

# Journal of The Association of Physicians of India



Editor-in-Chief:  
**Prof. Dr. Jyotirmoy Pal**

Executive-Editor:  
**Prof. Dr. Nandini Chatterjee**

## Editorial

The Darwinization  
of Diabetes

## Article

Incidence Of Infections  
in Renal Allograft  
Recipients and its  
Outcome in a Tertiary  
Care Center in  
North East India

## Article

From Clinic to  
Community: A Public  
Health Framework  
for MASLD  
Prevention in India

## Article

Curricular Integration of  
Point-of-Care Ultrasound  
(POCUS) in Medical  
Education in India: An  
Immediate Need

## Article

Imeglimin in Type 2  
Diabetes Mellitus: Expert  
Opinions and Consensus  
in Indian Context

# JAPI

[www.japi.org](http://www.japi.org)

app: myJAPI

Price: ₹ 800

Published on 1st of every month

“Raising the Standard of Cardiovascular Care”

# Telvas

Telmisartan



Cardiovascular Protection



Metabolic Correction



Technological Invention



Packaging Innovation

**Composition:** Telvas 40 Each tablet contains: Telmisartan IP 40 mg, Telvas- 80 Each tablet contains: Telmisartan IP 80 mg, Telvas20 Each tablet contains: Telmisartan IP 20 mg **Indication:** Hypertension - Treatment of essential hypertension in adults. Cardiovascular prevention - Reduction of cardiovascular morbidity in adults with: manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage. **Dosage and Administration:** Essential hypertension: The effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. Cardiovascular protection: The recommended dose is 80 mg once daily. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. 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 m<sup>2</sup>). **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 m<sup>2</sup>) 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/m<sup>2</sup> 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/m<sup>2</sup> 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



**Promise to Guard every hypertensive, now gets stronger...**



*with*  
**Telvas-BS™**

Telmisartan 40 mg + Bisoprolol Fumarate 2.5/5 mg

**Recommendation  
 1<sup>st</sup> Line therapy  
 in Hypertension with SIHD\***



**The dynamic... anti-ischemic!**

SIHD: Stable Ischemic Heart Disease \*ACC/AHA Guidelines  
 Hypertension. 2018;71:e13–e115

**Composition:** Each film coated tablet contains: Bisoprolol Fumarate IP 2.5mg/5mg Telmisartan IP 40mg  
**Indications:** The fixed dose combination of Bisoprolol fumarate and Telmisartan tablets is indicated for the treatment of stage 1 and stage 2 hypertension.  
**Dosage & Administration:** The recommended dose of the fixed dose combination of Bisoprolol and Telmisartan tablets is one tablet once a day or as directed by the Physician.  
**Mechanism of action:** Bisoprolol-Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and relevant membrane stabilising activity. 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 alicikiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m<sup>2</sup>).  
**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 alicikiren is therefore not recommended.  
**Drug Interactions:** Bisoprolol-Combination not recommended-Verapamil, Diltiazem, Methyl dopa, Lidocaine. Combinations to be used with caution- Amlodipine, Amlodipine, Amlodipine, Digitalis, 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, Alicikiren. **Special Populations: Pregnancy:** Bisoprolol is not recommended during pregnancy unless clearly necessary and breastfeeding. **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 overdosage.



# Magnesium + Vitamin D

## Supporting Better Glycaemic Outcomes in T2DM



RCT-published evidence in Indian patients.

PUBLISHED  
★ INDIAN RCT ★  
IN T2DM



### ORIGINAL ARTICLE

# JAPI



Journal of The Association of Physicians of India

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

Sanjay Tandon<sup>1</sup>, GM Prasad<sup>2</sup>, Dilip Kadam<sup>3</sup>  
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).

# <sup>Rx</sup> MGD3<sup>®</sup>

Magnesium Glycine Complex (Elemental Magnesium 250 mg)  
with Vitamin D<sub>3</sub> IP 1000 IU Tablets



### CLINICAL TRIAL STRENGTH

Published  
Indian RCT  
in T2DM<sup>1</sup>



### CLINICAL PRACTICE RELIABILITY

10+ Years  
of Doctors'  
Trust<sup>#</sup>

Dosage: 1 to 2 Tablets / Day

Note: Additional information will be provided on request. For further information, please write to: [medical@pharmed.in](mailto:medical@pharmed.in)

<sup>#</sup> 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. The Darwinization of Diabetes  
*Sanjay Kalra, Agam Vora, Mangesh Tiwaskar, Nishant Raizada, Madhur Verma, Nitin Kapoor* ..... 11

#### ORIGINAL ARTICLE

2. Incidence of Infections in Renal Allograft Recipients and Their Outcomes in a Tertiary Care Center in Northeast India  
*Sudipta Hajong, M Sharma, A Hakmaosa, PK Doley, G Pegu* ..... 13
3. Spectrum and Clinical Burden of Drug-induced Ataxia in Low-resource Settings: An Observational Study  
*Jayaram Saibaba, Murugesan P Subramaniam, Arunprakash P Thangavelu, Krithikaa Chitharanjan Renukaranjan* ..... 15
4. A Cross-sectional Study to Assess the Knowledge, Attitude, and Practice of Look-alike, Sound-alike Drugs among Healthcare Providers at a Tertiary Care Hospital  
*Nancy Bansal, Akash Ashok Kumar Khobragade, Aditya R Bawne, Ajinkya Bavlecha, Balbir Singh Kohli* ..... 20
5. Profile of Philadelphia Chromosome Negative (Ph-) Myeloproliferative Neoplasm with Special Emphasis on Vascular Thrombotic Events and the Response to Cytoreductive Therapy in Polycythemia Vera and Essential Thrombocythemia Patients: A Single Center Study from Kerala  
*Raghuvver Santhakumara Prabhu, Rahmathullah Sulaimankutty Nameera, Sayyid Muhammed Lukhmanulhakkim Thangal K, Priyanka R Nair* ..... 24
6. Evaluation of Presepsin as an Early Biomarker of Sepsis in Elderly Patients with Community-acquired Pneumonia  
*Shreya Sharma, Anita Tahlan, Monica Gupta, Anshu Palta, Nidhi Singla* ..... 28
7. Cardiac Magnetic Resonance Imaging Study on Cardiovascular Involvement >60 Days Post COVID-19 Recovery  
*Nihar Mehta, Tanushree Somir Banerjee, Chandresh O Karnavat, Rajesh M Parikh, Ritu Kashikar, Shraddha Sinhasan, Shruti Tandan-Pardasani, Susheel Bindroo, Anand Bhabhor, Indraneil Raut, Nimish Shah, Shrinivas B Desai, Munira Kapadia, Maherra Desai, Aarshree Kapoor* ..... 32
8. Clinical Presentations of Different Types of Nodopathies  
*Laxmi Khanna, Ish Anand, Praveen Kumar, Mandaville Gourie-Devi* ..... 38
9. Association of Hemoglobin–Albumin–Lymphocyte–Platelet Count (HALP) Score and Type 2 Diabetes Retinopathy  
*Vijay Kumar, Kadiri Gururaj, Pratibha Modi, Sanjeev Kumar, Anil Balivada, Amit Raj* ..... 42
10. Clinicopathological Features and Outcomes of Metastatic Colorectal Cancers Treated at a Tertiary Care Hospital: A Bidirectional Observational Study  
*Hema Sireesha Natti, Vishesh Gumdal, Deepak Koppaka, Swapna Nuguri, Sanjana Reddy Potu, Rudra Sanjeev Rudra, Rajeeva Moulasa Jaffer* ..... 49
11. Pregnancy Outcomes in Patients with Tuberculosis: A Systematic Review and Meta-analysis  
*Hemlata Sharma, Swati Garg, Saurabh Sharma, Urvashi Sharma, Ashok Kumar* ..... 60

#### REVIEW ARTICLE

12. From Clinic to Community: A Public Health Framework for Metabolic Dysfunction-associated Steatotic Liver Disease Prevention in India  
*Shambo Samrat Samajdar, Sanjay Bandyopadhyay, Shashank R Joshi* ..... 67
13. Continuous Glucose Monitoring—Purposes, Benefits, and Problems: A Review of the Indian Scenario  
*Anushtha Kushwaha, Aarti Niveditha Kodirekalla, Aruna Saharawat, Rashi Jaiswal* ..... 70
14. Navigating Bone Health in Epilepsy—A Detailed Review of Anticonvulsant-induced Osteomalacia: Its Mechanisms and Therapeutic Strategies  
*Sundar Sri MK, Karthickeyan Krishnan*, ..... 73

#### POINT OF VIEW

15. Consultation Fees as a Barrier to Regular Follow-up  
*Rajesh Agrawal* ..... 80

16. Curricular Integration of Point-of-care Ultrasound in Medical Education in India: An Immediate Need  
*Sushrut Ingawale, Vineet Upadhyaya, Vineet Chandak* ..... 82

#### PICTORIAL CME

17. Expanding the Spectrum: Isolated Acute Diencephalitis as the Initial Manifestation of Neuromyelitis Optica Spectrum Disorder  
*Jayaram Saibaba, Pushkar Pazhani, Vivek Venkataraman Iyer* ..... 86
18. When Febrile Seizures Are Not Benign: An Unusual Cause of Dyke–Davidoff–Masson Syndrome  
*Jashir Ahammed, Syed Ahmed Zaki, Kiran Kumar Reddy* ..... 88
19. Idiopathic Intracranial Hypertension Masquerading as Cerebral Venous Sinus Thrombosis: A Diagnostic Challenge  
*Nikhil Gupta, Tanvi Batra, Atul Kakar, Ashima Abbott Chandra* ..... 90

#### CORRESPONDENCE

20. Ipeglimin in Type 2 Diabetes Mellitus: Expert Opinions and Consensus in Indian Context  
*Jegan Duraiswamy, Nitin Chintaman Gawari, Tanvi Naik, Teja Achyut Deshpande* ..... 94
21. Assessing the Impact of the District Residency Program on Pre- and Paraclinical Postgraduate Training in India  
*Nitin Chintaman Gawari, Gampa Sarjanya, Sujata Prakash Shingare, Yasir Hassan* ..... 95
22. A Conversation with ChatGPT about Pleural Effusion  
*Srinivas Sadanand Pai* ..... 97

#### e-ONLY

#### ORIGINAL ARTICLE

23. Barriers to Timely Rheumatologic Care for Rheumatoid Arthritis: A Real-World Questionnaire-based Study from Karnataka Chapter of Indian Rheumatology Association (KRA)  
*Vineeta Shobha, Subramanian R, Prkruthi J, Sumithra Selvam, Shaleni V, Vikram Haridas, Mahabaleshwar Mamadapur, Ashwini Kamath, Arjun MN, Pramod Chebbi1, Jacob Mathews Vahaneyi, Silas Vinay VR, Abhishek Patil, Benzeeta Pinto, Yathish GC, Sachin R Jeevanagi, Sahana Baliga, Harshini AS, Shweta Singhai, Vijay K Rao, Veena Ramachandran, Matam Sri Anusha, Chandrashekara S, KM Mahendranath* ..... e1
24. A Study on Prehospital Factors Determining the Timely Arrival for Thrombolysis among Patients Presenting with Acute Ischemic Stroke at a Tertiary Care Center in South India  
*Naga Srinivas PS, Nidhi Prakash Vadanere, K Mugundhan, Sakthi Velayudham, Malcolm Jeyaraj, Sowmini PR* ..... e9
25. Clinical Characteristics Treatment Approaches and Survival Outcomes in Secondary Hemophagocytic Lymphohistiocytosis: A Retrospective Observational Study  
*Amratansh Varshney, Pratibha Satish Phadke, Anusree Prabhakaran, Dipak Patade, Yash Bhalani, Abhishek Kumar* ..... e18

#### REVIEW ARTICLE

26. Consensus Guidance for the Diagnosis and Management of Diabetic Kidney Disease: Executive Summary  
*Kavita Yadav, Vivekanand Jha, Georgi Abraham, Alan Fernandes Almeida, Sandeep Bansal, Shyam Bihari Bansal, Dipankar Bhowmik, Sujoy Ghosh, Natarajan Gopalakrishnan, Sanjeev Gulati, Shashank R Joshi, Sanjay Kalra, Jothydev Kesavadev, Vijay Kher, Dinesh Khullar, Ajay Umakant Mahajan, V Mohan, Abraham Oomman, Sreejith Parameswaran, Uday Phadke, CK Ponde, Sathyannarayana Rao Prakash, Narayan Prasad, Sree Bhushan Raju, A Ramachandran, Manisha Sahay, Rakesh Kumar Sahay, JPS Sawhney, Bipin Kumar Sethi, Daljit Singh Sethi, Parag Shah, Raj Kumar Sharma, Shivendra Singh, Rajana Sreedhara, Mangesh Tiwaskar, Subhash K Wangnoo* ..... e24

Your care, your dedication,  
your healing touch!

Doctor, You are the  
**ONE & ONLY** reason,  
the world remains healthier,  
happier, and stronger.

HAPPY

**DOCTORS' DAY!**



THERE IS  
**ONLY ONE**  
**ONCE-WEEKLY**  
**semaglutide injection**

Reference: Ozempic® CDSCO approved package insert version dated 23 Oct 2025.

Abbreviated prescribing information (and not full package insert)

**Generic Name:** Semaglutide Injection 0.5 mg (CDMO Origin) solution for injection in pre-filled pen, Semaglutide Injection 1 mg (CDMO Origin) solution for injection in pre-filled pen, Semaglutide Injection 1 mg (CDMO 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. **Black Box:** To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease, to reduce the risk of sustained weight loss, to reduce the risk of cardiovascular mortality in adults with type 2 diabetes mellitus and chronic kidney disease. **Description:** Ozempic® is a blue and white solution for injection in a pre-filled pen. **Pharmacology:** 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 food 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. **Pharmacokinetics:** Following a single dose, 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 insert carefully before administering Ozempic®. **Special Populations:** No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with hepatic impairment is limited. No dose adjustment is required for patients with hepatic impairment. **Use in children and adolescents:** The safety and efficacy of semaglutide in children and adolescents has 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 oral hypoglycaemic 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 diabetes before diagnosis. Use of GLP-1 receptor agonists has been associated with gastrointestinal adverse reactions. This should be considered when initiating treatment with semaglutide. In these patients, with impaired renal function or nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function. Increased risk of medical device failure due to dehydration. **Warnings:** Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued. Patients treated with semaglutide in combination with a sulphonylurea or insulin have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulphonylurea or insulin when initiated treatment with semaglutide. In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy 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. There are limited data regarding the use of semaglutide in pregnant women. Semaglutide should not be used during pregnancy. If a patient wishes to become pregnant or pregnancy occurs, semaglutide administration should be discontinued. **Drug Interactions:** Semaglutide should not be used in combination with insulin. Semaglutide does not change the overall exposure of atorvastatin following a single dose administration of atorvastatin 0.1 mg. Digoxin Semaglutide did not change the overall exposure or C<sub>max</sub> of digoxin following a single dose of digoxin 0.5 mg. Metformin Semaglutide did not change the overall exposure or C<sub>max</sub> of metformin following a single dose of 250 mg twice daily over 14 days. Warfarin Semaglutide did not change the overall exposure or C<sub>max</sub> of warfarin following a single dose of warfarin 25 mg. **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 3 trials, 4792 patients were exposed to semaglutide up to 1 mg. The most frequently reported adverse reactions in clinical trials were gastroenteric disorders, including nausea, vomiting, diarrhoea, constipation and abdominal pain. In general, these reactions were mild or moderate in severity and of short duration. **Overdose:** Overdose of up to 1 mg in a single case, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. **Caution:** Patients receiving treatment 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 to 8 °C). **Storage:** Store in a refrigerator (2 °C to 8 °C). Keep away from the cooling element. Do not freeze. Keep the pen cap on or under the pen cap. **Disclaimer:** The abbreviated package insert is updated from the CDSCO approved package insert (Ref No. B033M/25/00009) dated 19 Sep 2025 and subsequent approval (Ref No. INDM11011/1/2025) effective dated 23 Oct 2025.

