intensive respiratory care unit were included.

Aims and Objectives

- To study the perceived and mechanical side effects of noninvasive ventilation.

- To correlate the perceived and mechanical side effects with the average inspiratory positive airway pressure (IPAP) received during the NIV.
- To correlate the perceived and mechanical side effects with the duration of NIV.
- Noninvasive ventilation failure was defined as the need for endotracheal intubation due to worsening respiratory failure, hemodynamic instability, deteriorating mental status, or intolerance to NIV.

Statistical Analysis

Statistical analysis was performed using SPSS version 29 (IBM Corp., USA). Descriptive statistics were used to summarize demographic and clinical variables. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (IQR), while categorical variables were presented as frequencies and percentages. Appropriate inferential statistical tests (e.g., Chi-square test, t-test, logistic regression) were used, with a p -value < 0.05 considered statistically significant. NIV-related adverse effects such as skin irritation, abdominal distension, nasal bridge injury, eye irritation, and sleep disturbance were treated as binary variables (present = 1, absent = 0) for regression analysis. Variables with $p < 0.2$ in the univariate analysis were included in the multivariate logistic regression model.

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How to cite this article: Karpe SP, Khadekar V, Sidharth K, et al. Perceived and Observed Side Effects of Noninvasive Mechanical Ventilation in Patients at a Tertiary Care Center: A Prospective Observational Study. *J Assoc Physicians India* 2026;74(10):41–44.

RESULTS

A total of 300 subjects were enrolled; 59 subjects were excluded from the study due to incomplete data. Therefore, the total number of subjects in the study was 241. There were 114 males and 127 females. The average age of the study population was 52.39 years with an SD of 13.87 years. The most common addiction was smoking, found in 85 (35.26%) individuals. The average pack-years among smokers was 6.6 pack-years. There was a previous history of tuberculosis among 124 (51.4%) patients. All these patients had received NIV during the course of their stay in the hospital. The average days of NIV received were 5.56 days with an SD of 6.4 days. The average NIV IPAP was 19.9 ± 1.77 cmH₂O and was normally distributed. NIV intolerance leading to discontinuation due to side effects occurred in 8 patients (2.67%). The most common causes were severe mask discomfort, persistent nasal bridge pain, and anxiety related to mask intolerance.

The side effects perceived by the patients and noted by us were documented. The following is the frequency table (Table 1).

The most common reported side effect was oral dryness seen in 192 (79.67%), followed by fear in 180 (74.69%), disturbed sleep in 179 (74.27%), and pain in 179 (74.27%). The least common reported side effect was abdominal distention (15.35%). Abdominal distention was assessed clinically based on the patient's complaint of bloating or visible abdominal fullness during NIV therapy and was recorded as present or absent. Objective abdominal circumference measurement was not performed.

To study the relationship between the dependent variable, i.e., patient-reported adverse effects of NIV, and the average IPAP pressure, we performed logistic regression. We noticed that the relationship between the dependent and the independent variables was not statistically significant. Fear and pain

were subjectively evaluated on a scale of 1–10 for severity. The presence or absence of NIV-related discomforts and conditions was coded as 1 (present) and 0 (absent). The continuous data (fear score and pain score) in the study were found to be normally distributed with the help of Q–Q plots (Figs 1 and 2). Q–Q plots were generated for fear and pain scores to assess normality. They were all normally distributed.

As the data were normally distributed, Pearson's correlation coefficient was calculated for average IPAP, fear score, and pain score:

- For the average IPAP and fear scale: The correlation coefficient is 0.01. This was negligible.
- For the average IPAP and pain scale: The correlation coefficient is -0.02 . This was negligible.

As the majority of patients were post-TB OAD, overlap syndrome, and chronic obstructive pulmonary disease (COPD), others were clubbed into other diseases due to lower numbers (Table 2).

Therefore, we further did a subgroup analysis of patients with COPD and post-TB OAD.

The relationship between the IPAP and the patient-reported symptoms was not statistically significant in the case of post-TB OAD.

In cases of COPD, the complaints of skin irritation and oral dryness correlated significantly with the average IPAP pressure.

- There was a modest positive correlation between average IPAP and outcome (skin irritation) ($R = 0.229$, $SE = 0.492$). The correlation is statistically significant ($p = 0.029$). The coefficient was 0.069, suggesting that for every 1-unit increase in IPAP, there was a 0.069-unit increase in the probability of skin irritation.
- There is a moderate positive correlation between average IPAP and complaints of oral dryness ($R = 0.301$, $SE = 0.338$). This correlation is statistically significant (0.003). The coefficient was 0.065, suggesting that for every 1-unit increase in IPAP pressure, there was a 0.065-unit increase in the probability of oral dryness.

Table 2: Underlying diseases in the analytical cohort ($n = 241$)

Diseases	Frequency	Percentage
Post-TB OAD	101	41.90%
Overlap syndrome	39	16.18%
COPD	76	31.53%
Other diseases	25	10.37%
Total	241	

* $p < 0.05$, statistically significant. aOR, adjusted odds ratio; CI, confidence interval

The relationship between the duration of NIV days and NIV-related side effects was also studied by logistic regression (overall).

- The relationship between Abdominal distention and NIV duration was found to be statistically significant. The coefficient was 0.0127. For every additional day of NIV, abdominal distention is associated with increased odds by 0.013 units (p -value 0.000159, $R = 0.058$, $SE = 0.3513$).
- The relationship between Skin irritation and NIV duration was found to be statistically significant. The coefficient was 0.0125. For every additional day of NIV, skin irritation is associated with increased odds by 0.0125 units (p -value 0.0077, $R = 0.0293$, $SE = 0.0046$).
- The relationship between Nasal bridge injury and NIV duration was found to be statistically significant. The coefficient was 0.01258. For every additional day of NIV, nasal bridge injury is associated with increased odds by 0.0126 units (p -value 0.0046, $R = 0.0330$, $SE = 0.0044$).
- The relationship between pain and NIV duration was found to be statistically significant. The coefficient was 0.00922. For every additional day of NIV, the reported pain is associated with increased odds by 0.0092 units (p -value 0.025, $R = 0.0208$, $SE = 0.00409$).

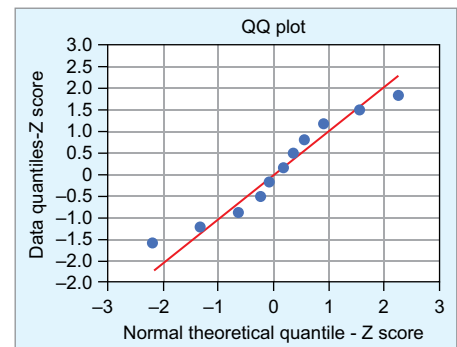


Fig. 1: Q–Q plot showing the normal distribution of fear

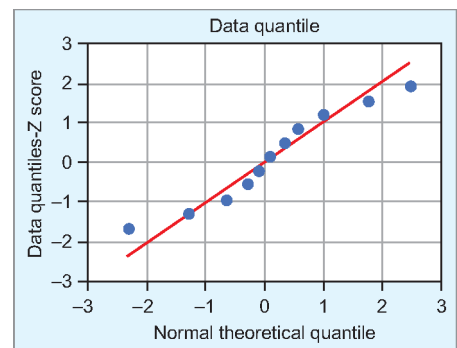


Fig. 2: Q–Q plot showing the normal distribution of pain

Table 1: Frequency of NIV-related side effects ($n = 241$)

Side effects	Frequency	Percentage
Disturbed sleep	179	74.27%
Nasal congestion	152	63.07%
Oral dryness	192	79.67%
Abdominal distention	37	15.35%
Skin irritation	115	47.72%
Nasal bridge injury	82	34.02%
Eye irritation	72	29.88%
Face injury due to mask	70	29.05%
Fear	180	74.69%
Pain	179	74.27%

Table 3: Multivariate logistic regression for skin irritation and oral dryness

Variable	Skin irritation (aOR, 95% CI)	p-value	Oral dryness (aOR, 95% CI)	p-value
Age	1.01 (0.99–1.03)	0.21	1.00 (0.98–1.02)	0.78
Female gender	1.12 (0.68–1.85)	0.64	1.25 (0.74–2.10)	0.39
Smoking	1.45 (0.82–2.56)	0.19	1.62 (0.90–2.91)	0.10
COPD	1.88 (1.05–3.36)	0.03*	2.15 (1.18–3.91)	0.01*
Post-TB OAD	1.22 (0.70–2.13)	0.47	1.31 (0.73–2.35)	0.36
Average IPAP	1.07 (1.01–1.14)	0.02*	1.06 (1.02–1.11)	0.003*
Duration of NIV	1.01 (1.00–1.02)	0.01*	1.01 (0.99–1.02)	0.12

* $p < 0.05$, statistically significant. aOR, adjusted odds ratio; CI, confidence interval

Table 4: Multivariate logistic regression for nasal bridge injury and abdominal distension

Variable	Nasal bridge injury (aOR, 95% CI)	p-value	Abdominal distension (aOR, 95% CI)	p-value
Age	1.02 (1.00–1.04)	0.04*	1.01 (0.98–1.03)	0.32
Female gender	1.38 (0.81–2.34)	0.22	0.92 (0.48–1.76)	0.80
Smoking	1.31 (0.72–2.38)	0.36	1.78 (0.88–3.59)	0.10
COPD	1.42 (0.78–2.57)	0.24	1.67 (0.81–3.44)	0.16
Post-TB OAD	1.19 (0.65–2.17)	0.56	1.08 (0.51–2.29)	0.83
Average IPAP	1.04 (0.99–1.09)	0.08	1.02 (0.96–1.08)	0.42
Duration of NIV	1.01 (1.00–1.02)	0.004*	1.02 (1.01–1.03)	<0.001*

* $p < 0.05$, statistically significant. aOR, adjusted odds ratio; CI, confidence interval

The duration of NIV was correlated with NIV-related side effects in COPD patients.

- A statistically significant association was observed between NIV duration and abdominal distension. The coefficient was 0.0207. For every day increase in the NIV duration, predicted abdominal distension by 0.0207 units ($R = 0.056$, $p = 0.0237$, $SE = 0.008971$).
- The relationship between Nasal bridge injury and NIV duration was found to be statistically significant (COPD). The coefficient was 0.0397. For every day increase in the NIV duration, predicted nasal bridge injury by 0.0398 units ($R = 0.1451$, $p = 0.0002$, $SE = 0.010286$).

The duration of NIV was correlated with NIV-related side effects in post-TB OAD patients.

- The relationship between Skin irritation and NIV duration was found to be statistically significant. The coefficient was 0.012111 units. For every day increase in the NIV duration, predicted skin irritation by 0.01211 units ($R = 0.045$, $p = 0.02439$, $SE = 0.005306$).
- The relationship between eye irritation and NIV duration was found to be statistically significant. The coefficient was 0.011471 units. For every day increase in the NIV duration, predicted eye irritation by 0.011471 units ($R = 0.0477$, $p = 0.020675$, $SE = 0.00488$).

A multivariate logistic regression analysis was performed to identify independent predictors of NIV-related adverse effects after adjusting for demographic and clinical variables.

Higher IPAP and longer duration of NIV were independently associated with increased odds of skin irritation and oral dryness. The duration of NIV was also independently associated with nasal bridge injury and abdominal distension. COPD patients had higher odds of developing skin irritation and oral dryness (Tables 3 and 4).

Noninvasive ventilation failure, defined as the need for endotracheal intubation after initiation of NIV, occurred in 36 patients, corresponding to a failure rate of 12% in the study population.

DISCUSSION

In this prospective observational study of 241 patients receiving NIV in a tertiary respiratory unit, we found that oral dryness, fear, disturbed sleep, pain, and skin/nasal bridge injury were among the most commonly perceived side effects, whereas abdominal distension was relatively uncommon. We also observed statistically significant associations of side effects with duration of NIV, especially nasal bridge injury, skin irritation, pain, and abdominal distension, and in COPD patients, higher IPAP correlated significantly with skin irritation and oral dryness. These results corroborate several recent studies on NIV use and are relevant, particularly in an Indian, post-TB-affected population. Impaired sleep quality has been reported in previous studies with NIV. Shah et al. found poor sleep quality among chronic NIV users, with mouth dryness, mask leak, aerophagia, and mask-related pain identified as contributors.¹ Similarly, a 2025 study on

nocturnal home NIV (without PSG guidance) reported that side effects like dry mouth, hoarseness, mask- or harness-related pain, pressure sores, and leaks were significantly associated with poor sleep quality.² These findings align with the high prevalence of disturbed sleep, pain, and oral dryness in our study. In our study, ~34% had nasal bridge injury, ~48% had skin irritation, ~29% had eye irritation, and ~29% had facial injury. These numbers are comparable to recent reports: A systematic review in 2025 reported the incidence of facial pressure injuries in adults receiving NIV to be ~25%, depending on mask interface, duration, and preventive measures.³ Other studies emphasize that risk increases with device duration, mask tightness, and lack of protective dressings.^{4,5} Prospective and retrospective cohorts have shown pressure injuries in 20–30% of patients on NIV, with the nasal bridge being the most vulnerable site.^{6,7} Nasal bridge injuries in patients receiving NIV are not an uncommon site in critical care settings, and despite protective measures applied, remain a cause of discomfort and concern. In multivariate analysis, duration of NIV emerged as the most consistent independent predictor across multiple adverse effects.

In the HAPPEN trial (2024), which compared high- vs low-intensity NIV in acute COPD, abdominal distension occurred significantly more frequently in the high-intensity group (37.4%) than in the low-intensity group (25.5%).⁸ This aligns with our finding of a statistically significant association between longer NIV duration (and in COPD, higher

IPAP) and abdominal distension, confirming aerophagia remains a relevant adverse event. Our observation that IPAP was significantly correlated with oral dryness and skin irritation in COPD patients is consistent with reports that higher pressure settings increase the risk of interface intolerance.^{9,10} Facial pressure injuries are also reported to rise with longer mask use, higher strap tension, and absence of protective interfaces.^{6,7} While objective mechanical side effects are often emphasized, subjective perceptions such as fear, pain, and anxiety were highly prevalent in our cohort (~74%). Studies underline that discomfort, claustrophobia, and anxiety can drive NIV intolerance and failure.^{11,12} Patient-reported side effects have also been shown to negatively impact adherence to long-term home NIV.¹³ During NIV therapy, several preventive measures were routinely implemented to reduce mask-related complications. These included periodic mask repositioning, adjustment of strap tension, application of protective gauze or hydrocolloid dressings over the nasal bridge, and intermittent breaks from NIV when clinically feasible. In patients experiencing oral dryness, humidification and adequate hydration were encouraged. These measures are recommended in previous studies to reduce NIV-related pressure injuries and improve patient tolerance.

Possible Mechanisms and Clinical Implications

- **Dryness:** NIV delivers dry air; mouth leaks and higher flows exacerbate oral dryness.^{1,2} Humidification, lower flows, and ensuring adequate hydration may help mitigate the oral dryness due to NIV.
- **Skin/nasal bridge injury:** Interface pressure and strap tension at bony prominences lead to injury.^{4,6,7} Softer interfaces and intermittent breaks can be attempted to reduce the incidence of nasal and skin injuries.
- **Abdominal distension:** Aerophagia from higher IPAP levels has been documented in COPD NIV trials.⁸ Mouth breathing can be discouraged, and a Ryle's tube insertion can be used to decompress the stomach to reduce abdominal distention.
- **Pain, fear, disturbed sleep:** Claustrophobia, mask leaks, airflow noise, and inability to speak/eat contribute.^{11,12} Patient education, counseling, and gradual increment of pressures might ease the patient's anxiety and fear over a period of time.
- **Duration effects:** Longer exposure to NIV increases the risk of both mechanical and subjective side effects.^{3,5,9} Addressing the underlying pathology mandating the

requirement of NIV should be optimized to ensure that the duration can be reduced as early as possible.

Our Findings Stress the Need for

- Routine side effect monitoring (skin checks, oral dryness, sleep disturbance).^{7,9}
- Preventive strategies: mask rotation, protective dressings, humidification.^{4,5}
- Patient education to reduce fear and improve adherence.^{12,13}
- Customized pressure titration and mask selection in vulnerable subgroups such as COPD.^{8,10}

The observed NIV failure rate in our cohort was 12%, which is comparable to previously reported rates of 10–20% in acute COPD exacerbations and higher rates in hypoxemic respiratory failure. NIV intolerance due to discomfort, anxiety, mask pressure injury, and aerophagia may contribute to early discontinuation and treatment failure. Recognition and early management of these complications may therefore improve NIV success. Although some correlations reached statistical significance, the magnitude of correlation coefficients was weak, suggesting limited clinical significance. These findings indicate that NIV-related side effects are likely influenced by multiple factors, including mask interface, patient tolerance, airflow leak, and duration of therapy, rather than pressure settings alone.

LIMITATIONS

This study has several limitations. First, it was a single-center study conducted at a tertiary respiratory care unit, which may limit generalizability to other settings. Second, several side effects, such as fear, pain, and sleep disturbance, were based on patient-reported measures and may be subject to reporting bias. Third, objective sleep assessment (such as polysomnography) and objective measurement of abdominal distension were not performed. Finally, mask interface type and humidification settings were not separately analyzed, which may influence the occurrence of NIV-related adverse effects. Multivariate analysis was limited by the lack of adjustment for mask type and humidification settings, which may act as confounders.

CONCLUSION

Our study demonstrates that although NIV remains an essential modality in respiratory care, it is associated with a substantial burden of both mechanical and subjective side effects. Longer duration of NIV appears to be an important determinant of these complications,

while higher pressures contribute to certain adverse effects in COPD patients. Recognition of these side effects, along with early preventive strategies and individualized NIV settings, may improve patient comfort, adherence, and overall success of NIV therapy.

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Beyond Rheumatoid Factor and Anticyclic Citrullinated Peptide: Role of 14-3-3 η Protein in the Diagnosis of Rheumatoid Arthritis and the Evaluation of Disease Severity

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Received: 31 May 2025; Accepted: 12 August 2026

ABSTRACT

Background: Rheumatoid arthritis (RA) is known to cause chronic inflammation of the joints, resulting in their destruction. Given the limitations of serological markers such as anti-cyclic citrullinated peptide antibodies (anti-CCP) and the autoantibody Rheumatoid Factor (RF), there is a need for additional markers to diagnose RA. A new promising marker for RA has been identified, known as 14-3-3 η (eta) protein.

Objective: To investigate the 14-3-3 η protein's role in the diagnosis of RA, to analyze its role in disease severity, and to distinguish between seropositive vs seronegative RA and early vs chronic RA.

Materials and methods: A total of 170 clinically suspected cases of RA met the inclusion criteria and were considered in this study. Data such as demographic details, clinical and laboratory findings, and DAS28 scores were collected from all participants. 14-3-3 η levels were estimated. Statistical analysis was done using R software.

Results: Out of 170 participants, 79 were definite RA, and 91 were disease controls, as per the defined criteria. At a cutoff value of 4.15 ng/mL, 14-3-3 η was 58% sensitive and 90% specific. There was a significant difference in 14-3-3 η positivity between RA cases and disease controls ($p < 0.05$). Likewise, the difference in 14-3-3 η positivity between SNRA cases and disease controls was also significant ($p = 0.0071$). The association of 14-3-3 η positivity with DAS28 score was statistically significant ($p < 0.001$). When 14-3-3 η was used in combination with anti-CCP and RF, the sensitivity of 14-3-3 η increased from 58% to 87%, but the specificity decreased from 84% to 63%.

Conclusion: The novel biomarker 14-3-3 η can be used as a diagnostic tool for assessing disease severity in RA and can distinguish definite cases and SNRA cases from disease controls. Also, adding this 14-3-3 η to the traditional markers enhances their diagnostic capacity.

Keywords: 14-3-3 η , Anticyclic citrullinated peptide antibodies, Disease severity, Rheumatoid arthritis, Rheumatoid factor.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1742

INTRODUCTION

Rheumatoid arthritis (RA) is known to cause chronic inflammation of the joints, resulting in their destruction.¹ According to WHO, in 2019, 18 million people in the world were living with RA, of whom 13 million had severe or moderate levels of disease, who could benefit from rehabilitation.² RA can affect men, women, and children at any age, but globally, 70% of people affected are women, and among them, 55% are older than 55 years.² In India, it is estimated that 0.7% of people have RA.³

Early and accurate diagnosis is important for RA for its proper management and also to prevent long-term damage. Early RA is the initial stage of the disease, with a duration of less than 1 year, while established RA is with symptoms that have lasted for more than one year,⁴ which includes pain, tenderness, swelling, and stiffness, especially in the hands, wrists, and feet joints.² The 2010 classification criteria developed by the American College

of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) identify anti-cyclic citrullinated peptide antibodies (anti-CCP) and an autoantibody, Rheumatoid Factor (RF), as key serological markers for diagnosing RA.⁵ However, there are limitations to the two markers. The sensitivity of RF ranges between 60% and 80%, with a specificity of about 85%.⁶ Also, RF can be present in other autoimmune diseases and even in healthy individuals (about 5% of cases⁷), leading to false positive results.⁵ The anti-CCP has also been found to be equally sensitive at about 67%, but has a better specificity of about 98%.⁶ However, anti-CCP is positive only in a set of RA patients.⁸ This seronegativity observed in both established and early RA cases highlights the need for additional biomarkers to improve the diagnostic sensitivity, ensure accurate detection across all RA patients, and provide them with timely, accurate treatment. When either of the two tests, anti-CCP and RF, is positive, it is known as seropositive RA (SPRA), while in RA cases when both anti-CCP and RF

are negative, it is classified as seronegative RA (SNRA).⁹

Serum 14-3-3 η (eta) is an emerging marker in RA. The family of 14-3-3 proteins has 7 isoforms: β , γ , ϵ , η , σ , θ , and ζ , out of which 14-3-3 η plays an important role in the onset and progression of RA.⁵ Serum 14-3-3 η was seen significantly higher in synovial fluid and serum of patients with arthritis as compared to healthy individuals. Studies have shown that 14-3-3 η may play a role in cartilage destruction through regulation of matrix metalloproteinases (MMPs). Also, studies have shown that combining 14-3-3 η protein with anti-CCP and/or RF, the diagnostic rate of RA is increased.⁵

While many Indian studies have focused on the role of 14-3-3 η protein in diagnosing RA, to the best of our knowledge, this is the first Indian study that analyses its significance in disease severity, distinguishing seropositive vs. seronegative RA, and early vs. established RA.

MATERIALS AND METHODS

This was an observational study that was conducted over 18 months, from May 2023 to October 2024, in the Department of Microbiology at a tertiary care hospital in North India. The study was approved by the Institute's Ethics Committee. (IEC No. 12/23, dated 8/5/2023). The sample size was calculated based on a previously published study by Shovman et al.¹⁰ Adding 10% loss

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How to cite this article: Aravindh A, Gupta A, Agarwal J, et al. Beyond Rheumatoid Factor and Anticyclic Citrullinated Peptide: Role of 14-3-3 η Protein in the Diagnosis of Rheumatoid Arthritis and the Evaluation of Disease Severity. *J Assoc Physicians India* 2026;74(10):50–54.

of data, we got an optimum sample size of 90 patients. Patients attending the Rheumatology OPD in the Internal Medicine Department for the first time during the study period with chief complaints suggestive of RA (joint pain, swelling, tenderness, and stiffness, especially in the hands, wrists, and feet) and consenting to participate were enrolled in the study.

Exclusion Criteria

Follow-up RA patients, patients who are diagnosed with non-RA conditions like osteoarthritis, ankylosing spondylitis, systemic sclerosis, chronic kidney disease, subjects not consenting to participate, and repeat samples from the same patient were excluded from the study.

Data Collection

After the enrollment of participants, their demographic, clinical, and laboratory data were collected, such as age, gender, and duration of disease from the initial appearance of symptoms. Tender joint count (TJC) and swollen joint count (SJC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were collected to calculate the DAS28 score, which is derived from assessing 28 joints. The serostatus of RF autoantibodies and anti-CCP antibodies was collected. The ACR criteria of each patient were recorded according to the 2010 ACR/EULAR criteria. This criterion assigns a score ranging from 0 to 10, with a score of 6 or higher indicating RA.¹¹ Those with a score of <6 are classified as non-RA patients. Depending on the presence/absence of joint erosions as seen in radiographic evaluations, RA was further classified into erosive and non-erosive types.

Sample Collection

Two mL of peripheral blood was drawn from each patient. The serum was separated from each blood sample and aliquoted at -20°C for further analysis. The serum concentration of 14-3-3 η protein was quantified by enzyme-linked immunosorbent assay (ELISA) using

the Human YWHAH (14-3-3 protein eta) ELISA kit, Fine Biotech, Wuhan, China. The ELISA tests were performed according to the manufacturer's instructions.

Statistical Analysis

R software version 4.3.1 was used for Statistical analysis. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic accuracy of the indexes, and the results were presented as the area under the curve (AUC) along with 95% confidence intervals (CI). The optimum cutoff value and diagnostic accuracy criteria were determined using Youden's index.

RESULTS

In total, 170 patients presenting with clinical suspicion of RA were included. Of these, 79 study participants were categorized as definite RA as they fulfilled the ACR criteria, and the remaining 91 participants were non-RA patients and were taken as disease controls.

Patients' Disease Characteristics

Out of the 79 definite RA cases, females were the majority (64 cases, 81.01%), while males accounted for only 15 cases (18.98%). The median age of the patients was 45 years, with a range of 19 to 71 years. The disease activity was moderate to severe in 63% of the patients, and the mean DAS28 score

was 5.13. The median duration of RA was 1.02 years. Out of all the definitive RA cases, 30 were negative for anti-CCP, whereas 49 tested positive. Additionally, 36 patients tested RF positive, while 43 were RF negative. SPRA was identified in 56 patients, whereas 23 patients had SNRA.

Diagnostic Value of 14-3-3 η

According to the ROC curve, using ACR criteria as the gold standard, the AUC for 14-3-3 η was 0.758, with a Youden's index of 0.483 and a 95% CI of 0.684–0.832. At a cut-off value of 4.15 ng/mL, 14-3-3 η was 58% sensitive and 90% specific (Fig. 1)

Correlation of 14-3-3 η with Clinicopathological Characteristics of RA

The median 14-3-3 η in the study was 2.53 ng/mL. No significant correlation was found between 14-3-3 η expression with age or sex. The correlation of 14-3-3 η with the clinicopathological characteristics is detailed in Table 1. Correlation of demography with various biomarkers is summarized in Table 2.