Ozempic®, NovoPen® and NovoPen® 3 are registered trademarks owned by Novo Nordisk A/S and registered in Denmark. Imported by Novo Nordisk India Private Limited, Bangalore. For full prescribing information, please contact +914040303200 or write to us at: IN@genova.novonordisk.com or reach us at: Novo Nordisk India Pvt. Ltd., Tower 1, 1st Floor, Embassy Mangala Business Park, Nagercoil Village, Kottur Taluk, Bangalore - 560 065, India.

Note: For detailed information on this product, please refer to full package insert.

This material is developed by Novo Nordisk India, Private Limited, NOT Tower 1, Floor 1 & 2, Embassy Mangala Business Park, Nagercoil Village, Kottur Taluk, Bangalore-560 065, India. For the use of registered medical practitioner or a registered pharmacist or a hospital or laboratory only. The photographs are only for illustrative purposes.

IN26Z0M00169 | Review date: 25 June 2026



novonordisk®



## Editorial Board (2026–2027)

Editor-in-Chief	<b>Jyotirmoy Pal</b>
Executive Editor	<b>Nandini Chatterjee</b>
Associate Editors	<b>KK Pareek • GS Wander • Anupam Prakash Amit Saraf • Ashish Thakur</b>
Assistant Editors	<b>Ashok Taneja • Sekhar Chakrabarty • Sangram Biradar NP Singh • Saif Quaiser • Ashutosh Chaturvedi • Ananda Bagchi</b>
Members	<b>Puneet Saxena • V Palaniappen • Amit Das • Munish Prabhakar MPS Chawla • Nikhil Balankhe • Dwijen Das • Jayant Kr Panda YSN Raju • Alladi Mohan • SS Dariya • Bhupen Barman Pradip Bhaumik • Bidita Khandelwal • Rajesh Kumar Ghanashyam Pangtey • Ravikeerthy M • Srikant Behera N K Soni • H S Pathak • Kamlesh Tiwari • Smarajit Banik</b>
Ex-Officio	<b>Girish Mathur • G Narsimulu • A Muruganathan</b>
Jt. Secretary	<b>Rakesh Bhadade</b>
Tech and Podcast Editor	<b>Nihar Mehta</b>
Team	<b>SV Kulkarni • R Chandni • S Sreenivasa Kamath Hem Shankar Sharma • Tanuja Manohar • JK Mokta BK Singh • Saikat Datta • Debashis Chakraborty • SM Baruah</b>

## Advisory Board (2026–27)

Philip Abraham	Bhavin Jankharia	Aniruddha Phadke
VK Arora	SK Jindal	M Premanath
S Arulrhaj	Ameya Joshi	Girish Rajadhyaksha
Smrati Bajpai	Sanjay Kalra	Neelam N Redkar
Tushar Bandgar	Mala Kaneria	BB Rewari
D Behera	Surya Kant	Mrinal Kanti Roy
Sudhir Bhandari	Dilip Karnad	Manisha Sahay
Atul Bhasin	Nitin Karnik	Rakesh Sahay
Abhay Bhawe	NK Karnik	Santosh Salagre
Nitin Burkule	SV Khadilkar	Manoj Saluja
Vasudeo Charan	Umesh Khanna	Rohini Samant
Ved Chaturvedi	Uday Khopkar	SK Sarin
Dhruv Chaudhry	Parvez Koul	RN Sarkar
M Chenniappan	Virnda Kulkarni	Vinayak Sawardekar
RM Chhabra	Charulata V Londhey	PS Shankar
PK Deshpande	Anuj Maheshwari	Aman Sharma
Raja Dhar	Sanjiv Maheshwari	OP Sharma
Suhas Erande	Ketan K Mehta	Akash Shingada
SB Ganguly	Sudhir Mehta	Akash Shukla
Vijay Garg	AP Misra	Awadhesh K Singh
Liyakat Ali Gauri	Minal Mohit	Pratibha Singhal
Soumitra Ghosh	K Mugundhan	Rajeev Soman
Sujoy Ghosh	Vasant Nagwekar	Archana Sonawale
Udas Chandra Ghosh	SN Narasingan	Shyam Sunder
Nithya Gogoi	CL Nawal	Sanjay Tandon
Yojana Gokhale	Benny Negalur	BB Thakur
Mohit Goyal	Vijay Negalur	Urmila Thatte
Virender Kr Goyal	Shailesh Palekar	Mohankumar Thekkinkattil
Rohini Handa	Vijay Panikar	Rajesh Upadhyay
DK Hazra	Falguni Parikh	Prema Varthakavi
Manish Itoliker	Deepak Patkar	Vijay Viswanathan

## International Advisory Board (2026–2027)

M P Kafle	Suranga Manilgama	Hany Eteiba
Sanjeev Sharma	Eric Livingstone	Roman Jaeshke

### 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.

### Copyright and Photocopying

No part of this publication may be reproduced, or transmitted in any form or by any means, electronic or mechanical, including photocopy without written permission from the Hon. Editor.

### Business Correspondence

Enquiries concerning subscription, advertisement, etc. should be addressed to **Prof. Dr Jyotirmoy Pal**, Editor-in-Chief, JAPI, Unit No. 3301, Prestige Turf Tower 'D', Shakti Mill Lane, Off. Dr. E. Moses Road, Near Mahalaxmi Station (West), Mumbai-400 011.

Mobile number: 7710020034/7710029211

**e-mail: [onlinejapi@gmail.com](mailto:onlinejapi@gmail.com)**

**[j\\_pal2004@rediffmail.com](mailto:j_pal2004@rediffmail.com)**

**[api.hdo@gmail.com](mailto:api.hdo@gmail.com)**

### 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.  
Editor-in-Chief: **Prof. Dr Jyotirmoy Pal**.

### Advertorial Enquiry:

**Prof. Dr Jyotirmoy Pal**, Editor-in-Chief, JAPI, Unit No. 3301, Prestige Turf Tower 'D', Shakti Mill Lane, Off. Dr. E. Moses Road, Near Mahalaxmi Station (West), Mumbai-400 011.

Mobile number: 7710020034/7710029211

**e-mail: [onlinejapi@gmail.com](mailto:onlinejapi@gmail.com)**

**[j\\_pal2004@rediffmail.com](mailto:j_pal2004@rediffmail.com)**



Jaypee Brothers Medical Publishers (P) Ltd.  
New Delhi

**JAPI App: myJAPI**  
**[www.japi.org](http://www.japi.org)**



# Association of Physicians of India

## GOVERNING BODY (2026–2027)

**President-Elect**  
**Ashok K Taneja** (Gurugram) (2027)

**MPS Chawla** (New Delhi) (2027)

**Hon. General Secretary**  
**Puneet Saxena** (Jaipur) (2027)

**Nihar Mehta** (Mumbai) (2027)  
**Aditya Prakash Misra** (New Delhi) (2027)  
**Jyotirmoy Pal** (Kolkata) (2027)  
**Gautam Bhandari** (Jodhpur) (2027)  
**AK Gupta** (Agra) (2027)  
**L Srinivasa Murthy** (Bengaluru) (2027)

North Zone **AK Singh** (Varanasi) (2029)  
North West Zone **Ajay Mahajan** (Hisar) (2029)  
Central Zone **GD Ramchandani** (Kota) (2029)  
West Zone **Anil Kumar Kulshrestha** (Ahmedabad) (2029)  
North East Zone **Dwijen Das** (Silchar) (2029)

### Invited Members

*Editor-in-Chief, API Textbook*  
**KK Pareek** (Kota)  
*Editor-in-Chief, JAPI*  
**Jyotirmoy Pal** (Kolkata)  
*Chairman, API House Committee*  
**Anil Kumar Kulshrestha** (Ahmedabad)

*Chairman, Finance Committee*  
**Amal Kumar Banerjee** (Kolkata)  
*Chairman API Credential Committee*  
**YSN Raju** (Hyderabad)

**President**  
**G Narsimulu** (Hyderabad) (2027)

**Vice Presidents**  
**Sekhar Chakraborty** (Siliguri) (2027)

**Jt. Secretary (HQ)**  
**Rakesh Bhadade** (Mumbai) (2028)

### Members

**Soumitra Ghosh** (Kolkata) (2028)  
**Pradeep Bhaumik** (Agartala) (2028)  
**Sangram S Biradar** (Gulbarga) (2028)  
**Anupam Prakash** (New Delhi) (2028)  
**M Pavan Kumar** (Warangal) (2028)  
**Pramod Kumar Sinha** (Gaya) (2028)

### Zonal Members

Mid South Zone  
South Zone  
Mid East Zone  
East Zone

**Past President**  
**Jyotirmoy Pal** (Barrackpur) (2027)

**Ravikeerthy M** (Bengaluru) (2029)

**Hon. Treasurer**  
**Amit Saraf** (Mumbai) (2029)

**Mahesh Kumar Dave** (Udaipur) (2029)  
**Udas C Ghosh** (Kolkata) (2029)  
**L Muthumani** (Trichy) (2029)  
**Jayanta Kumar Panda** (Cuttack) (2029)  
**R Chandani** (Kozhikode) (2029)  
**Braj Kishore Singh** (Aurangabad) (2029)

**KR Jawaharlal** (Kakinada) (2029)  
**S Chandrasekhar** (Chennai) (2029)  
**Amit Kumar Das** (Muzaffarpur) (2029)  
**Debasis Chakrabarti** (Siliguri) (2029)

### Ex-Officio Members

*Dean, ICP*  
**Girish Mathur** (Kota)  
*Director, PRF*  
**A Muruganathan** (Tirupur)

### Co-opted Members

*Jt. Secretary (President's Place)*  
**G Vishesh** (Hyderabad)  
*Armed Forces Medical Services*  
**Vivek Hande** (Delhi)  
*Organizing Secretary, APICON 2026 (Patna)*  
**Kamlesh Tewary** (Muzaffarpur)  
*Organizing Secretary, APICON 2027 (Gurgaon)*  
**Munish Prabhakar** (Gurgaon)



# Indian College of Physicians

## FACULTY COUNCIL (2026–2027)

**Chairman**  
**G Narsimulu** (Hyderabad) (2027)

**Vice Deans**  
**K Mugundhan** (Chennai) (2027)  
**V Palaniappan** (Dindigul, TN) (2028)  
**Prakash Keshwani** (Jaipur) (2029)

**Jt. Secretary (HQ)**  
**Rakesh Bhadade** (Mumbai) (2028)

**Munish Prabhakar** (Gurugram) (2027)  
**S Sreenivasa Kamath** (Kochi) (2027)  
**E Prabhu** (Chennai) (2027)  
**Mahesh Marda** (Hyderabad) (2027)  
**Sandeep Garg** (New Delhi) (2028)

*President-Elect*  
**Ashok Taneja** (Gurgaon)

*Editor-in-Chief, JAPI*  
**Jyotirmoy Pal** (Kolkata)

**Dean**  
**Girish Mathur** (Kota) (2027)

**Hon. Gen. Secretary**  
**Puneet Saxena** (Jaipur) (2027)

**Jt. Secretary (Dean's Place)**  
**Ashutosh Chaturvedi** (Jaipur) (2027)

**Elected Members**  
**Hem Shankar Sharma** (Bhagalpur) (2028)  
**Ashis Kumar Saha** (Kolkata) (2028)  
**Suresh V Sagarad** (Raichur) (2028)  
**Partha Sarkar** (Kolkata) (2029)  
**Naval Chandra** (Hyderabad) (2029)

### Ex-Officio Members

*Director, PRF*  
**A Muruganathan** (Tirupur)

**Invited Member**  
*Chairman, Credentials Committee*  
**Shyam Sundar** (Varanasi)

**Dean-Elect**  
**S Arulrhaj** (Tuticorin) (2027)

**Past Dean**  
**Kamlesh Tewary** (Muzaffarpur) (2027)

**Hon. Treasurer**  
**Amit Saraf** (Mumbai) (2029)

**Prasanta Dhingia** (Dibugarh) (2029)  
**Rabindra Kumar Modi** (Purnia) (2029)  
**Anil Gomber** (New Delhi) (2029)  
**Vikram Londhey** (Mumbai) (2029)

*Editor-in-Chief, API Textbook*  
**KK Pareek** (Kota)



# Physicians Research Foundation

## BOARD OF DIRECTORS (2026–2027)

**Chairman**  
**G Narsimulu** (Hyderabad) (2027)

**Hon. General Secretary**  
**Puneet Saxena** (Jaipur) (2027)

**Devendra Prasad Singh** (Bhagalpur) (2027)  
**Puneet Rihwani** (Jaipur) (2027)  
**Sudhir Mehta** (Jaipur) (2028)

*Editor-in-Chief, JAPI*  
**Jyotirmoy Pal** (Kolkata)

**Director**  
**A Muruganathan** (Tirupur) (2027)

**Jt. Secretary (Director's Place)**  
**R Rajasekaran** (Kumbakonam) (2027)

**Members**  
**Ghanshyam Pangtey** (New Delhi) (2028)  
**SS Dariya** (Jaipur) (2029)

### Invited Members

*Dean, ICP*  
**Girish Mathur** (Kota)

**Director Elect**  
**Sanjeev Maheshwari** (Ajmer) (2027)

**Hon. Treasurer**  
**Amit Saraf** (Mumbai) (2029)

**Ramesh Aggarwal** (New Delhi) (2029)  
**Prabhat Pandey** (Durg) (2029)

*Editor-in-Chief, API Textbook*  
**KK Pareek** (Kota)

# *Endoscopically proven healing of Erosive Esophagitis*



# **Pantop**-D SR

Pantoprazole 40 mg + Domperidone 30 mg (SR) Capsules

## **Once-a-day control in GERD**



**ARISTO**  
PHARMACEUTICALS PRIVATE LIMITED

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Nutraceutical. Not for Medicinal Use. For the Use of a Healthcare provider.  
This is only a trade mark and does not represent its true nature.  
For the Use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.



# Your Absolute Clinical Choice for **Daily Micronutrients**



**Absolut<sup>®</sup> 3G<sup>®</sup>**  
Extracts of Ginkgo, Ginseng, Green Tea and Grape Seed | Omega-3-Acid Triglycerides | Antioxidants | Vitamins | Minerals & Trace Elements Capsules



**Absolut<sup>®</sup> WOMAN**

Vit D<sub>3</sub> 1000 IU, Ginkgo biloba 40 mg, Lycopene 2.5 mg, Green Tea Polyphenols, L-Carnitine, Lysine, Inositol, Vitamins A C E & B-Complex, Chromium, Selenium, Zinc & Iodine with EPD 250 mg Capsules



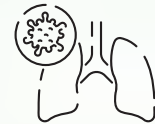
**Absolut<sup>®</sup> DM**

Alpha Lipoic Acid 100 mg, Benfotiamine 100 mg, Mecobalamin 1500 mcg, Folic Acid 1.5 mg and Pyridoxine 3 mg Capsules



*Recommended*  
**Absolut<sup>®</sup> GOLD<sup>+</sup>**  
Capsules

Resveratrol, Astaxanthin (AstaReal<sup>®</sup>), Alpha Lipoic Acid, Lycopene, Beta Carotene, Vitamin C, Vitamin D<sub>3</sub> (Vitamin D<sub>3</sub>), Vitamin E, Chromium, Selenium, Zinc, Lutetin, Green Tea Extract, Curcuma Longa Extract, Citrus Aurantifolia Juice Extract, Glycyrrhiza Glabra Extract & Ocimum Sanctum Extract Capsules.



**Dosage: OD**

\*Data on file. Note: Additional information will be provided on request.  
For further information, please write to: [medical@pharmed.in](mailto:medical@pharmed.in)  
\*OD: Once a day; EPO: Evening Primrose Oil.; IU: International Unit.

# The Darwinization of Diabetes

Sanjay Kalra<sup>1\*</sup>, Agam Vora<sup>2</sup>, Mangesh Tiwaskar<sup>3</sup>, Nishant Raizada<sup>4</sup>, Madhur Verma<sup>5</sup>, Nitin Kapoor<sup>6</sup>



*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1562

## INTRODUCTION

Diabetes is a dynamic disease, an ever-evolving entity. In existence for centuries, the prevalence of diabetes has increased manifold over the past few decades.<sup>1</sup> This evolution is associated with a change in classification, clinical features, comorbidities, complications, and clinical management strategies. These changes are what we describe as the Darwinization of diabetes. Charles Darwin was one of the most important scientists in human history. His research forms the basis of evolutionary biology. His hypothesis on natural selection, created along with Alfred Wallace, is accepted as the most important mechanism of evolution.<sup>2</sup> A similar situation occurs with diabetes.

## THE GLUCOCENE ERA

From a geological perspective, mankind has entered the Anthropocene Era, in which the world's environment is being modified by human activity. The term Barocene Era highlights the bidirectional impact of obesity and the environment on each other.<sup>3</sup> Similarly, the term Glucocene Era may describe the changes related to the exploding diabetes epidemic. The Glucocene Era is marked by diabetogenic changes in the environment, e.g., lack of open spaces for exercise, as well as by environmental changes due to the "endemic" nature of diabetes, e.g., production of sugar-free foods and beverages, provision of diabetes-friendly services, and the environmental impact of plastic used in insulin and its ancillaries.

## TYPES AND TAXONOMY

The Darwinization of diabetes, however, goes beyond this. As the human phenotype shifts toward heavier body weight and the immunotype toward enhanced autoimmunity, the "type" of diabetes is also changing. There is more diabetes and a greater incidence of type 1 diabetes than before. The incidence of malnutrition-modulated diabetes mellitus has declined so much so that the World Health Organization discontinued this terminology in its 1995 classification.<sup>4</sup> Darwin's laws of natural selection will govern recent efforts at "creating" a type 5 diabetes: only the fittest will survive.

## TARGETS AND TERMINI

The Darwinization of diabetes is evident in our understanding as well. We are now better evolved in terms of strategies, style, science, and substance while managing diabetes. The earlier glucocentric approach has been supplanted by comprehensive care, aimed at achieving pan-metabolic as well as psychosocial well-being. This is a perfect example of natural selection: only the fittest theories and tools survive; the most appropriate targets and termini are aimed for.<sup>5</sup>

## BURDEN OR BUOYANCY?

There is a paradox here, however. Better care has helped increase survival rates in diabetes. This is especially true for persons with type 1 diabetes. This has led to an exponential increase in the number of persons living with diabetes. This creates an enigmatic situation: while the challenge of diabetes on society and the individual is higher, society and individuals can shoulder this burden better and live longer. Should we view the increasing number of persons living with diabetes as a failure of the preventive health care system or a success of the curative services? This question is open to debate.

## MALTHUSIAN MALADAPTATION

Will the unchecked rise in our dysglycemic population lead to a Malthusian situation? Thomas Malthus argued that population growth, which occurs exponentially or logarithmically, will one day outstrip food supply, which grows arithmetically.<sup>2</sup> He felt that this would lead to a survival crisis, characterized by autocorrective man-made or natural disasters, which would drastically reduce the population.

Such pessimistic predictions have also been made earlier in the context of diabetes. There was a fear that bovine and porcine insulins would go out of stock because we did not have sufficient animals to produce insulin. The production of recombinant insulin resolved this Cassandra concept, and then came analog insulins.<sup>6</sup> Today, newer challenges of diabetes, such as renal and cardiac disease, are met by novel drugs, which have been proven to enhance complication-free survival.

## DIAGNOSTICS AND THERAPEUTICS

The Darwinization of diabetes extends to diagnostics as well. Newer methods such as HbA1c are available to diagnose diabetes. The World Health Organization has also accepted using glucometers for diagnosis, albeit with slightly higher capillary glucose levels.<sup>7</sup> Diabetes monitoring now includes time in range, and complication screening can easily be done by point-of-care devices.<sup>8</sup> All these are examples of evolution through natural selection, of affirmative action against adversity.

The same holds for treatment systems. Not only medication but the method of delivering health care is changing. Diabetes is increasingly being managed at the primary care level, using drugs that do not need dose adjustment or frequent monitoring. Modern medications developed for glucose control also help in weight management and metabolic protection, thus offering survival benefits and evolutionary advantage.<sup>9</sup> The lack of side effects, such as hypoglycemia, is an added strength.

## LINEARITY AND CYCLICITY

The Darwinian theory of evolution is a linear one. This contrasts with the Indian philosophy of cosmic evolution, which is cyclic. Hindu philosophy views the cosmos as undergoing continuous cycles, or kalpas and yugas, of creation, preservation, and destruction. Will diabetes care limit itself

<sup>1</sup>Consultant, Department of Endocrinology, Bharti Research Institute of Diabetes & Endocrinology, Karnal, Haryana; <sup>2</sup>Medical Director, Vora Clinic; <sup>3</sup>Physician, Department of Medicine, Shilpa Medical Centre, Mumbai, Maharashtra; <sup>4</sup>Professor, Department of Endocrinology, Centre for Diabetes, Endocrinology and Metabolism, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi; <sup>5</sup>Associate Editor, Department of Community and Family Medicine, All India Institute of Medical Sciences, Bathinda, Punjab; <sup>6</sup>Editor, Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India; \*Corresponding Author

**How to cite this article:** Kalra S, Vora A, Tiwaskar M, et al. The Darwinization of Diabetes. *J Assoc Physicians India* 2026;74(7):11–12.

to linear growth and evolution? Or will it follow a cyclic path?

We do see signs of both. Linear and short-term secular trends are visible to all stakeholders in the diabetes care ecosystem. Long-time observers can discern examples of cyclic Darwinization, as we revisit older drugs and ancient wisdom in our effort to tame diabetes. Examples include a resurgence in interest in malnutrition-related diabetes mellitus, the use of hydroxychloroquine for diabetes, a return to vials and syringes in many parts of the world, and efforts to use ketosis as a treatment for obesity.

## DYNAMICITY OF DARWINIZATION

Darwinization is dynamic, just as evolution is eternal. Despite progress in physiology and pharmacology, we continue to struggle with poor control of diabetes. This means that we still need to improve further. Better diagnostics, therapeutics, and enhanced

motivational and behavioral change skills are required. These will be effective only if we focus on awareness and advocacy about diabetes, the ill effects of poor control, and the advantages of good control.

This represents another paradox: awareness and education are seemingly the simplest of therapies to impart but the most arduous to achieve. This is what we try to do, along with our readers, at our journal. Let us evolve together, toward a Eugluocene Era.

## ORCID

*Sanjay Kalra*  <https://orcid.org/0000-0003-1308-121X>

*Agam Vora*  <https://orcid.org/0000-0002-9632-1807>

*Madhur Verma*  <https://orcid.org/0000-0002-1787-8392>

*Nitin Kapoor*  <https://orcid.org/0000-0002-9520-2072>

## REFERENCES

1. IDF. Diabetes Atlas. Available from: <https://diabetesatlas.org/> [Last accessed June, 2026].
2. Vorzimmer P. Darwin, Malthus, and the theory of natural selection. *J Hist Ideas* 1969;30(4):527.
3. Kalra S, Verma M, Kapoor N. The Barocene era. *J Pak Med Assoc* 2024;74(2):402–403.
4. Rao RH, Yajnik C. Commentary: time to rethink malnutrition and diabetes in the tropics. *Diabetes Care* 1996;19(9):1014–1017.
5. Kalra S, Baruah MP, Sahay R, et al. Pentads and hexads in diabetes care: numbers as targets; numbers as tools. *Indian J Endocrinol Metab* 2017;21(6):794–796.
6. Mohan V. Which insulin to use? Human or animal? *Curr Sci* 2002;83(12):1544–1547.
7. HEARTS D: diagnosis and management of type 2 diabetes. Available from: <https://www.who.int/publications/i/item/who-ucn-ncd-20.1>. [Last accessed June, 2026].
8. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S27–S49.
9. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S181–S206.



# Incidence of Infections in Renal Allograft Recipients and Their Outcomes in a Tertiary Care Center in Northeast India

Sudipta Hajong<sup>1\*</sup>, M Sharma<sup>2</sup>, A Hakmaosa<sup>3</sup>, PK Doley<sup>4</sup>, G Pegu<sup>5</sup>

Received: 17 January 2024; Revised: 27 March 2026; Accepted: 21 April 2026

## ABSTRACT

**Introduction:** The advent of modern potent immunosuppression has significantly reduced the occurrence of rejection in renal allograft recipients but has increased the risk of infection, which remains the major cause of death in these patients.

**Materials and methods:** This single-center retrospective observational study was conducted at a tertiary care center in India. Data were collected from medical records of renal allograft recipients admitted for infection-related complications over a 10-year duration.

**Results and conclusion:** Out of 238 admissions, 63 (26.47%) were due to infection-related complications involving 59 unique patients. The most common infections were urinary tract infections (UTIs) ( $n = 24$ ) and pneumonia ( $n = 19$ ). Of the two patients requiring multiple admissions, one patient had two episodes of pneumonia and one episode of UTI, and the other patient needed three admissions for diabetic foot. Six patients succumbed to their illness, resulting in a mortality rate of 10.16%, with sepsis due to UTI being the most common cause of death.

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1614

## INTRODUCTION

Patients with end-stage kidney disease (ESKD) have various treatment options, including hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation. Kidney transplant patients generally experience a better quality of life compared to those on dialysis.<sup>1</sup> However, the use of potent immunosuppressive drugs, while reducing rejection rates, increases the risk of infections in renal allograft recipients. Infection remains the leading cause of death both in the early and late post-transplant period.<sup>2</sup> Diagnosing infections in these patients can be challenging due to atypical presentations, potentially increasing morbidity and mortality.<sup>3</sup>

Infections are highly prevalent in the post-transplant period. For instance, a study conducted in Chandigarh found that 68.4% of patients experienced at least one infection episode within the first 6 months post-transplant.<sup>4</sup> Kumar et al. also identified urinary tract infections (UTIs) as the most common infection among Indian renal transplant recipients.<sup>1</sup> This study aims to provide further insights into infection profiles in renal allograft recipients.

## AIMS AND OBJECTIVES

- To estimate the incidence of infection in renal allograft recipients.
- To estimate the pattern of infection in renal allograft recipients.
- To estimate the outcome of infection in renal allograft recipients.

## MATERIALS AND METHODS

This retrospective descriptive study was conducted at a tertiary care center in India. Medical records of renal allograft recipients admitted over a 10-year duration were reviewed, focusing on admissions due to infection-related complications. Baseline characteristics, including age and sex, were recorded, along with infection sources, etiological agents, comorbid conditions, and outcomes.

## RESULTS

During the study period, there were a total of 238 admissions of renal allograft recipients. After adjusting for multiple admissions, the actual number of patients was 218, comprising 187 males and 31 females, resulting in a male-to-female ratio of 6.03:1. Among these patients, 63 admissions were due to infection-related complications, accounting for 26.47% of the total admissions. Two patients required multiple admissions, leading to a total of 59 individual patients, with 52 males and 7 females, reflecting a male-to-female ratio of 7.42:1 (Table 1).

Among the patients with multiple admissions, one had two episodes of

pneumonia and one episode of UTI, while the other patient required three admissions due to diabetic foot complications. The most common infection necessitating hospitalization was UTI, with 24 cases, followed by pneumonia, with 19 cases (Table 2). Urine cultures from UTI patients most frequently isolated *E. coli*, with 11 isolates (45.83%), followed by *K. pneumoniae*, with 7 isolates (29.16%) (Table 3).

**Table 2:** The profile of infections and the frequency of occurrence

Infection	Frequency (%)
UTI	24 (36.92)
Pneumonia	19 (29.23)
Cellulitis	7 (10.77)
Tuberculosis	4 (6.15)
CMV (2 Pneumonia)	4 (6.15)
Diabetic foot	3 (4.61)
CSOM with Meningitis	1 (1.54)
Perinephric abscess	1 (1.54)
BK virus (1 had concomitant pneumonia)	2 (3.07)
Esophageal candidiasis	1 (1.54)
Varicella	1 (1.54)
Total	65

**Table 3:** Organisms causing UTI

Organism	Frequency (%)
<i>E. coli</i>	11 (45.83)
<i>K. pneumoniae</i>	7 (29.16)
<i>Staphylococcus</i>	2 (8.33)
<i>Candida albicans</i>	1 (4.16)
Culture-negative	3 (12.5)

<sup>1</sup>DM Trainee; <sup>2</sup>Professor, Department of Nephrology, Gauhati Medical College and Hospital; <sup>3</sup>Associate Professor, Department of Community Medicine, Pragjyotishpur Medical College and Hospital; <sup>4</sup>Professor and Head; <sup>5</sup>Associate Professor, Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam, India; \*Corresponding Author

**How to cite this article:** Hajong S, Sharma M, Hakmaosa A, et al. Incidence of Infections in Renal Allograft Recipients and Their Outcomes in a Tertiary Care Center in Northeast India. *J Assoc Physicians India* 2026;74(7):13–14.

**Table 1:** Baseline patient characteristics

Baseline characteristics	Total no of patients (n = 59)
Age (mean ± SD)	39.48 ± 14.13
Male, n (%)	52 (88.13)
Female, n (%)	7 (11.86)

The spectrum of infections in these patients was diverse. There were four patients diagnosed with tuberculosis, each presenting with a different form of the disease: one with pulmonary TB, one with pleural TB, one with TB meningitis, and one with spinal TB. This highlights the varied clinical presentations of tuberculosis in immunocompromised patients, such as those who have received renal allografts.

Additionally, four patients tested positive for cytomegalovirus (CMV). Of these, two had lung involvement, manifesting as CMV pneumonia, one had gastrointestinal tract involvement, and one had viremia accompanied by a UTI. The presence of CMV in these patients underscores the importance of monitoring for viral infections in post-transplant care, as they can significantly impact patient outcomes.

Post-transplant diabetes mellitus (PTDM) was observed in four patients, indicating a significant post-transplant complication. Among these patients, one presented with pneumonia and three with UTIs. This suggests that PTDM patients may be at increased risk for certain infections. Additionally, among patients with type 2 diabetes mellitus (T2DM), two were admitted for pneumonia, one for a UTI, and one for diabetic foot. This data indicates that diabetic patients, whether PTDM or T2DM, have a higher susceptibility to infections that require hospitalization.

Leukopenia, associated with infection, was noted in three patients. Of these, two had pneumonia, and one had cellulitis. Leukopenia can further complicate the clinical course of infections, making management more challenging.

Out of the 59 patients admitted for infections, 6 succumbed to their illness, resulting in a mortality rate of 10.16%. The leading cause of death was sepsis secondary to UTI (Table 4). This high mortality rate underscores the severe impact that infections can have on renal

**Table 4:** Causes of sepsis causing death

Cause of sepsis	Frequency
UTI	2
Pneumonia	1
Meningitis with CSOM	1
CMV of GI tract	1
Cellulitis	1
Total	6

allograft recipients, emphasizing the need for vigilant infection control and prompt treatment protocols in this vulnerable population.

## DISCUSSION AND CONCLUSION

In this single-center study on infectious complications in renal transplant patients, the incidence of infection was found to be 26.47%. This rate is slightly lower than a previous study, which reported that 72.5% of patients experienced at least one major infectious episode after their transplant.<sup>5</sup> Tuberculosis was found in 6.15% of the patients in our study, a figure slightly lower than the 17.8% incidence reported in a study on renal allograft recipients in India.<sup>1</sup>

The most common infection in our study was UTI, affecting 36.92% of patients, followed by pneumonia at 29.23%. This finding aligns with the study by Kumar et al.,<sup>1</sup> where UTI was also the most common infection among postrenal transplant recipients. Similarly, another study conducted in South India reported UTI as the most prevalent infection in renal allograft recipients.<sup>5</sup>

In our study, the most common causative organisms were Gram-negative bacteria, with *E. coli* and *K. pneumoniae* being the predominant pathogens, accounting for 45.38% and 29.16% of infections, respectively. This is consistent with the findings of Halim et al.,<sup>6</sup> who reported that *E. coli* and *K. pneumoniae* were responsible for 42% and 39% of UTIs, respectively. Mukherjee et al.<sup>7</sup> also found gram-negative organisms to

be the leading cause of infections, with *E. coli* isolated in 72% of cases.

The most common cause of infection-related death in our study was UTI, which contrasts with the findings of Washer et al.,<sup>2</sup> where pneumonia was the leading cause of infection-related mortality.

Renal allograft recipients are chronically immunosuppressed, placing them at an increased risk of various infections. These infections are associated with significant morbidity and mortality. Therefore, it is essential to implement robust preventive measures and ensure early, aggressive treatment to enhance outcomes for these patients. Overall, these findings underscore the urgent need for comprehensive infection surveillance and management strategies to improve the prognosis for renal allograft recipients.