Table 1: Comparing the median values of 14-3-3 η and their significance values

Condition	Median value of 14-3-3 η (ng/mL)	p-value
Definite RA	4.6	0.001
Disease control	1.7	
Early RA	3.125	0.972
Established RA	2.175	
Anti-CCP positive	4.16	0.184
Anti-CCP negative	4.64	
RF positive cases	4.7	0.832
RF negative cases	4.42	
SPRA	5.1	0.758
SNRA	4.312	
Erosive	24	0.132
Nonerosive	8.85	

SPRA, seropositive RA; SNRA, seronegative RA

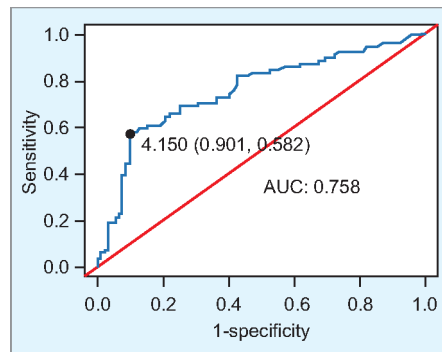


Fig. 1: ROC curve showing 14-3-3 η sensitivity and specificity for diagnosing RA

Table 2: Correlation of demography with biomarkers

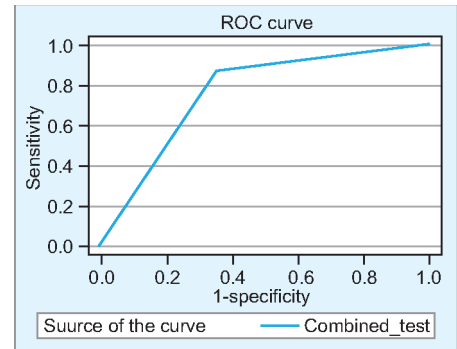
Group, (n)	Mean age (years)	Sex (% female)	Median 14-3-3 η (ng/mL)	14-3-3 η positive	Anti-CCP positive	RF positive
Total cases (n = 170)	44	134 (78%)	2.53	55 (32%)	71 (41.4%)	50 (29.4%)
RA (n = 79)	45	64 (81%)	4.6	46 (58.2%)	49 (62%)	36 (45.5%)
Disease control (n = 91)	42	70 (77%)	1.7	9 (9.89%)	22 (24%)	14 (15%)
Early RA (n = 51)	45	38 (74.5%)	3.125	32 (62.7%)	27 (53%)	17 (33.3%)
Established RA (n = 28)	45.5	26 (93%)	2.175	14 (50%)	22 (78.57%)	19 (68%)
SPRA (n = 56)	44.5	45 (80%)	5.1	33 (59%)	49 (87.5%)	36 (64.2%)
SNRA (n = 23)	50	19 (82.6%)	4.312	13 (56.5%)	0	0

SPRA, seropositive RA; SNRA, seronegative RA

Table 3: 14-3-3 η positivity and value of significance in different categories

Categories	Total 14-3-3 η positive	p-value
Female	64	0.46
RA	46	0.0001
Disease controls	9	
High DAS28 score (>5.1)	37	0.007
Moderate-low DAS28 score ($\leq$ 5.1)	9	
Early	32	0.38
Established RA	14	
SPRA	31	0.9
SNRA	13	
SNRA	13	<0.001
Disease controls	9	

SPRA, seropositive RA; SNRA, seronegative RA

**Fig. 2:** The ROC curve analysis showing the sensitivity, specificity, and AUC for the combination of 14-3-3 η , RF, and anti-CCP**Table 4:** The results of the diagnostic value of RF, anti-CCP, 14-3-3 η alone, and in combination with 14-3-3 η

Biomarker tested (s)	Sensitivity(95%CI)	Specificity(95%CI)	PLR	NLR	DOR
14-3-3 η	0.58 (0.46–0.69)	0.90 (0.82–0.95)	5.9	0.463	12.74
RF	0.45 (0.34–0.57)	0.84 (0.75–0.91)	3	0.64	4.68
Anti-CCP	0.62 (0.46–0.75)	0.75 (0.62–0.86)	2.6	0.500	5.2
14-3-3 η or/and RF	0.77 (0.67–0.86)	0.76 (0.65–0.84)	3.2	0.30	10.66
14-3-3 η or/and Anti-CCPs	0.84 (0.77–0.93)	0.68 (0.57–0.77)	2.6	0.23	11.30
14-3-3 η or/and RF or/and anti-CCP	0.87 (0.77–0.93)	0.63 (0.52–0.73)	2.35	0.21	11.19

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio

Positivity of 14-3-3 η in RA and Disease Controls ($n = 170$)

Among the 170 cases, 14-3-3 η was positive in 46 RA cases (58.2%) and negative in 33 RA cases (41.8%). The disease control group had 82 cases (90.1%) with 14-3-3 η being negative, and 9 cases (9.9%) with it being positive. The difference in 14-3-3 η positivity between RA patients and disease controls was significant ($p < 0.05$) (Table 3).

14-3-3 η Levels and Disease Activity

Out of the 79 definite RA patients, the DAS28 score was mild to moderate in 28 cases, and high in 51 cases. 14-3-3 η was positive in 37 (72.5%) and negative in 14 (27.5%) of the 51 patients with a high DAS28 score. Among those with a mild to moderate DAS28 score, 14-3-3 η was positive in 9 cases and negative in 19 cases. The association between 14-3-3 η positivity and DAS28 score was highly significant ($p = 0.0071$) (Table 3).

14-3-3 η in Early vs Established RA ($n = 79$)

Out of 51 cases of early RA, 14-3-3 η was tested positive in 32 cases (62.7%) and negative in 19 cases (37.3%). It was also positive in 14 of the 28 cases of established RA and negative in 14 of the cases. The difference in 14-3-3 η positivity between early and established RA was not statistically significant ($p > 0.05$) (Table 3).

Correlation of 14-3-3 η Positivity with SPRA and SNRA ($n = 79$)

Among the 79 definite RA cases, 14-3-3 η was positive in 26 anti-CCP-positive cases ($n = 49$) and negative in 10 anti-CCP-negative cases ($n = 30$). Similarly, 14-3-3 η was positive in 20 RF-positive cases ($n = 36$) and negative in 17 RF-negative cases ($n = 43$). Out of the 56 SPRA cases, 14-3-3 η was positive in 33 cases, while out of the 23 SNRA cases, it was positive in 13 cases. The prevalence of this marker in the seropositive population was found to be 59%, and in the seronegative population, it was 57% (Table 2).

Comparison of 14-3-3 η Positivity in SNRA and Disease Controls

Of the SNRA cases, 13 had a positive 14-3-3 η and 10 had a negative 14-3-3 η . In the disease control group, the majority were 14-3-3 η negative (82 cases), and only 9 cases were positive. The difference in 14-3-3 η positivity between SNRA cases and disease controls was highly significant ($p < 0.001$) (Table 3).

Diagnostic Value of Combining 14-3-3 η with RF and Anti-CCP

The sensitivity increased from 45% to 77.26% when 14-3-3 η was combined with RF, but the specificity decreased from 84% to 76.25%. Similarly, combining 14-3-3 η with anti-CCP raised sensitivity from 62% to 84.14%, with a reduction in specificity to 68.32% (Table 4).

Use of 14-3-3 η in Combination with RF and/or Anti-CCP

The combination of 14-3-3 η with RF and anti-CCP increased the sensitivity from 58% to 87%, and the specificity was 63% (Table 4 and Fig. 2)

DISCUSSION

This study evaluated the significance of 14-3-3 η among various subgroups of RA and disease controls to explore its clinical relevance and potential diagnostic utility. The median 14-3-3 η was significantly higher in definite RA cases (4.6 ng/mL) when compared to disease controls (1.7 ng/mL). This is similar to the findings from Yarlagadda et al.,¹² where RA patients exhibited higher median 14-3-3 η levels than individuals with other autoimmune diseases. Yarlagadda et al.¹² also studied the activity of 14-3-3 η in the Indian population, focusing on its use as a biomarker for RA. Additionally, no association between 14-3-3 η and age or sex was found in our study.

In this study, the median value of 14-3-3 η did not show any significant differences between early and established RA. This contrasts with findings from Gong et al.,¹³ where median levels of 14-3-3 η were higher in early RA group. This result could be because of a smaller number of early RA cases in our study. In our study, the ROC curve of 14-3-3 η differentiating RA cases from disease controls exhibited a sensitivity and specificity of 58%

and 90%, respectively, with an AUC of 0.758 at a cutoff of 4.15 ng/mL. Whereas in a study done by Tu et al.¹⁴ where 14-3-3 η was compared between RA cases with osteoarthritis (OA), at a cutoff of 0.656 ng/mL, 14-3-3 η showed a sensitivity of 60% and specificity of 84.4%.

While higher 14-3-3 η positivity was seen in anti-CCP and RF-positive cases in our study, the association was statistically insignificant. The study conducted by Tu et al.¹⁴ also reported a positive association of serum 14-3-3 η levels with both RF and anti-CCP.¹⁴ This is because all three markers release proinflammatory factors, such as IL-1 β and IL-6.¹³ The prevalence of 14-3-3 η was only marginally higher in SPRA (59%) when compared to SNRA (57%) in our study. Whereas, in a study done by Yarlagadda et al., the prevalence of 14-3-3 η was 71% in SNRA and 78% in SPRA cases.¹² Our study also analyzed the median 14-3-3 η levels in SPRA and SNRA, which were 5.1 and 4.31, respectively, showing no significant difference.

Although 14-3-3 η could not differentiate early from established RA in this study (p -value = 0.389), its prevalence was higher in early RA cases (62.7%) compared to established RA cases (50%). Conversely, Gong et al. reported a significantly higher incidence of 14-3-3 η positivity in the established RA group compared to the early RA group.¹³ In another study done by Maksymowych et al.,¹⁵ 14-3-3 η could distinguish early and chronic RA cases from those of the healthy population and disease controls.

In our study, a significant association was observed between 14-3-3 η and disease activity, with a p -value of 0.0071. The study by Gong et al.¹³ stated that 14-3-3 η positive cases in RA showed significantly higher DAS28 scores when compared to 14-3-3 η negative cases. Research has shown that 14-3-3 η positivity is associated with worse outcomes or higher disease severity because elevated expression of 14-3-3 η promotes the overproduction of RANKL, MMP-1, MMP-3, IL-1 β , and IL-6, which exacerbates inflammation and contributes to cartilage and bone destruction, ultimately leading to higher disease activity.¹⁴ Kilani et al.¹⁶ were the first to establish a correlation between 14-3-3 η and RA in 2007, demonstrating that 14-3-3 η was elevated in both serum and synovial fluid of RA patients. They also found a positive association between 14-3-3 η and matrix metalloproteinases (MMPs).¹⁶ MMPs cause structural erosions that contribute to progressive joint destruction and eventually lead to increased disease activity in RA.¹⁶

In the present study, 14-3-3 η levels were markedly elevated in RA cases than in disease controls with a significant p -value of <0.0001.

These findings are similar to those of a study by Huang et al.,¹⁷ which showed elevated 14-3-3 η in RA cases when compared to other non-RA cases and even in healthy controls, suggesting its role in differentiating RA cases from non-RA cases. Another study by Tu et al.¹⁴ also reported that 14-3-3 η can differentiate RA from osteoarthritis (OA) and healthy controls (HCs), potentially due to its role in upregulating pro-inflammatory cytokines. A study by Salman et al.¹⁸ reported a significant positive association between 14-3-3 η and SNRA when compared to healthy controls. Similarly, our study also found a significant association with 14-3-3 η positivity in SNRA and disease controls, yielding a p -value of <0.0001. This finding is of much significance as many SNRA cases can be misdiagnosed as non-RA, leading to wrong treatment and thus increased morbidity.

Multiple studies have evaluated the diagnostic utility of 14-3-3 η in RA.^{10,13,15} 14-3-3 η showed a PLR of 5.9 and an NLR of 0.46, suggesting that 14-3-3 η is clinically useful in making an appropriate diagnosis (Table 4). An increased DOR indicates better diagnostic accuracy, meaning the test is more effective at differentiating between individuals with and without the condition. With a DOR of 15.90, 14-3-3 η indicates high diagnostic accuracy. This suggests that the test is quite effective in distinguishing between the presence and absence of RA. When 14-3-3 η was combined with RF, the DOR was 10.66, which was greater than that of RF alone (DOR was 4.68). Likewise, when combining 14-3-3 η to anti-CCPs, DOR improved from 5.2 to 11.30. These findings indicate that the combination of 14-3-3 η with RF or anti-CCP improves diagnostic accuracy over using a single marker. Although the combined DOR of all three markers (11.19) is higher than those of individual RF and anti-CCP, it is similar to the DOR of 14-3-3 η alone and its combination with anti-CCP. This indicates that while the combined use of markers enhances diagnostic performance relative to RF and anti-CCP alone, the improvement is marginal when compared to 14-3-3 η and its combinations; thus, testing any of the two traditional markers (Anti-CCP or RF), preferably anti-CCP (DOR 11.30) with 14-3-3 η will be sufficient to support a diagnosis of RA. According to Maksymowych et al.,¹⁵ the addition of 14-3-3 η provides incremental benefits in diagnosing RA compared to using a single indicator (RF or anti-CCP). However, the study by Wu et al.¹⁹ stated that adding 14-3-3 η does not provide any added advantage in diagnosing RA. Few studies have shown that the combined specificity of the three markers (14-3-3 η , anti-CCP and RF) increases significantly,^{12,20}

unlike our study, which has shown a significant increase in sensitivity of the three markers but a slight decrease in specificity of the three markers combined. Our study has shown an overall increased diagnostic accuracy on combining 14-3-3 η with either anti-CCP or RF, thus making the testing cost more reasonable (using two tests as compared to combining three tests).

This study has certain limitations. It lacks a follow-up period to assess the correlation of 14-3-3 η with treatment response. Also, this study did not compare the levels of 14-3-3 η in RA patients and healthy controls.

CONCLUSION

In conclusion, the serum of RA patients has been confirmed to contain elevated levels of 14-3-3 η , establishing it as a promising new biomarker for diagnosing RA. 14-3-3 η in serum can also be employed for assessing the disease severity. Additionally, we have demonstrated that 14-3-3 η can effectively distinguish definite cases of RA from disease controls. Furthermore, adding the 14-3-3 η alongside anti-CCP increases the positive likelihood ratio and diagnostic odds ratio, leading to a more accurate and reliable diagnosis of RA.

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ANNOUNCEMENT

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Organised by: API TRIPURA STATE BRANCH

Date: 08/09/10th January, 2027

Venue: Rabindra Shatabarshiki Bhavan, Agartala, West Tripura

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Multiple Choice Question Metamorphosis—Enhancing Question Quality through Faculty Training: A Pragmatic Study

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Received: 07 October 2025; Accepted: 05 August 2026

ABSTRACT

Background: Faculty in medical colleges often lack formal training in developing multiple-choice questions (MCQs) that target higher-order thinking skills (HOTS). Poorly constructed MCQs can negatively impact the assessment's effectiveness and the examinee's outcomes, ultimately impacting students' learning. The study aimed to compare item-writing flaws and item-analysis metrics after a faculty-training program among medical college faculty in Karnataka.

Materials and methods: A quasi-experimental study was conducted from March to June 2024 at a private medical college in Karnataka, involving 32 medical faculty members trained to identify item flaws and analyze item-analysis metrics. After the second training program, MCQs prepared and administered by the faculty were analyzed to determine the effect of the training program. Descriptive variables were expressed as percentages and proportions, and inferential statistics were used to determine changes in item flaws and analysis metrics before and after the training programs. Statistical analysis was conducted using MS Excel 365 and SPSS version 29.0, with a significance level of $p < 0.05$.

Results: MCQ questions between two training programs reduced recall questions from 737 (87.1%) to 75 (63.6%). The proportions of analytical MCQs increased from 2.8% (24) to 13.6% (16), application MCQs from 9.1% (77) to 17.8% (21), and evaluation MCQs from 0.9% (8) to 5.1% (6). A significant reduction in the difficulty index from 86.0 (66.67–95.1) to 61.1 (44.4–93.5), an increase in the discriminator index from 23.3 (11.0–34.5) to 34.4 (18.1–46.1), and an increase in zero nonfunctional distractors from 26 (12.2%) to 45 (39.5%) were noted after the second training program.

Conclusion: The training programs significantly improved assessment quality by improving item-analysis scores for higher-order thinking skills in MCQs prepared by the faculty. However, they were not effective in reducing MCQ item-writing flaws.

Keywords: Faculty training, Higher-order thinking, Item analysis, Medical education, Multiple-choice questions.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1739

INTRODUCTION

Multiple-choice questions (MCQs) are widely used in medical assessments because of their efficiency, reliability, and standardization.¹ The quality of MCQs affects students' competency levels. Well-constructed MCQs assess higher-order cognitive skills using Bloom's taxonomy and the knowledge domain of Miller's pyramid.¹ Poorly constructed MCQs can negatively affect assessment effectiveness and examinee outcomes, ultimately affecting student learning.² Framing MCQs is challenging, but a carefully curated question bank aids academic institutions in conducting assessments.¹

The formulation of MCQs and items is entrusted to faculty members, but many need to become familiar with standard MCQ guidelines for using higher-order thinking skills. One reason cited for poor MCQ/item formulation is a lack of faculty training, which contributes to flaws in MCQ writing.² Item analysis provides information on the validity and reliability of MCQs and is highly dependent on students' level of preparation.¹ Item-analysis metrics are often

used as indices for optimizing questions and preparing question banks.³ Optimization of MCQs produces more valid results, and pre-examination review based on feedback from previous item-analysis scores can augment the reliability of MCQs in the long term.⁴ These findings highlight the need to review and enhance the quality of test items, particularly by adjusting difficulty levels, improving item discrimination, and increasing distractor effectiveness to foster deeper engagement and learning. This may be possible by developing standard operating guidelines for setting MCQs.⁵

Research in the Indian context, in which item analysis was used to improve faculty skills after a single-day workshop on framing multiple-choice questions, found an improvement in item-writing flaws from 27.7 to 15% and reduced heterogeneity from 27.1 to 5.8%, with little improvement in MCQ writing.¹ Other studies conducted in Iran showed that faculty training in one-best MCQ writing significantly improved MCQ quality, decreasing flaw scores from pretest

to posttest, with common flaws found in the stem and lead-in.⁶ However, very few studies have looked at the residual effect of training programs on higher-order thinking skills related to multiple-choice questions in the Indian context.

Towards this end, a study was undertaken to compare item flaws before and 1 month after a training program for single-best-response, higher-order-thinking-skills MCQs prepared by faculty in a medical college, as well as item-analysis scores—facility value (FV), difficulty index (DFI), discrimination index (DI), nonfunctional distractors (NFDs), and distractor effectiveness (DE)—before and 1 month after the training program.

MATERIALS AND METHODS

Study Design and Participants

The study was an interventional, quasi-experimental study involving 32 consenting medical college faculty members at a private medical college in Karnataka, India. Participants were trained to frame single-best-response, higher-order-thinking-skills multiple-choice questions. The study was conducted for 4 months (1 March 2024–30 June 2024).

Data Collection

MCQ Writing Training Needs Assessment of the Faculty

Item-writing flaws and item-analysis metrics were obtained from the College Learning Management System (LMS). The study considered 889 multiple-choice questions available in the participating departments' question banks in the LMS; the questions were carefully evaluated by one of the authors to ascertain item-writing flaws.

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How to cite this article: Jacob AM, Hosapatna Laxminarayana KP. Multiple Choice Question Metamorphosis—Enhancing Question Quality through Faculty Training: A Pragmatic Study. *J Assoc Physicians India* 2026;74(10):55–58.

Because the multiple-choice questions had already been administered to medical students as part of their formative assessments, the built-in item analysis of the administered questions—difficulty index (P), discrimination index (D), and distractor efficiency (DE)—was used to establish baseline item-analysis metrics before the training among the faculty in the participating departments.

Training Intervention

The training was held in two consecutive sessions, 1 month apart, with the same faculty members trained in the first session. The training sessions broadly focused on:

- The principles of writing effective MCQs.
- The development of higher-order thinking skills (HOTS) questions.
- Methods to enhance item-analysis metrics.

The training program was administered in two interactive sessions, each lasting 3 hours. The first session trained the faculty in reducing item-writing flaws, and the second trained them in conducting item analysis. Hands-on training in developing higher-order thinking skills (HOTS) MCQs, such as application, analysis, evaluation, interpretation, critical thinking, case-vignette analysis, scenario-based reasoning, and problem-solving, rather than recall-based questions considered lower-order thinking skills (LOTS), was conducted during the first session. The second session provided hands-on training in conducting item analysis using the LMS of the department's course webpage and Microsoft Excel item-analysis sheets available through the Carlo Excels YouTube channel. The supplied resource link is retained in the source manuscript.

The faculty were provided with handouts at the end of both training sessions on strategies for creating effective MCQs, developing higher-order thinking skills (HOTS) questions, and improving item-analysis metrics. The faculty members were allowed to use any method of their choice to develop MCQs and administer them to students before the next training session. Each trained faculty member was required to complete 5–10 higher-order-thinking-skills questions in their specialty, administer them to medical students, and provide the LMS link or anonymized physical copies of the students' answer scripts to the authors for analysis of item-writing flaws and item-analysis metrics after the second training session.

After both training sessions, MCQs created by 27 of the 32 faculty members ($n = 154$) were evaluated for item-writing flaws and item-analysis metrics, including difficulty index (P), discrimination index (D), and distractor efficiency (DE), by one of the authors using standard methods for item analysis.

Statistical Analysis

Descriptive Statistics

The study analyzed faculty MCQ-writing flaws, including approximately 11 major item-writing flaws, rather than subject content per se. These included vague terms, negative statements, and long, complex options in the stem, lead-in, and option set, as shown in Table 1. The results are expressed as percentages and proportions.

The item analysis metrics included pre-training and after the second training program values of the DIF I/difficulty index, discriminatory index/ d value, and distractor efficiency index,

expressed as mean and standard deviation or median and interquartile range (IQR), as appropriate. Non-functioning distractors were graded as poor, moderate, good, or excellent, with percentages and proportions.

Inferential Statistics

For item-writing flaws: The Z test for proportions was used to compare frequencies between the pretraining values obtained from the LMS and the post-second-training-program item-writing flaws among faculty members.

For item analysis: The Mann-Whitney U test was used to compare item-analysis metrics between MCQs evaluated before training and those evaluated after the second training program. For faculty knowledge scores, paired t-test and Wilcoxon signed-rank test were used to compare pretest and posttest scores. The item-analysis metrics of faculty value/difficulty index, discrimination index, and distractor effectiveness in framing MCQs before training and after the second training program were expressed as frequencies and percentages and analyzed using chi-square tests and Z tests for proportions; $p < 0.05$ was considered statistically significant.

For faculty feedback at the end of each training program: Feedback on a 5-point Likert scale collected using Google Forms was expressed as frequencies and proportions. All data were entered in Microsoft Excel and analyzed using SPSS software, version 29.0. A p -value of <0.05 was considered statistically significant.

Ethics Considerations

The study involved faculty members attending training programs on framing

Table 1: Types of common flaws seen in framing multiple-choice questions before and after the training program among the faculty

Types of flaws in writing multiple-choice questions	Before training ($N = 889$) n (%)	After two training programs ($N = 153$) n (%)	Z value	p-value
Flaws related to the question stem				
Use of vague terms like frequent, most common, never, and always	0 (0)	0 (0)	–	–
The case scenario included is not related to the question	7 (0.8)	4 (2.6)	–2.04	0.041*
Flaws related to lead-in				
Negative statement (which is NOT/FALSE in the characteristic type of question)	24 (2.7)	9 (5.9)	–2.08	0.038*
Questions ending with ALL EXCEPT	137 (15.4)	9 (5.9)	3.14	0.002*
Flaws related to the option set				
Dissimilar length of the answer probe	103 (11.6)	19 (12.4)	–0.30	0.767
Long, complex options	29 (3.3)	4 (2.6)	0.42	0.673
Numbers in the option set are not in ascending/descending order	43 (4.8)	5 (3.3)	0.86	0.393
Use of overlapping numbers in the options ($n = 85$)	17 (1.9)	0 (0)	1.73	0.085
Words could have been added in the lead-in	145 (16.3)	21 (13.7)	0.81	0.420
Unfamiliar acronyms	55 (6.2)	5 (3.3)	1.43	0.152
Use of “none of the above” or “all of the above”	38 (4.3)	4 (2.6)	0.96	0.335

Z test for proportions; * $p < 0.05$ considered statistically significant

single-best-response multiple-choice questions and analyzing student scores. It adhered to ethical considerations and complied with the World Medical Association's Code of Ethics (Declaration of Helsinki) for human experiments. Faculty participants provided informed consent and a participant information sheet outlining the study purpose, risks, benefits, and the right to withdraw without penalty. The study ensured the confidentiality and anonymity of faculty and student data, preventing individual identification in reports or publications. The Institutional Ethics Committee (IEC) approved the study via letter INST.EC/EC/106/2024 dated 5 April 2024.

RESULTS

The training workshop was attended by 32 faculty members from the first to the fourth professional years, ranging from lecturers to professors and department

heads. There were 12 (37.5%) male and 20 (62.5%) female faculty members.

Item-writing Flaws

The faculty members' item flaws before and after the second training program are described in Table 1. Although the frequency of several item-writing flaws decreased after the second training program, a statistically significant reduction was observed in the use of questions ending with "ALL EXCEPT" (15.4% before training vs. 5.9% after training; $p = 0.002$). Though the number of negatively worded and instances where the case scenario was not related to the question apparently increased it may be attributable to the fewer questions evaluated in the post training session. The relative frequency of questions also varied significantly, with improved question quality resulting from a shift from recall (lower-order thinking skills) to application, analysis, evaluation, and case-based scenarios (higher-order thinking skills), as shown in Table 2.