## ACKNOWLEDGMENTS

None.

## SOURCE OF FUNDING

None.

## REFERENCES

1. Kumar A, Agarwal C, Hooda AK, et al. Profile of infections in renal transplant recipients from India. *J Family Med Prim Care* 2016;5:611–614.
2. Washer GF, Schröter GP, Starzl TE, et al. Causes of death after kidney transplantation. *JAMA* 1983;250(1):49–54.
3. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012;7(12):2058–2070.
4. Gupta KL, Bagai S, Joshi K, et al. Opportunistic infections occurring in renal transplant recipients in tropical countries. *Indian J Transplant* 2019;13:110–114.
5. Kumar A, Dhanapriya J, Dineshkumar T, et al. Post-renal transplant infections: a two decade experience. *ISN WCN 2020*, Abu Dhabi, UAE.
6. Halim I, Goel N, Gupta A, et al. Prevalence and antibiogram of urinary tract infections in renal transplant recipients at a tertiary care hospital in North India. *J Assoc Physicians India* 2020;68(5):30–31.
7. Mukherjee D, Sharma S, Nair RK, et al. Urinary tract infection in renal transplant recipients at a tertiary care center in India. *Saudi J Kidney Dis Transpl* 2018;29(2):361–368.



# Spectrum and Clinical Burden of Drug-induced Ataxia in Low-resource Settings: An Observational Study

Jayaram Saibaba<sup>1</sup>, Murugesan P Subramaniam<sup>2</sup>, Arunprakash P Thangavelu<sup>3\*</sup>, Krithikaa Chitharanjan Rennukaranjan<sup>4</sup>

Received: 22 February 2026; Accepted: 30 April 2026

## ABSTRACT

**Background:** The clinical manifestation of drug-induced ataxia (DIA) is well established clinically but often becomes unrecognized until actual ataxia occurs. DIA may include ataxia as its primary clinical symptom or may be one of multiple manifestations. This study aimed to characterize the development of DIA types and the timing of clinical resolution.

**Materials and methods:** Between January 2016 and March 2025, a prospective observational study of subjects diagnosed with DIA based on the development of ataxia after starting a drug and no prior history of ataxia was conducted. Collected data included the drug involved, timing to onset of symptoms, type of DIA (cerebellar vs sensory), and time required for resolution of symptoms.

**Results:** A total of 63 subjects met the criteria for inclusion in this analysis. Ataxia was most commonly attributed to antiepileptic drugs (AED) (44 subjects, 69.8%), with the remaining 19 subjects having ataxia after the use of chemotherapeutic or other drugs (30.2%). The most frequent drug associated with ataxia was phenytoin (22 subjects). The majority of ataxia experienced by the subjects was of the cerebellar variety (58.7%), whereas only 41.3% experienced a sensory form of ataxia. Symptoms of ataxia following the use of a drug were most commonly noted >72 hours after starting the drug (79.4%). In subjects with symptomatic improvement after intervention, 39.7% of subjects demonstrated improvement within 72 hours after intervention.

**Conclusion:** DIA may typically be caused by AEDs and chemotherapeutic drugs, with symptoms commonly manifesting >72 hours after initiation of drug therapy. Early recognition and treatment of DIA may improve clinical outcomes for individuals diagnosed with DIA.

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1571

of DIA from low-resource settings such as India. Most existing literature consists of case reports or reviews from high-income countries, limiting the generalizability of findings to populations with different genetic backgrounds, drug prescription patterns, and monitoring capabilities. This study was therefore conducted to provide a detailed characterization of the clinical and temporal profile of DIA in a tertiary care cohort in India, with the objective of enhancing clinical surveillance and enabling earlier therapeutic intervention.

## AIMS AND OBJECTIVES

### Primary Objective

This study was designed with the primary aim of characterizing the clinical and temporal profile of DIA in patients receiving antiepileptic and chemotherapeutic agents.

### Secondary Objectives

The secondary objectives were to identify and quantify the most common drugs associated with ataxia within our clinical cohort and to classify the predominant type of ataxia—sensory versus cerebellar—while describing its associated clinical features. Furthermore, the study sought to analyze the temporal patterns of both symptom onset and clinical resolution following drug intervention, as well as to evaluate potential risk factors for DIA, including dose duration, drug levels, and patient demographics. Finally, we aimed to compare the clinical profiles and outcomes of ataxia induced by AEDs vs chemotherapeutic or other agents to determine whether distinct patterns exist between these drug classes.

## INTRODUCTION

Ataxia, derived from the Greek meaning “lack of order,” is defined as the loss of coordinated voluntary movement, affecting gait, limb use, and speech. This impairment typically results from dysfunction of the cerebellum or its afferent/efferent pathways, including the sensory proprioceptive system. The etiology of ataxia is broad, encompassing genetic disorders, neurodegenerative conditions, vascular events, and metabolic disturbances.<sup>1</sup>

Drug-induced ataxia (DIA) is a significant iatrogenic condition that is often underrecognized in clinical practice despite being a prevalent adverse effect of numerous medications.<sup>2</sup> A systematic review has highlighted that DIA can result from a wide array of pharmaceuticals, including but not limited to antiepileptic drugs (AEDs), chemotherapeutic agents, psychotropic medications, and certain antibiotics.<sup>2</sup> The true incidence of DIA is difficult to ascertain, but it represents a considerable burden, particularly in polypharmacy and specialized clinical settings.

The pathophysiological mechanisms of DIA are complex and drug specific. Common mechanisms include: (1) direct neurotoxicity, particularly to the Purkinje

cells of the cerebellum, which are highly susceptible to metabolic and excitotoxic injury; (2) disruption of key neurotransmitter pathways, such as the gamma-aminobutyric acid (GABA)-ergic system, leading to impaired cerebellar inhibition; and (3) damage to the peripheral sensory nerves or dorsal root ganglia, resulting in sensory ataxia.<sup>3,4</sup> For instance, phenytoin is believed to cause cerebellar toxicity through voltage-gated sodium channel blockade and subsequent Purkinje cell loss, while chemotherapeutic agents such as cytarabine can cause a dose-dependent cerebellar syndrome.<sup>5,6</sup>

Clinically, DIA can present on a spectrum from acute onset following a single dose or dose adjustment to an insidious, chronic progression with prolonged exposure.<sup>2</sup> The clinical phenotype can be purely cerebellar (e.g., gait ataxia, nystagmus, dysmetria), sensory (e.g., positive Romberg sign, impaired proprioception), or a mixed picture. While many cases of DIA are reversible with dose reduction or drug withdrawal, some agents, particularly certain chemotherapies, can cause permanent neurological sequelae.<sup>7</sup>

Despite its clinical importance, there is a paucity of comprehensive data on the clinical spectrum, temporal profiles, and outcomes

<sup>1</sup>Assistant Professor; <sup>2</sup>Professor and Head;

<sup>3</sup>Associate Professor, Department of Neurology;

<sup>4</sup>Postgraduate, Department of Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry, India; \*Corresponding Author

**How to cite this article:** Saibaba J, Subramaniam MP, Thangavelu AP, *et al.* Spectrum and Clinical Burden of Drug-induced Ataxia in Low-resource Settings: An Observational Study. *J Assoc Physicians India* 2026;74(7):15–19.

## MATERIALS AND METHODS

### Study Design and Setting

This was a prospective, longitudinal observational study conducted in the Department of Neurology and General Medicine at Mahatma Gandhi Medical College and Research Institute, Puducherry, a tertiary care hospital in South India, from January 2016 to March 2025. The study protocol was approved by the Institutional Ethics Committee (MGM/IHEC/85/2016). Written informed consent was obtained from all patients willing to participate in the study.

### Inclusion and Exclusion Criteria

The inclusion criteria for this study required patients to be aged 4 years or older, presenting with new-onset ataxia—as previously defined—following the initiation or dose modification of a drug. Eligible patients must have had no prior history of ataxia, cerebellar disease, or hereditary ataxia and must have had normal neuroimaging [computed tomography (CT) or magnetic resonance imaging (MRI) of the brain] to exclude structural causes. Exclusion criteria included a history of significant alcohol use disorder as per World Health Organization (WHO) criteria,<sup>8</sup> uncontrolled metabolic disorders such as hypothyroidism or Wilson disease, or an active central nervous system infection. Additionally, patients with preexisting peripheral neuropathy from causes other than the suspected drug—such as diabetes mellitus or vitamin B12 deficiency—were not eligible. Those with psychiatric or cognitive disorders that would preclude the ability to provide reliable clinical history or informed consent were also excluded.

### Data Collection

For all enrolled participants, a standardized case report form was used to collect the following data:

Demographics: Age, sex.

Drug history: Name of the suspected drug, indication for use, daily dose, duration of therapy before symptom onset, and any recent dose modifications.

Clinical assessment: All patients underwent a comprehensive neurological examination performed by a neurologist. The type of ataxia was classified based on predefined clinical criteria adapted from standard neurological texts.<sup>9</sup>

Cerebellar ataxia: Presence of at least two of the following: gait ataxia (broad-based, unsteady), limb ataxia (dysmetria on finger-to-nose or heel-to-shin test), dysdiadochokinesia (impaired rapid alternating movements),

hypotonia, and cerebellar ocular motor signs (e.g., gaze-evoked nystagmus, saccadic dysmetria).

Sensory ataxia: Presence of ataxia with impaired proprioception [positive Romberg's sign (which worsens with eye closure)] and signs of peripheral neuropathy (diminished or absent ankle jerks, impaired vibration sense), in the absence of classical cerebellar signs.

Investigations: Serum drug levels were measured where clinically indicated and available. These were categorized as therapeutic or supratherapeutic based on standard laboratory reference ranges.

Outcome: The time to clinical resolution (defined as return to premorbid baseline neurological function or significant improvement in ataxia symptoms) was recorded following drug withdrawal, dose reduction, or specific intervention (e.g., levocarnitine for valproate toxicity). Patients were followed until clinical resolution or for a maximum of 30 days.

### Definitions and Categorization

Onset time: The time from the last drug dose modification (initiation or dose increase) to the first appearance of ataxia symptoms, categorized as follows:

Group A:  $\leq 24$  hours

Group B: 24–72 hours

Group C:  $> 72$  hours

Resolution time: The time from drug intervention (withdrawal or dose reduction) to documented clinical improvement, categorized as follows:

Group I:  $\leq 72$  hours

Group II: 72–144 hours

Group III:  $> 144$  hours

### Sample Size Calculation

The sample size was calculated based on the primary outcome of mean recovery time between the antiepileptic and chemotherapy groups. Assuming a two-sided alpha of 5% and power of 80%, and anticipating a clinically significant difference of 3 days in recovery time with a pooled standard deviation (SD) of 2.5 days (based on pilot data and previous literature), the minimum required sample size was estimated to be 11 patients per group (using the formula for comparing two means). Our final sample of 44 patients in the AED group and 19 in the chemotherapy group was therefore adequately powered to detect the observed differences between the drug classes.

### Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM

Corp., USA). Descriptive statistics were presented as mean  $\pm$  standard deviation (SD) for continuous variables and frequencies (percentages) for categorical variables. The primary outcome of resolution time was compared between drug classes (AEDs vs chemotherapeutic/other drugs) using an independent-samples *t*-test. Categorical variables were analyzed using the Chi-squared test or Fisher's exact test, as appropriate. A *p*-value  $< 0.05$  was considered statistically significant for all tests. Risk ratios (RRs) along with 95% confidence intervals (CIs) were computed where applicable to quantify effect sizes.

## RESULTS

### Participant Demographics and Clinical Profile

A total of 63 patients met the inclusion criteria and were enrolled in the study. The mean age was 48.2 years (SD 21.5, range: 4–89 years), with a near-equal sex distribution (34 males, 29 females). The primary drug class implicated was AEDs in 44 cases (69.8%), while chemotherapy and other drugs accounted for the remaining 19 cases (30.2%). Baseline demographics are detailed in Table 1.

### Pharmacological Agents Linked to Ataxia

Phenytoin was the single most common offending agent, responsible for 34.9% ( $n = 22$ ) of all cases. Carbamazepine was implicated in 19% ( $n = 12$ ) of cases. Other AEDs included gabapentin ( $n = 3$ ), zonisamide ( $n = 2$ ), and lamotrigine ( $n = 2$ ). Among chemotherapeutic and miscellaneous drugs, cytarabine and lithium each caused ataxia in 6.3% ( $n = 4$ ) of cases. The antidepressant amitriptyline was implicated in 7.9% ( $n = 5$ ) of cases. Other medications noted were ketamine, acyclovir, methotrexate, and mebendazole,

**Table 1:** Baseline demographic and clinical characteristics of study cohort ( $N = 63$ )

Characteristics	Value
Total patients	63
Mean age ( $\pm$ SD)	48.2 $\pm$ 21.5 years
Age range	4–89 years
Gender (male:female)	34:29
Primary drug category	
AEDs	44 (69.8%)
Chemotherapeutic/other drugs	19 (30.2%)
Most common indication	Seizure disorder ( $n = 28$ )

**Table 2:** Frequency and percentage of drugs associated with ataxia

Drug	Number of cases (N = 63)	Percentage (%)	Drug class
Phenytoin	22	34.9%	Antiepileptic
Carbamazepine	12	19%	Antiepileptic
Amitriptyline	5	7.9%	Antidepressant
Cytarabine	4	6.3%	Chemotherapeutic
Lithium	4	6.3%	Mood stabilizer
Gabapentin	3	4.8%	Antiepileptic
ketamine	4	6.3%	Anesthetic
5-fluorouracil	2	3.2%	chemotherapeutic
Methotrexate	2	3.2%	Chemotherapeutic
Others*	5	7.9%	Miscellaneous

Others\*—Zonisamide, Lamotrigine, Acyclovir, Mebendazole, Neem Oil, Immunoglobulin, Hep B Vaccine, Amiodarone, Cyclophosphamide

**Table 3:** Distribution of ataxia type and temporal onset groups

Variable	Sensory ataxia (n = 26)	Cerebellar ataxia (n = 37)	Total (N = 63)
Onset group, n (%)			
Group A (≤24 hours)	3 (11.5%)	4 (10.8%)	7 (11.1%)
Group B (24–72 hours)	2 (7.7%)	4 (10.8%)	6 (9.5%)
Group C (>72 hours)	21 (80.8%)	29 (78.4%)	50 (79.4%)
Most common signs			
Impaired proprioception	22 (84.6%)	–	–
Positive Romberg	19 (73.1%)	–	–
Dysmetria/dysdiadochokinesia	–	28 (75.7%)	–
Nystagmus/abnormal eye movements	–	18 (48.6%)	–
Ataxic gait	26 (100%)	37 (100%)	63 (100%)

**Table 4:** Time to clinical resolution after intervention

Resolution group	AEDs (n = 44)	Chemotherapeutic/other drugs (n = 19)	Total (N = 63)
Group I (≤72 hours)	19 (43.2%)	6 (31.6%)	25 (39.7%)
Group II (72–144 hours)	13 (29.5%)	4 (21.1%)	17 (27%)
Group III (>144 hours)	12 (27.3%)	9 (47.4%)	21 (33.3%)
Mean resolution time (days)	5.1 ± 2.3	8.2 ± 3.1	6.0 ± 2.9

**Table 5:** Clinical improvement by onset group

Onset group	Resolution <72 hours (group I)	Resolution 72–144 hours (group II)	Resolution >144 hours (group III)	Total
Group A (≤24 hours)	5	2	0	7
Group B (24–72 hours)	3	2	1	6
Group C (>72 hours)	17	13	20	50
Total	25	17	21	63

**Table 6:** Risk factor analysis in phenytoin induced ataxia (n = 22)

Factor	Sensory ataxia (n = 14)	Cerebellar ataxia (n = 8)	Total (n = 22)
Dose duration >1 week	12 (85.7%)	7 (87.5%)	19 (86.4%)
High serum drug level	10 (71.4%)	5 (62.5%)	15 (68.2%)
Dose increased prior to ataxia	6 (42.9%)	3 (37.5%)	9 (40.9%)
Mean resolution time (days)	6.2 ± 1.8	5.8 ± 1.5	6 ± 1.7
Peripheral neuropathy present	9 (64.3%)	2 (25%)	11 (50%)

highlighting the wide range of drugs that can precipitate ataxia (Table 2).