Item-analysis Metrics

The difficulty index decreased from 86.0 (66.67–95.07) before training to 61.11 (44.44–93.38) after the second training program. The discrimination index increased from 23.33 (11.34–34.40) to 34.15 (18.18–45.45). Distractor effectiveness also increased from 36.36 (17.95–52.20) to 43.62 (26.70–62.25) after the second training program. There was a significant increase in the proportion of MCQs with zero nonfunctional distractors, from 26 (12.2%) to 44 (38.9%), and a significant reduction in those with two nonfunctional distractors, from 57 (26.8%) to 19 (16.8%). The proportions of MCQs with three nonfunctional distractors decreased from 83 (39.0%) to 33 (29.2%), while those with one nonfunctional distractor decreased from 47 (22.1%) to 17 (15.0%); these reductions were not statistically significant. Overall changes in item-analysis metrics are presented in Table 3. Table 4 shows a statistically significant increase in posttest scores for item-analysis knowledge

Table 2: Cognitive levels of multiple-choice questions before and after the training program among the faculty

Cognitive level	Pretraining (N = 889) n (%)	After two training programs (N = 153) n (%)	Z test value	p-value
Lower-order thinking (recall-based)	772 (86.8)	98 (64.1)	7.01	<0.001*
Higher-order thinking skills MCQ				
Application	84 (9.4)	26 (17.0)	-2.81	0.005*
Analytical	25 (2.8)	21 (13.7)	-6.07	<0.001*
Evaluation	8 (0.9)	8 (5.2)	-4.02	<0.001*
Case-vignette/scenario-based	68 (7.6)	44 (28.8)	-7.79	<0.001*

Z test for proportions; * $p < 0.05$

Table 3: Item analysis of single-best-response MCQs created by the faculty after two training programs ($n = 27$)

Item-analysis metrics	Pre-training median (IQR) (n = 213)	After two training programs, median (IQR) (n = 113)	Z† value	p-value
Difficulty index	86.0 (66.67–95.07)	61.11 (44.44–93.38)	3.37	<0.001*
Discrimination index	23.33 (11.34–34.40)	34.15 (18.18–45.45)	-4.10	<0.001*
Distractor effectiveness	36.36 (17.95–52.20)	43.62 (26.70–62.25)	-2.21	0.027*
Distractor efficiency	Pretraining (n = 213)	After two training programs (n = 113)	Z value	p-value
3 nonfunctional distractors (poor)	83 (39.0%)	33 (29.2%)	1.8	0.07
2 nonfunctional distractors (moderate)	57 (26.8%)	19 (16.8%)	2.05	0.039*
1 nonfunctional distractor (good)	47 (22.1%)	17 (15.0%)	1.55	0.121
Zero nonfunctional distractors (excellent)	26 (12.2%)	44 (38.9%)	5.7	<0.001*

IQR, interquartile range; †Mann-Whitney U test; Z test for proportions; * $p < 0.05$

Table 4: Knowledge scores of the faculty on item analysis at the end of two training programs ($n = 27$)

Characteristics	Pretest (out of 10)	Posttest (out of 10)	T value	p-value
Mean	4.1 ± 2.2	7.7 ± 2.1	5.83 [#]	<0.001
Range	1–8	3–10		
Median	3 (2–6.5)	8 (7–9)	-3.83 [‡]	<0.001

[#]Paired t-test; [‡]Wilcoxon signed-rank test; p-value < 0.05

Table 5: Feedback on the training program by the participants ($n = 22$)

Question	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
The workshop content on item analysis was clear and easy to understand	18 (81.8) [§]	2 (9.1)	1 (4.5)	1 (4.5)	0 (0.0)
The workshop provided a good balance between theory and practical application	15 (68.2) [§]	6 (27.3)	1 (4.5)	0 (0.0)	0 (0.0)
The resource persons were knowledgeable and engaging	19 (86.4) [§]	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)
After attending this workshop, I am confident that I can conduct an item analysis of MCQs	16 (72.7) [§]	5 (22.7)	0 (0.0)	1 (4.5)	0 (0.0)
I can understand the basics of item analysis in quality-assurance multiple-choice questions (MCQs)	15 (68.2) [§]	6 (27.3)	1 (4.5)	0 (0.0)	0 (0.0)
I can critically analyze MCQs for medical undergraduates that I framed myself using item analysis	15 (68.2) [§]	5 (22.7)	2 (9.1)	0 (0.0)	0 (0.0)
I am willing to conduct an item analysis for MCQs and am prepared to improve the quality of the multiple-choice questions I frame	15 (68.2) [§]	5 (22.7)	1 (4.5)	1 (4.5)	0 (0.0)

[§]represents the highest percentage

among faculty members participating in the workshop.

Feedback from the Faculty ($N = 22$)

Table 5 shows that the training program was successful, with participants finding the content clear, engaging, and practical; feeling confident in applying item-analysis techniques; and being highly motivated to implement their learning.

DISCUSSION

The study shows improvement in item-analysis metrics after training, with marked improvements in difficulty, distractor efficiency, and discrimination indices. Nonfunctional distractors decreased, and the number of questions based on recall decreased. Analytic, application, evaluation-related, and case-scenario-based multiple-choice questions increased. Significant reductions were observed in questions ending with "ALL EXCEPT."

Changes in Item-writing Flaws

The shift from lower-order thinking skills to higher-order thinking skills (HOTS) MCQs was an important outcome of the training. The proportion of recall-based questions decreased from 86.8% (772/889) pretraining to 64.1% (98/153) posttraining, while the proportion of questions assessing application increased from 9.4% (84/889) to 17.0% (26/153), analysis from 2.8% (25/889) to 13.7% (21/153), and evaluation from 0.9% (8/889) to 5.2% (8/153). This shift indicates a move away from predominantly recall-based assessment toward greater representation of higher-order cognitive skills following the training.

Changes in Item-analysis Metrics

The distribution of nonfunctional distractors differed significantly between pretraining

and posttraining items. In particular, there was a significant increase in items with zero nonfunctional distractors, from 26 (12.2%) to 44 (38.9%), and a significant reduction in items with two nonfunctional distractors, from 57 (26.8%) to 19 (16.8%). Items with three nonfunctional distractors decreased from 83 (39.0%) to 33 (29.2%), while those with one nonfunctional distractor decreased from 47 (22.1%) to 17 (15.0%); these individual reductions were not statistically significant.

CONCLUSION AND LIMITATIONS

The training program for faculty members in MCQ construction significantly improved assessment quality by reducing item flaws and increasing higher-order thinking skills. Regular training can improve MCQ assessment through item-flaw reduction and improvement in item-analysis metrics. However, the study's limitations include subjective bias in faculty selection and the need for training sessions to reinforce item writing flaws and item analysis to sustain the training program efforts.

CONFLICT OF INTEREST

None.

SOURCE OF SUPPORT

None.

AUTHOR CONTRIBUTIONS

AMJ: Conceptualization, study design, data curation and analysis, manuscript drafting—original draft, manuscript review and editing, final approval of manuscript; KPHL: Conceptualization, study design, manuscript drafting—original draft, manuscript review and editing, final approval of manuscript.

ARTIFICIAL INTELLIGENCE DISCLOSURE

During the preparation of this work, the authors used Turnitin to estimate the level of purported plagiarized content and QuillBot to paraphrase content flagged as supposedly plagiarized. After using these tools, the authors reviewed and edited the content as needed and took full responsibility for the final published article.

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ANNOUNCEMENT

ELECTION RESULTS OF API, PRF AND ICP

RESULTS OF THE ELECTION OF THE ASSOCIATION OF PHYSICIANS OF INDIA, PHYSICIANS OF RESEARCH FOUNDATION AND INDIAN COLLEGE OF PHYSICIANS 2027-2030

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Increasingly Recognized Long-term Side Effects of Proton Pump Inhibitors



CL Nawal¹, Govind Rankawat^{2*}, Hazari Lal Saini³, Radhey Shyam Chejara⁴

Received: 21 August 2025; Accepted: 10 March 2026

ABSTRACT

Proton pump inhibitors (PPIs) are the most commonly prescribed medicines to treat gastroesophageal reflux disease (GERD) and peptic ulcers. However, prolonged use of PPIs has been connected to many complications. These include pneumonia and *Clostridioides difficile* infection (CDI), which may result from impaired nutrient absorption due to hypochlorhydria; cognitive decline associated with reduced amyloid beta peptide clearance and decreased acetylcholine production; osteoporosis caused by a calcium absorption defect and transient receptor potential melastatin 6/7 (TRPM6/7)-linked dysregulation of bone remodeling; chronic kidney disease (CKD) driven by acute interstitial nephritis and vascular calcifications resulting from hypomagnesemia; and an increased risk of metabolic syndrome with type 2 diabetes mellitus. Given these potential adverse effects, health care providers must use PPIs carefully, ensuring that treatment is necessary at the start and continually reevaluated during long-term use.

Keywords: Adverse events, Gut microbiota, Hypergastrinemia, Proton pump inhibitors.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1656

INTRODUCTION

Proton pump inhibitors (PPIs) have become a mainstay in modern medical treatment, widely endorsed by clinicians due to their proven efficacy and strong safety profile in managing gastroesophageal reflux disease (GERD). In addition, PPIs play a significant role in healing peptic ulcer-related disease and minimizing the risk of gastropathy related to nonsteroidal anti-inflammatory drugs (NSAIDs), reinforcing their position as a go-to therapeutic option.¹ These agents act on parietal cells and block the H⁺/K⁺-ATPase enzyme. However, these very properties have also led to the widespread overuse and inappropriate prescribing of PPIs. Many physicians continue recommending them for extended durations, while a substantial number of patients use them without medical oversight, often purchasing them over the counter. Additionally, aggressive marketing by pharmaceutical companies has contributed to this trend. Adverse outcomes such as lupus erythematosus, acute interstitial nephritis (AIN), hypomagnesemia, bone fractures, and vitamin deficiency—several of which have been highlighted in Food and Drug Administration (FDA) warnings—are increasingly associated with long-term use.² Numerous international studies have reported that PPIs are frequently used in both inpatient and outpatient settings. The two major concerns tied to prolonged PPI use are the elevated cost of therapy and the heightened risk of side effects.

EVIDENCE-BASED DEPLOYMENT OF PROTON PUMP INHIBITOR: NAVIGATING THE PITFALLS OF OVERUTILIZATION

Proton pump inhibitors have provided significant therapeutic benefits, greatly improving the lives of patients with refractory GERD and the risk of iatrogenic upper gastrointestinal issues. Short-term use of PPIs has shown effectiveness in managing various gastrointestinal disorders, including peptic ulcer disease. However, excessive prescribing of PPIs remains common in both primary and secondary care settings. While their use is justified for patients with persistent acid-related symptoms or a high risk of developing such conditions, irrational prescribing practices have become widespread. This inappropriate use not only raises the risk of adverse drug reactions but also leads to unnecessary health care expenses.

A large part of this excessive use originates in primary health care centers, where patients are often kept on long-term PPI therapy without reevaluation.³ A study conducted at different centers revealed that PPI use was highest in intensive care units (ICUs), where 95% of patients received PPIs, with pantoprazole being the most commonly prescribed, accounting for nearly 90% of cases. Additionally, about one-third of PPI administrations were intravenous, mainly within medical wards. Almost 90% of admitted patients were prescribed a PPI.⁴ Self-

medication and unmonitored use of PPIs are also major concerns, frequently leading to drug interactions and side effects. A prospective survey from a rural teaching hospital suggests that almost 50% of patients used PPIs without clear clinical indications. Among them, 64% either received prescriptions from unqualified sources or purchased the medications without medical approval.

Patient-specific factors, such as age, underlying health conditions, genetic traits, and concurrent medications, play a crucial role in determining the likelihood and severity of side effects from PPI use. Including patient perspectives in future research can help better understand the risks and improve therapeutic outcomes through patient-centered care.⁵ Another concern is rebound acid hypersecretion that may occur after stopping PPIs following several weeks of use, often resulting in resumed therapy and potential long-term dependence.⁶ To improve appropriate PPI use, health care providers should conduct personalized risk assessments to identify individuals most vulnerable to adverse outcomes. Evidence indicates that 82% of complications associated with PPIs are seen in patients with preexisting risk factors, highlighting the need for tailored prescribing of PPIs.⁷ Alarming, more than two-thirds of patients continue PPI therapy after discharge from the hospital without valid justification.

Clinicians are recommended to follow best practices, including prescribing intermittent therapy at the lowest effective dose. Suggested durations of PPI therapy are 4–8 weeks for GERD and peptic ulcers, 10–14 days for *Helicobacter pylori* eradication, up to 12 months for short bowel syndrome, and 12 weeks (extendable to 6 months) for high-risk NSAID users to minimize ulcer risk. In some cases, such

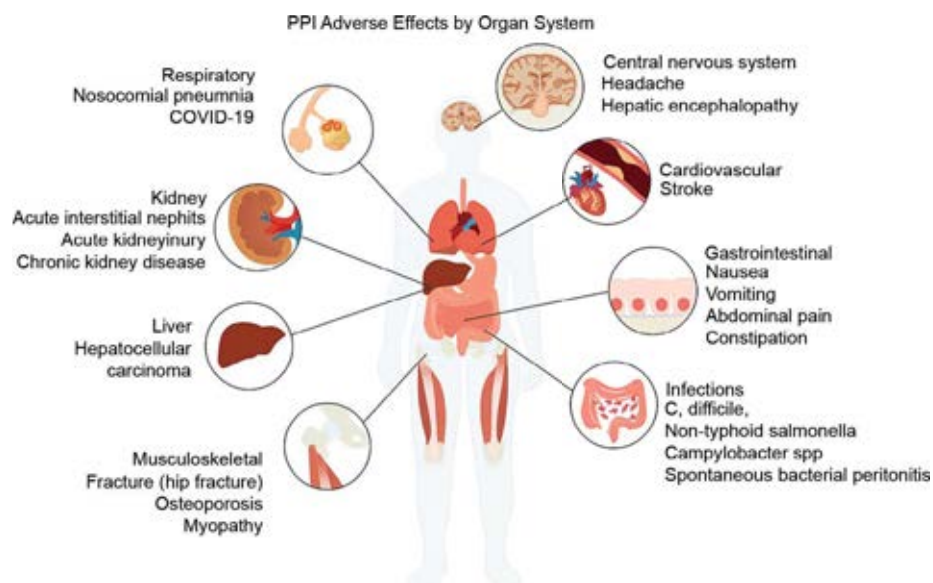
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How to cite this article: Nawal C, Rankawat G, Saini HL, et al. Increasingly Recognized Long-term Side Effects of Proton Pump Inhibitors. *J Assoc Physicians India* 2026;74(10):60–69.

Table 1: Extended PPIs therapy and its risks with their proposed mechanisms⁹

S. No.	Adverse effect	Proposed mechanism(s)
1	Renal complications	Accumulation of PPI in the tubulo-interstitium → immune-mediated interstitial inflammation → acute interstitial nephritis (AIN) → progression to acute kidney injury (AKI) → chronic interstitial fibrosis → CKD → end-stage renal disease (ESRD)
2	Cardiovascular risks (myocardial infarction, stroke)	Increased asymmetric dimethylarginine (ADMA) → reduced nitric oxide → endothelial dysfunction; reduced vitamin C and B12 levels; enhanced oxidative stress
3	Fractures	Impaired calcium absorption due to insoluble calcium salts in hypochlorhydric conditions and PPI-induced hypergastrinemia
4	Infections (<i>C. difficile</i> , community-acquired pneumonia)	Suppressed gastric acid → diminished barrier function → increased bacterial colonization with subsequent overgrowth in the GI tract
5	Micronutrient deficiencies (Mg ²⁺ , Iron, and vitamin B12)	Reduced acid-dependent mineral absorption, altered transporter activity, and gut microbiota dysbiosis
6	Hypergastrinemia	Chronic suppression of gastric acid → persistent stimulation of G-cells → elevated gastrin secretion
7	Cancer risk (GIT and hepatic cancer)	Long-term acid suppression → enterochromaffin-like (ECL) cell hyperplasia, bacterial overgrowth, and hypergastrinemia
8	Hepatic encephalopathy	Reduced gastric acid → impaired absorption of vitamin B12, magnesium, and iron; increased β -amyloid accumulation
9	Type 2 diabetes mellitus	Altered gut microbiota, magnesium depletion, reduced incretin response, and weight gain

**Fig. 1:** PPI therapy-associated adverse effects¹⁰

as after lung transplantation, long-term or indefinite use may be necessary.⁸ PPIs are not advised for infants because of limited efficacy and safety data. Dosing should always be conservative to lower the risk of complications.

LONG-TERM CONSEQUENCES OF PROTON PUMP INHIBITOR THERAPY

Excessive use of PPIs has become a growing concern, highlighting the need to understand their potential long-term adverse outcomes. Over the last decade, several complications linked to prolonged PPI therapy have been documented. Recent studies increasingly

report significant associations between extended PPI use and conditions such as type 2 diabetes mellitus (T2DM), metabolic syndrome, cognitive decline, including dementia, vitamin B12 deficiency, and an elevated risk of bone fractures in adults (Tables 1 and 2; Fig. 1).

INFECTIONS

Clostridioides difficile Infection

Numerous studies have explored the potential link between PPIs and infections, particularly *Clostridioides difficile* infection (CDI)¹¹ and pneumonia.¹² PPIs may disrupt the balance of gut flora, thereby fostering an environment conducive to the development

of various infections. Gastric hydrochloric acid acts as a primary defense and neutralizes pathogens present in ingested food or accidentally swallowed bacteria. Long-term suppression of stomach acid through PPI therapy compromises this barrier, permitting microbes to survive and multiply in the gastrointestinal system. PPIs raise gastric pH, creating conditions favorable for gut microbial growth, promoting bacterial translocation, and influencing anti-inflammatory and immune-regulatory functions.¹³

A meta-analysis conducted by Deshpande et al. reviewed 30 studies across 29 journals and reported that PPI therapy is associated with a doubled risk of CDI.¹¹ Additional research carried out in hospital settings further supported this association, revealing a significant increase in CDI cases among general ward patients receiving PPI therapy.¹⁴ In a study by Lewis et al., hospital-acquired CDI incidence and severity outcomes were analyzed between patients receiving PPIs and those who were not. The findings demonstrated that PPI use correlated with a higher frequency and greater severity of hospital-acquired CDI.¹⁵ Moreover, a retrospective observational study indicated that prolonged PPI use was linked with a high risk of CDI, with PPIs posing a greater threat than histamine-2 receptor antagonists (H2RAs).¹⁶ Within pediatric populations, PPIs also showed a stronger association with CDI and recurrent infections when compared with H2RAs.¹⁷ In response to these findings, the Food and Drug Administration (FDA) has issued warnings about the potential association between the use of PPIs and CDI. It advises that patients taking PPIs who develop

Table 2: PPI-related adverse events: mechanism and their effects

Mechanism	Effect
Clostridium difficile infection	
↑ Gastric pH	↓ Acid barrier → <i>C. difficile</i> spores survive
Altered gut microbiota	↓ Colonization resistance → spore germination
Antibiotic synergy	↑ Combined risk of CDI
↓ Immune response (theoretical)	↓ Host clearance of <i>C. difficile</i> and its toxins
Community-acquired pneumonia	
Hypochlorhydria	PPIs suppress gastric acid, reducing the stomach's natural barrier to ingested pathogens
Bacterial overgrowth in upper GI tract	Pathogens like <i>S. pneumoniae</i> and <i>Haemophilus influenzae</i> may colonize the oropharynx and esophagus
Microaspiration	Overgrown gastric contents can be aspirated into the lungs, especially during sleep, leading to CAP
Impaired immune function	Long-term PPI use may affect neutrophil and macrophage function, although this is less clearly proven
Vitamin B12 deficiency	
In food, vitamin B12 is attached to proteins and is liberated through the action of gastric acid	Suppression of gastric acid by PPIs limits the release of vitamin B12 from ingested food
In the stomach, free B12 complexes with intrinsic factor, enabling absorption in the ileum	Chronic hypochlorhydria reduces IF activity and alters gastric environment
Hypomagnesemia	
↑ Gastric pH (from PPI)	↓ Mg salt solubilization
↓ TRPM6/TRPM7 activity	↓ Active Mg absorption in intestine
↓ Mg absorption	Chronic hypomagnesemia
(Rare) renal Mg loss	Contributes in susceptible individuals
Osteoporosis	
↓ Stomach acid	↓ Calcium absorption
Hypomagnesemia	Impaired PTH and bone regulation
Hypergastrinemia	↑ Bone resorption
↓ Vitamin B12	↑ Homocysteine → weak bone matrix
Potential direct bone cell effects	Possible ↓ bone formation
Reduced TRPM 7 channel protein expression	Reduced bone proliferation
Dementia	
↓ Gastric acid → ↓ B12	Cognitive decline, ↑ homocysteine
↓ Mg ²⁺ and Fe absorption	Neuronal dysfunction, poor neurotransmission
↑ β-amyloid production	Alzheimer-like pathology
Microbiota alteration → inflammation	Neuroinflammation, cognitive decline
↓ Choline acetyltransferase	↓ Acetylcholine → memory impairment
Kidney impairment	
Acute interstitial nephritis	Tubular damage → interstitial fibrosis
Hypomagnesemia	Tubular injury, nephrocalcinosis
Oxidative stress	Endothelial damage → glomerulosclerosis
Altered microbiome	Uremic toxin accumulation
Volume depletion	Ischemic injury → CKD progression

persistent diarrhea ought to be investigated for possible *C. difficile*-associated diarrhea (CDAD).¹⁸

Pneumonia

The characteristics of pneumonia include inflammation of the lung tissue, often resulting in fluid or pus accumulation in the alveoli. The most common bacterial pathogens responsible for pneumonia include *Streptococcus pneumoniae* and *Mycoplasma*

pneumoniae. A growing body of research has suggested an association between the use of PPIs and the diagnosis of pneumonia. In October 2011, the American College of Chest Physicians (ACCP) conducted a meta-analysis comprising 1,20,863 pneumonia cases reported between 1987 and 2006 to explore this association, focusing specifically on community-acquired pneumonia (CAP). The analysis, which considered variables such as PPI dose, duration, and timing of

use, concluded that PPIs were significantly associated with an increased risk of CAP.¹⁹

Another systematic review involving 33 studies further examined the risk of CAP among outpatient PPI users. The findings showed a 1.49-fold increase in CAP risk, regardless of age or PPI dosage, with the highest risk occurring within the first month of initiating therapy. PPI use also correlated with a greater likelihood of hospitalization due to CAP during this early treatment period.²⁰

The underlying mechanisms proposed for this association include a reduction in gastric acidity, which diminishes the stomach's defense against ingested pathogens. This altered environment facilitates bacterial survival and potential colonization of the upper gastrointestinal tract, increasing the chance of aspiration. Additionally, changes in the oropharyngeal and gastric microbiota, coupled with impaired immune responses such as neutrophil dysfunction, may further elevate the risk.

Research indicates that the likelihood of developing CAP is nearly three times higher in individuals who begin PPI therapy within 30 days. Although the oropharyngeal bacterial profile remained similar among current, former, and nonusers of PPIs, users were more frequently diagnosed with infections caused by *S. pneumoniae*, which contributes to the observed rise in CAP cases.^{21,22}

Another meta-analysis involving nearly 10 lakh participants supported the connection between PPI use and CAP, with new users of PPIs having a twofold higher risk of CAP than those not using the medication.²³ In a primary care cohort of 75,050 individuals aged 60 years and above, those on a 1-year PPI regimen demonstrated a heightened risk of developing pneumonia in the subsequent years following initiation of the medication, with this pattern being consistent across various age and comorbidity groups.²⁴ Altogether, CAP is increasingly recognized as a possible adverse outcome associated with prolonged or inappropriate PPI use.