### Classification and Clinical Presentation of Ataxia

The most frequent disorder observed in this group was cerebellar ataxia, with 37 patients (58.7%) affected. Other common cerebellar signs included dysmetria (n = 28, 75.7%) and dysdiadochokinesia (n = 25, 67.6%). Nystagmus or other oculomotor deficits were present in 18 patients (48.6%). Sensory ataxia was diagnosed in 26 patients (41.3%), characterized by impaired proprioception (n = 22, 84.6%), a positive Romberg sign (n = 19, 73.1%), and diminished tendon reflexes (n = 17, 65.4%). While phenytoin was associated with both types, it produced sensory ataxia more frequently (14/22 patients, 63.6%). In contrast, cytarabine caused exclusively cerebellar manifestations. The distribution of ataxia subtype by onset is presented in Table 3.

### Timing of Symptom Onset and Recovery

A striking finding was the delayed onset of symptoms, with the vast majority of patients (n = 50, 79.4%) experiencing ataxia >72 hours after the last drug modification (group C). Only 11.1% (n = 7) had onset within 24 hours (group A), and 9.5% (n = 6) had onset between 24 and 72 hours (group B).

Following drug intervention, clinical recovery occurred within 72 hours (group I) in 39.7% (n = 25) of patients. A further 27.0% (n = 17) recovered within 72–144 hours (group II), and 33.3% (n = 21) had a prolonged recovery taking >144 hours (group III). Ataxia related to chemotherapeutic agents was associated with significantly longer recovery periods. The time to clinical recovery by drug class is shown in Table 4, and a cross-tabulation of onset and resolution groups is presented in Table 5.

### Analysis of Contributing Factors

Within the phenytoin subgroup (n = 22), 15 subjects were determined to have elevated serum concentrations of phenytoin. The combination of high serum levels and a therapy duration of >3 weeks appeared to enhance symptom severity and prolong recovery time. Other risk factors associated with phenytoin-induced ataxia are shown in Table 6. Similar to phenytoin, carbamazepine demonstrated a comparable risk profile. For drugs that are not typically monitored, duration of treatment and cumulative dosage were the primary identified risk factors. Age >60 years was associated with both an increased frequency of ataxia and a longer

**Table 7:** Comparative profile of ataxia by drug class (N = 63)

Parameter	AEDs (n = 44)	Chemotherapeutic/other drug (n = 19)	p-value
Mean age (years)	45.3 ± 19.2	54.1 ± 24.7	0.12
Male:female ratio	22:22	12:7	0.32
Ataxia type, n (%)			0.03
Sensory	21 (47.7%)	4 (21.1%)	
Cerebellar	23 (52.3%)	15 (78.9%)	
Onset group C (>72 hours)	36 (81.8%)	14 (73.7%)	0.46
Resolution group III (>144 hours)	12 (27.3%)	9 (47.4%)	0.02
Abnormal drugs levels	28/34 (82.4%)	5/12 (41.7%)	<0.01

mean recovery time across all medication types.

### Comparison between Drug Classes

The clinical profile of ataxia due to AEDs was different from that attributed to chemotherapy. Sensory ataxia was more frequent with AEDs (47.7%) than with chemotherapy (21.1%,  $p = 0.03$ ). Conversely, cerebellar ataxia was the dominant phenotype in the chemotherapy group (78.9%). While the onset of symptoms was delayed (>72 hours) in the majority of both groups, the mean time to recovery from AED-related ataxia was significantly shorter than that from chemotherapy-related ataxia (5.1 vs 8.2 days,  $p = 0.02$ ). A comparison of clinical features according to drug class is shown in Table 7.

## DISCUSSION

The current study describes the clinical and temporal characteristics of DIA and supports its identification as a preventable iatrogenic disorder.<sup>2</sup> The predominance of AEDs, particularly phenytoin, aligns with global literature that identifies these agents as common culprits due to their narrow therapeutic index and direct effects on the central nervous system (CNS).<sup>5</sup> The high proportion of phenytoin-related cases in our cohort likely reflects its widespread and often unmonitored use in the management of epilepsy in resource-limited settings.<sup>10</sup> Our finding that elevated serum phenytoin levels were present in a majority of these cases (68.2%) underscores the critical need for accessible and routine therapeutic drug monitoring to prevent neurotoxicity.<sup>5</sup>

The significant association between AEDs and sensory ataxia, as opposed to the predominantly cerebellar ataxia associated with chemotherapy, suggests divergent pathophysiological pathways.<sup>3,4</sup> Phenytoin's neurotoxicity, while classically linked to cerebellar Purkinje cell damage, also involves peripheral nerve injury,

possibly through folate antagonism or direct axonal damage, leading to the sensory deficits observed in our patients.<sup>6</sup> In contrast, chemotherapeutic agents such as cytarabine are known for their selective toxicity to cerebellar granule cells, explaining the pure cerebellar syndrome seen in our cohort.<sup>11</sup>

Importantly, the majority (79.4%) of the subjects experienced a delayed onset of symptoms, indicating that DIA cannot solely be considered an acute toxic event. The presence of delayed symptom expression indicates that there may be other mechanisms at work; for example, cumulative neurotoxicity, progressive neuronal injury, or the unmasking of previously compensated subclinical deficits.<sup>2,12</sup> This finding reinforces the need for ongoing clinical monitoring of patients receiving chronic therapy because symptoms may develop many weeks after initiation of pharmacological treatment. This latency period creates a diagnostic challenge, as the temporal link between the drug and the symptom may not be immediately apparent to the clinician, potentially leading to delayed diagnosis and unnecessary investigations.<sup>12</sup>

The observed differences in recovery times between drug classes are clinically important. The relatively rapid recovery (mean 5.1 days) following withdrawal of most AEDs supports the concept of functional, reversible neurotoxicity in many cases. However, the significantly prolonged recovery (mean 8.2 days) and higher proportion of patients in Resolution group III for chemotherapy-associated ataxia highlight the potential for more irreversible, structural damage from these agents.<sup>7,11</sup> This finding is consistent with studies on high-dose cytarabine, where neurotoxicity can be dose limiting and recovery incomplete.<sup>11</sup>

Our risk factor analysis reinforces the importance of both pharmacokinetic and pharmacodynamic factors. The strong link between high serum drug levels and ataxia,

even within the "therapeutic window" for some patients, highlights the interindividual variability in drug metabolism and CNS susceptibility.<sup>13</sup> Furthermore, age emerged as a significant nonmodifiable risk factor. The increased vulnerability in older adults is likely multifactorial, stemming from age-related declines in hepatic and renal clearance, reduced neurological reserve, and an increased likelihood of polypharmacy.<sup>14</sup>

### Clinical Implications

In low-resource settings where access to frequent serum drug-level monitoring may be limited, our findings underscore the importance of high clinical vigilance. Physicians should maintain a high index of suspicion for DIA in any patient presenting with new-onset ataxia, particularly those receiving long-term AED therapy or chemotherapy. A detailed drug history, including recent dose changes, is important. Given the delayed onset, the absence of a recent dose change does not rule out DIA. Patients receiving high-risk medications, such as phenytoin, should undergo regular neurological assessments of gait and proprioception and serum monitoring. Patient and caregiver education regarding the early warning signs of ataxia is also vital to facilitate early reporting and intervention.

### Strengths and Limitations

The main strength of our study is its prospective, longitudinal design with a well-characterized cohort from a real-world clinical setting. The systematic neurological phenotyping of ataxia is another key strength. However, several limitations must be acknowledged. First, as a single-center study, the findings may not be fully generalizable to other populations. Second, the observational nature of the study precludes the establishment of definitive causality, although the Naranjo Adverse Drug Reaction Probability Scale<sup>15</sup> was used implicitly in clinical assessment. Third, serum drug levels were not available for all patients, particularly for non-AEDs,

limiting our ability to perform a complete pharmacokinetic analysis for all cases. Finally, the sample size, while adequate for descriptive analysis, limited the statistical power for subgroup analyses of rarer drugs.

## FUTURE DIRECTIONS

Multicenter prospective studies with standardized drug monitoring and biomarker integration should be the focus of future research. Additionally, exploring genetic polymorphisms in drug-metabolizing enzymes and drug transporters may support personalized medicine approaches to identify at-risk individuals before drug exposure, ultimately moving toward the prevention of DIA.<sup>16</sup>

## CONCLUSION

Ataxia secondary to pharmacotherapy demonstrates specific clinical and temporal characteristics. Antiepileptic medications, especially phenytoin, account for the majority of cases, and chemotherapeutic agents lead to longer recovery courses. The frequently delayed onset of symptoms mandates ongoing, vigilant clinical surveillance throughout the course of therapy, not

just immediately after initiation. Optimal management involves timely identification, prompt dose modification or drug withdrawal, and an understanding of the unique neurotoxic mechanisms of each causative agent. To protect patient safety and improve outcomes, the implementation of structured neurological assessments into the care plans of patients receiving high-risk medications is essential.

## ORCID

Jayaram Saibaba  <https://orcid.org/0009-0003-0736-5141>

## REFERENCES

- Ashizawa T, Xia G. Ataxia. *Continuum (Minneapolis)* 2016;22(4 Movement Disorders):1208–1226.
- van Gaalen J, Kerstens FG, Maas RP, et al. Drug-induced cerebellar ataxia: a systematic review. *CNS Drugs* 2014;28(12):1139–1153.
- Sarna JR, Hawkes R. Patterned Purkinje cell death in the cerebellum. *Prog Neurobiol* 2003;70(6):473–507.
- Dolbec K, Dobbs MR, Ibraheem M. Toxin-induced cerebellar disorders. *Neurol Clin* 2020;38(4):843–852.
- Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008;49(7):1239–1276.
- Zaccara G, Gangemi PF, Cincotta M. Central nervous system adverse effects of new antiepileptic drugs. A meta-analysis of placebo-controlled studies. *Seizure* 2008;17(5):405–421.
- Adityanjee, Munshi KR, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005;28(1):38–49.
- World Health Organization. International guide for monitoring alcohol consumption and related harm. Geneva: World Health Organization; 2000.
- Ropper AH, Samuels MA, Klein JP, et al. *Adams and Victor's Principles of Neurology*. 11th ed. New York: McGraw-Hill; 2019.
- Radhakrishnan K. Challenges in the management of epilepsy in resource-poor economies. *Epilepsia* 2009;50(Suppl 8):52–55.
- Smith GA, Damon LE, Rugo HS, et al. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. *J Clin Oncol* 1997;15(2):833–839.
- Bhattacharyya S, Darby RR, Raibagkar P, et al. Antibiotic-associated encephalopathy. *Neurology* 2016;86(10):963–971.
- Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol* 2006;61(3):246–255.
- Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol* 2003;38(8):843–853.
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239–245.
- Löscher W, Klotz U, Zimprich F, et al. The clinical impact of pharmacogenetics on the treatment of epilepsy. *Epilepsia* 2009;50(1):1–23.

# A Cross-sectional Study to Assess the Knowledge, Attitude, and Practice of Look-alike, Sound-alike Drugs among Healthcare Providers at a Tertiary Care Hospital



Nancy Bansal<sup>1\*</sup>, Akash Ashok Kumar Khobragade<sup>2</sup>, Aditya R Bawne<sup>3</sup>, Ajinkya Bavlecha<sup>4</sup>, Balbir Singh Kohli<sup>5</sup>

Received: 08 November 2025; Accepted: 30 April 2026

## ABSTRACT

**Background:** Sometimes, drug names or their appearances create confusion among healthcare providers. These look-alike or sound-alike (LASA) drugs have the potential to cause medication errors leading to patient harm. Such errors can occur during prescribing, dispensing, and administration of drugs. Therefore, this study was conducted to assess the knowledge, attitudes, and practice of LASA drugs among healthcare providers at a tertiary care hospital in India.

**Materials and methods:** This cross-sectional, observational, single-center, questionnaire-based study was conducted among healthcare providers at a tertiary care hospital in India. The study was conducted over a duration of 2 months between November and December 2024.

**Results:** Out of the 400 participants, 81% were doctors, followed by 12.75% nurses, 3.25% pharmacists, and 3% interns. The majority of them were aware of the term LASA drugs. The majority of them were slightly concerned about the risks of LASA drugs. Whereas, only 10% of them had ever reported LASA errors, as the majority of them were unaware about medication error reporting form.

**Conclusion:** This study suggests that lack of awareness about LASA drugs among healthcare providers contributes to medication errors. To address this, solutions can be implemented at different levels via a multidisciplinary approach.

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1593

## INTRODUCTION

Look-alike, sound-alike (LASA) drugs are drugs that have orthographic (look-alike) and phonetic (sound-alike) similarities. Look-alike drugs appear the same in terms of packaging, shape, color, and size, while sound-alike drugs are similar in terms of names, doses, and strengths.<sup>1,2</sup> Confusion due to LASA drugs can occur between brand-brand, brand-generic, or generic-generic names of drugs.<sup>3</sup> The appearance of drugs can be confusing either because different drugs look the same or same drugs look different.<sup>1</sup> Thus, LASA drugs can lead to a specific type of medication error known as LASA errors.<sup>4</sup>

Look-alike, sound-alike errors can occur during the prescribing, dispensing, and administration of drugs.<sup>5</sup> While prescribing, illegibility in prescriptions on which the diagnosis is not mentioned makes it difficult to identify the drug. Also, errors may occur during dispensing if the pharmacists are not aware of LASA drugs and during administering if the nursing staff does not cross-check LASA drugs. Thus, LASA errors can lead to overdosing, underdosing, or inappropriate dosing of drugs.<sup>6</sup> LASA errors have more detrimental effects in children, elderly patients, and those with organ

failures.<sup>7</sup> They may culminate in serious adverse events, including death.

Regulators are accountable for the naming and packaging of new drugs to avoid LASA errors.<sup>8</sup> The Central Drugs Standard Control Organization (CDSCO) is the regulatory authority in India. Naming bodies such as the World Health Organization International Nonproprietary Names program (WHO INN program) can prevent the designation of highly confusing names.<sup>2,9</sup>

In India, very few studies have been conducted on awareness of LASA drugs, one of which concluded that only 34% of doctors and 17% of pharmacists were aware of LASA drugs.<sup>10</sup> As tertiary care hospitals provide highly specialized care, awareness of LASA drugs is critically important to reduce medication errors and for better patient outcomes. Therefore, this study aimed to assess the knowledge, attitude, and practice of LASA drugs among healthcare providers at a tertiary care hospital in India.

## MATERIALS AND METHODS

### Study Design

This study was a cross-sectional, observational, single-center, questionnaire-based study conducted among healthcare providers at a

tertiary care hospital in an urban metropolitan city of India. The study was conducted over a 2-month duration between November and December 2024.

### Sample Size

The sampling method used for this study was consecutive sampling, where all eligible participants available during the study period were approached. Approximately 500 healthcare providers were approached during the study period, out of whom 400 responded to the questionnaire, yielding a response rate of approximately 80%. Respondents included postgraduate residents, nurses, and pharmacists working at a tertiary care hospital, selected using a convenience sampling approach.

### Study Procedure

Before starting this study, Institutional Ethics Committee approval was taken (IEC Number: IEC/Pharm/RP/335/Oct/2024). Informed consent was taken over the "Google Form" platform before data collection. Participants were informed that their participation was voluntary and that they could choose not to answer any question. Participants' confidentiality was maintained as no information related to identity was collected.

The questionnaire was validated by six doctors, two nurses, and two pharmacists. The questionnaire had four parts. The first part consisted of demographic details such as age, gender, profession, and years of

<sup>1</sup>Junior Resident, Department of Pharmacology, Grant Government Medical College, Mumbai;

<sup>2</sup>Professor, Department of Pharmacology, Government Medical College, Raigad; <sup>3</sup>Junior Resident; <sup>4</sup>Senior Resident, Department of Pharmacology, Grant Government Medical College; <sup>5</sup>Consultant, Department of Internal Medicine, Hira Mongi Navneet Hospital, Mumbai, Maharashtra, India; \*Corresponding Author

**How to cite this article:** Bansal N, Kumar Khobragade AA, Bawne AR, et al. A Cross-sectional Study to Assess the Knowledge, Attitude, and Practice of Look-alike Sound-alike (LASA) Drugs among Healthcare Providers at a Tertiary Care Hospital. *J Assoc Physicians India* 2026;74(7):20–23.

experience. In the second part, questions were based on knowledge about awareness of LASA drugs. In the third and fourth parts, questions based on attitude and practice, respectively, were put forth to the participants. The questionnaire used in the study is provided as an appendix.

**Statistical Analysis**

Cronbach’s alpha value was calculated to validate the questionnaire, which was 0.9. The data obtained were analyzed in Microsoft Excel (Version 2502). Data were analyzed using descriptive statistics.

**RESULTS**

Out of the total 400 participants who participated in the study, most of the participants ( $n = 305, 76.25\%$ ) were between 20 and 30 years of age, followed by those between 31 and 40 years ( $n = 56, 14\%$ ). The number of male participants ( $n = 222, 55.5\%$ ) was greater than that of female participants ( $n = 178, 44.5\%$ ). The majority of participants in the study were doctors ( $n = 324, 81\%$ ), followed by nurses ( $n = 51, 12.75\%$ ), pharmacists ( $n = 13, 3.25\%$ ), and interns ( $n = 12, 3\%$ ). Most of the participants had less than 5 years of work experience ( $n = 281, 70.25\%$ ), followed by those with 11–15 years of experience ( $n = 39, 9.75\%$ ) and those with 16–20 years of experience ( $n = 29, 7.25\%$ ). A majority of the participants were aware of LASA drugs ( $n = 243, 60.75\%$ ), with most of them believing that they were drugs with similar names ( $n = 315, 78.75\%$ ), with similar appearances ( $n = 227, 56.75\%$ ), or with similar packaging ( $n = 153, 38.25\%$ ) (Fig. 1). Most of them ( $n = 268, 67\%$ ) were able to identify at least one LASA drug pair (Fig. 2), while almost all of them ( $n = 375, 93.75\%$ ) were aware of at least one potential risk which could arise from prescribing LASA drugs (Fig. 3).

Most of them were aware ( $n = 355, 88.75\%$ ) that a thorough understanding of LASA drugs was necessary to prevent medication errors, while a majority were slightly concerned regarding the risks posed by LASA drugs. A majority of the participants demonstrated that they were able to identify the category of a given pair of LASA drugs ( $n = 211, 52.75\%$ ) and how to correctly use tall man lettering (TML) ( $n = 266, 66.5\%$ ).

Most of the participants strongly agreed ( $n = 220, 55\%$ ) that additional training on LASA drugs was vital for healthcare professionals, while they were unsure whether the precautions at their workplace regarding LASA drugs were

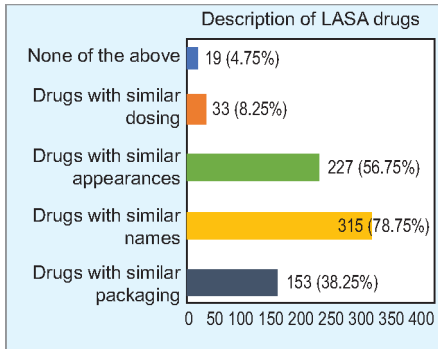


Fig. 1: Description of LASA drugs

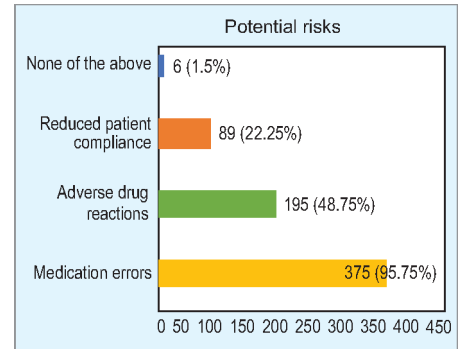


Fig. 3: Potential risks

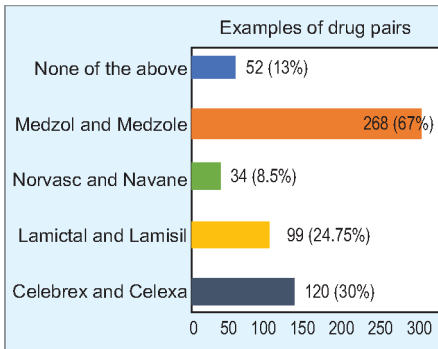


Fig. 2: Examples of drug pairs

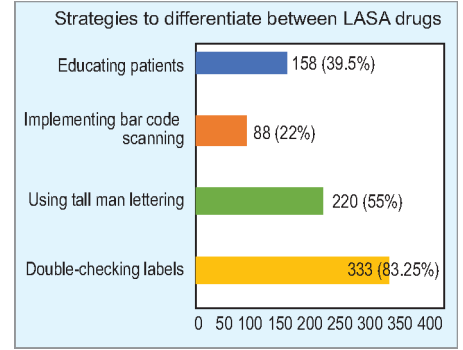


Fig. 4: Strategies to differentiate between LASA drugs

Table 1: Double-checking for LASA drugs prior to medication

Sr. No	Double-check for LASA drugs before administering medication	Number of participants (%)
1	Never	34 (8.5)
2	Rarely	60 (15)
3	Sometimes	136 (34)
4	Often	60 (15)
5	Always	110 (27.5)

sufficient ( $n = 115, 28.75\%$ ). Also, a large number of participants responded that they only checked sometimes ( $n = 136, 34\%$ ) for LASA drugs before administering drugs (Table 1).

The strategies favored by healthcare professionals to differentiate between LASA drugs were double-checking labels (333, 83.25%) and using tall man lettering ( $n = 220, 55\%$ ) while few of them implemented barcode scanning (88, 22%) (Fig. 4).

More than half of the participants had never seen the medication error reporting form ( $n = 241, 60.25\%$ ), while a very small number had attended any CME, webinar, or conference regarding LASA drugs ( $n = 19, 4.75\%$ ). The use of generic names in prescriptions helps prevent LASA errors. More than half of the participants ( $n = 207, 51.75\%$ ) frequently wrote or encountered

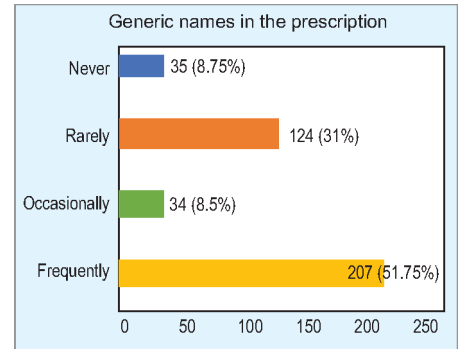


Fig. 5: Generic names in prescriptions

generic names of drugs in the prescriptions of patients (Fig. 5).

Only 10% ( $n = 42$ ) of participants had ever reported LASA errors. Few of the participants also suggested additional measures that could be employed to prevent LASA drug errors at their workplaces.

**DISCUSSION**

This study assessed the awareness, knowledge, attitude, and practice of LASA drugs among healthcare providers at a tertiary care teaching hospital in an urban metropolitan city. Our findings showed that 60% of healthcare providers were aware of the term “LASA drugs,” while 67% of them could identify at least one pair of LASA drugs. These results are inconsistent with the study conducted

by Munshi et al.,<sup>10</sup> which showed that 34% of resident doctors and 17% of pharmacists were aware of the term "LASA drugs". 55% of healthcare providers strongly agreed that additional training on LASA drugs was necessary to avoid medication errors and for better patient safety outcomes. 34% of healthcare providers sometimes double-check before administering LASA drugs.

A notable discrepancy was observed between knowledge and practice among healthcare providers. While a large proportion of participants recognized double-checking labels as an important strategy to prevent LASA errors, only a smaller proportion reported consistently implementing this practice. This highlights a gap between knowledge and actual practice, which may be attributed to factors such as high workload, time constraints, lack of standardized protocols, or insufficient reinforcement through training. Addressing this gap requires system-level interventions, including regular training programs, implementation of standard operating procedures, and incorporation of double-checking mechanisms into routine clinical workflows.

There are various strategies that can be used to differentiate between LASA drugs, such as double-checking labels, using tall man lettering, implementing barcode scanning, and educating patients. The majority of participants had never seen a medication error reporting form, whereas only 10% of healthcare providers had ever reported LASA errors. This is because of a lack of awareness about reporting of medication errors among healthcare providers. Few healthcare providers gave suggestions to prevent LASA errors at their workplace, such as conducting educational seminars on awareness of LASA drugs, workshops on reporting of LASA errors, prescription audits, double-checking the labels before administration and confirming once with the doctor, and storing LASA drugs in different cabinets with proper labeling.

The interventions to mitigate and prevent LASA errors could be taken at various levels. Regulatory authorities such as the United States Food and Drug Administration (USFDA), CDSCO, can contribute to reducing LASA errors by not approving those brand names that can create confusion with International nonproprietary names (INNs) and ones that incorporate INNs into them.<sup>11,12</sup> At the drug policy level, immediate withdrawal of drugs with misleading names should be done, and regular updates or advisories on a list of misleading names should be released, along with the use of tall man lettering on drug labels.<sup>13</sup> At the level of healthcare providers,

mentioning diagnosis and indications on prescriptions can help to avoid errors while dispensing, writing generic prescriptions, avoiding distraction while prescribing drugs, use of tall man lettering on prescriptions, timely training of healthcare providers on the updated list of LASA drugs, and use of computerized drug prescriptions.<sup>14</sup> At the level of drug dispensing, using a double-check system to match the drugs dispensed with those prescribed, to confirm the dispensed drug is appropriate for the mentioned indication, and separately storing LASA drugs.

A limitation of this study is the possibility of recall bias. Respondents may not have been able to recall past experiences with LASA errors, resulting in either underreporting or overreporting of actual events, and thereby affecting the reliability of the findings. Also, social desirability bias is another limitation, as participants may have provided responses they believed were acceptable or expected, rather than being entirely truthful. If respondents were disinterested or hesitant to admit to errors, the data collected might not accurately reflect real practices or attitudes.

Another limitation is that a large proportion of participants in this study were doctors (81%), with relatively fewer nurses (12.75%) and pharmacists (3.25%). This uneven distribution may limit the generalizability of the findings, as nurses and pharmacists are also actively involved in dispensing and administration of medications, where LASA errors commonly occur.

## CONCLUSION

This study highlights gaps in awareness and reporting of LASA errors among healthcare providers. While a considerable proportion of participants were aware of LASA drugs, inconsistencies between knowledge and practice were observed, along with poor reporting of medication errors. To address these issues, a multidisciplinary approach involving healthcare professionals, nursing staff, and pharmacists is required.

## SOURCE OF FUNDING

None.

## CONFLICT OF INTEREST

None.

## APPENDIX

Questionnaire on knowledge, attitude, and practice of look-alike sound-alike (LASA) drugs.

## Section 1: Demographics

1. Age:

1. 20–30 years
2. 31–40 years
3. 41–50 years
4. 51–60 years
5. 61 years and above

2. Gender:

1. Male
2. Female
3. Other

3. Profession:

1. Doctor
2. Nurse
3. Pharmacist
4. Other (please specify): \_\_\_\_\_

4. Years of experience:

1. 0–5 years
2. 6–10 years
3. 11–15 years
4. 16–20 years
5. More than 20 years

## Section 2: Knowledge

5. Have you ever heard of look-alike, sound-alike (LASA) drugs?

1. Yes
2. No

6. Which of the following best describes LASA drugs? (Select all that apply.)

1. Drugs with similar packaging
2. Drugs with similar names
3. Drugs with similar appearances
4. Drugs with similar dosing
5. None of the above

7. Which of the following are examples of LASA drug pairs? (Select all that apply.)

1. Celebrex and Celexa
2. Lamictal and Lamisil
3. Norvasc and Navane
4. Medzol and Medzole
5. All of the above

8. What are the potential risks associated with LASA drugs? (Select all that apply.)

1. Medication errors
2. Adverse drug reactions
3. Reduced patient compliance
4. None of the above

9. Which organization issued recommendations for LASA drugs?

1. World Health Organization guidelines
2. Institute for Safe Medication Practices guidelines

3. Central Drugs Standard Control Organization guidelines

4. Food and Drug Administration guidelines

10. What is the primary purpose of understanding LASA drugs?

1. To reduce the cost of drug development
2. To increase pharmaceutical sales
3. To discover new brand names for existing drugs
4. To prevent medication errors

11. The following pair belongs to which category of LASA drugs?

Cetralon (cetirizine) and Cetro (cetirizine)

1. Similar brand names with different generic compositions
2. Similar brand names with the same generic composition
3. Generic drug pairs
4. Similar brand names with an additional letter

12. Which of the following LASA pairs is written in tall man lettering (TML)?

1. ALPRAZolam and LORazepam
2. HYDROcodone and oxyCODONE
3. Paroxetine and fluoxetine
4. Tramadol and trazodone

### Section 3: Attitude

13. How concerned are you about the risks associated with LASA drugs?

1. Not concerned
2. Slightly concerned
3. Moderately concerned
4. Very concerned
5. Extremely concerned

14. Do you believe that additional training on LASA drugs is necessary for healthcare professionals?

1. Strongly disagree
2. Disagree
3. Neutral
4. Agree
5. Strongly agree

15. Do you think your workplace takes sufficient measures to prevent LASA drug errors?

1. Strongly disagree
2. Disagree
3. Neutral
4. Agree

5. Strongly agree

### Section 4: Practice

16. How often do you check for LASA drugs before administering medication?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always

17. What strategies do you use to differentiate between LASA drugs? (Select all that apply.)

1. Double-checking labels
2. Using tall man lettering
3. Implementing barcode scanning
4. Educating patients
5. Other (please specify): \_\_\_\_\_

18. Have you ever reported an incident involving LASA drugs?

1. Yes
2. No

18.1. If yes, what kind of incident was it?

Answer: \_\_\_\_\_

18.2. If yes, how often do you report such incidents?

1. Always
2. Often
3. Sometimes
4. Rarely
5. Never

19. Have you ever seen the medication error reporting form?

1. Yes
2. No

20. How often do you write or see generic names in prescriptions given to patients?

1. Frequently
2. Occasionally
3. Rarely
4. Never

21. Have you ever attended continuing medical education (CME) sessions, webinars, or conferences regarding LASA drugs?

1. Yes
2. No

22. What additional measures would you suggest to prevent LASA drug errors in your workplace? (Open-ended).

### ORCID

Nancy Bansal  <https://orcid.org/0009-0008-9307-4143>

### REFERENCES

1. World Health Organization. (2023). Medication safety for look-alike, sound-alike medicines. [online] Available from: <https://www.who.int/news-room/events/detail/2023/10/20/default-calendar/medication-safety-webinar--medication-safety-for-look-alike--sound-alike-medicines> [Last accessed June, 2026].
2. Bryan R, Aronson JK, ten Hacken P, et al. Patient safety in medication nomenclature: orthographic and semantic properties of international nonproprietary names. *PLoS One* 2015;10(12):e0145431.
3. Institute for Safe Medication Practices (ISMP). (2015). ISMP safe practice guidelines for adult IV push medications. [online] Available from: <https://www.ismp.org/guidelines/iv-push> [Last accessed June, 2026].
4. Bryan R, Aronson JK, Williams A, et al. The problem of look-alike, sound-alike name errors: drivers and solutions. *Br J Clin Pharmacol* 2021;87(2):386–394.
5. Moore SJ, Jenkins AT, Poppe LB, et al. Significant publications about the medication use process in 2012. *J Pharm Pract* 2015;28(4):387–397.
6. Ministry of Public Health, Lebanon. (2024). Look-alike sound-alike medicines. [online] Available from: <http://www.moph.gov.lb/en/DynamicPages/view/68527/look-alike-sound-alike-medicines> [Last accessed June, 2026].
7. Zakharov S, Tomas N, Pelclova D. Medication errors: an enduring problem for children and elderly patients. *Ups J Med Sci* 2012;117(3):309–317.
8. Health Canada. (2014). Guidance document for industry: review of drug brand names. [online] Available from: <https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/guidance-document-industry-review-drug-brand-names.html> [Last accessed June, 2026].
9. World Health Organization. (2026). International nonproprietary names program and classification of medical products. [online] Available from: <https://www.who.int/teams/health-product-and-policy-standards/inn> [Last accessed June, 2026].
10. Munshi RP, Tople GD, Munot SR. Assessment of the degree of awareness among post-graduate medical physicians and pharmacists about look-alike, sound-alike drug and potential medication errors. *Int J Basic Clin Pharmacol* 2019;8(8):1771–1775.
11. Neelakantan M, Sharma P, Kulkarni A. Look-alike, sound-alike (LASA) drugs in India. *Lancet Reg Health Southeast Asia* 2024;26:100425.
12. World Health Organization. (2026). Guidance on INN. [online] Available from: <https://www.who.int/teams/health-product-and-policy-standards/inn/guidance-on-inn> [Last accessed June, 2026].
13. Bryan R, Aronson JK. A systematic literature review of LASA error interventions. *Br J Clin Pharmacol* 2021;87(2):336–351.
14. Tariq RA, Vashisht R, Sinha A, et al. Medication dispensing errors and prevention. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2026.