NUTRITIONAL DEFICIENCY

Vitamin B12 Deficiency

Vitamin B12 is necessary for the proper functioning of the central nervous system, myelin formation, red blood cell synthesis, and DNA replication.²⁵ It also acts as an important cofactor involved in fatty acid as well as amino acid metabolism during DNA synthesis. The leading cause of vitamin B12 deficiency is malabsorption, typically resulting from insufficient intrinsic factor or reduced acid-pepsin activity, such as in cases of hypochlorhydria.²⁶ Vitamin B12 absorption involves a two-step process. In the first stage, hydrochloric acid in the stomach helps release vitamin B12 from dietary proteins. In the next stage, intrinsic factor (a glycoprotein necessary for its absorption in the ileum) attaches to vitamin B12 for absorption.²⁷ Consequently, long-term suppression of gastric acid by PPIs may hinder this process, elevating the likelihood of developing vitamin B12 deficiency.²⁸

This risk is particularly pronounced among older adults. Prolonged use of PPIs is linked with declining vitamin B12 levels in geriatric populations.²⁹ For example, institutionalized elderly individuals taking PPIs for 1 year exhibited a significant reduction in vitamin B12 levels compared with those not using the drugs.³⁰ Moreover, when PPIs are used in combination with medications such as metformin, the reduction in vitamin B12 levels can be more pronounced.²⁸ A study examining older adults showed a strong association between chronic use of PPIs and histamine-2 receptor antagonists (H2RAs) and vitamin B12 deficiency, which may manifest through hematologic, neurological, and psychiatric symptoms. However, this association was not observed with short-term PPI use. Collectively, chronic PPI use can interfere with vitamin B12 absorption, potentially resulting in clinically significant deficiency, particularly in elderly populations.³¹

Hypomagnesemia

A study exploring the association between chronic PPI use and hypomagnesemia identified two cases in which individuals developed severe deficiencies of magnesium, potassium, and calcium. These symptoms improved after the discontinuation of PPI therapy, highlighting a potential causal relationship.³² A large cohort study involving 9,818 participants demonstrated that PPI users were twice as likely to develop hypomagnesemia compared with those not taking PPIs. The risk further increased when PPIs were used alongside loop diuretics, suggesting a compounding effect.³³ Interestingly, switching to a different PPI did not alleviate the hypomagnesemia, indicating a class effect across all PPIs. According to the Food and Drug Administration Adverse Event Reporting System (FAERS), pantoprazole presented the highest association with hypomagnesemia, while esomeprazole had the lowest. The data also showed that older individuals and males were more susceptible to this adverse effect, and cases of PPI-induced hypomagnesemia were frequently accompanied by concurrent hypokalemia and hypocalcemia. Females, in contrast, exhibited a significantly lower risk of developing hypomagnesemia.³⁴

In another study comparing hospitalized adults on PPIs with nonusers, the average magnesium level measured in PPI users was 1.19 mg/dL, compared with 2.0 mg/dL in those not using PPIs. Even after adjusting for confounding variables, the likelihood of hypomagnesemia remained approximately doubled in those receiving PPIs.³⁵ The risk

of developing hypomagnesemia increases with higher PPI dosages. Severe magnesium deficiency due to PPI therapy has the potential to cause severe neuromuscular and cardiac issues, often presenting in combination with low calcium and potassium levels.³⁶ Magnesium uptake occurs through two pathways: passive diffusion and an active transport mechanism within the gastrointestinal tract. Active absorption is primarily mediated by transient receptor potential melastatin 6 and 7 (TRPM6 and TRPM7) channels, which are present on the apical membrane of enterocytes. These channels facilitate the movement of magnesium into the bloodstream. However, PPIs may alter intestinal pH levels, potentially impairing the function of TRPM6/TRPM7 channels and disrupting magnesium transport. As a result, prolonged PPI use can hinder both active and passive absorption of magnesium, contributing to hypomagnesemia.³⁷

Hypocalcemia and Hypokalemia

Evidence from over 10 million adverse event submissions available in the Food and Drug Administration Adverse Event Reporting System (FAERS) suggests a significant link between PPI use and electrolyte disturbances such as hypocalcemia and hypokalemia. Prolonged PPI therapy may impair calcium absorption, predisposing patients to hypocalcemia. In addition, hypokalemia observed in PPI users may be secondary to PPI-induced chronic kidney disease (CKD).³⁸

Anemia

Several case reports and observational studies have documented PPI-associated anemia. Multiple mechanisms have been proposed, including impaired iron absorption resulting from PPI-induced hypochlorhydria.³⁹ Furthermore, PPIs may reduce iron availability by increasing the expression of hepcidin, a peptide hormone that regulates iron homeostasis and inhibits duodenal ferroportin-mediated iron export.⁴⁰

OSTEOPOROSIS AND FRACTURE

Skeletal complications, including osteoporosis and fragility fractures, remain an important concern with chronic use of PPIs. A large population-based study in Canada reported an elevated risk of nontraumatic fractures among chronic PPI users. Notably, this association persisted even after adjusting for traditional risk factors such as femoral neck bone density, suggesting that PPI therapy independently contributes to an increased incidence of fragility fractures in both men and women.⁴¹

PPI-induced achlorhydria decreases calcium solubility, thereby impairing its absorption.⁴² Prolonged use of PPIs, particularly beyond 7 years, has been strongly associated with osteoporosis-related fractures, while use exceeding 5 years is linked to an elevated risk of hip fracture.⁴³ Among postmenopausal women, PPI therapy has been correlated with a significant increase in osteoporosis risk. According to the Women's Health in Lund Area (WHILA) study, use of PPIs was associated with a nearly twofold rise in osteoporosis risk and premature fractures during extended monitoring.⁴⁴ Similarly, a German cohort study revealed that the risk of osteoporosis and associated fractures escalates with the duration of PPI treatment, further emphasizing a time-dependent relationship.⁴⁵

A multicenter Canadian osteoporosis study reported that individuals using PPIs exhibited lower baseline bone mineral density (BMD), particularly at the neck of the femur and total hip, compared with those not using PPIs. However, PPI use did not significantly influence the rate of BMD loss over time. Nonetheless, prolonged PPI therapy used at higher doses has been associated with a heightened risk of hip fractures.^{46,47}

The profound reduction in stomach acid caused by PPIs, particularly among older adults, can impair calcium absorption, a critical factor for bone health.⁴⁸ Various other studies have demonstrated that PPI treatment may hinder calcium uptake and contribute to reduced bone density.⁴⁹ Although PPIs reduce bone resorption by inhibiting osteoclastic vacuolar-type H⁺-ATPase pumps, they also compromise calcium absorption because of the hypochlorhydric environment they create.⁴⁷

A meta-analysis suggested that PPI users faced a 26% higher risk of hip fractures relative to those who did not use these medications. Several epidemiological investigations have similarly linked PPI therapy to a higher occurrence of hip fractures.^{47,50} Further insight into the mechanism was provided by research into the transient receptor potential melastatin 7 (TRPM7) channel, which is expressed in osteoblasts as well as osteoclasts and plays a vital role in bone development. An *in vitro* study examining pantoprazole's effect on TRPM7 demonstrated dose-dependent inhibition of cell viability and a reduction in TRPM7 protein expression in both osteoblastic and osteoclastic cells.⁵¹ This suggests that PPIs may negatively impact bone remodeling by disrupting cellular pathways essential to bone turnover.⁵²

Moreover, extended use of PPIs has repeatedly been correlated with an increased

fracture risk involving the hip, spine, and wrist. This elevated risk may stem from reduced calcium solubility and absorption secondary to hypochlorhydria, as well as hypergastrinemia induced by long-term acid suppression.⁵³ A meta-analysis encompassing 11 studies suggested a modest increase in fracture incidence at various anatomical sites among PPI users, reinforcing the link between prolonged PPI therapy and skeletal fragility.⁵⁴

DEMENTIA

Dementia encompasses a wide range of conditions, with Alzheimer's disease accounting for the largest proportion of cases among the elderly. Several studies have indicated a potential link between chronic use of PPIs and a heightened risk of dementia and Alzheimer's disease in the elderly.⁵⁵ A review study has also identified a strong association between the use of PPIs and cognitive decline.⁵⁶ National Health and Nutrition Examination Survey (NHANES) data (1999–2012) reported a notable rise in PPI prescriptions among US adults aged 40–60 years, increasing from 4.9 to 8.3%. This growing trend, particularly among the aging population, has raised safety concerns because of possible cognitive side effects.⁵⁷ Evidence suggests that elderly individuals regularly taking PPIs may face a significantly higher risk of developing dementia.⁵⁸

A pharmacoepidemiologic cohort study compared dementia risk among users of histamine-2 receptor antagonists (H2RAs) and PPIs with nonusers. Results indicated that both medication groups were associated with an increased incidence of dementia.⁵⁹ Several mechanisms have been proposed to explain this relationship. For instance, *in vitro* research has shown that chronic use of PPIs may impede the clearance of amyloid beta (Aβ), a hallmark of Alzheimer's pathology. Microglial elimination of fibrillary Aβ requires proper lysosomal acidification, a process disrupted by PPI-mediated inhibition of V-ATPase proton pumps, leading to reduced Aβ degradation and accumulation.⁶⁰

Additionally, PPIs are inverse modulators of γ-secretase while also enhancing the activity of β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), both of which are involved in Aβ production and plaque formation.⁶¹ Another contributing factor is vitamin B12 deficiency, commonly associated with prolonged PPI use. This deficiency can impair cognitive function by disrupting DNA synthesis and methylation pathways and by increasing neurotoxic homocysteine levels.⁶² Vitamin B12 is essential for one-carbon metabolism, supporting the synthesis

of neurotransmitters, phospholipids, and nucleotides. A deficiency can lead to hyperhomocysteinemia, which, along with reduced methylation, has been implicated in dementia and Alzheimer's disease. Elevated homocysteine levels and impaired methylation may also reduce protein phosphatase 2A activity, promoting tau protein hyperphosphorylation and aggregation, a key feature of Alzheimer's pathology.^{63–65}

Animal model studies have further supported these findings, demonstrating that PPI treatment increases brain Aβ levels by modulating β- and γ-secretase activity⁶⁶ and contributes to vitamin B12 deficiency, which has been correlated with cognitive dysfunction.⁶¹ Moreover, PPIs inhibit choline acetyltransferase, which reduces the synthesis of acetylcholine, a neurotransmitter critical for learning and memory.⁶⁷ A reduction in acetylcholine production can significantly affect cognitive performance, increasing the risk of dementia. Overall, current evidence indicates a concerning link between long-term PPI use and the onset of dementia.⁶⁸ This highlights the necessity of monitoring chronic PPI administration, especially in older adults, by weighing the therapeutic benefits against potential cognitive risks.

KIDNEY DISEASES

A potential causal relationship has been found between the utilization of PPIs and the development of CKD.⁶⁹ A study identified an independent correlation between PPI therapy and a 20–50% elevation in the risk of CKD. Notably, the study indicated that PPI therapy alone could be a contributing factor to kidney dysfunction.⁷⁰ The association was more clearly demonstrated in patients aged 18 years and above with no previous history of kidney disease. When these individuals initiated PPI therapy and were followed longitudinally, they exhibited a significantly increased frequency of acute kidney injury compared with those not taking PPIs.⁷¹ Extended PPI therapy has been associated with a 1.3-fold higher likelihood of developing CKD or advancing to end-stage renal disease (ESRD), relative to those treated with histamine-2 receptor antagonists (H2RAs). Importantly, such a correlation was not found in the H2RA group, indicating a distinct risk pattern unique to PPI exposure.⁷² Various clinical trials related to PPI-associated kidney impairment are shown in Table 3.

Several studies have investigated the underlying mechanisms through which PPIs may lead to kidney function decline. One proposed pathway involves PPI-

Table 3: Evidence linking PPIs with renal and vascular complications⁷³

Study	Study characteristics	Key outcome
Lee et al., 2018	Included patients >18 years who received PPIs for 1–2 years	PPI use was longer in patients with CKD compared to non-CKD patients
Fusaro et al., 2013	Evaluated aortic and iliac artery calcification among PPI users	PPI utilization was significantly associated with increased arterial calcifications
Giusti et al., 2021	Utilized the US Veterans Affairs database to assess PPI use and kidney function decline	PPI use accelerated kidney dysfunction; hazard ratio 1.82 with 95% CI: 1.53–2.9

induced hypomagnesemia, which can lead to increased renal calcification.⁷⁴ In patients undergoing hemodialysis, chronic PPI use has been associated with a higher incidence of vascular calcification. Magnesium serves as a natural inhibitor of calcification, so a PPI-related reduction in magnesium levels may exacerbate vascular calcification, particularly in individuals with CKD. Another well-documented mechanism is characterized by the emergence of acute interstitial nephritis (AIN) triggered by PPI use.⁷⁵ The metabolites of PPIs may function as haptens,⁷⁶ binding with larger peptides and contributing to immune complex formation, which is later deposited within renal tubular structures. This stimulates an immune response, predominantly mediated by T cells, which release inflammatory cytokines and chemotactic agents that contribute to interstitial inflammation and kidney injury.⁷⁷

CARDIOVASCULAR COMPLICATIONS: MYOCARDIAL INFARCTION AND STROKE

The use of PPIs has been associated with increased concentrations of asymmetric dimethylarginine (ADMA), which suppresses nitric oxide synthase activity. PPI therapy may interfere with the normal functioning of dimethylarginine dimethylaminohydrolase (DDAH), thereby increasing circulating ADMA concentrations. This imbalance reduces nitric oxide (NO) bioavailability, resulting in heightened vascular tone, impaired vasodilation, and a predisposition to cardiovascular adverse outcomes, including myocardial infarction (MI) and ischemic stroke.⁷⁸

Clinical evidence supports this proposed mechanism. A cohort study involving 27,624 participants without prior ischemic heart disease revealed that chronic or high-dose exposure to PPIs was significantly linked with the onset of acute MI.⁷⁹ Furthermore, chronic PPI use has been statistically correlated with cerebral small vessel disease, particularly deep white matter disease, as revealed through multivariate Cox regression, which

is a well-recognized precursor of stroke and cognitive decline.⁸⁰

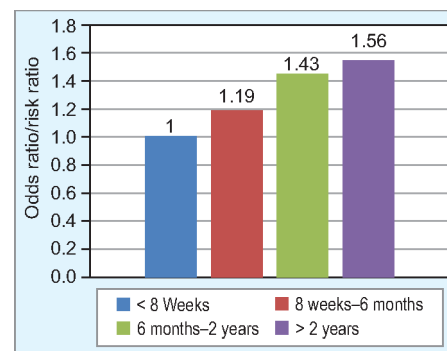
Large population-based studies corroborate these findings. A Danish nationwide cohort study of nearly 214,000 individuals reported that sustained PPI therapy was associated with a greater incidence of primary ischemic stroke and myocardial infarction.⁸¹ Similarly, retrospective cohort data from Taiwan showed that PPI therapy was associated with higher rates of hospitalization for ischemic stroke.⁸²

METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS

Several studies have demonstrated an association between long-term PPI use and an elevated likelihood of developing type 2 diabetes mellitus (T2DM) and metabolic syndrome. A large retrospective study including 7,77,429 new PPI users identified 50,535 patients with diabetes and compared them with matched controls by age, sex, and clinical characteristics, revealing an association between PPI therapy and the development of diabetes.⁸³

The risk appears to be duration-dependent. Patients receiving PPIs for durations between 8 weeks and 2 years exhibited a higher incidence of diabetes than those exposed for shorter durations (Fig. 2).⁸³ Furthermore, frequent PPI users showed a 24% greater chance of developing diabetes relative to nonusers, with the risk escalating progressively with prolonged treatment. This finding has been consistently validated in three large prospective cohort studies.⁸⁴

In another investigation, research found that 73.9% of elderly patients were inappropriately prescribed PPIs. The excessive prescribing was strongly associated with underlying cardiac and metabolic conditions, underscoring concerns about the overutilization of these medications in elderly individuals with multiple comorbidities.⁸⁵ One of the mechanisms potentially connecting PPI use to diabetes is PPI-induced hypomagnesemia.⁸⁶ Hypomagnesemia is repeatedly observed to worsen blood

**Fig. 2:** Relationship between PPI duration and odds ratio (risk ratios)⁷³

glucose control in patients with type 1 as well as type 2 diabetes. Magnesium supplementation has been demonstrated to enhance insulin sensitivity while lowering insulin requirements. In one study, diabetic individuals receiving 250 mg of magnesium hydroxide twice daily showed reduced insulin requirements compared with healthy controls.⁸⁷ Similarly, another case-control study involving 200 subjects suggested that magnesium depletion in obese patients with diabetes is influenced by the degree of metabolic control.⁸⁸

Four weeks of oral magnesium administration in elderly patients with type 2 diabetes led to reduced fasting glucose levels, increased intracellular magnesium, and a modest but statistically significant improvement in pancreatic β -cell responsiveness. These findings suggest that chronic magnesium deficiency, possibly exacerbated by PPI use, may impair glucose metabolism, insulin signaling, and overall glycemic control.⁸⁹ Additional studies have linked hypomagnesemia in diabetic individuals with complications such as retinopathy, nephropathy, and diabetic foot ulcers.⁹⁰ Mather et al. found hypomagnesemia in approximately 25% of the diabetic patients studied.⁹¹ Given that PPIs may contribute to or worsen magnesium deficiency, there is a plausible link between their use and impaired glycemic control. This underscores the need for ongoing monitoring of both diabetic and nondiabetic individuals on long-term PPI therapy.

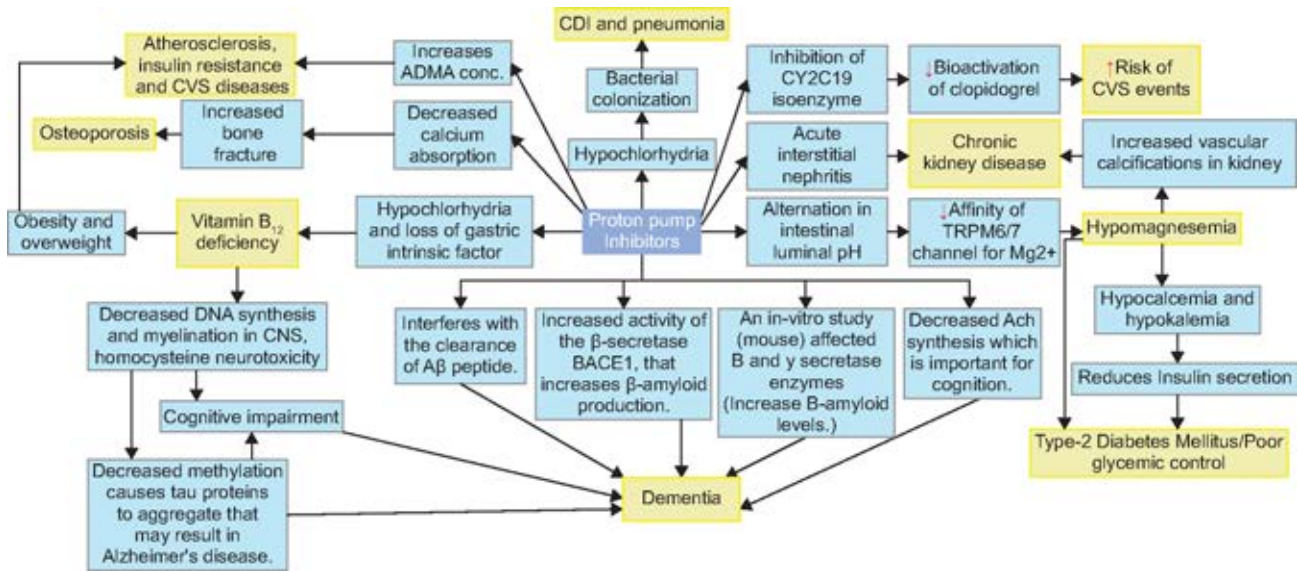


Fig. 3: Cascade of adverse outcomes associated with long-term PPI use⁷³

Nitric Oxide, Asymmetric Dimethylarginine, and Cardiovascular Risk

Nitric oxide (NO), a critical molecule synthesized by endothelial cells *via* endothelial nitric oxide synthase (eNOS), plays a fundamental role in maintaining vascular health.⁹² It regulates vascular tone, inhibits platelet aggregation, and limits leukocyte adhesion, making it essential for cardiovascular protection.⁹³ Asymmetric dimethylarginine (ADMA) is a naturally occurring inhibitor of eNOS, and elevated levels have been linked to increased cardiovascular risk.⁹⁴ PPIs have been shown to raise plasma levels of ADMA by inhibiting dimethylarginine dimethylaminohydrolase (DDAH), the enzyme responsible for its degradation. This inhibition reduces NO synthesis, impairs endothelium-dependent vasodilation, and contributes to vascular dysfunction. Because individuals with diabetes already tend to have higher ADMA levels, the addition of PPI therapy may exacerbate their cardiovascular risk.⁹⁵

Secondary Hypergastrinemia and Other Long-term Risks

Chronic PPI use suppresses gastric acid secretion, resulting in compensatory hypergastrinemia. Elevated gastrin levels stimulate enterochromaffin-like (ECL) cell proliferation, potentially increasing the risk of gastric carcinoid tumors and various histopathological modifications in the gastric lining. Moreover, this persistent elevation may trigger rebound acid hypersecretion when PPI therapy is discontinued, complicating the management of acid-related disorders. Extended PPI therapy has also been linked with a variety of other complications, including

an increased risk of infections, nutrient deficiencies (notably calcium, magnesium, and vitamin B12), and osseous fractures, especially in geriatric individuals or those with underlying liver disease.

Given these risks, medical professionals are urged to adopt judicious prescribing practices. Trials such as STOPPIT have explored the outcomes of deprescribing PPIs in high-risk groups. Alternative approaches, including the use of histamine-2 receptor antagonists (H2RAs), lifestyle changes, or step-down strategies, are recommended to reduce long-term PPI dependence while maintaining effective symptom control. Routine reevaluation of the need for PPI therapy, informed by clinical guidelines and patient-specific factors, is vital for achieving better outcomes and lowering the likelihood of adverse effects (Figs 3 and 4).

EXPLORING THE CONNECTION BETWEEN EXTENDED PROTON PUMP INHIBITOR THERAPY AND CANCER SUSCEPTIBILITY

Emerging evidence suggests that extended PPI therapy has been linked to a potentially higher risk of several cancers, such as gastric, pancreatic, colorectal, and liver malignancies. A comprehensive umbrella review of 21 meta-analyses, covering 65 observational studies, found that PPI use is associated with a statistically significant higher risk of these cancers.⁹⁷

Gastric Cancer

Multiple studies identified a positive correlation between chronic PPI use and the development of gastric cancer. Prolonged exposure to PPIs has been linked

to more than double the risk of gastric cancer. Potential mechanisms include profound acid suppression, which can contribute to gastric atrophy, chronic hypergastrinemia, enterochromaffin-like (ECL) cell hyperplasia, and bacterial overgrowth, all of which may contribute to carcinogenesis in the gastric mucosa.⁹⁸ An analytical study demonstrated a notable link between chronic PPI therapy and the development of fundic polyps as well as gastric cancer.⁹⁹ Another large-scale meta-analysis involving 9,26,386 individuals reported a twofold higher risk of gastric cancer among chronic users of PPIs.¹⁰⁰

Pancreatic Cancer

A nationwide study conducted using the French National Health Data System (SNDS) found that chronic PPI use was associated with an increased risk of pancreatic cancer. The hypothesized mechanisms include hypergastrinemia and bacterial overgrowth associated with reduced gastric acidity, both of which may create a microenvironment conducive to pancreatic tumor development.¹⁰¹

Colorectal Cancer

Extended PPI therapy has also been implicated in a higher likelihood of developing colorectal malignancy. A Swedish population-based cohort study found that long-term PPI users had higher rates of both all-cause and colorectal cancer-specific mortality.¹⁰² Mechanistically, chronic PPI use may contribute to hypergastrinemia, which promotes proliferation of colonic and rectal epithelial cells. Additional factors such as activation of the Yes-associated protein (YAP), disruption of the gut microbiota, and increased fecal pH may also play roles in colorectal tumorigenesis.¹⁰³

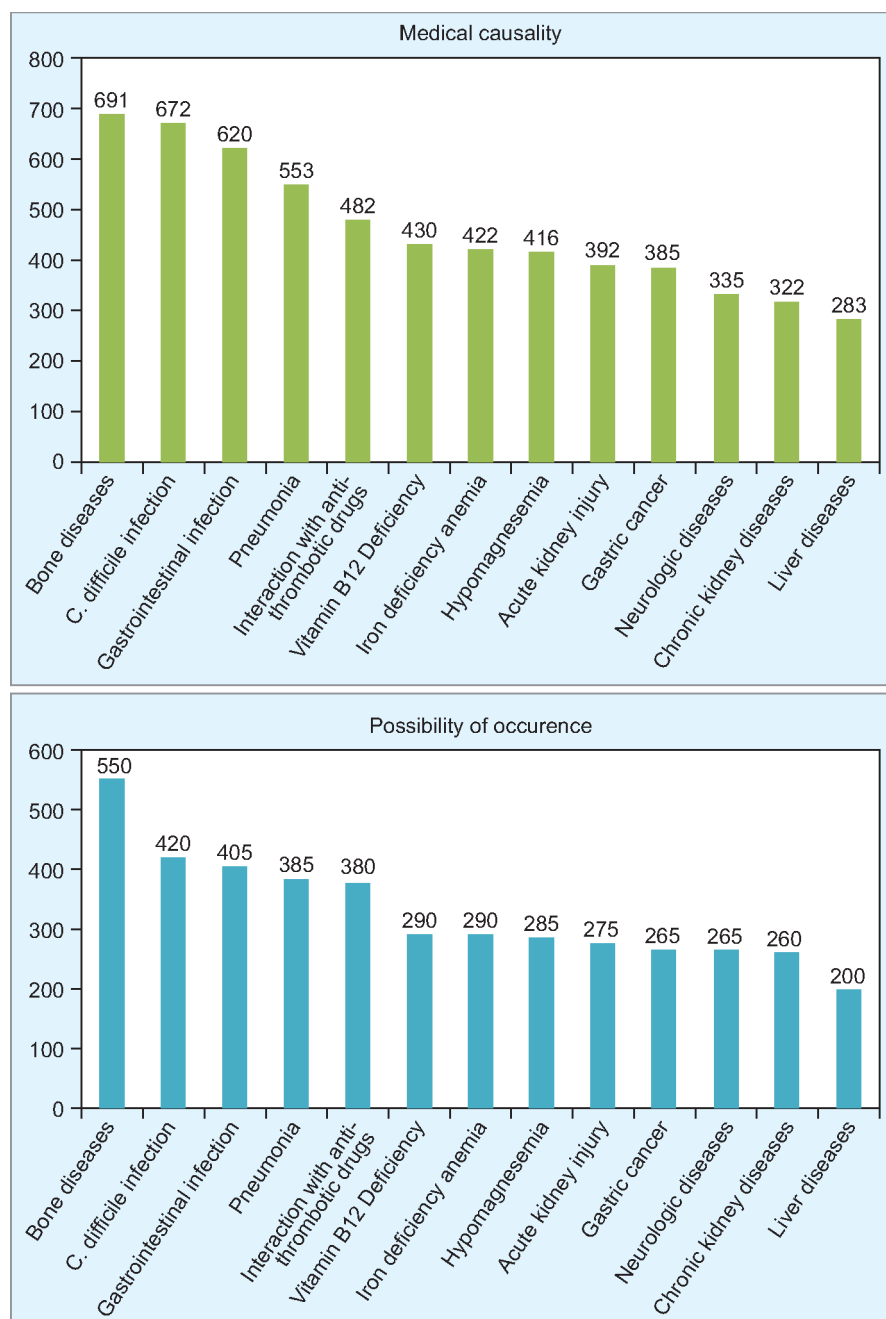


Fig. 4: Assessment of clinical causation and the likelihood of occurrence of established major adverse effects associated with PPIs⁹⁶

Hepatic Cancer

Prolonged PPI use may increase the likelihood of developing hepatocellular carcinoma (HCC), particularly in patients with preexisting liver disease. An analysis of 11 studies suggested that PPI use in individuals with chronic liver disease was associated with a significantly elevated risk of developing HCC and increased mortality. The underlying mechanism may again involve sustained hypergastrinemia, which has been associated with hepatic cellular proliferation and oncogenesis.¹⁰⁴

CONCLUSION

Although PPIs are widely accessible and commonly prescribed, their long-term use has been linked with a range of potentially serious adverse effects. Reported complications include osteoporosis, CDI, respiratory infections such as pneumonia, magnesium deficiency, CKD, vitamin B12 deficiency, and type 2 diabetes mellitus (T2DM). These health risks not only pose significant clinical concerns but also contribute to increased health care expenditures, placing a financial strain on patients.

Given these risks, it is imperative that clinicians carefully evaluate the necessity of PPI therapy, particularly for prolonged or continuous use. Treatment decisions should be based on a clear and justified indication, and ongoing reevaluation is essential to ensure that continued use remains appropriate. This review highlights the various biological pathways through which PPIs may contribute to adverse outcomes, including their impact on glucose and lipid metabolism in relation to T2DM. Nonetheless, further clinical research is warranted to validate these associations and to determine whether PPI use significantly affects glycosylated hemoglobin (HbA1c), low-density lipoprotein (LDL), and triglyceride levels.

AUTHOR CONTRIBUTIONS

Dr C Nawal and Dr H Saini contributed to the concept and design of this expert opinion document. The manuscript draft was developed by Dr G Rankawat and critically reviewed by all the authors. The manuscript was edited and revised by Dr G Rankawat and Dr R Chejara. The final draft of the manuscript was approved by all contributing authors.

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Pycnodysostosis—A Sparsely Diagnosed Entity and an Underrecognized Cause of Growth Hormone Responsive Reversible Short Stature: An Update



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Received: 09 August 2025; Accepted: 12 August 2026

ABSTRACT

Context: Pycnodysostosis (PYCD) is an osteopathic disorder usually present with dental or bony abnormalities. Though short stature is universal in this condition and responds to growth hormone treatment, the majority of subjects cannot reach target height because of late presentation to an endocrinologist.

Evidence acquisition: A literature review was undertaken to analyze clinical presentation and management of the disease. The rarity of the disease revealed very few case reports. The maximum number of cases were reported from India, the US, and Brazil. Most cases were concerned about their dental or osseous complications and consulted accordingly.

Evidence synthesis: Short stature, both prenatal and postnatal, is the most important but remediable complication of this disease, not adequately taken care of so far. Growth hormone deficiency has been found in some of these patients. Growth hormone treatment is effective in reaching target height whether or not its deficiency is overt.

Conclusion: All patients with facial dysmorphism, dental crowding, dense bones, recurrent fractures, and short stature should be genetically screened for PYCD. Growth hormone treatment should be considered after excluding contraindications.

Keywords: Growth hormone deficiency, Pycnodysostosis, Short stature.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1738

INTRODUCTION

Pycnodysostosis (PYCD) is a rare autosomal recessive disorder with a reported prevalence of 1–1.7 per million, with equal sex distribution.¹ It is due to a mutation of the lysosomal cysteine protease enzyme cathepsin K (*CTSK*), expressed adequately in osteoclasts and involved in their function. It helps in the degradation of type 1 collagen, maximally present in bones. So, a loss-of-function mutation of *CTSK* causes less osteoclast-directed bone resorption and consequent deranged bone remodeling, leading to osteosclerosis. PYCD presents with facial dysmorphism, unerupted and crowded teeth, acro-osteolysis, repeated fractures, and short stature. Parental consanguinity is common but not universal. Though it is primarily an osteopathic disorder often leading to short stature, the maximum number of cases reported are from faciomaxillary and dental specialties, and the most common presentation of this disorder is tooth crowding and the presence of multiple deciduous teeth. A proper diagnosis and consequent precautions should be taken before doing any dental surgery, as mandibular osteomyelitis is very common. Local vascularity and immunity of the affected region are affected by the

disease, which may be the cause of infection and osteomyelitis.

GENETICS

PYCD has been recognized for a long time, but it was known as osteopetrosis or other bone disorders. It was Maroteaux and Lamy who, in 1962, first conclusively described it as a separate entity. Genotype–phenotype relationship is very strong in PYCD. Those with more complete genetic aberrations manifest at a younger age with marked skeletal changes, repeated fractures, and growth retardation. Subjects with fewer mutations show normal height velocities and reach target height. Recurrent fractures are also sparse in this group. The *CTSK* gene has been located on the long arm of chromosome 1 (1q21.3, OMIM 601105). It contains 8 exons. Most mutation points are found in exons 6 and 7.² A study in a Mexican family, reported as early as 1996, detected a mutation in nucleotide 862, from C to T, of the *CTSK* coding sequence.³ Another study reported in the same year confirmed a gene mutation in the *CTSK* gene.⁴ Mutation analysis done in 1999 showed that an affected protein reduction of up to 80% in parents of affected subjects did not show any disease manifestation. Only complete absence of *CTSK* leads to

disease manifestations.⁴ In the same study, they found a nonsense mutation of A to T at DNA 154 and a missense mutation of G to A at DNA 236.⁵ In the year 2000, four cases of PYCD were analyzed; they found mutations A277V and L9P, and a single-base deletion, 531delT.⁶ In a report from Egypt of eight cases, all offspring of consanguineous marriages, homozygous missense mutations, DNA 164, A to C, and DNA 433, G to A, were found.⁷

CLINICAL PRESENTATION

The most common clinical presentation is persistent deciduous teeth and delayed teeth eruption. This persistence of deciduous teeth along with erupted permanent teeth causes supernumerary teeth and crowding. Teeth show enamel hypoplasia, caries, obliteration of pulp chambers, and malocclusion. The next common presentation is generalized increase of bone density, recurrent fractures, delayed closure of fontanelle, and short stature. The maximum reported cases are from dental and faciomaxillary surgery departments. The typical facial dysmorphism, like midface hypoplasia, retrognathia, obtuse mandibular gonial angle, frontal and sometimes occipital bossing, dolichocephaly, beaked nose, and ocular proptosis, often leads to diagnosis. Extremities show short, stocky hands and feet, dystrophic nails, and osteolysis of terminal phalanges. Clavicular dysplasia of the acromial end should be differentiated from more common cleidocranial dysplasia. A classical presentation of short stature with increased bone density is present in PYCD. All biochemical parameters of bone

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How to cite this article: Chakraborty J, Chakraborty S. Pycnodysostosis—A Sparsely Diagnosed Entity and an Underrecognized Cause of Growth Hormone Responsive Reversible Short Stature: An Update. *J Assoc Physicians India* 2026;74(10):70–72.

metabolism are usually normal. Thyroid and other hormones are normal. Growth hormone (GH) and IGF-1 are often low, but this finding is not universal. Others have hypothesized that when exogenous GH is administered, there is less degradation of IGF-1 at the growth plate due to *CTSK* deficiency.⁸ This may be the cause of growth stimulation of subjects with otherwise normal GH secretion. A recent case report from India has reported multiple pituitary hormone deficiencies in a case of PYKD.⁹ A report from Egypt has shown that seven out of a series of eight children reported were born short; length SDS was -3 to -1.5 . There was also postnatal growth retardation. All of them had height SDS below -3 at the third birthday. Combined genetic and hormonal factors were responsible, as they found impaired GH response on provocative tests in 50% of children. Moreover, these subjects with GH hyposecretion also had pituitary hypoplasia on MRI.¹⁰

Due to alteration of the anatomy of the palate, maxillae, and mandibles, these patients may present with obstructive sleep apnea. A study has found 37.5% of PYCD patients had sleep apnea.¹¹ They have recommended polysomnography for all patients with PYCD. Presence of a long soft palate and maxillary and mandibular deficiencies are the principal etiological factors of upper airway obstruction.¹²

A case of bilateral optic atrophy with blindness due to thickening of optic canals as a result of bone thickening has been recently reported. So, all these patients should undergo careful optic nerve examination so that early intervention could prevent blindness.¹³

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of PYCD is suggested by typical clinical features supported by radiological findings. It is confirmed by molecular genetic diagnosis of *CTSK* gene mutation. The three Ds should point to suspicion—they are dysmorphic face, dental crowding, and dense bones.

The four main differential diagnoses are osteopetrosis, cleidocranial dysostosis, idiopathic acro-osteolysis, and genetic asymmetric short stature with facial dysmorphism. The main presenting feature of osteopetrosis is multiple cranial nerve palsies over years due to strangulation at cranial foramina, along with signs of extramedullary hematopoiesis due to bone marrow dysmyelopoiesis, which often results in hepatosplenomegaly. Cleidocranial dysostosis shares many of the features of

PYCD, but the main difference is that there is no increase in bone density in the former. It usually presents with a frontal groove due to incomplete closure of the suture and open fontanelle. The clavicles are either hypoplastic at the acromial end or, in extreme cases, completely absent. Idiopathic acro-osteolysis does not show other features of PYCD. Distal phalanx osteolysis may be due to connective tissue disorder or primary Raynaud's phenomenon. But if there is midshaft osteolysis of the terminal phalanx, also called "band osteolysis," then idiopathic acro-osteolysis is the most probable diagnosis. However, a combination of osteosclerosis along with acro-osteolysis is almost diagnostic of PYCD.

MANAGEMENT

Management of this disease is primarily fivefold: (1) Management of dental and faciomaxillary aberrations; (2) Management of bone and joint fractures and deformities; (3) Management of sleep apnea; (4) Management of hematologic complications arising out of bone thickening and consequent compromise of bone marrow; (5) Management of short stature.

As we have already discussed, the most common presentation of PYCD is dental crowding and delayed eruption. Patients often consult initially for enamel hypoplasia and periodontal disease. Enamel hypoplasia leads to carious teeth and needs strict oral hygiene to prevent it. So, maintenance of dental and oral hygiene is of utmost importance. Mandibular osteomyelitis is very common, which may be spontaneous or secondary to tooth extraction. Infection with both aerobic and anaerobic organisms prevails. Antibiotics often fail to reach the site of infection due to compromised circulation to bones as a result of osteosclerosis. Midface hypoplasia is one of the important causes of dental malocclusion and consequent recurrent injury. Midface advancement surgery may help to minimize osteomyelitis. But any elective operation on these already vascularity-compromised bones may also precipitate osteomyelitis. There is a report from Istanbul of three cases that underwent successful similar operations.¹⁴

The management of fractures is according to the site affected. Utmost care should be taken to prevent osteomyelitis in these vascularity-compromised bones.

The management of upper airway obstruction depends on the site of obstruction, namely nasal, oropharyngeal, or hypopharyngeal obstruction. Long soft palate, increased tongue mass and its retroposition, and maxillary and mandibular deficiencies

produce obstruction in this region commonly. Uvulopalatopharyngoplasty and other surgical maneuvers are undertaken for these.¹⁵ Orthognathic surgery, such as maxillary and mandibular advancement, is often done.¹⁶ Due to exaggerated bone growth, there is less pneumatization of paranasal sinuses and less space inside the orbit, which may require corrective surgeries.

Hematological complications like anemia, though rare in PYCD, have been reported in some cases. Treatment is usually symptomatic.

Management of short stature is very important. Though, till date, only GH deficiency has been found, other endocrine evaluations may be done for better understanding. Growth hormone (GH) treatment for PYCD started long back in 1996, when Soliman et al. found low IGF-1 and a positive GH stimulation test in three out of four patients with PYCD. In his report from Oman of four children, all were born of consanguineous marriages. All subjects had height standard deviation (HtSDS) below -3 before starting GH treatment, and there was a significant increase in height velocity in all subjects after GH treatment.¹⁷ The same author, in another report of eight subjects, among whom four had GH hyposecretion, successfully treated short stature with GH, resulting in increased HtSDS.

Recently, there have been several studies of GH treatment of PYCD subjects. Rothenbühler et al., in a study of three patients, found a considerable increase in height velocities. They concluded that PYCD is the only form of short stature that could be totally corrected by GH therapy.⁸ In another study, they took eight children between 3 and 6 years, all of whom had height standard deviations below -3.5 , and all had delayed bone age and subnormal GH response to clonidine. They were treated with GH. There was a significant increase in height velocity as long as GH treatment was continued but significant slowing after stopping. So, from this study, it is obvious that GH treatment should be continued for a sufficient period until height velocity plateaus.¹⁸ In another single-case study, GH treatment was started at the age of 7 years when height velocity was 3.9 cm/year. GH treatment caused a rapid spurt to 9.4 cm/year.¹⁹ So, the above evidence supports that further research, including a meta-analysis, is needed on the role of GH treatment in PYCD, so that a guideline can be formulated.

CONCLUSION

PYCD is a disease with multisystem involvement. Though bone and oropharyngeal complications and their management have

been adequately addressed and advanced, growth disorder in this condition has not been studied enough. Further studies of central and peripheral causes of growth retardation in this disorder are needed for better management.

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Monoclonal Gammopathy of Renal Significance: Clinical Insights and Therapeutic Advances

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Received: 30 June 2026; Accepted: 20 August 2026

ABSTRACT

Monoclonal gammopathy of renal significance (MGRS) describes a group of kidney disorders driven by nephrotoxic monoclonal immunoglobulins arising from small, indolent clones of B cells or plasma cells. Although these clones fall short of the diagnostic thresholds used for hematological malignancy, the monoclonal protein they secrete can injure the kidney directly or through tissue deposition. The renal compartment affected—glomerulus, tubule, interstitium, or vasculature—and the resulting clinical picture depend largely on the physicochemical behavior of the paraprotein, and untreated disease tends to progress to chronic kidney failure.

Diagnostic precision in MGRS has improved considerably with refinements in renal biopsy interpretation and wider use of immunofluorescence, electron microscopy, and mass spectrometry-based proteomics. Linking hematological work-up with renal diagnostics now permits earlier disease recognition and more precisely targeted intervention. Management has moved away from nonspecific immunosuppression toward clone-directed regimens—proteasome inhibitors, monoclonal antibodies, and immunomodulatory agents—chosen to suppress the underlying clone while sparing renal function.

Because no single specialty can manage MGRS alone, close cooperation between nephrologists, hematologists, and renal pathologists has become the standard of care, and early clone-directed treatment is associated with better renal and survival outcomes. Open questions remain around biomarker development, standardized diagnostic pathways, and minimization of treatment toxicity; addressing these will require sustained multidisciplinary research. This review summarizes current understanding of MGRS pathophysiology, diagnosis, and treatment, and outlines the gaps that future work should address.

Keywords: Amyloidosis, Diagnostic advancements, Light chain deposition disease, Monoclonal gammopathy of renal significance, Monoclonal immunoglobulin deposition disease, Plasma cell dyscrasia, Renal pathology, Targeted therapy.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1746

INTRODUCTION

The term monoclonal gammopathy of renal significance (MGRS) was coined in 2012 by the International Kidney and Monoclonal Gammopathy Research Group (IKMG) to capture a specific category of kidney disease.¹ Two features define MGRS: the disease is driven by a nephrotoxic monoclonal immunoglobulin, and that immunoglobulin is secreted by a B-cell or plasma cell clone too small to meet criteria for multiple myeloma or malignant lymphoma.² This review traces how the definition and terminology of MGRS have evolved, summarizes recent diagnostic and therapeutic progress, and considers what these advances mean for everyday clinical practice.

The International Kidney and Monoclonal Gammopathy Research Group revisited the classification of MGRS-related renal lesions in 2017 and sharpened the definition further.^{2,3}

Why Did the Definition Need Revision?

The original concept of MGRS cast a wide net, covering any small B-cell clone capable

of producing a harmful monoclonal protein. That breadth created ambiguity: it was unclear whether smoldering multiple myeloma (SMM) or smoldering Waldenström macroglobulinemia (SWM) belonged under the MGRS umbrella, and a similar question arose for indolent chronic lymphocytic leukemia (CLL) or low-grade lymphomas that, although technically malignant, do not yet warrant treatment.⁴

The revised definition narrows MGRS to B-cell and plasma-cell disorders that produce a nephrotoxic monoclonal immunoglobulin but do not themselves require immediate oncological treatment. SMM, SWM, monoclonal B-cell lymphocytosis (MBL), and indolent lymphomas causing renal injury are all captured by this updated definition, which explicitly excludes any requirement for overt malignancy; once a clone progresses to frank malignancy, management follows disease-specific protocols rather than the MGRS framework.⁵

With this clarified definition as a foundation, the discussion can now turn to

the range of renal histopathological patterns seen in MGRS and what they mean for clinical care.

THE SPECTRUM OF RENAL HISTOPATHOLOGY IN MGRS

Because of their size, intact monoclonal immunoglobulins do not cross the glomerular basement membrane; free light chains, being considerably smaller, pass through the filter and are normally reclaimed and degraded by proximal tubular cells. Nephrotoxicity in MGRS arises through several overlapping mechanisms—tissue deposition with direct cellular interaction, intratubular precipitation, and activation of complement and inflammatory cytokine pathways. The paraprotein deposited in the kidney may be an intact immunoglobulin, an isolated light or heavy chain, a light-heavy chain combination, or a fragment of any of these. Any of the four renal compartments—glomerulus, tubule, interstitium, or vessel—may be involved, alone or together.⁶ Which compartment is affected, and how severely, depends largely on the structural and physicochemical properties of the specific paraprotein, properties that can render it nephrotoxic even at low circulating concentrations.^{7,8} Recognizing this histopathological spectrum is central to interpreting the clinical significance of MGRS and to choosing an appropriate management strategy.⁹

Table 1 summarizes the classification and salient clinical, immunofluorescence, ultrastructural, and extrarenal features of the principal MGRS-associated lesions.^{9–13}

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How to cite this article: Rajan A, Mahapatra HS, Balakrishnan M, et al. Monoclonal Gammopathy of Renal Significance: Clinical Insights and Therapeutic Advances. *J Assoc Physicians India* 2026;74(10):73–78.

Table 1: Monoclonal gammopathy of renal significance (MGRS) classification

Category	Kidney symptoms	Immunofluorescence (Ig type)	Ultrastructural features	Extrarenal manifestations
AL Amyloidosis	Proteinuria, nephrotic syndrome (NS), CKD; occasionally hypertension and hematuria	Light chain (λ predominant)	Unbranched fibrils, 7–14 nm	Heart, liver, nerves
AH Amyloidosis	Same as AL	Heavy chain ($\gamma 1$, $\gamma 4$, or α)	Same as AL	Same as AL
AHL Amyloidosis	Same as AL	Light + Heavy ($\gamma + \lambda$ or $\alpha + \kappa$)	Same as AL	Same as AL
ITGN / GOMMID	Proteinuria, NS, CKD, microhematuria, hypertension, AKI, nephritic syndrome	Monotypic IgG (IgG1–3), κ or λ ; C3, C4, C1q deposits	Microtubules (10–60 nm), hollow	Rare: nerves, skin
Type I Cryoglobulinemic GN	Proteinuria, NS, CKD, microhematuria, hypertension, AKI, nephritic syndrome	Monotypic IgG/IgM/IgA (κ or λ); C3, C4, C1q deposits	Microtubules (10–90 nm), crystals possible	Skin, nerves, joints
Light Chain Fanconi Syndrome	Proximal tubular dysfunction, gradual CKD progression	Mostly κ (Vk1 or Vk3)	Rhomboid crystals in lysosomes	Osteomalacia, bone disease
Crystal-Storing Histiocytosis	Proximal tubulopathy, CKD	Predominantly κ (Vk1 or Vk3)	Needle-like crystals in histiocytes	Multi-organ: liver, lungs, cornea
MIDD (LCDD / HCDD / LHCCD)	Proteinuria, NS, CKD, microhematuria, hypertension	Linear Ig deposits (LCDD: LC, HCDD: HC, LHCCD: LC+HC)	Amorphous deposits in GBM, TBM, mesangium	Heart, liver, lungs
PGNMID	Proteinuria, NS, CKD, microhematuria, hypertension	Monotypic IgG, usually IgG3	Non-organized granular deposits	None
C3 Glomerulopathy with MG	Proteinuria, NS, CKD, microhematuria, hypertension	Sparse/absent Ig; prominent C3	Intramembranous & mesangial dense deposits	None

Table 2: Summary of methods for detecting monoclonal free light chains (FLCs)

Method	Type	Detection limit (sensitivity)	Advantages	Disadvantages
Serum protein electrophoresis (SPE)	Semiquantitative	500–2000 mg/L	Affordable and simple to perform	Limited sensitivity for low levels of M-proteins, especially FLCs.
Urine protein electrophoresis (UPE)	Semi-quantitative	20–50 mg/L	Inexpensive and straightforward	Detects FLCs only when tubular reabsorption is saturated; requires 24-hour urine collection; interpretation can be subjective; challenging with concentrated urine or high protein levels.
Serum Immunofixation Electrophoresis (IFE)	Qualitative	150–500 mg/L	About 10 times more sensitive than serum EP	Detects urinary FLCs only once reabsorption is overwhelmed; needs 24-hour urine collection.
Urine Immunofixation Electrophoresis (IFE)	Qualitative	20–50 mg/L	Useful as a prognostic tool and for monitoring treatment effectiveness	Requires 24-hour urine collection; similar limitations to serum IFE.
Serum free light chain assay (sFLC)	Quantitative	κ : 1.5 mg/L; λ : 3 mg/L	Precise κ/λ measurement and ratio; helpful for prognosis and treatment monitoring	More expensive; inter-assay variability; needs further refinement for certain diseases.

When to Suspect MGRS

A nonmalignant or premalignant monoclonal gammopathy is found incidentally in a substantial proportion of patients investigated for unexplained renal impairment or proteinuria, particularly among older adults.

Clinicians should consider MGRS whenever renal disease coexists with a detectable M-protein, especially when conventional cardiovascular risk factors—diabetes, hypertension, atherosclerosis—are either absent or already well controlled. The same suspicion should extend to patients with C3 glomerulopathy or thrombotic microangiopathy (TMA), both of which show a recognized association with M-protein-driven kidney disease, again more so in older patients. MGRS is most often diagnosed

beyond age 50, though it is not confined to this group.¹⁴

Monoclonal Protein Testing

Because the underlying clone in MGRS is small, circulating M-protein levels are typically low. Serum protein electrophoresis (SPE)—with a detection floor of roughly 500–2000 mg/L—frequently misses these low-level paraproteins, particularly free light chains (FLCs), which clear from the circulation faster than intact immunoglobulins. Serum immunofixation electrophoresis (IFE) improves sensitivity roughly tenfold over SPE, but reliably identifying the M-protein usually still requires urine IFE and/or a serum free light chain assay.^{9,15–17} Table 2 compares the sensitivity, advantages, and limitations

of the principal methods used to detect monoclonal free light chains.

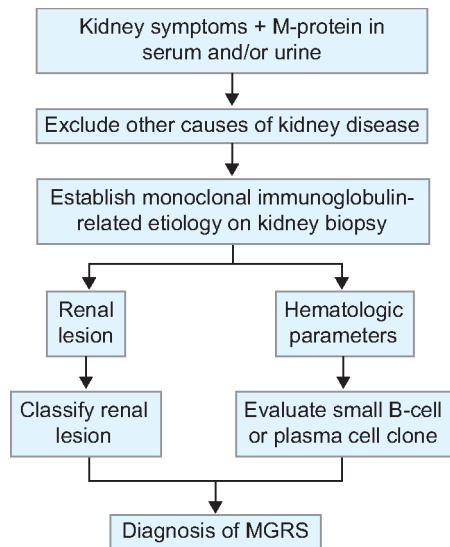
Kidney Biopsy and Bone Marrow Evaluation in MGRS Diagnosis

A kidney biopsy is the pivotal investigation in MGRS, distinguishing an incidental M-protein from one that is actually driving the renal lesion. A full assessment—immunofluorescence (IF), immunohistochemistry (IHC), and electron microscopy (EM)—is needed to characterize deposit composition and ultrastructure. EM is especially valuable for fibrillary glomerulonephritis (FGN), immunotactoid glomerulopathy (ITG), type 1 crystalline glomerulopathy, and crystalline light-chain proximal tubulopathy (LCPT). When AL amyloidosis is suspected, however, a surrogate

Table 3: Special stains used on renal biopsy tissue in MGRS

Disease	PAS	Silver stain	Masson's trichrome	Congo red
Amyloid	–	–	Blue	+++
ITG/FGN	+++	–	Blue	–
FN	–	–	Red	–
DN	+++	+	Blue	–
MIDD	–	–	Blue	–
INS	+++	+	Blue	–
CG	–	–	Blue	–

PAS, periodic acid–Schiff stain; ITGN, immunotactoid glomerulopathy; FGN, fibrillary glomerulonephritis; FN, fibronectin glomerulopathy; DN, diabetic nephropathy; MIDD, monoclonal immunoglobulin deposition disease; INS, idiopathic nodular sclerosis; CG, crystalline glomerulopathy


Fig. 1: Diagnostic algorithm for MGRS

tissue sample such as abdominal fat may sometimes substitute for renal biopsy if there is clinical evidence of renal involvement.¹⁴

Certain dense or unusual deposits require more specialized methods—immunogold EM or proteomic analysis by laser microdissection coupled with mass spectrometry (LMD/MS). LMD/MS is now the reference standard for amyloid typing and is also useful in other MGRS subtypes, though it typically requires referral to a specialized laboratory and is reserved for diagnostically ambiguous cases.^{18,19}

Identifying the causative B-cell or plasma-cell clone calls for a thorough hematological evaluation that excludes overt multiple myeloma or Waldenström macroglobulinemia. Bone marrow aspirate and biopsy in MGRS usually show only a modest, morphologically unremarkable increase in plasma cells or B cells (under 10%). A Congo red stain of the marrow can flag amyloidosis, which is detectable there in roughly 60% of AL amyloidosis cases, while immunohistochemistry and flow cytometry confirm clonality and correlate it with the circulating M-protein.²

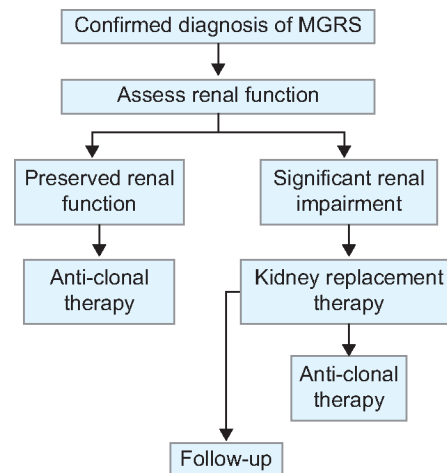

Fig. 2: Treatment algorithm for MGRS

Table 3 lists the special stains used on renal biopsy tissue and the patterns they reveal across the major MGRS-related lesions, and Figure 1 sets out a diagnostic algorithm that brings these elements together.

TREATMENT AND ADVANCES IN THE FIELD OF MGRS

Management of MGRS targets the underlying B-cell or plasma-cell clone. Historically, clinicians were reluctant to treat MGRS aggressively, worried about toxicity—particularly the risk of secondary malignancy with alkylating agents—at a time when the condition was generally regarded as indolent. Autologous peripheral blood stem cell transplantation has since proven a workable option for B-cell clones, and ongoing monitoring remains essential to catch complications such as thrombosis or infection, especially when nephrotic-range proteinuria is present.²⁰ Figure 2 outlines the basic treatment strategy.