# Profile of Philadelphia Chromosome Negative (Ph<sup>-</sup>) Myeloproliferative Neoplasm with Special Emphasis on Vascular Thrombotic Events and the Response to Cytoreductive Therapy in Polycythemia Vera and Essential Thrombocythemia Patients: A Single Center Study from Kerala

Raghuveer Santhakumara Prabhu<sup>1\*</sup>, Rahmathullah Sulaimankutty Nameera<sup>2</sup>, Sayyid Muhammed Likhmanulhakkim Thangal K<sup>3</sup>, Priyanka R Nair<sup>4</sup>

Received: 23 December 2025; Accepted: 04 May 2026

## ABSTRACT

**Introduction:** Thrombotic events are a major morbidity among Philadelphia chromosome-negative myeloproliferative neoplasm (Ph-MPN) patients. There is a lack of data from Kerala regarding the profile of Ph-MPN and the prevalence of thrombosis among these patients.

**Aims:** To study the clinical profile, driver mutations, incidence of thrombotic events among Ph-MPN patients, and the response to hydroxyurea therapy.

**Methods:** We reviewed the medical records of 84 Ph-MPN patients who were on follow-up from April 2019 to June 2023 in a tertiary care hospital in Kerala.

**Results:** There were 48 polycythemia vera (PV), 16 essential thrombocythemia (ET), 14 primary myelofibrosis (PMF), and six unclassifiable MPN (MPN-u) patients. The incidence of Janus kinase 2 (JAK2) mutation was 96, 62.5, and 79% among PV, ET, and PMF patients, respectively. The incidence of calreticulin (CALR) mutation was 37.5 and 21% among ET and PMF patients, respectively. The incidence of thrombotic events was 23/48 (48%), 7/16 (43.5%), and 6/14 (42.8%) among PV, ET, and PMF patients, respectively. All ET and PMF patients with thrombotic events were JAK2V617F-mutated. Eighty-seven percent of the evaluable patients on hydroxyurea for PV achieved freedom from therapeutic phlebotomies. ET patients who were on hydroxyurea achieved a median platelet count of 4.3 lakhs/ $\mu$ L (3.16–6.08).

**Conclusion:** There is a higher incidence of thrombosis among Ph-MPN patients from Kerala, which needs to be ascertained in a population-based study. JAK2V617F mutation is the major determinant of thrombotic episodes in ET and PMF. Hydroxyurea is an effective cytoreductive therapy in PV and ET.

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1583

## INTRODUCTION

Philadelphia chromosome-negative myeloproliferative neoplasm (Ph-MPN) is a heterogeneous group of clonal hematopoietic stem cell disorders that are classified into polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic neutrophilic leukemia (CNL), mastocytosis, and myeloproliferative neoplasm-unclassifiable (MPN-u).<sup>1</sup> The diagnosis of Ph-MPNs typically involves a combination of clinical evaluation, peripheral blood counts, bone marrow examination, and molecular testing to identify specific mutations. The identifiable driver mutations in MPN are Janus kinase 2 (JAK2), calreticulin (CALR), and thrombopoietin receptor/myeloproliferative leukemia (MPL) mutations.<sup>2</sup> Major complications include thrombotic events such as stroke, myocardial infarction, and venous thrombosis. PV and

ET can progress to secondary myelofibrosis and, rarely, to leukemia. Transformation to acute leukemia is relatively more common with PMF in comparison to other Ph-MPNs. Management of Ph-MPN mainly aims to control disease symptoms, reduce the risk of thrombotic or hemorrhagic complications, and tackle disease-related complications such as secondary myelofibrosis or transformation to leukemia. Treatment options include therapeutic phlebotomy, cytoreductive therapy, and/or targeted agents such as JAK inhibitors. Patients diagnosed with PV, ET, or primary/secondary myelofibrosis have an increased risk of mortality when compared with the general population.<sup>3</sup>

Hydroxyurea has been the conventional first-line treatment for patients with myeloproliferative neoplasms (MPNs) requiring cytoreductive therapy.<sup>4</sup> In PV, hydroxyurea is used primarily to suppress exaggerated hematopoiesis, thereby reducing the risk of thrombotic events associated with

increased blood viscosity. In ET, hydroxyurea helps to mitigate the elevated platelet count by inhibiting megakaryocytic proliferation, thereby reducing the risk of thrombotic events such as stroke or myocardial infarction. Treatment with hydroxyurea requires regular monitoring for potential side effects, including myelosuppression, nonhealing leg ulcers, and gastrointestinal disturbances. An additional concern with hydroxyurea is the risk of secondary malignancies, such as leukemia and skin carcinoma, necessitating careful consideration of its benefits and risks.

There is a lack of data from Kerala regarding the clinical profile, incidence of thrombotic events, prevalence of driver mutations, and response to therapy among MPN patients.

## METHODS

This was a single-center, retrospective observational study.

We analyzed the medical records of Ph-MPN patients above 18 years of age who were on follow-up from April 2019 to June 2023 in a tertiary care hospital in Kerala, South India. The procedures followed in the study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as

<sup>1</sup>Senior Consultant; <sup>2</sup>Clinical Pharmacist, Department of Hematology; <sup>3</sup>Assistant Quality Manager; <sup>4</sup>Senior Consultant, Department of Molecular Biology, IQRAA International Hospital and Research Center, Kozhikode, Kerala, India; \*Corresponding Author

**How to cite this article:** Prabhu RS, Nameera RS, K S, *et al.* Profile of Philadelphia Chromosome Negative (Ph<sup>-</sup>) Myeloproliferative Neoplasm with Special Emphasis on Vascular Thrombotic Events and the Response to Cytoreductive Therapy in Polycythemia Vera and Essential Thrombocythemia Patients: A Single Center Study from Kerala. *J Assoc Physicians India* 2026;74(7):24–27.

revised in 2013. The diagnosis of Ph-MPN was made according to the revised 2016 World Health Organization (WHO) classification. The main objectives were to evaluate the clinical characteristics, laboratory parameters, driver mutations (JAK2 V617F, JAK2 exon 12, CALR, and MPL mutations), therapy given, and response to therapy, especially hydroxyurea. Thrombotic events were analyzed in each subtype of Ph-MPN. Thromboembolic complications related to MPN were defined as thrombotic events that occurred up to 2 years before the MPN diagnosis or afterward. The occurrence of a thromboembolic event was recorded as the date of imaging when the event was objectively confirmed. Patients were categorized as high risk if they were above 60 years of age or had a history of a thrombotic event.

Categorical variables were represented by frequencies in numbers and rates in percentages. Continuous variables were expressed as median values and ranges.

## RESULTS

A total of 84 patients were diagnosed with Ph-MPN. Table 1 depicts their baseline characteristics. The median age was 61 years (21–85). Fifty-three patients were men (63%) and 31 were women (37%). Of the 84 patients, 48 had PV (including four with post-PV myelofibrosis), 16 had ET, 14 had PMF, and six had MPN-u.

Among the PV group, the median age of the patients was 59.5 years (21–76), with 36 (75%) men and 12 (25%) women. Forty-five (94%) PV

patients harbored the JAK2 V617F mutation, 1/48 (2%) had a JAK2 exon 12 mutation, one was negative for both mutations, and in one patient, mutations were not examined (Fig. 1). Of these, 34 (71%) patients belonged to the high-risk (HR) group and 14 (29%) patients belonged to the low-risk (LR) group. Thrombotic events at or before diagnosis were reported in 23/48 (48%) patients. Thrombotic events included cerebrovascular accident (CVA) in 12 patients, transient ischemic attack (TIA) in two patients, coronary artery disease (CAD) in five patients, deep venous thrombosis (DVT) of the lower limbs in one patient, pulmonary thromboembolism (PTE) in one patient, and digital gangrene in one patient. Portal vein and mesenteric vein thrombosis occurred simultaneously in one patient. The median hemoglobin (Hb) level was 18 gm/dL (14–22.7), the median hematocrit was 55.9% (42.5–75.9), the median white blood cell (WBC) count was 11,590/μL (5,130–34,200), and

the median platelet count was 4.34 lakhs/μL (1.2–10). One patient had covert PV, that is, blood counts were normal but JAK2 V617F positivity was detected during the evaluation of portal vein thrombosis (PVT). The median follow-up was 14.5 months. Low-risk patients were treated with low-dose aspirin and therapeutic phlebotomy to keep packed cell volume (PCV) <45%. Hydroxyurea was added to the above regimen for HR patients. Of the 23 evaluable HR patients on hydroxyurea, 20 (87%) were free from therapeutic phlebotomies by 3 months of therapy. None of the patients developed a new thrombotic event during follow-up. One patient with post-PV myelofibrosis (PV-MF) progressed to acute myeloid leukemia.

The ET group had a median age of 57.5 years (22–73), with four men (25%) and 12 women (75%). Ten patients were JAK2 V617F-positive, and six patients had a CALR mutation (Fig. 2). A total of 10/16

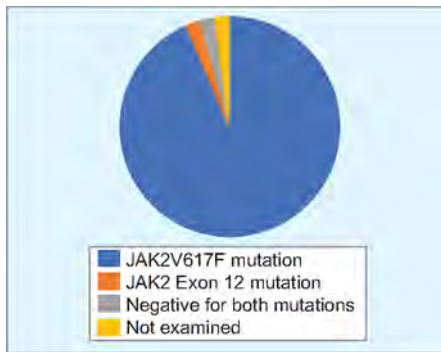


Fig. 1: Prevalence of driver mutations in PV

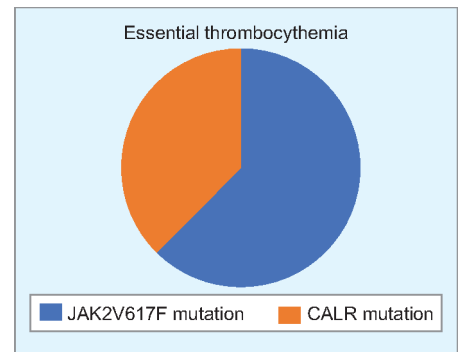
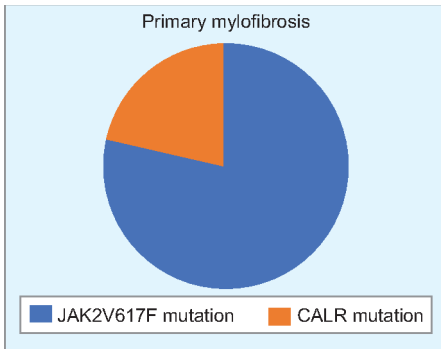


Fig. 2: Prevalence of driver mutations in ET

Table 1: Baseline characteristics of MPN patients

	MPN (n = 84)	PV (n = 48)	ET (n = 16)	PMF (n = 14)	MPNu (n = 6)
Age (years)	61 (21–85)	59.5 (21–76)	57.5 (22–73)	68 (50–78)	80.5 (53–85)
Gender	Male 53 (63%) Female 31 (37%)	Male 36 (75%) Female 12 (25%)	Male 4 (25%) Female 12 (75%)	Male 9 (64%) Female 5 (36%)	Male 4 (67%) Female 2 (33%)
Hb (gm/dL)	15.4 (6.5–22.7)	18 (14–22.7)	13 (9.9–16.3)	10.8 (6.5–16.9)	11.1 (10.5–14.9)
WBC (cells/μL)	11,245 (3,900–96,600)	11,590 (5,130–34,200)	8,335 (6,000–17,310)	12,200 (3,900–72,260)	29,055 (16,000–96,600)
Platelets (lakhs/μL)	4.88 (1.1–21.11)	4.34 (1.2–10)	8.84 (4.96–21.11)	4.15 (1.1–12.7)	5.04 (1.9–13.7)
Hematocrit (%)	47 (20.2–75.9)	55.9 (42.5–75.9)	39.6 (29.1–50.8)	34.35 (20.2–53.6)	34.95 (33.4–51.9)
Mutations					
JAK2	69 (82%)	46 (96%)	10 (62.5%)	11 (79%)	2 (33.3%)
CALR	9 (11%)	0	6 (37.5%)	3 (21%)	0
MPL	0	0	0	0	0
Triple neg	4 (5%)	1 (2%)	0	0	3 (50%)
Not done	2 (2%)	1 (2%)	0	0	1 (16.7%)
Thrombotic events	37 (44%)	23 (48%)	7 (44%)	6 (43%)	4 (67%)
Vasomotor events	17 (20%)	13 (27%)	1 (6%)	3 (21%)	0
Bleeding events	4 (5%)	3 (6%)	0	0	1 (17%)
Aquagenic pruritus	7 (8%)	6 (12.5%)	0	1 (7%)	0

CALR, calreticulin; ET, essential thrombocythemia; JAK2, Janus kinase 2; MPL, myeloproliferative leukemia virus oncogene; MPN, myeloproliferative neoplasm; MPN-u, myeloproliferative neoplasm, unclassifiable; PMF, primary myelofibrosis; PV, polycythemia vera; WBC, white blood cell



**Fig. 3:** Prevalence of driver mutations in PMF

(62.5%) patients belonged to the HR group. Seven patients (43.75%) had thrombotic events, which included five CVAs, one case of digital gangrene, and one patient with a combination of PVT and abdominal aortic thrombus with renal infarction. All patients with thrombotic events were JAK2 V617F-positive. The median platelet count at diagnosis was 8.84 lakhs/ $\mu$ L (4.96–21.11). The median follow-up was 9 months. ET patients were treated with antiplatelet agents, and hydroxyurea was added for HR patients. The median platelet count at the last follow-up for patients on hydroxyurea was 4.3 lakhs/ $\mu$ L (3.16–6.08).

The PMF group had a median age of 68 years (50–78), with nine men (64.7%) and five women (35.7%). Eleven of the 14 patients had a JAK2 V617F mutation, and three had a CALR mutation (Fig. 3). Five patients were in the prefibrotic phase. Eleven PMF patients had anemia, eight had leukocytosis, six had thrombocytosis, and one had thrombocytopenia at presentation. Six patients (42.8%) had thrombotic events, and all of them were JAK2 V617F-positive. There were two CAD events, three cases of peripheral arterial disease (one patient had a combination of CAD and peripheral arterial disease), one DVT of the lower limbs, and one PVT.

## DISCUSSION

In this observational study of Ph-MPN cases, driver mutations were assessed in all but two cases (one of which was PV and the other MPN-u). Ninety-six percent of our PV patients had driver mutations, with JAK2 V617F in 94% and JAK2 exon 12 mutation in 2%. In a study by Tefferi et al., 98% of PV patients had a driver mutation in the JAK2 gene.<sup>5</sup> The remaining patients can have noncanonical mutations in the pseudokinase domain of the JAK2 gene in exons 12–15.<sup>6</sup> We did not check for noncanonical mutations in the JAK2 gene, as sequencing for these alterations

was not easily available. Also, we tested for driver mutations by real-time polymerase chain reaction (RT-PCR) techniques and not by deep sequencing. Deep-sequencing techniques may have identified cases in which the driver mutation allele burden was low. A meta-analysis of 29 studies, which included 13,436 MPN patients from Europe, North America, Asia, and Australia, reported that the pooled prevalence of arterial or venous thrombotic events at the diagnosis of MPN was 20% [95% confidence interval (CI), 16.6–23.8%], and the pooled prevalence in PV patients was 28.6% (95% CI, 22.0–36.3%).<sup>7</sup> Contrary to this meta-analysis and another study from India,<sup>8</sup> thrombotic events were more frequent in our study, with 44% of the total Ph-MPN cohort and approximately half of our PV patients affected. Whether this higher incidence of thrombosis in MPN patients in Kerala (a small state in southern India) reflects the higher prevalence of vascular disorders secondary to the high burden of diabetes and hypertension in Kerala or a unique feature of MPN in this locality needs to be ascertained in larger population studies. Hydroxyurea was well tolerated and very effective in controlling the red blood cell (RBC) mass in our HR-PV patients; 87% of the evaluable patients did not require further therapeutic phlebotomy, and none developed a new thrombotic event while on hydroxyurea.