For patients with CKD stages 1–3, early chemotherapy aimed at suppressing monoclonal immunoglobulin production and achieving a deep hematological response is advised.²¹ Autologous stem cell transplantation (ASCT) can deepen

and prolong both the hematological and renal response. Conservative measures—bicarbonate, phosphate binders, and vitamin D—help offset CKD-related mineral and bone disease, and renin–angiotensin–aldosterone blockade (ACE inhibitors or ARBs) is appropriate for hypertension. Dialysis becomes necessary once patients reach end-stage renal disease (ESRD), with kidney transplantation the preferred long-term option, although recurrent nephropathy after transplant remains common, particularly when the underlying clone was not adequately controlled beforehand. While no MGRS-specific trial has yet proven a survival benefit, large trials of SGLT2 inhibitors and finerenone have shown improved renal outcomes and reduced mortality in CKD more broadly, and these agents are reasonable to consider in MGRS as well.²²

In CKD stage 4 or ESRD, chemotherapy is generally reserved for patients who remain transplant candidates or who have significant extrarenal disease—cardiac, hepatic, or pulmonary. A complete hematological response before transplantation is important to limit the risk of MGRS recurrence and graft loss in the new kidney; ASCT may be used pre-transplant to help achieve this, and treating extrarenal disease can separately improve organ-specific outcomes.^{7,23}

Plasma Cell Dyscrasia with IgG, IgA, or LC Only

When a non-IgM MGUS clone secretes only IgG, IgA, or light chains, treatment is directed at clone eradication to protect renal function. Bortezomib, a proteasome inhibitor that is cleared largely independent of the kidney, is the workhorse agent, usually paired with dexamethasone. It produces rapid reduction in tumor burden and improves renal function in multiple myeloma patients with renal impairment, and in dialysis-dependent myeloma patients, bortezomib-based induction has outperformed conventional chemotherapy in lowering transplant-related mortality. The same regimen—often combined with melphalan-conditioned ASCT—produces high complete and very good partial response rates in AL amyloidosis; giving bortezomib both before and after ASCT can help offset the impact of renal failure on outcomes.²⁴

Eligibility for ASCT matters as much as drug choice. Patients under 70 with adequate cardiopulmonary reserve, stable renal disease, and good performance status are generally suitable candidates; ASCT remains feasible even on dialysis, albeit with a higher risk of transplant-related death, and is best avoided in patients with active infection or otherwise unmet eligibility

Table 4: Treatment recommendations and transplant considerations

MGRS Entity	Treatment recommendation	Transplant notes
MIDD	CKD I–III: Bortezomib-based therapy ± ASCT if eligible; CKD IV–V: same, with continued therapy if not transplant eligible	Success depends on effective hematologic treatment before transplant
PGNMID	CKD I–II, stable: symptom management; progressive CKD or CKD III–V: chemotherapy ± ASCT if eligible	High recurrence risk without treatment; histologic monitoring crucial
ITG	Treat CLL-associated cases with bendamustine + rituximab; non-CLL: bortezomib-based regimens	Outcome depends on underlying hematologic response
Type 1 Cryoglobulinemic GN	Plasma cell clone: myeloma-directed therapy ± ASCT; LPL clone: WM-like therapy (rituximab-based)	Transplant success relies on pre-transplant therapy and hematologic response
Type 2 Cryoglobulinemic GN	HCV+: antivirals ± immunosuppression; rapid progression: add plasma exchange	Viral management key; monitor vasculitis pre/post-transplant
LCPT with Fibrillary Structures	CKD I–III: chemotherapy (bortezomib ± ASCT); CKD IV–V: similar, with symptom focus if transplant ineligible	High recurrence risk without hematologic control; pre-transplant therapy is critical

criteria. Those who are not ASCT candidates typically receive six to eight cycles of bortezomib with dexamethasone and cyclophosphamide, or bortezomib with melphalan-prednisone. Thalidomide and lenalidomide are reasonable immunomodulatory alternatives, with lenalidomide generally favored on efficacy grounds.²⁵

B-cell Clone with IgM M-protein

IgM MGUS-driven MGRS is uncommon, so the supporting evidence base is correspondingly thin. Where the clone is IgM-secreting and B-cell in origin, rituximab—typically combined with dexamethasone plus either cyclophosphamide or bendamustine—is the preferred approach. Rituximab needs no dose adjustment for renal impairment; cyclophosphamide elimination is affected by renal function, though recommended dose adjustments vary across the literature, and bendamustine appears reasonably safe in moderate renal impairment but carries more toxicity risk as kidney function falls further. ASCT remains an option for patients likely to achieve a substantial hematological response.²⁶

Transplant in MGRS

Whether and when to transplant a kidney in MGRS remains unsettled. Recurrence risk is higher than in the general transplant population, and there is no consensus on optimal timing. Nonetheless, kidney transplantation can be appropriate for MGRS patients reaching ESRD, since effective hematological treatment improves both renal prognosis and overall survival; patients who respond well to rescue therapy tend to have correspondingly better graft survival, which is why transplantation is generally reserved for those who have already achieved a good hematological response, even though some recurrence risk persists regardless.^{5,14,27–29}

Outcomes after transplant differ by the structural type of the deposit. MGRS entities with organized Ig deposits—

fibrillary, microtubular, or crystalline—have outcomes that hinge on how well, and how promptly, the clone was treated before transplant. Nonorganized deposits, as in C3 glomerulopathy or TMA, carry a particularly high risk of early recurrence if the underlying clone is left untreated; a Mayo Clinic series reported an 89% recurrence rate without prior hematologic control, vs 30% when control was achieved.³⁰

Treatment of PGNMID should follow the suspected or confirmed clone: regimens built around cyclophosphamide, bortezomib, and dexamethasone suit a plasma-cell clone, while rituximab-based therapy is preferred for a B-cell clone; when no clone can be identified, empirical therapy is chosen based on the most likely cell of origin.

Table 4 summarizes treatment recommendations and transplant considerations across the major MGRS entities.

NOVEL THERAPEUTIC AGENTS AND DRUG CLASSES

Clone-directed therapy in MGRS has broadened substantially in recent years, with monoclonal antibodies, proteasome inhibitors, and complement blockers reshaping outcomes.

Monoclonal antibodies: Daratumumab, an anti-CD38 antibody, has become central to treating plasma-cell-mediated MGRS, AL amyloidosis in particular. In the phase III ANDROMEDA trial, adding daratumumab to CyBorD (cyclophosphamide, bortezomib, dexamethasone) nearly tripled the complete hematological response rate compared with CyBorD alone (53% vs 18%) and substantially improved the renal response rate (53% vs 24%).³¹ Daratumumab has also shown encouraging activity in LCDD and in PGNMID without an identifiable clone,³² while rituximab remains the standard for IgM-associated and other B-cell-driven MGRS.³³

Proteasome inhibitors: Bortezomib-based regimens remain first-line for plasma-cell MGRS such as AL amyloidosis and LCDD, valued for rapid tumor-cell lysis and renal recovery.³⁴ Carfilzomib and oral ixazomib are increasingly used in relapsed or refractory disease.

Immunomodulatory drugs (IMiDs): Lenalidomide and pomalidomide have a role in refractory disease but are used cautiously in amyloidosis because of toxicity concerns; their evidence base is stronger in nonamyloid lesions.³⁴

BCL-2 inhibitors: Roughly half of AL amyloidosis cases carry the t(11;14) translocation, making venetoclax—a BCL-2 inhibitor—a rational option; deep hematological responses have been reported in relapsed MGRS with this translocation.³⁵

Complement inhibitors: The C5 blocker eculizumab has been used in MGRS-associated TMA and C3 glomerulopathy, achieving dialysis independence in over half of TMA patients in one cohort,³⁶ though clone-directed therapy is still considered essential alongside complement blockade in complement-mediated disease.³⁷

Key Clinical Trials in MGRS

1. ANDROMEDA (2020–2021): adding daratumumab to CyBorD produced superior hematological and renal responses in AL amyloidosis.³¹
2. Daratumumab in PGNMID (2021): an open-label Mayo Clinic phase II trial found that daratumumab monotherapy produced a renal response in every enrolled patient.³²
3. C3G and clone therapy study (2017): clone-directed therapy improved renal survival compared with immunosuppression alone in MGRS-associated C3 glomerulopathy.³⁷
4. Ongoing studies: trials of CAEL-101 (an anti-light-chain amyloid antibody), in AL amyloidosis, and of isatuximab, and subcutaneous daratumumab in non-amyloid MGRS lesions, are currently underway.³⁸

Table 5: Response to therapy in MGRS

Response category	Criteria
Complete response	Normal free light chain (FLC) ratio; negative serum and urine immunofixation
Very good partial response	Difference between involved and uninvolved FLC < 40 mg/L
Partial response	≥50% reduction in the difference between involved and uninvolved FLC
No response	No significant change in FLC levels

RESPONSE TO THERAPY

In AL amyloidosis, LCDD, and Fanconi syndrome, response is graded by free light chain (FLC) kinetics. A complete response requires a normalized FLC ratio together with negative serum and urine immunofixation. A very good partial response is defined as a difference between involved and uninvolved FLC of under 40 mg/L, and a partial response as a fall of more than 50% in that difference; no meaningful change in FLC levels is classed as no response (Table 5).

Where the causal protein is an intact immunoglobulin, the response criteria used in multiple myeloma apply instead. If no causative immunoglobulin can be measured at all, response is instead assessed by repeat bone marrow examination. Complete hematological remission should be achieved before transplantation wherever possible, since recurrence risk is substantial across all MGRS subtypes and graft loss can occur particularly quickly in PGNMID.³⁹ Post-transplant care therefore requires close surveillance of immunoglobulin parameters, with therapy resumed promptly if the clonal disorder shows signs of progression.

RESEARCH GAPS AND FUTURE DIRECTIONS

Despite growing recognition of MGRS as a distinct entity, several gaps in knowledge persist:

1. *Few disease-specific clinical trials:* Most current treatment strategies are extrapolated from trials conducted in multiple myeloma, AL amyloidosis, or indolent B-cell lymphoma rather than in MGRS itself. Randomized trials specifically addressing non-amyloid MGRS subtypes—PGNMID, LCPT, immunotactoid glomerulopathy—are essentially absent, which limits the field's ability to build subtype-specific, evidence-based treatment algorithms.
2. *Delayed diagnosis and under-recognition:* Diagnosis is commonly delayed because of low-level, subclinical M-protein that conventional serum electrophoresis fails to detect; limited awareness of

MGRS among general nephrologists and hematologists; and reluctance to biopsy patients labeled simply as having "monoclonal gammopathy of unknown significance." Because delayed treatment risks irreversible renal damage, earlier recognition is a priority.

3. *No validated biomarkers:* There is currently no validated, noninvasive biomarker that reliably distinguishes MGRS from a benign monoclonal gammopathy. Mass-spectrometry-based proteomics, complement-activation assays, and urinary monoclonal light-chain profiling are promising but remain investigational.
4. *Difficulty monitoring disease activity:* Monitoring is complicated by discordance between hematological and renal responses, by clones that cannot be quantified in the first place (as in PGNMID without a detectable serum clone), and by the lack of a renal response standard that applies uniformly across histological subtypes. Serum free light chains and M-protein levels, the current mainstays of monitoring, do not necessarily track ongoing kidney injury.
5. *High recurrence after kidney transplantation:* Even though transplantation is now considered feasible in carefully selected patients, recurrence remains common, especially when hematological remission was incomplete beforehand. How long clone suppression should be maintained before transplant, and what role maintenance therapy should play afterward, are both still undefined.
6. *Need for multidisciplinary care models:* MGRS care depends on coordinated input from nephrology, hematology, pathology, and transplant teams, yet integrated care pathways are far from universal, particularly in resource-limited settings—a gap that risks fragmented care and missed opportunities for early treatment.

LIMITATIONS

This review has certain limitations inherent to its narrative format. It draws on published trial and cohort data rather than a systematic

or meta-analytic synthesis, so the selection of studies discussed, while intended to be representative, is not exhaustive. Much of the therapeutic evidence cited is extrapolated from trials conducted in multiple myeloma or AL amyloidosis rather than from MGRS-specific randomized trials, which remain lacking for most non-amyloid subtypes. Treatment recommendations for individual MGRS entities are therefore largely consensus- and expert-opinion-based rather than derived from high-level evidence, and outcome data—particularly for transplant recurrence and long-term renal survival—come mainly from retrospective, single-center, or registry series that carry their own selection and reporting biases.

CONCLUSION

Monoclonal gammopathy of renal significance comprises a wide range of kidney disorders unified by their relationship to a monoclonal protein rather than by a single histological pattern. Progress in understanding its pathophysiology, refining its diagnosis, and individualizing its treatment has materially improved how these patients are managed, and the experience reviewed here underscores how much that progress depends on close collaboration between nephrology, hematology, and pathology.

Three points are worth emphasizing:

1. Early diagnosis limits the risk of irreversible kidney damage.
2. Treatment succeeds or fails largely on how effectively the underlying B-cell or plasma-cell clone is controlled.
3. Newer clone-directed agents—daratumumab, venetoclax, and complement blockers among them—offer real grounds for optimism, even though kidney transplantation in this setting still calls for caution given the persistent risk of disease recurrence.

Further progress will depend on continued, cross-disciplinary research into MGRS-specific biomarkers, standardized response criteria, and disease-specific trials, with the shared goal of improving outcomes for patients living with this condition.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This is a narrative review article based on previously published literature and does not involve original patient data, identifiable patient information, or new human or animal experimentation. Ethics committee approval and participant consent are therefore not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable—this manuscript does not report a clinical trial.

AUTHOR CONTRIBUTIONS

HSM contributed to the conception and design of the review. AR performed the literature search and drafted the manuscript. MSB and LSP critically revised the manuscript for important intellectual content. HSM supervised the work and provided final approval of the version to be published. All authors read and approved the final manuscript.

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Expert Opinion Review on the Shift from Dual Antiplatelet Therapy to Single Antiplatelet Therapy in Indian Clinical Practice



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Received: 13 April 2026; Accepted: 04 June 2026

ABSTRACT

Background: The management of antiplatelet therapy post-percutaneous coronary intervention (PCI) has evolved, balancing ischemic protection with bleeding risk mitigation. Dual Antiplatelet Therapy (DAPT) remains the standard, but emerging evidence supports early de-escalation to Single Antiplatelet Therapy (SAPT), particularly in high bleeding risk (HBR) patients. However, real-world adoption varies, and data on prescribing trends in India are limited.

Aim: The objective of this expert opinion was to understand prevailing clinical practices among Indian cardiologists related to DAPT duration, SAPT transition, and maintenance therapy in post-PCI management of ACS and CCS patients.

Materials and methods: A structured questionnaire was developed by an expert panel and disseminated among 162 cardiologists across multiple centers in India. The questionnaire covered key topics such as bleeding risk stratification, the shift from DAPT to SAPT, and preference for clopidogrel versus aspirin in real-world practice. Data were collected and analyzed using descriptive statistics, with responses compared against contemporary guidelines such as the 2023 ESC Guidelines for ACS and the ACC/AHA updates on DAPT duration, as well as key clinical trials including STOPDAPT-2, SMART-CHOICE, HOST-EXAM, HOST-EXAM Extended, OPT-BIRISK trial, and POPular AGE trial.

Results: Among respondents, 71.4% routinely screen for HBR patients, primarily using clinical parameters (66.7%), with 51.2% preferring a 3-month DAPT duration in HBR patients, favoring Clopidogrel plus Statin Fixed-Dose Combination (44.2%) for SAPT. In elderly ACS patients, 60.5% adopted an abbreviated DAPT strategy, with clopidogrel monotherapy (48.7%) as the preferred regimen. Clopidogrel was also favored over aspirin for long-term maintenance (90%), aligning with the HOST-EXAM trial.

Conclusion: Expert opinions largely align with contemporary guidelines, emphasizing individualized risk stratification and early DAPT de-escalation in patients with high HBR and low ischemic risk. Clopidogrel-based monotherapy or fixed-dose combinations are preferred, reflecting real-world adaptations to optimize long-term cardiovascular protection post-PCI.

Keywords: Acute coronary syndrome, Antiplatelet de-escalation, Chronic coronary syndrome, Clopidogrel monotherapy, Dual antiplatelet therapy, High bleeding risk, Percutaneous coronary intervention, Postpercutaneous coronary intervention management, Real-world clinical practice in India, Single antiplatelet therapy.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1637

INTRODUCTION

The management of acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) has undergone significant advancements, with dual antiplatelet therapy (DAPT) remaining the cornerstone of secondary prevention following percutaneous coronary intervention (PCI). The transition of antiplatelet therapy has been from prolonged DAPT with aspirin and clopidogrel toward more personalized therapy regimens. Most ACS cases use commonly preferred ticagrelor and prasugrel, due to their superior efficacy compared with clopidogrel. Current ECS guidelines (2025) now focus on customizing DAPT duration based on individual factors,

such as high bleeding risk, which may require early transition to monotherapy (often ticagrelor) after just 1 month, while those at higher ischemic risk may benefit from extended DAPT. The integration of genetic and platelet function testing supports precise adjustment of therapy. The overall approach prioritizes maximizing protection from ischemia while minimizing bleeding risk, with a strong focus on individualized care. DAPT, typically consisting of aspirin and a P2Y₁₂ inhibitor (clopidogrel, ticagrelor, or prasugrel), effectively reduces the risk of stent thrombosis, recurrent myocardial infarction, and stroke.^{1,2} As per the existing literature, such as high bleeding risk (HBR) patients, the elderly, and those with comorbidities such as chronic

kidney disease (CKD) or prior bleeding events have increased risk with continued prolonged DAPT.^{3,4} Major trials such as ticagrelor with Aspirin or Alone in High-risk Patients after Coronary Intervention (TWILIGHT), Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-eluting Cobalt-chromium Stent-2 (STOPDAPT-2), and Smart Management of Antiplatelet Regimen by Tailoring CHOICE of therapy (SMART-CHOICE) suggest that shortened DAPT (3–6 months) followed by single antiplatelet therapy (SAPT) can provide noninferior ischemic protection while reducing bleeding complications.^{5–7}

Although there is growing evidence supporting patient-centric de-escalation strategies, SAPT post-DAPT is still not widely accepted in real-world clinical settings. The low acceptability can be attributed to demographic features such as differences in patient characteristics, clinical opinion owing to physician preference, and drug availability. The choice of SAPT, which can include aspirin, clopidogrel, or ticagrelor, is variable in different settings, with paucity in data on prescribing trends in India. The transition from DAPT to

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How to cite this article: Ezhilan J, Manoria PC, Gupta R, et al. Expert Opinion Review on the Shift from Dual Antiplatelet Therapy to Single Antiplatelet Therapy in Indian Clinical Practice. *J Assoc Physicians India* 2026;74(10):80–85.

SAPT after initiating the treatment is aimed at reducing the risk of significant bleeding events while still effectively preventing thrombotic events. Transitioning to SAPT after 6–12 months, as supported by clinical evidence, in those at higher bleeding risk should be individualized on the basis of assessment of patient risk as per the current guidelines.⁸

The main benefit of this shift is a lower bleeding risk without a meaningful increase in ischemic complications. For understanding Indian cardiologists' approach to DAPT duration and DAPT-to-SAPT transition, and long-term secondary prevention, this expert opinion was compiled by gathering feedback on clinical practices from cardiologists across multiple centers. The expert opinion review aims to assess screening practices for HBR patients, preferred timelines for transitioning from DAPT to SAPT, and commonly used antiplatelet regimens in real-world practice, based on insights gathered through focus group discussions with cardiologists across India, to better understand current prescribing patterns and identify opportunities to optimize post-PCI antiplatelet therapy.

MATERIALS AND METHODS

This expert opinion was designed to evaluate prevailing clinical practices and preferences regarding antiplatelet therapy following PCI, with particular focus on HBR patients and elderly individuals with ACS. An expert panel of interventional cardiologists developed and finalized a structured questionnaire comprising nine focused questions. These questions were organized into three thematic categories: (1) bleeding risk stratification, (2) transition from DAPT to SAPT, and (3) preference for clopidogrel versus aspirin in long-term maintenance therapy. The questionnaire explored key areas such as screening methods for HBR patients, timing of de-escalation from DAPT to SAPT, and preferred monotherapy regimens for elderly and stabilized patients. Responses were collected to capture real-world clinical patterns and to evaluate how Indian cardiologists' decision-making aligns with

current guideline recommendations and evidence from major clinical trials.

Development of Expert-framed Questionnaire

The expert opinion developed by a panel of experienced interventional cardiologists was based on a structured set of questions initially framed after a thorough literature review. Depending on their clinical expertise, nine key questions were decided upon to explore ongoing practices in antiplatelet therapy across various patient archetypes. These questions were designed to elicit clinical insights into decision-making regarding DAPT duration, timing of DAPT-to-SAPT transition, and long-term maintenance strategies, with a comparative analysis of clopidogrel and aspirin, particularly focusing on high bleeding risk and elderly ACS patients.

Study Population and Data Collection

The approved questionnaire was discussed during regional-level advisory board meetings held across India. Each meeting was moderated by a senior expert cardiologist and attended by approximately 162 practicing cardiologists with expertise in managing ACS and CCS patients post-PCI. The expert responses were evaluated based on clinical experience, interpretation of current scientific evidence, and consensus-based judgment. Opinions and clinical perspectives gathered from these discussions were compiled and analyzed for the development of this expert opinion review.

Data Analysis

Expert responses were qualitatively assessed and categorized based on the overall level of agreement among participating cardiologists (Table 1).

RESULTS

Bleeding Risk Stratification

A total of 162 cardiologists participated in this expert opinion survey, with a substantial majority, 77.8%, routinely screening for HBR in patients who have undergone revascularization following ACS or CCS. Among the respondents,

over half (56.2%) relied on clinical parameters and the patient's medical history to identify bleeding risk despite various other approaches (score-based) existing for HBR assessment. Structured bleeding risk scores such as the DAPT score or the PRECISE-DAPT score, which incorporate laboratory and clinical variables to predict bleeding complications during antiplatelet therapy, were seemingly utilized by 39.5% of respondents. A smaller proportion, 9.3%, incorporated the ARC-HBR (Academic Research Consortium for High Bleeding Risk) score, which is a consensus-based standardized tool encompassing major and minor bleeding criteria. The most commonly acknowledged risk factors cited by cardiologists, presented in decreasing order of occurrence are advancing age (71.0%), underlying kidney disease (65.4%), prior history of stroke or bleeding events (64.2%), anemia or low platelet count (59.9%), liver disease (59.3%), current use of oral anticoagulants (56.8%), active cancer (50.6%), and prior blood transfusion (24.7%). These findings highlight the central role of thorough clinical evaluation supplemented with validated scoring systems in identifying patients at elevated bleeding risk, which is crucial for tailoring antiplatelet therapy post-revascularization and optimizing patient outcomes (Fig. 1).

Shift from DAPT to SAPT

The expert opinion with the cardiologist panel, it was recorded that more than half (56.2%) reported moving from DAPT to SAPT at 3 months in HBR patients with low ischemic risk, reflecting a preference for early de-escalation to reduce bleeding complications. Approximately one-fourth (25.9%) opted for a 1-month transition, while 18.5% continued DAPT for 6 months before shifting to SAPT. In the context of preferred monotherapy regimens following a

Table 1: Classification of expert opinion strength

Level of agreement	Definition	Threshold
Strong agreement	Broad consensus among experts	≥75% endorsement
Moderate agreement	Majority support, though less than strong consensus	50–74% endorsement
Mild agreement	Limited support from experts	25–49% endorsement
Neutral/no clear consensus	Opinions varied significantly or limited endorsement	<25% endorsement

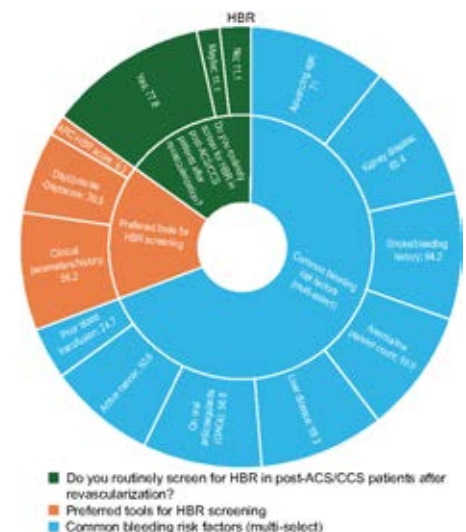


Fig. 1: Expert opinions on bleeding risk stratification



Fig. 2: Expert opinions on switching from DAPT to SAPT

shorter DAPT, 42.6% preferred the fixed-dose combination (FDC) of clopidogrel with a statin, followed by clopidogrel alone (40.7%). Among the less commonly chosen were ticagrelor and aspirin monotherapy, at 20.4% and 12.3%, respectively. However, a majority (56.2%) showed inclination towards abbreviated DAPT selectively in elderly patients with ACS, while 31.5% used it most of the time, reflecting a trend towards balancing ischemic and bleeding risks through individualized antiplatelet strategies (Fig. 2).

Preference for Clopidogrel vs Aspirin

In the present expert survey involving 162 cardiologists, clopidogrel-based regimens emerged as the dominant preference for long-term antiplatelet therapy, particularly among elderly patients with ACS. Among the various antiplatelet regimens reported, clopidogrel monotherapy emerged as the most prescribed (43.8%), followed by the FDC of clopidogrel and statin (35.2%). In contrast, aspirin monotherapy (9.8%) and ticagrelor monotherapy (9.2%) were less frequently used. A strong consensus (81.5%) was observed in agreement with the HOST-EXAM trial findings that clopidogrel is superior to aspirin for long-term secondary prevention. Continued use of clopidogrel + statin FDC postcompletion of 12-month DAPT was approved and followed by 77.8% of cardiologists, indicating a progressive landscape of confidence in clopidogrel-centric maintenance therapy for sustainable vascular protection in stable post-ACS patients (Fig. 3).

DISCUSSION

The management of antiplatelet therapy in patients with ACS and CCS post-PCI continues to evolve, particularly in the context of

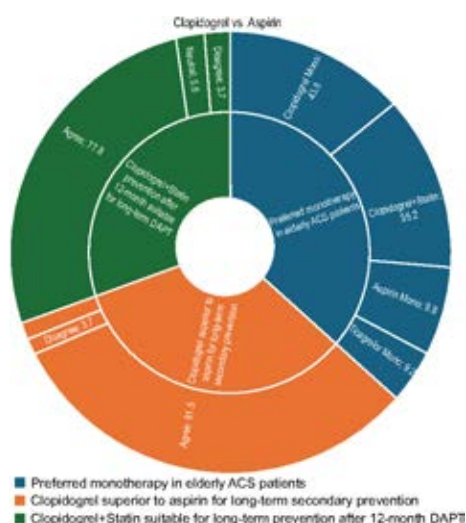


Fig. 3: Expert opinions on preferred monotherapy

balancing ischemic protection with bleeding risk mitigation. While DAPT has been the standard of care, recent clinical evidence suggests that abbreviated DAPT strategies followed by SAPT may provide a safer and equally effective alternative for select patients, especially those at high bleeding risk. Given these evolving paradigms, it is critical to evaluate both published literature and expert clinical perspectives to determine the optimal approach in Indian clinical practice.

Evolution of DAPT and Shift Toward Individualized Strategies Based on Bleeding Risks

Since the inception of PCI in 1977, developments in antithrombotic therapy have enhanced patient outcomes. The advancement of DAPT has been propelled by improvements in stent design and an enhanced comprehension of thrombosis and hemorrhagic dangers. Initially, bare-metal stents (BMS) necessitated extended dual antiplatelet therapy (DAPT) due to elevated thrombosis rates, whereas first-generation drug-eluting stents (DES) prolonged the recommended period to 12 months. Next-generation DES enhance safety, and studies advocate for abbreviated DAPT (3–6 months) followed by SAPT for patients with elevated bleeding risk. The current ESC guidelines (2023) advise a duration of 3–6 months for stable CAD, 12 months for ACS, and 1 month of DAPT in situations of high bleeding risk.⁸ A comprehensive study on stroke in India underscores its increasing impact, positioning it as the fourth major cause of mortality and the fifth leading cause of disability. Analysis of data from nine studies conducted in large cities revealed that stroke incidence varied from 108 to 172 per 100,000 annually, with 1-month case fatality rates between 18% and 42%, elevated in

males. The scarcity of high-quality data throughout India obstructs policy formulation. The research underscores the necessity for enhanced stroke surveillance, improved hospital accessibility, and consistent data collection, promoting population-based registries and WHO surveillance frameworks to advance stroke prevention and treatment methodologies.⁹

The review by Tersalvi et al. highlights the critical balance between ischemic prevention and bleeding risk in DAPT for ACS.¹⁰ Unexpected discontinuation of DAPT is frequently prompted by bleeding events, a complication that significantly increases the risk of subsequent ischemic episodes. Furthermore, following a bleeding incident, patients often cease use of other cardioprotective medications, including beta-blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, and statins, further elevating their risk for adverse cardiovascular outcomes. Given the strong association between bleeding and poor prognosis, including increased mortality, contemporary clinical guidelines emphasize the implementation of bleeding-avoidance strategies starting at the revascularization stage and recommend maintaining these preventive measures well beyond the initial acute phase.¹⁰ While DAPT reduces stent thrombosis and recurrent ischemic events, it significantly increases bleeding risk, necessitating individualized therapy. The study endorses abbreviated DAPT (3–6 months) followed by SAPT in HBR patients, using instruments such as PRECISE-DAPT and ARC-HBR to enable risk evaluation. Urban et al. established HBR criteria and identified significant risk variables including advanced age, chronic kidney disease (CKD), malignancy, previous stroke, and anticoagulant usage. In relation to the Bleeding Academic Research Consortium (BARC), HBR in patients receiving PCI is defined as having at least a 4% risk of significant bleeding (category 3 or 5) or a 1% risk of cerebral hemorrhage within 1 year of PCI.¹¹

The ARC-HBR criteria include a combination of major and minor clinical factors, such as older age (≥ 75 years), anemia, use of oral anticoagulants, and recent bleeding events. These patients have a higher chance of bleeding problems, so DAPT needs to be carefully managed. In HBR patients, DAPT duration is often shortened to minimize bleeding risk while maintaining protection against ischemic events such as stent thrombosis. This approach balances the benefits of reducing clot formation with the increased risk of bleeding in patients. The study shows that people with a high bleeding

risk (HBR) are often left out of PCI trials. This makes it difficult to create standard treatment guidelines. These findings demonstrate that decreasing DAPT for 6 months or less by switching to SAPT can minimize bleeding risk without increasing ischemic events. This highlights the need for personalized antiplatelet strategies in post-PCI care.¹¹

A fixed-duration approach to DAPT toward a more personalized, risk-based strategy has been largely shaped by evidence showing that shorter DAPT followed by SAPT can benefit patients with HBR. Although current guidelines recommend using risk assessment tools such as PRECISE-DAPT and ARC-HBR to identify these high-risk patients, their real-world use differs widely among clinicians and healthcare settings. In our study, 77.8% of experts reported that they routinely screen HBR patients after revascularization, emphasizing its critical role in informing antiplatelet therapy decisions. 39.5% of patients used DAPT or PRECISE-DAPT scores, but most (56.2%) depended on clinical parameters and patient history. This shows individuals in the real world prefer individualized assessment to tools.

Advancing age (71.0%) was the most reported bleeding risk factor, followed by kidney disease (65.4%), prior stroke or bleeding history (64.2%), and anemia or low platelet count (59.9%). These findings reinforce the importance of personalized risk stratification to balance ischemic and bleeding risks in post-PCI management.

Expert Opinion

The experts emphasized that individualized risk assessment remains central to determining the optimal duration of dual antiplatelet therapy (DAPT), particularly among patients with a high bleeding risk profile. While validated tools such as the PRECISE-DAPT and ARC-HBR scores were acknowledged for structured evaluation, the panel noted that clinical decision-making in real-world settings is more often guided by patient history, comorbid conditions, and physician judgment. According to the experts, key factors influencing early transition to single antiplatelet therapy (SAPT) include advanced age, renal impairment, prior bleeding episodes, and low platelet counts, which together help balance ischemic protection with bleeding safety in post-revascularization management.

Optimizing Antiplatelet Therapy (DAPT to SAPT transition): SAPT and De-escalation Strategies

The management of antiplatelet therapy post-PCI is increasingly shifting toward individualized risk-based strategies, especially in HBR patients. According to the 2023 ESC Guidelines recommendations, it is highly advised for individualized antiplatelet therapy following PCI for HBR patients in particular (Fig. 4).² While considering the low ischemic risk in HBR patients, DAPT can possibly be shortened to 3–6 months, with

a preference for a P2Y₁₂ inhibitor over aspirin for maintaining long-term patient on SAPT.

In elderly patients, the higher bleeding risk necessitates early DAPT de-escalation, with clopidogrel favored over potent P2Y₁₂ inhibitors. For HBR cases, 1-month DAPT may be considered. The guidelines also propose alternative antiplatelet therapy to reduce bleeding risk within the first 12 months after ACS. In stabilized patients, early de-escalation from potent P2Y₁₂ inhibitors (ticagrelor/prasugrel) to clopidogrel after 1 month can decrease bleeding while maintaining ischemic protection.

Optimal antiplatelet strategies for patients undergoing complex PCI were discussed in a review by Bhatt, and emphasis was given on individualized therapy based on ischemic and bleeding risk.¹² 1-month DAPT regimen followed by clopidogrel monotherapy was recommended for HBR patients. A 3-month DAPT followed by ticagrelor (90 mg BID) is suggested, with a potential dose reduction (60 mg BID) after 1 year in patients with moderate ischemic risk. For those with high ischemic risk but low bleeding risk, 12-month DAPT is maintained, with reassessment of bleeding risk annually. This patient-specific approach balances the risk of bleeding against ischemic protection, emphasizing therapy guided by clinical judgment, platelet function testing, or genotyping where available. The recommendation highlights that while shorter DAPT followed by SAPT is suitable for stable or HBR patients, those with higher thrombotic risk require prolonged DAPT to optimize outcomes.¹²

The SHARE trial evaluated P2Y₁₂ inhibitor monotherapy after 3 months of DAPT compared with 12-month DAPT in patients undergoing PCI with a drug-eluting stent.¹³ The study demonstrated that early aspirin withdrawal with P2Y₁₂ monotherapy was noninferior to 12-month DAPT regarding net adverse clinical events, including major bleeding and ischemic outcomes. The occurrence of major bleeding was lower in the monotherapy group (0.2% vs 0.8%), with no significant increase in ischemic events. These results support a shorter DAPT duration in selected patients, particularly those at high bleeding risk, aligning with recent trends favoring individualized antiplatelet strategies. The OPT-BIRISK randomized clinical trial evaluated extended clopidogrel monotherapy against continued DAPT in ACS patients at both high ischemic and bleeding risk who had completed 9–12 months of DAPT after PCI.¹⁴ Among 7,758 patients, those randomized to clopidogrel monotherapy experienced a 25% reduction in BARC types 2, 3, or 5 bleeding (2.5% vs 3.3%; HR: 0.75, $p = 0.03$). Importantly, major adverse cardiac and cerebral events

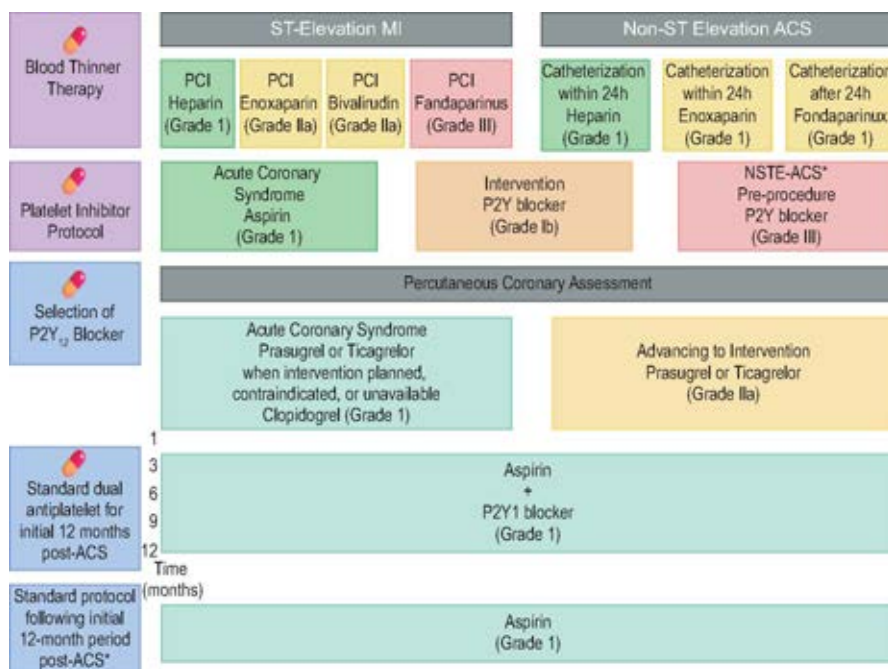


Fig. 4: Algorithm for the management of acute coronary syndromes (ACS), including ST-elevation myocardial infarction and non-ST-elevation ACS. Adapted from the European Society of Cardiology (ESC) Heart Failure Guidelines, 2023

(MACCE) were also significantly lower in the monotherapy group (2.6% vs 3.5%; HR: 0.74, $p = 0.02$ for superiority), demonstrating that clopidogrel alone maintained ischemic protection while reducing bleeding risk. These findings emphasize extended P2Y₁₂ monotherapy as a safer alternative for bi-risk patients post-DAPT, aligning with recent trends favoring aspirin-free long-term antiplatelet regimens to optimize bleeding safety without compromising ischemic outcomes.

The POPular AGE study examined clopidogrel in comparison to ticagrelor/evaluating bleeding risk and clinical outcomes in elderly patients aged 70 years and above with NSTEMI-ACS (non-ST-elevation acute coronary syndrome) over a 12-month period.¹⁵ In nearly 1,002 patients, clopidogrel noticeably reduced bleeding incidences (18% against 24%, $p = 0.02$) while being noninferior in attributed clinical benefit (comprising mortality, myocardial infarction, stroke, and bleeding) in comparison to ticagrelor/prasugrel (28% vs 32%, $p = 0.03$). In nearly 47% of patients on ticagrelor/prasugrel therapy, therapy was ceased early owing to hemorrhage, dyspnea, or the necessity for anticoagulation. In accordance with the data, it can be inferred that clopidogrel is a safer and effective alternative, especially for elderly individuals at elevated bleeding risk, as it balances the management regimen by reducing bleeding complications without raising ischemic events. The reduction of DAPT is mostly determined by the rationalized balance between ischemic and hemorrhagic events. Current guidelines advocate for 6 months of dual antiplatelet therapy (DAPT) for stable coronary artery disease (CAD) following drug-eluting stent (DES) implantation and 12 months for acute coronary syndrome (ACS). In HBR patients, DAPT may be reduced to 3–6 months without elevating ischemic events.¹⁶

Among participating clinicians, 56.2% preferred switching from DAPT to SAPT at 3 months in HBR patients with low ischemic risk, aligning with guideline-backed de-escalation strategies. The clopidogrel + statin FDC was the most preferred for SAPT (42.6%), closely followed by clopidogrel monotherapy (40.7%) and ticagrelor monotherapy (20.4%), whereas aspirin alone was the least favored (12.3%). Among elderly ACS patients, 56.2% selectively adopted abbreviated DAPT, with clopidogrel monotherapy (43.8%) being the preferred choice, reinforcing real-world preference for individualized, bleeding-conscious strategies.

Expert Opinion

The experts agreed that early de-escalation from dual antiplatelet therapy (DAPT) to

single antiplatelet therapy (SAPT) is a safe and appropriate approach, particularly in high bleeding risk and elderly patients. They identified clopidogrel-based regimens, either as standalone therapy or as fixed-dose combinations with statins, as the most preferred options due to their favorable balance between efficacy and safety. According to the panel, timely transition to SAPT helps minimize bleeding complications without compromising ischemic protection, especially in clinically stabilized patients following revascularization.

Long-term Maintenance Therapy Post-DAPT

The HOST-EXAM trial investigated the optimal antiplatelet monotherapy in patients undergoing PCI with DES and who had completed 6–18 months of DAPT without adverse events.¹⁷ The study randomized 5,438 patients to receive either clopidogrel (75 mg daily) or aspirin (100 mg daily) for 24 months. The primary composite endpoint, comprising all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC type 3 or greater bleeding, was significantly lower in the clopidogrel group (5.7%) than in the aspirin group (7.7%; HR 0.73, $p = 0.0035$). Clopidogrel also showed lower rates of stroke (0.7% vs 1.6%), readmission due to ACS (2.5% vs 4.1%), and major bleeding (1.2% vs 2.0%).¹⁷ The SMART-CHOICE 3 trial also demonstrated that in high-risk patients post-PCI who had completed standard DAPT, after which the patients were randomized to clopidogrel or aspirin monotherapy. Clopidogrel monotherapy was more effective than aspirin for long-term maintenance. Over a 3-year follow-up, clopidogrel significantly reduced the composite endpoint of all-cause death, myocardial infarction, and stroke in comparison to aspirin (4.4% vs 6.6%; HR 0.71; $p = 0.013$), primarily driven by lower rates of MI (1.0% vs 2.2%) and mortality, without an increase in bleeding events (3.0% vs 3.0%) or other adverse outcomes.¹⁸ These findings establish clopidogrel as a superior option to aspirin for chronic maintenance therapy post-PCI, reducing both ischemic and bleeding risks in stable patients transitioning from DAPT in both ACS and CCS populations.

In the current study, 81.5% of the respondents came to an agreement that clopidogrel monotherapy is preferable to aspirin for long-term maintenance. This aligns with the findings of the HOST-EXAM trial with its lower ischemic and bleeding risk profile. Considering low-risk ACS patients who have completed 12 months of DAPT,

the clopidogrel + statin FDC stood out as a practical long-term strategy for secondary prevention. Among the respondents, 77.8% supported FDC usage, reflecting real-world endorsement of dual-benefit therapy beyond standard monotherapy.

Expert Recommendation

The experts indicated that clopidogrel is predominantly preferred over aspirin for long-term maintenance therapy following completion of dual antiplatelet therapy (DAPT), aligning with evidence from major trials such as HOST-EXAM. They further endorsed the use of fixed-dose combinations of clopidogrel and statins as a practical, dual-benefit approach that enhances both antiplatelet efficacy and lipid control. According to the panel, this regimen is particularly suitable for stable, low-risk patients with acute coronary syndrome (ACS) who have completed 12 months of DAPT, as it supports better adherence, sustained vascular protection, and a lower risk of bleeding complications.

CONCLUSION

This expert opinion survey highlights real-world practices of Indian cardiologists regarding antiplatelet therapy post-PCI, emphasizing individualized risk stratification and early de-escalation strategies. A majority of clinicians (77.8%) routinely screen for high bleeding risk (HBR), predominantly relying on clinical parameters and patient history rather than formal scoring tools, reflecting a pragmatic, experience-driven approach. Regarding DAPT duration, 56.2% of experts favored de-escalation to SAPT at 3 months in HBR patients with low ischemic risk, consistent with contemporary ESC recommendations and evidence from trials such as SHARE, STOPDAPT-2, and SMART-CHOICE. The clopidogrel + statin fixed-dose combination (42.6%) was the most preferred SAPT strategy, closely followed by clopidogrel monotherapy (40.7%), while aspirin monotherapy was the least favored. Among elderly ACS patients, 56.2% selectively adopted abbreviated DAPT, with clopidogrel monotherapy (43.8%) as the preferred regimen, supporting findings from the POPular AGE trial. For long-term maintenance, 81.5% of experts endorsed clopidogrel over aspirin, aligning with the HOST-EXAM and SMART-CHOICE 3 trials, and 77.8% supported continued use of the clopidogrel + statin FDC beyond 12 months of DAPT. Collectively, these findings demonstrate that Indian cardiologists' practices largely align with contemporary international guidelines, while also reflecting regional adaptations, most notably a stronger reliance

on clopidogrel-based regimens and fixed-dose combinations. These real-world insights underscore the need for further prospective research and India-specific recommendations to optimize post-PCI antiplatelet therapy.

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Rising Violence against Doctors: Roots and Remedies

Rajesh Agrawal*

Received: 08 December 2024; Accepted: 02 January 2025



ABSTRACT

Medical violence [MV] includes any Violence by anybody in health care setting. MV may be against doctors or among themselves or towards the patient or other staff members or by the public to an institution. Violence Against Health Care Professionals [HCPs] is rising in recent years, and it refers to any aggression, physical assault, verbal abuse, harassment and threats. World Medical Association said violence against HCP is an international emergency that can undermine health systems and impact patient health and it has become part of the profession worldwide & India is no exception.

Various reasons for violence against HCWs are unrealistic expectations, Unacceptability of complications, poor health literacy, death of the patient, Perception of medical profession as a business, Short tempered, long waiting, Lack of health infrastructure, High cost, Media portraying a negative image of medical profession and Public impression is HCPs are earning Easy money and handsome amount. Non communication between HCP and relatives of the patient and Provocation by the politicians, local leaders, legal advisors to run their profession are other important reasons for MV.

There is no sympathy towards medical profession or HCP facing the issues, from any corner of the society and most painful is their own medical colleagues are also not supportive.

Violence against HCP is better avoided by fairer and clear explanation about the expenses, fees, duration of hospitalization and treatment and at the same time you can provide cheaper alternatives elsewhere will improve confidence in you. Giving them liberty to consult the consultant and centre of their choice and sympathetic attitude, towards patient and relatives may avoid many violences. If we do not rightly communicate then we may have to face legal complications and hire advocates and attend court of law and all these are much more expensive and time consuming.

Last and most important is to be vigilant and understand the psychology of the patient and at that point of time leave aside the ego and make certain compromises though they are very bitter to swallow. "It is better to lose a penny today than a pound tomorrow" what I mean is in case of dispute compromise some amount of money and time because most of the time financial issues are at the back of mind.

Keywords: Healthcare professional, Healthcare setting, Healthcare workers, Lack of trust, Medical violence, Violence against doctors.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1740

DEFINITION OF MEDICAL VIOLENCE

Medical violence (MV) is a broad term that includes any violence by anybody in a healthcare setting or healthcare institution. MV may be against or by doctors (Drs) themselves or toward the patient or other staff members or by the public to an institution, healthcare professional (HCP), healthcare worker (HCW), hospital, or health infrastructure. "Medical violence" includes harmful, abusive behavior, physical, psychological, and emotional abuse by any of the HCWs or institutions or patients or their family members or the public in a healthcare setting that may harm the patient or HCWs and/or infrastructure.

Medical violence may be:

- Verbal: Racial abuse, cursing, yelling, or torture.
- Sexual harassment: Insulting gestures, sexual-type verbal or physical contact.

- Physical violence: Spitting, biting or beating, tearing clothes using weapons, or any unwanted physical contact.

World Health Organization (WHO) definition of violence: "The intentional use of physical force, threatened or actual, against one, another or against a group or community, resulting in injury, psychological harm, maldevelopment or death."

VIOLENCE AGAINST HEALTHCARE PROFESSIONALS

Violence against Drs is rising alarmingly in recent years, and it refers to any aggression, verbal or sexual abuse, or physical threat directed to HCWs or HCPs. The violence is usually done by patients, their family members, or sometimes provoked by colleagues. Here, we are discussing only rising violence against Drs or HCPs or

HCWs, usually used synonymously. HCWs are a group of people that includes doctors, nurses, paramedical staff, peons, ward boys, lab assistants, technicians, etc.

The World Medical Association said violence against HCWs is an international emergency that is affecting healthcare systems and affects patient health.

Violence against Drs has become part of their profession worldwide, and India is no exception; the Indian healthcare system is facing many challenges, including workplace violence (WPV), multiple causative nexuses leading to substandard performance by HCWs.¹

A study conducted to compare the pattern of violence in a tertiary care government teaching hospital and a multispecialty private trust hospital in Sagar, Madhya Pradesh, India, revealed 96.5% verbal, 43.4% emotional, and 6.2% physical violence, and violence was more common in government hospitals compared to private hospitals. Most HCWs (87.6%) silently resolved without reporting, and only 1.8% reported to fight. Reasons at the root of violence were illiteracy and lack of morality (83.2%) among patients and relatives, lack of proper facilities, and a lack of trust in HCWs.²

Census of Fatal Occupational Injuries (CFOI), a Bureau of Labor Statistics, reported 5,333 fatal workplace injuries in 2019 in the USA, and 761 were intentional in nature.³

Occupational Safety and Health Administration (OSHA) reported that HCWs are five times more likely to be exposed to verbal and physical violence than those in other sectors.⁴ Violence against HCWs affects their performance negatively and alters doctor-patient relationships, leading to substandard healthcare; they may also get burned out or experience depression or sleep disorders.

National Institute for Occupational Safety and Health (NIOSH) 2018 survey found 20%

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How to cite this article: Agrawal R. Rising Violence against Doctors: Roots and Remedies. J Assoc Physicians India 2026;74(10):86–88.

of nurses experienced physical violence at work.⁵

Medical violence is globally increasing and leading to increasing stress. At the root of all violence, cost of treatment and financial issues are present, and sensitivity and tenderness of the profession allow them to carry out all nuisances.⁶

Reports from Syria and Yemen are really worrying, highlighting that healthcare facilities are the targets, leading to loss of life and disruption of medical care significantly.⁷

Indian Medical Association (IMA) revealed 75% of Drs in India have experienced violence at some point in their lives, mostly verbal abuse. A cross-sectional study of 326 resident Drs from six departments of a tertiary care hospital in New Delhi in June 2022 showed WPV was present in 80.4% of HCPs; 75.6–84.5% experienced verbal violence, and 21.7% faced physical violence. Perceived delay in treatment and patient deaths were the most common causes of violence. HCPs were hesitant to report WPV due to time-consuming processes and a lack of organizational support. WPV had a negative impact on 73.3% of Drs' mental and personal well-being. The negative impact of WPV is not only limited to the psychosocial well-being of Drs but alters their approach to the patient and the surgical and medical interventions. Appropriate actions to safeguard HCPs and improve patient outcomes are necessary.⁸

A narrative review showed that:

- 156 HCWs were killed at workplaces between 2011 and 2018 in the US, equal to about 20 deaths a year.
- 10 Drs have been killed since 2017 in the Philippines because of their perceived political connections.
- 21 Drs were killed between 1988 and 2019 in Italy by patients and relatives.
- 101 serious MV incidents occurred between 2003 and 2013 in China, which claimed the lives of 24 Drs and nurses.⁹

A study found that violence against doctors is most prevalent in government hospitals. In general, the public used to say to Drs that you are the GOD or next to GOD, but in reality, there is no sympathy toward the medical profession or HCPs or HCWs facing the issues from any corner of society, be it the press, media, journalists, public, politicians, administration, police, and, most painfully, their own medical colleagues as well.

REASONS FOR INCREASED MEDICAL VIOLENCE?

- Public impression is that Drs are earning easy money and handsome amounts.

- Drs are a sophisticated class of people and the creamy layer of society, and the medical profession is very tender and sensitive, so they are very easily targeted.
- Litigations by way of female physical or sexual abuse (whether it is right or fake) will spoil the reputation of Drs, so it is very often easy and common.
- Noncommunication between Drs and relatives of the patient and nonunderstanding or lack of knowledge of the disease are common factors.
- Expensive and rising cost of treatment.
- Provocation by politicians, local leaders, and legal advisors to run their profession are common.
- Unrealistic expectations and unacceptability of complications and death of the patient.
- It's a bitter truth, but many a times violence is provoked by your own colleague because of jealousy or the competitive world or any other unknown reason.
- High expenditure in corporate hospitals.
- Ignorance of medical problems and perception of the medical profession as a business because of obvious reasons like referral practice, unnecessary investigations, blanket sets of investigations for every patient, and extraction of the Medclaim facilities by the corporate hospitals are the key reasons behind this belief.
- Lack of morality, short-tempered nature, and long waiting before speaking to a doctor.
- Lack of adequate health-related infrastructure.
- Role of media in portraying a negative image of the medical profession.

HOW TO AVOID VIOLENCE AGAINST HEALTHCARE PROFESSIONAL

"It is better to lose an hour today than to lose days, months, and years thereafter" and "It is better to lose a penny today than a pound tomorrow" by way of proper communication about the disease, complications, and outcome information with the patient and his or her most influential relative or friend. If it is not rightly communicated, then you may have to face legal complications and pay and spend time on advocates and attend court of law, and all these are much more expensive and time-consuming than an hour. Also, do compromise some amount of money because most of the time, financial issues are at the root of all issues.

Fair and clear explanation about the expenses, fees, duration of hospitalization, and treatment, and at the same time, you

can provide cheaper alternatives elsewhere, will improve your acceptability as well as confidence in you.

Give them liberty to consult the consultant and center of their choice.

Try to be sympathetic with patients and their relatives and never lose patience and never be aggressive.

Paramedical staff must be sympathetic and well behaved while talking or caring for the hospitalized patient in the wards. For example, chitchatting or laughing when a patient is asking for help or a patient's attendant comes to you to complain about his patient can make them irritable and aggressive.

Teaching and implementing communication skills and conflict management skills should be injected into Indian doctors for avoiding WPV. Joint efforts by the doctors, media, society, and governance will help find a solution for this epidemic.¹

Always avoid prolonged waiting as patients are the sufferers, and prolonged waiting increases suffering. It's a bitter truth that "no one, nowhere in the world, for any reason, likes to wait," and this issue of waiting should be addressed properly; it will also improve your efficiency or improve your efficiency.

Developing stress management programs, creating safe working environments, staff training on preemptive risk analysis, recognizing warning signals, de-escalation, restraints, evasion, and breakaway techniques must be an integral part of healthcare settings.

Infrastructure-related issues should be well addressed, like improving visibility through better lighting, transparent doors, CCTV, security with door locks, secured furniture, and weapons-screening guards, etc.

Last but not least, most of the violence can be avoided if you are vigilant and understand the psychology or mindset of the patient and if you leave aside the ego and make certain compromises like some amount of money and time.

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Atma and Medicine: Bridging Ancient Wisdom and Modern Understanding of Life and Consciousness

HNS Bhatnagar*

ABSTRACT

Modern medicine has achieved remarkable advances in understanding the human body, yet the fundamental nature of life and consciousness remains incompletely understood. The ancient Indian concept of Atma offers a philosophical perspective on life, consciousness, and individual existence. This editorial explores possible interfaces between the concept of Atma and contemporary medicine, particularly in relation to energy, cellular organization, consciousness, unconsciousness, electrophysiology, and death. Atma should not be equated with any currently recognized physical form of energy or biological structure; rather, it may provide a philosophical framework for reflecting upon questions that remain at the boundaries of science and human understanding. Such dialogue can enrich medicine while maintaining the distinction between philosophical concepts and scientific evidence.

Keywords: Atma, Consciousness, Death, Energy, Indian philosophy, Life, Neuroscience.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1737

INTRODUCTION

Medicine is fundamentally empirical. It observes, measures, and seeks reproducible explanations for biological phenomena. We can measure blood pressure, oxygen saturation, biochemical parameters, cardiac electrical activity, and cerebral electrical activity. Modern imaging and molecular biology can reveal the structure and function of the human body with extraordinary precision.

Yet one fundamental question remains unanswered:

What makes a living human being different from a collection of living cells?

We understand many mechanisms necessary for sustaining life, but the nature of consciousness, subjective experience, and the transition from biological activity to awareness remains incompletely understood.

Indian philosophical traditions contemplated these questions thousands of years ago. The concept of Atma has traditionally been associated with the essential principle of life, consciousness, and individual existence. Chetana, or consciousness, is closely related to this concept.

The universe, or Brahmand, may be conceptualized as a vast reservoir of energy manifesting in different forms. Within this philosophical framework, Atma may be viewed as a manifestation of this universal principle, continuing through different forms of existence.

Although such concepts belong primarily to philosophy and spirituality, they raise questions of considerable relevance to medicine.

ATMA AND THE ENERGY OF LIFE

Modern physics recognizes energy as a fundamental and measurable property that exists in different forms and undergoes transformation. Biology is similarly dependent on continuous energy transformation. Cells utilize chemical energy, generate adenosine triphosphate (ATP), maintain electrochemical gradients, and perform mechanical and synthetic work.

Atma, however, should not be equated with physical energy in the scientific sense. Energy in physics has a precise operational definition, whereas Atma is a philosophical and spiritual concept.

Nevertheless, the conceptual parallel is intriguing. Life is characterized by continuous transformation of energy and information. Atma may therefore be considered philosophically as a principle underlying the continuity and organization of life rather than as a measurable energy particle or physical substance.

FROM CONCEPTION TO THE LIVING ORGANISM

Life begins with an extraordinarily complex biological process. Fertilization brings together the genetic contributions of two individuals and initiates cellular division, differentiation, and progressive organization.

The developing organism receives nutrients and energy through the mother and, after birth, through nutrition. Throughout life, energy is continuously acquired, transformed, and utilized to maintain cellular and organ function.

This raises a deeper question:

At what point does biological existence become consciousness?

Developmental biology can increasingly describe the structural and functional maturation of the nervous system, but the emergence of subjective consciousness remains difficult to define.

This is one area where the philosophical concept of Atma and modern science address a common question from very different perspectives.

THE LIVING CELL

Every cell is a highly organized system of energy, information, and regulation. Mitochondria generate ATP, membrane potentials maintain cellular communication, and intracellular organelles coordinate the synthesis, modification, and transport of essential molecules.

Atma may be conceptualized as being present in minute form within living cells and as contributing philosophically to their vitality and organization.

The Golgi apparatus has well-established functions in protein and lipid modification, sorting, and intracellular trafficking. Describing it as a "step-up transformer" for Atma is therefore best regarded as a conceptual hypothesis or metaphor rather than an established biological mechanism.

The broader idea remains interesting: a living cell is much more than the sum of its biochemical constituents. Its remarkable organization depends upon continuous integration of energy, information, and structure.

ATMA AND CONSCIOUSNESS

Perhaps the most important interface between Atma and medicine is consciousness.

Atma or Chetana may be regarded philosophically as closely associated with consciousness and awareness. Modern

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How to cite this article: Bhatnagar HNS. Atma and Medicine: Bridging Ancient Wisdom and Modern Understanding of Life and Consciousness. J Assoc Physicians India 2026;74(10):89–90.

neuroscience, however, has not identified a single anatomical “seat” of consciousness. Consciousness appears to involve complex interactions among cortical and subcortical networks, including the cerebral cortex, thalamus, and ascending arousal systems.

Neuroscience has identified numerous neural correlates of conscious states, but identifying these correlates does not necessarily explain why neural activity is accompanied by subjective experience.

We can record brain activity associated with pain, memory, emotion, and awareness. Yet why an individual experiences these phenomena as a personal, subjective reality remains one of the major unanswered questions in science.

Atma therefore remains relevant as a philosophical concept—not necessarily as an alternative biological mechanism, but as a reminder that the mystery of consciousness has not yet been completely resolved by neuroscience.

UNCONSCIOUSNESS IS NOT DEATH

Clinically, an important distinction exists between unconsciousness and death.

Anesthesia, hypoglycemia, metabolic disorders, intoxication, and several neurological conditions can produce profound unconsciousness while brain function remains potentially reversible. Restoration of normal physiology may restore consciousness.

The concept of Atma may interpret this as a state in which consciousness becomes inactive while Atma continues to exist within the body.

Modern medicine does not require this explanation. Nevertheless, both perspectives highlight an important clinical principle:

Absence of consciousness does not necessarily mean death.

Death requires appropriate clinical determination and cannot be defined simply by lack of responsiveness.

ELECTRICAL MANIFESTATIONS OF LIFE

Living tissues have complex electrical properties. Cardiac electrical activity can be recorded through the electrocardiogram (ECG), while electrical activity of neuronal populations can be recorded through the electroencephalogram (EEG).

Atma may be compared metaphorically with an electrical current: it cannot be directly seen, but its manifestations may be inferred through measurable physiological activity.

However, ECG and EEG are not direct measurements of Atma. They record specific

electrical phenomena generated by the heart and brain.

Nevertheless, they demonstrate an important principle: living organisms continuously express measurable electrical, chemical, and informational activity.

This provides an interesting conceptual bridge between the philosophical idea of an underlying life principle and the measurable manifestations of biological function.

DEATH: AN EVENT OR A PROCESS?

Death is often perceived as an instantaneous event, but biology reveals a more complex process. Following cessation of circulation, different organs and tissues lose function at different rates. Cellular processes may continue for varying periods, and under appropriate conditions, some organs can remain viable for transplantation.

This does not establish persistence of consciousness or Atma after death. Rather, it demonstrates that death of the organism and cessation of every cellular process are not necessarily simultaneous events.

Modern transplantation medicine makes practical use of this biological window. The ability to preserve and transplant organs after death is one of the remarkable achievements of medicine.

The observation that tissues may remain viable for a period after death therefore invites philosophical reflection, but should not itself be interpreted as scientific evidence for the existence or persistence of Atma.

SCIENCE AND ATMA: COMPLEMENTARY QUESTIONS

Can Atma be scientifically demonstrated?

At present, if Atma is defined as a nonmaterial or transcendent principle, it cannot readily be investigated using conventional scientific methods. A scientific hypothesis requires operational definition, measurable parameters, and reproducible observations.

This does not make Atma meaningless. It simply places the concept in a different epistemological category.

Science asks:

What happens? How does it happen? Can it be measured and reproduced?

Philosophy asks:

What does existence mean? What is consciousness? What constitutes the self?

Medicine encounters both sets of questions every day.

The challenge is therefore not to prove a philosophical concept using inappropriate scientific measurements, nor to dismiss it because it lies beyond current scientific

methods. The challenge is to maintain scientific rigor together with intellectual humility.

BEYOND REDUCTIONISM

Modern medicine has achieved much of its success by analyzing complex systems into measurable components—genes, proteins, cells, organs, and neural circuits.

Yet the patient is more than a collection of these components.

Pain is more than a laboratory value. Suffering cannot be completely represented by imaging. Compassion cannot be reduced to a biochemical pathway. The physician–patient relationship contains dimensions that remain difficult to quantify.

The concept of Atma may therefore encourage medicine to retain a sense of wholeness.

This does not require accepting Atma as a biological entity. Rather, it reminds us that medicine deals not only with biological mechanisms but also with consciousness, subjective experience, dignity, relationships, and the meaning of illness.

CONCLUSION

Modern medicine has become extraordinarily proficient at understanding and manipulating the physical processes that sustain human life. Yet the deeper questions remain:

What is life? What is consciousness? What makes a human being a person rather than merely an organized collection of cells?

Atma offers one philosophical response to these questions, while modern biology provides explanations based on cellular organization, metabolism, electrophysiology, and neural networks.

These perspectives should neither be conflated nor unnecessarily placed in opposition.

The greatest value of bringing Atma into medical discourse may not be to propose a new biological mechanism, but to encourage medicine to remain open to questions that lie at the boundaries of science and philosophy.

Medicine must remain firmly grounded in evidence. At the same time, it must acknowledge the limits of present knowledge.

What we can measure may not yet encompass everything we seek to understand.

The mystery of consciousness remains one of the greatest frontiers of human knowledge. The dialogue between Atma and medicine may therefore serve an important purpose—not by replacing science with spirituality, but by reminding us that understanding the human body is not necessarily the same as understanding the human being.



Letter to Editor (Correspondence) on “Correlation of Conventional and Extended Lipid Profiles with Plaque Burden in Statin-naïve Patients with Acute Coronary Syndrome: A Prospective Observational Study from South India”

Nitin Chintaman Gawari¹, Sujata Prakash Shingare^{2*}, Bhalchandra Tryambak Rane³, AV Tilak⁴

Keywords: Acute coronary syndrome, Extended Lipid Profiles, Lipid parameters, Plaque burden.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1651

Dear Sir,

The study by Periasamy et al. offers valuable data on lipid metrics and plaque burden in statin-naïve acute coronary syndrome (ACS) patients¹; however, a few methodological issues require clarification. Lipid measurements obtained within 48 hours may be influenced by acute-phase declines in total and low-density lipoprotein (LDL) cholesterol, a well-described phenomenon following myocardial infarction,² which may attenuate true associations. Acknowledgment of this or repeat convalescent profiling would improve interpretability.

Although multivariable models were presented, several key confounders—diabetes, body mass index (BMI), smoking status, thrombolysis, and timing of angiography—were not included together. These variables influence both lipid indices and Gensini scores and may affect the robustness of the correlation.^{3,4}

The wide range of time-to-angiography (median 7 days overall, 24 days for unstable

angina) may also alter plaque assessment due to thrombus resolution or interim therapy. Prior work shows that delayed angiography can affect coronary assessment⁵; adjustment or subgroup analysis could help clarify this effect.

The study is commendable, and addressing these points would further strengthen its conclusions.

Thank you.

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How to cite this article: Gawari NC, Shingare SP, Rane BT, et al. Letter to Editor (Correspondence) on “Correlation of Conventional and Extended Lipid Profiles with Plaque Burden in Statin-naïve Patients with Acute Coronary Syndrome: A Prospective Observational Study from South India”. *J Assoc Physicians India* 2026;74(10):91.

Therapeutic Wheel for Hypertension: A Squared Critique

Ankit Kumar Sahu^{1*}, Arshad Nazir², Aditya Kapoor³



Keywords: Comorbidities, Fixed-dose drug combinations, Hypertension, Medical management, Tailored approach.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1686

The multispecialty consensus by Wander et al.¹ proposes a visually intuitive “therapeutic wheel” to guide individualized antihypertensive therapy across diverse comorbid conditions. While this framework is educational and innovative, its clinical utility is limited by several conceptual, scientific, and practical shortcomings. This commentary critically appraises the wheel in the context of contemporary hypertension management, with emphasis on special populations, resistant hypertension, evolving pharmacotherapy, multimorbidity, and interventional strategies. We shall be discussing the potential deficiencies in the proposed concept of the hypertension wheel in light of currently available evidence.

OMISSION OF KEY HIGH-RISK POPULATIONS

Hypertension in Pregnancy

Hypertensive disorders of pregnancy (HDP) represent a distinct pathophysiological entity characterized by abnormal placentation, endothelial dysfunction, and heightened cardiovascular risk later in life. Management of HDP differs fundamentally from nonpregnant hypertension. RAAS inhibitors, mineralocorticoid receptor antagonists, and SGLT2 inhibitors are contraindicated because of fetal toxicity, whereas labetalol, nifedipine, and methyldopa are first-line agents. Blood pressure thresholds and targets are gestation-specific. The absence of this phenotype from the therapeutic wheel undermines its claim of comprehensive, multispecialty guidance.

Hypertension in the Elderly

Older adults account for the majority of hypertensive patients. Aging is associated with arterial stiffening, isolated systolic hypertension, orthostatic hypotension, frailty, and polypharmacy. Excessive BP lowering in this group increases the risk of syncope, falls, cognitive decline, and renal dysfunction. Current guidelines recommend individualized systolic targets, cautious titration, and avoidance of

aggressive multidrug therapy in frail elderly patients. The therapeutic wheel does not address these complexities, limiting its relevance in geriatric care.

OVERSIMPLIFICATION OF HEART FAILURE PHENOTYPES

The wheel groups all heart failure patients together without distinguishing HFpEF from HFrEF. This is clinically important, as HFpEF is driven by systemic inflammation, endothelial dysfunction, and ventricular stiffness, while HFrEF is characterized by neurohormonal activation and myocardial injury. Recent trials have demonstrated benefits of SGLT2 inhibitors, mineralocorticoid receptor antagonists, and Finerenone in HFpEF.² These phenotype-specific strategies are not reflected in the wheel, which risks promoting uniform treatment for heterogeneous conditions.

RESISTANT HYPERTENSION: BEYOND PHARMACOLOGY

Resistant hypertension requires a systematic approach that extends beyond drug escalation. The wheel remains pharmacocentric and omits device-based strategies. Renal sympathetic denervation has demonstrated sustained BP reductions in multiple sham-controlled trials.³ In selected patients, baroreflex activation therapy has also shown benefit.⁴ The absence of these options limits the wheel’s relevance in refractory cases.

OMISSION OF NEWER THERAPIES

Emerging agents such as brexdrostat, an aldosterone synthase inhibitor, have shown significant BP reductions in resistant hypertension but are not included.⁵ More concerning, Finerenone is depicted as contraindicated in CKD, despite being approved for diabetic CKD down to an eGFR of 25 mL/min/1.73 m² with potassium monitoring.⁶ This misclassification risks discouraging evidence-based therapy.

MULTIMORBIDITY: A MISSING DIMENSION

Most hypertensive patients have more than one comorbidity. Treating each condition in isolation does not reflect clinical reality. Multimorbidity requires prioritization of therapies, balancing competing risks, and minimizing polypharmacy. The wheel provides no guidance for such scenarios.

LIMITED GRANULARITY IN PULMONARY DISORDERS

Chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea, and pulmonary hypertension differ markedly in pathophysiology and treatment interactions. Cardioselective β -blockers are often safe in COPD, but not in asthma. These nuances are not captured.

SEMANTIC INACCURACY OF BEING “CONTRAINDICATED”

The outer red ring is labeled “contraindicated”, yet many agents are only relatively contraindicated or require monitoring. Absolute contraindication implies a drug should never be used, which is misleading. A term such as “use with caution” would be more accurate.

CONCLUSION

The therapeutic wheel is a valuable educational concept but oversimplifies the complexity of contemporary hypertension management. Greater phenotypic granularity, inclusion of special populations, resistant hypertension pathways, interventional strategies, and accurate drug classification are required for it to function as a robust, evidence-aligned decision-support tool.

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How to cite this article: Sahu AK, Nazir A, Kapoor A. Therapeutic Wheel for Hypertension: A Squared Critique. *J Assoc Physicians India* 2026;74(10):92–93.

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Can We Have Paperless Conferences in the Era of Digitalization?

Abhijit Anil Trailokya*¹



Keywords: Digitalization, Paperless conferences, Seminars and symposiums.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1685

Dear Sir,

These days, medical knowledge changes almost by the hour. New technologies appear, fresh studies are published, and updated guidelines keep rolling out. For a busy clinician, staying current with all of this can be challenging. Yet it has become essential because the landscape of health care is shifting quickly with new tools, changing patient profiles, and evolving disease patterns.¹

Scientific meetings and congresses help bridge this gap. They give clinicians a chance to review the latest evidence, learn from the real-world experiences of peers, exchange practical solutions, and pick up new skills. In the end, these interactions shape our daily practice and support safer, more effective care for our patients.¹

Nothing truly replaces the learning that happens at in-person events. Conferences, workshops, seminars, and symposiums offer a mix of exposure, interaction, and practical insight that is hard to recreate in local meetings or standard classroom programs. These gatherings create opportunities for growth, networking, and skill development that go well beyond routine training.²

Traditionally, medical conference gatherings have depended on printed materials such as registration forms, conference agendas, abstract booklets, schedules, certificates, posters, and many more. However, in the era of digitalization, it is worth asking whether our conferences can transition to a paperless model while maintaining scientific depth and interaction.

The logistics of printing, transportation, and waste management surrounding conferences increase the overall carbon footprint.

Digital alternatives now make paperless conferences a practical reality. Electronic abstract books, QR-based e-posters, and mobile applications for scientific schedules provide delegates with immediate access to conference materials. Digital badges, e-certificates, and virtual feedback systems can replace printed counterparts effectively. Advances in technology have made this shift both practical and beneficial. Mobile applications can integrate scientific programs, speaker profiles, and discussion forums. QR-code-based e-posters, digital abstract books, and e-certificates now offer a seamless experience for participants.

This will also reduce the load on clinicians, as most delegates do not carry printed literature back home and often leave it at the venue. A fully digital model avoids this waste. Moving away from paper not only helps the environment but also saves significant printing and logistics costs. These funds can be directed toward more meaningful initiatives such as scholarships, research support, and educational programs that benefit the medical community and society. With joint responsibility from conference organizers and pharmaceutical teams, events can move toward a cleaner, more efficient, and socially responsible digital format.

Nonetheless, challenges must be acknowledged. Dependence on technology

requires stable internet connectivity, digital literacy, and robust cybersecurity measures.

In conclusion, paperless conferences in the era of digitalization are not only achievable but imperative. Transitioning to sustainable, technology-driven formats can reduce environmental impact, improve efficiency, and align scientific gatherings with global sustainability goals. At this point, both conference organizers and pharmaceutical companies need to take shared responsibility to limit paper use and support a completely digital conference experience. This will make meetings more efficient, sustainable, and aligned with modern scientific communication. As the medical community continues to embrace innovation, it must also lead the way toward environmentally responsible academic practices.

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How to cite this article: Trailokya AA. Can We Have Paperless Conferences in the Era of Digitalization? *J Assoc Physicians India* 2026;74(10):94.



A Study on Electrocardiography, Echocardiography, and Cardiac Biomarkers in Aluminum Phosphide Poisoning and Their Prognostic Correlation

Gaurav Ashok Chaudhary¹, Sharveen Kumbhar^{2*}, Siddharth Gharge³

Keywords: 2D echocardiography, Aluminum phosphide poisoning, ECG.

Journal of The Association of Physicians of India (2026); 10.59556/japi.74.1736

Dear Sir,

We read with great interest the article by Harshvardhan Tiwari et al. titled "A Study on Electrocardiography, Echocardiography, and Cardiac Biomarkers in Aluminum Phosphide Poisoning and Their Prognostic Correlation" published in JAPI.¹ The authors should be congratulated for addressing the clinically significant issue of prognostic indicators in aluminum phosphide (AIP) poisoning, which is associated with high mortality in developing countries.

The study highlights the role of electrocardiographic abnormalities, echocardiographic findings, and cardiac biomarkers in predicting mortality. However, we would like to seek clarification regarding certain inconsistencies in the reporting of multivariate analysis results. In the discussion section, the authors report odds ratios for positive troponin-I, global hypokinesia, abnormal ECG, and abnormal PaO₂ as 0.31, 0.42, 0.44, and 0.03, respectively. However, Table 4 reports very different values for the same variables, namely 20.31, 8.42, 6.44, and 9.03, respectively. Since odds ratios below 1 and above 1 carry entirely different clinical implications, clarification regarding the correct estimated value would help to interpret and reproduce the study findings more correctly.

Additionally, the simultaneous inclusion of multiple cardiac biomarkers such as troponin-I, CPK-MB, CPK-NAC, and LDH in the prognostic model raises the possibility of multicollinearity, as all these variables are a reflection of myocardial injury. It would be valuable to know whether the use of collinearity diagnostics or variable selection methods was done before multivariate regression analysis was performed. Identification of the single most predictive and feasible biomarker may be more clinically useful than using multiple independent markers correlating with each other.

We also believe that serial echocardiographic assessment may further help in predicting the prognosis in AIP poisoning, as previous studies have reported the possibility of reversible myocardial dysfunction and transient ventricular stunning.²⁻⁵

Nevertheless, the study makes a valuable contribution to the growing literature on AIP cardiotoxicity and reinforces the importance of early cardiac evaluation in these patients.

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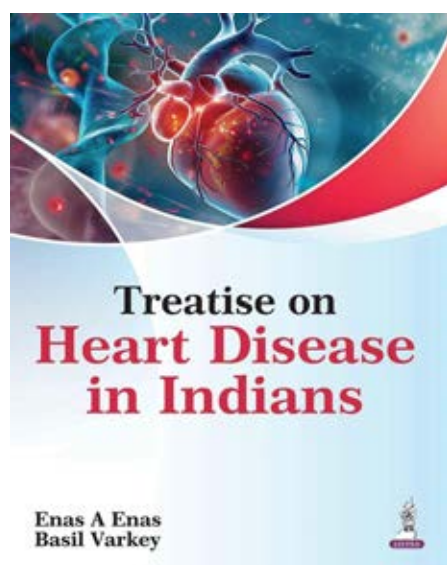
How to cite this article: Chaudhary GA, Kumbhar S, Gharge S. A Study on Electrocardiography, Echocardiography, and Cardiac Biomarkers in Aluminum Phosphide Poisoning and Their Prognostic Correlation. *J Assoc Physicians India* 2026;74(10):95.

Treatise on Heart Disease in Indians

Enas A Enas¹, Basil Varkey^{2*}

Keyword: Heart disease.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1752



A timely, evidence-informed call for earlier recognition, prevention, and treatment of cardiovascular disease among Indians and other South Asians.

MP Ravindra Nathan

A PERSISTENT CARDIOVASCULAR DISPARITY

Cardiovascular disease remains the foremost cause of death worldwide despite the extraordinary advances made in its prevention, diagnosis, and treatment. Yet, within this global epidemic lies a particularly troubling paradox: people of Indian and South Asian origin continue to experience coronary artery disease (CAD) at an earlier age and, in many instances, with greater severity than many other populations. The burden is not confined to India. It extends to Indians and other South Asians living throughout the world. In India, CAD and stroke have increased in both urban and rural populations, and the future trajectory remains deeply concerning.

A LIFELONG SCIENTIFIC MISSION

Treatise on Heart Disease in Indians addresses this important and long-overlooked disparity.

The book is the culmination of Dr. Enas's decades-long clinical observation, research, and advocacy. Beginning in the 1970s, while practicing in Chicago, he observed young Indian physicians developing serious CAD despite having few conventional risk factors. This led to a lifelong investigation into the distinctive cardiovascular risk of Indians.

Through his work with AKMG (Association of Kerala Medical Graduates) and AAPI (American Association of Physicians of Indian Origin), and the establishment of the CADI Research Foundation, he helped bring greater scientific attention to this problem. Dr. Enas also collaborated with world-renowned researchers including Drs. Salim Yusuf, Jeremiah Stamler, and Michael Davidson. Dr. Enas then teamed up with Dr. Basil Varkey, whose meticulous attention to detail has contributed greatly to the clarity, coherence, and readability of every chapter.

DISTINCTIVE RISK AND EARLY DISEASE

The book highlights several important messages: CAD can occur early, may be extensive and clinically aggressive, can remain silent until a catastrophic event occurs, and may begin developing much earlier in life than in other populations. Particular emphasis is placed on atherogenic lipoproteins, especially LDL cholesterol and Lp(a), with a dedicated chapter on each, underscoring their importance in the prevention of premature cardiovascular disease.

Coronary artery disease can occur early, may be extensive and clinically aggressive, and can remain silent until a catastrophic event occurs.

COMPREHENSIVE AND PRACTICAL

Across 17 chapters, the book provides a comprehensive review of the risk factors, prevention, and treatment of CAD. It covers established therapies such as statins, emerging nonstatin treatments, and related cardiovascular conditions, including heart

attack, angina, atrial fibrillation, stroke, metabolic syndrome, and heart failure. Three chapters are devoted to prevention, including diet and the Life's Essential 8 framework for promoting cardiovascular health.

CLEAR, PRECISE, AND ACCESSIBLE

A major strength of the book is its concise, precise, and lucid presentation, supported by current and well-selected references. Clear illustrations, graphs, and tables make complex concepts easy to understand without compromising scientific depth. The book is valuable not only for cardiologists and other physicians caring for South Asian patients, but also for patients and families seeking to understand and prevent premature heart disease.

PREVENTION CANNOT WAIT

Coronary artery disease has now become highly preventable and treatable. The United States and many other countries have witnessed remarkable reductions in age-standardized mortality from heart disease over the past several decades, largely as a result of advances in prevention, risk-factor modification, early detection, and effective treatment. This book provides essential knowledge and practical guidance for policymakers, physicians, and the general public to help arrest and ultimately reverse the CAD epidemic in India.

What began as an observation by a young cardiologist in Chicago grew into a decades-long scientific and educational mission. *Treatise on Heart Disease in Indians* is the product of that journey and a timely call for earlier recognition, prevention, and treatment of cardiovascular disease among Indians. The enduring lesson is a simple but powerful one: we cannot wait for the first heart attack to begin preventing heart disease.

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How to cite this article: Enas EA, Varkey B. *Treatise on Heart Disease in Indians*. J Assoc Physicians India 2026;74(10):96–97.

For Indians and other South Asians, cardiovascular prevention must begin early, continue throughout life, and be guided by a clear understanding of their distinctive risk profile. In that regard, *Treatise on Heart Disease in Indians* is not merely a book about disease. It is a timely appeal

for greater awareness, earlier intervention, and a renewed commitment to preventing premature cardiovascular death.

The enduring message is "Prevention is powerful. We cannot wait for the first heart attack to occur before taking the first steps to prevent heart disease."

MP Ravindra Nathan

Retired cardiologist

The author of '*Stories from My Heart*' and

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