In the ET group, JAK2 V617F mutation was found in 63% of patients, and the remainder were CALR mutation-positive. The incidence of JAK2 V617F mutation in our ET group concurs with previous reports.<sup>9,10</sup> We did not find any MPL-mutated ET cases. Previous studies reported that ET patients with JAK2 V617F mutation have a higher risk of thrombotic events than CALR- or MPL-mutated patients.<sup>11,12</sup> In our cohort, 44% of ET patients had major thrombotic events, and all of them were positive for JAK2 V617F mutation. This incidence of thrombotic events is higher compared to a previous Mayo Clinic study, in which 22% of patients had a thrombotic event.<sup>13</sup> There is no correlation between platelet count per se and the incidence of thrombosis in ET. However, it is a known fact that good control of thrombocytosis is essential to prevent further thrombotic events in ET. HR ET patients in our study who were treated with hydroxyurea achieved good control of thrombocytosis, as evidenced by a median platelet count of 4.3 lakhs/ $\mu$ L. Resistance to hydroxyurea leads to an increased risk of transformation to myelofibrosis (MF) and acute myeloid leukemia (AML).<sup>14,15</sup> All our

patients tolerated hydroxyurea well and did not develop resistance during the follow-up period, and there were no new thrombotic events.

Among the PMF cohort in this study, JAK2 V617F and CALR mutations were found in 79 and 21% of patients, respectively. The incidence of JAK2 V617F mutation in our PMF group is higher compared to previous reports.<sup>16</sup> In this small group of PMF patients, none had MPL mutations. As was the case with ET, all PMF patients who had thrombotic events were JAK2 V617F-mutated. This concurs with the previously reported higher frequency of thrombotic events in JAK2-mutated PMF.<sup>17,18</sup> As with our other two Ph-MPN groups, the PMF cohort also had a higher incidence of thrombotic events (43%) compared with the previously reported 24% from an East Asian cohort.<sup>19</sup>

As our HR-PV patients had an excellent response to hydroxyurea, ruxolitinib was not required in our PV cohort. One patient with post-PV MF was started on ruxolitinib but rapidly progressed to AML. None of the PMF patients were treated with ruxolitinib, primarily because of the high cost of the drug, which was beyond their means. A second malignancy was seen in only one patient who had PV, which progressed to MF after 18 years and later to AML. The low rate of second malignancy in patients on hydroxyurea concurs with the previous analysis from the New Haven group of a large cohort of 2,683 MPN patients on hydroxyurea.<sup>20</sup>

To summarize, thrombotic events were seen in 48, 44, and 43% of our PV, ET, and PMF cohorts, respectively. This higher incidence of thrombosis, compared to previous studies, needs to be studied prospectively in population-based research. Consistent with previous reports, JAK2 V617F mutation remains a major determinant of thrombotic episodes in ET and PMF patients. Hydroxyurea is an efficient cytoreductive therapy in PV and ET, and none of our patients developed further thrombotic events after initiating therapy.

Our data reveal the real-life characteristics of MPN in South India. This will help research initiatives in this field, the fair allocation of limited healthcare resources, the understanding of disease trends, and disease management. Larger population studies of Ph-MPNs from developing countries such as India are required in order to enhance knowledge regarding the clinical and molecular profile of MPN. This is essential in an era of emerging targeted therapies and will help in tailoring patient-centric therapies.

## ACKNOWLEDGMENTS

The authors acknowledge their gratitude to the patients who were part of this study.

## ORCID

Raghuvveer Santhakumara Prabhu  <https://orcid.org/0000-0002-9870-6639>

## REFERENCES

- Li W. The 5th edition of the World Health Organization classification of hematolymphoid tumors. In: Li W, editor. *Leukemia* [Internet]. Brisbane (AU): Exon Publications; 2022 Oct 16. Chapter 1. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK586208/> DOI: 10.36255/exon-publications-leukemia-who-5th-edition-hematolymphoid-tumors
- Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood* 2022;140(11):1200–1228.
- Mesa R, Miller CB, Thyne M, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. *BMC Cancer* 2016;16:167.
- Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia* 2018;32(5):1057–1069.
- Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. *Blood Adv* 2016;1(1):21–30.
- Lee TS, Ma W, Zhang X, et al. Structural effects of clinically observed mutations in JAK2 exons 13-15: comparison with V617F and exon 12 mutations. *BMC Struct Biol* 2009;9:58.
- Rungjirajitranon T, Owattanapanich W, Ungprasert P, et al. A systematic review and meta-analysis of the prevalence of thrombosis and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms. *BMC Cancer* 2019;19:184.
- Singh S, Singh J, Mehta A, et al. Distinctive attributes of Indian patients with classical BCR::ABL1-negative myeloproliferative neoplasms: unified clinical and laboratory data. *Clin Lymphoma Myeloma Leuk* 2023;23(5):360–369.
- Schafer AI. Molecular basis of the diagnosis and treatment of polycythemia vera and essential thrombocythemia. *Blood* 2006;107(11):4214–4222.
- Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood* 2014;123(10):1544–1551.
- Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. *Blood* 2014;123(10):1552–1555.
- Torregrosa JM, Ferrer-Marin F, Lozano ML, et al. Impaired leucocyte activation is underlining the lower thrombotic risk of essential thrombocythaemia patients with CALR mutations as compared with those with the JAK2 mutation. *Br J Haematol* 2016;172(5):813–815.
- Gangat N, Karrar O, Al-Kali A, et al. One thousand patients with essential thrombocythemia: the Mayo Clinic experience. *Blood Cancer J* 2024;14:11.
- Harrison CN, Mead AJ, Panchal A, et al. Cross, Ruben Mesa, Mary Frances McMullin; Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. *Blood* 2017;130(17):1889–1897.
- Park YH, Lee S, Mun YC, et al. Prognostic value of modified criteria for hydroxyurea resistance or intolerance in patients with high-risk essential thrombocythemia. *Cancer Med* 2023;12:8073–8082.
- Easwar A, Siddon AJ. Genetic landscape of myeloproliferative neoplasms with an emphasis on molecular diagnostic laboratory testing. *Life (Basel)* 2021;11(1):1158.
- Tevet M, Ionescu R, Dragan C, et al. Influence of the JAK2 V617F mutation and inherited thrombophilia on the thrombotic risk among patients with myeloproliferative disorders. *Maedica (Bucur)* 2015;10(1):27–32.
- Zhang Y, Zhou Y, Wang Y, et al. Thrombosis among 1537 patients with JAK2V617F -mutated myeloproliferative neoplasms: risk factors and development of a predictive model. *Cancer Med* 2020;9(6):2096–2105.
- Kim J, Byun JM, Hong J, et al. Incidence, characteristics and risk factors of thromboembolic events in East Asian patients with BCR-ABL1 negative myeloproliferative neoplasms. *Sci Rep* 2021;11(1):17819.
- Wang R, Shallis RM, Stempel JM, et al. Second malignancies among older patients with classical myeloproliferative neoplasms treated with hydroxyurea. *Blood Adv* 2023;7(5):734–743.

# Evaluation of Presepsin as an Early Biomarker of Sepsis in Elderly Patients with Community-acquired Pneumonia



Shreya Sharma<sup>1</sup>, Anita Tahlan<sup>2\*</sup>, Monica Gupta<sup>3</sup>, Anshu Palta<sup>4</sup>, Nidhi Singla<sup>5</sup>

Received: 14 January 2025; Accepted: 04 May 2026

## ABSTRACT

Pneumonia is the most prevalent cause of sepsis. Early detection of sepsis is essential. Presepsin is an emerging biomarker. To analyze the diagnostic efficacy of presepsin for identifying sepsis and evaluate its predictive accuracy, a study was conducted for 18 months involving 100 elderly ( $\geq 60$  years) patients diagnosed with community-acquired pneumonia (CAP) and fulfilling the Systemic Inflammatory Response Syndrome (SIRS) criteria. Clinical details were recorded, and the quick Sequential Organ Failure Assessment (qSOFA) score was calculated. Presepsin values were determined and correlated with culture findings. All patients were divided into two groups: the diagnostic group (based on culture findings) and the prognostic group (based on clinical outcome). Subgroups of the diagnostic group were culture-proven and culture-sterile, and those of the prognostic group were survivors and nonsurvivors. Presepsin values were higher in culture-proven patients and nonsurvivors. Presepsin and qSOFA scores correlated positively. Presepsin can be used to predict mortality from sepsis in addition to being a superior biomarker for predicting bacteremia.

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1603

## INTRODUCTION

Pneumonia is defined as an acute infection of the respiratory system parenchyma. The types of pneumonia identified by the clinical settings in which the infection was contracted include community-acquired pneumonia (CAP), ventilator-associated pneumonia, healthcare-associated pneumonia, and hospital-acquired pneumonia.<sup>1</sup>

Community-acquired pneumonia is a pulmonary parenchymal infection in otherwise healthy individuals that is acquired from a normal environment.<sup>2</sup> The most frequent antecedent infection, pneumonia, is responsible for almost half of sepsis cases.<sup>3</sup> Globally, CAP incidence ranges from 5 to 11/1,000 population, with higher rates noted in the elderly.<sup>4</sup> The most common etiologic agents causing CAP are bacterial; however, viral and fungal agents have also been reported.<sup>5</sup>

Sepsis is a potentially fatal condition marked by organ dysfunction, most often affecting the cardiovascular, renal, respiratory, or hematological systems, as a consequence of an uncontrolled host response to infection. A significantly elevated risk of death might result from the underlying circulatory and metabolic abnormalities in septic shock, a subtype of sepsis.<sup>6</sup> Elderly patients are especially vulnerable to sepsis because their immunity is weakened due to certain underlying conditions, such as diabetes or any malignancy.<sup>7</sup>

To assist with the early detection and risk assessment of individuals suffering from sepsis and septic shock, a variety of criteria and scoring systems have been proposed. One very simple method for quickly assessing those who may be prone to sepsis is the quick Sequential Organ Failure Assessment (qSOFA) scoring system. It was designed for use in the emergency room as an immediate diagnostic tool at the bedside.<sup>8,9</sup>

The assessment of several sepsis-related biomarkers that could be employed in infection diagnosis and early detection has recently drawn interest. Procalcitonin, C-reactive protein, cytokines (IL-6), presepsin, among others, are examples of these biomarkers. With these, sepsis could be suspected even when there is not an obvious source of infection, particularly in older adults who frequently exhibit nonspecific symptoms.<sup>8</sup>

Presepsin is a soluble component of cluster of differentiation 14 (CD14) that stimulates toll-like receptor 4, initiating a proinflammatory signaling cascade that induces an inflammatory response against microbes. CD14 appears in two forms: membrane-bound (mCD14) and soluble form (sCD14). It is located in plasma and is cleaved by cathepsin D to produce a 13 kDa fragment, which is referred to as presepsin. Plasma levels of presepsin increase after bacterial infections and decrease following antibiotic treatment.<sup>10</sup>

Blood culture serves as the gold-standard diagnostic method to identify any bacterial bloodstream infection. Once the organism is identified, the antibiotic susceptibility profile can help in making therapeutic decisions.<sup>11</sup> Sputum culture aids in the microbiological diagnosis of CAP in cases where expectorated sputum is a readily available specimen.<sup>12</sup> However, the turnaround time is relatively longer compared to that of other methods, and many times the condition of the patient warrants immediate intervention.<sup>11</sup>

Biomarkers are one of the most important aspects of antibiotic stewardship programs. The assessment of presepsin's function as a biomarker in the early diagnosis of sepsis is underrepresented in the Indian scientific literature. Hence, this study aims to evaluate the role of presepsin as an early biomarker of sepsis and its correlation with blood and sputum culture in cases of CAP.

## METHODOLOGY

### Study Design and Population

At a tertiary care hospital in Chandigarh, 100 consecutive patients with a clinical diagnosis of CAP took part in an 18-month cross-sectional observational study. Every participant in this study provided written informed consent. The study was ethically approved by the Institutional Ethics Core Committee at GMCH, Chandigarh, per letter no. GMCH/IEC/2020/497R/160 dated 8<sup>th</sup> April 2021. It was carried out in compliance with the Declaration of Helsinki and the guidelines established by the Central Ethics

<sup>1</sup>Junior Resident, Department of Pathology, Government Medical College and Hospital; <sup>2</sup>Professor, Department of Pathology; <sup>3</sup>Professor, Department of General Medicine; <sup>4</sup>Professor, Department of Pathology; <sup>5</sup>Professor, Department of Microbiology, Government Medical College Hospital, Chandigarh, India; \*Corresponding Author

**How to cite this article:** Sharma S, Tahlan A, Gupta M, et al. Evaluation of Presepsin as an Early Biomarker of Sepsis in Elderly Patients with Community-acquired Pneumonia. *J Assoc Physicians India* 2026;74(7):28–31.

Committee on Human Research (CECHR) of the Indian Council of Medical Research (ICMR), New Delhi.

The study included elderly patients (aged  $\geq 60$  years) diagnosed with CAP and fulfilling the criteria for Systemic Inflammatory Response Syndrome (SIRS),<sup>13</sup> that is, the presence of two or more of the following: respiratory rate (RR)  $>20$ /minute or  $\text{PaCO}_2 < 32$  mm Hg, heart rate  $>90$ /minute, total leukocyte count  $>12 \times 10^9/\text{L}$  or  $<4 \times 10^9/\text{L}$ , or the presence of  $>10\%$  immature neutrophils, and temperature  $>38.0^\circ\text{C}$  or  $<36.0^\circ\text{C}$ . Patients with known malignancies, such as leukemia, who were undergoing radiation or chemotherapy were excluded from the study.

A comprehensive clinical examination was completed upon admission, which included recording vital parameters, namely respiratory rate, oxygen saturation, body temperature, blood pressure (BP), heart rate, etc. The three criteria that determined the qSOFA score were altered mental state (Glasgow Coma Scale  $<15$ ), systolic BP  $\leq 100$  mmHg, and RR of  $>22$  breaths per minute. One point was given for each of the three parameters, and a score of  $\geq 2$  was considered highly suggestive of sepsis.<sup>8,9</sup>

Two milliliters of blood was obtained for complete blood counts (CBC), peripheral blood film analysis, and erythrocyte sedimentation rate (ESR) estimation. Additionally, 2 mL of blood was obtained for measuring presepsin levels in serum; 10 mL of blood was obtained in two bottles (5 mL each) for culture; and a sterile container containing a sputum sample was obtained for microbiological analysis and culture before initiating any antibiotic treatment. CBC was performed using 2 mL of ethylenediaminetetraacetic acid (EDTA) blood sample and run on the Sysmex XN-1000 automated cell counter.<sup>14</sup> ESR was calculated using a 2 mL EDTA blood sample via an automated method on the VES-MATIC Cube 80.<sup>15</sup> The Human Presepsin Enzyme-Linked Immunosorbent Assay (ELISA) Kit (Cat. No. E3745Hu) from Bioassay Technology Laboratory, Shanghai, China, was used to determine presepsin levels in serum samples.<sup>16</sup>

## Outcomes

Clinical outcomes and sputum/blood culture findings were used to further subdivide these patients. Patients were tracked from the time they were admitted until discharge or death. Identifying the diagnostic accuracy of presepsin blood levels in predicting sepsis was the primary outcome. Evaluation of presepsin's predictive accuracy for mortality was a secondary outcome.

## Statistical Analysis

Mean and standard deviation were used to describe presepsin. Diagnostic accuracy was evaluated using the area under the receiver operating characteristic curve (AUROC), which comprised the test's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Presepsin was compared between bacteremia and nonbacteremia causes of CAP. Patients were tested for significance of difference using Student's *t*-test. The association between presepsin and outcomes was tested using the Chi-square test of significance. Correlation between presepsin and qSOFA score was assessed using Spearman correlation. The most recent release of Statistical Package for the Social Sciences (SPSS) was used to analyze the data.

## RESULTS

### Clinical Profile

The study participants' average age was 70.69 years. Sixty-five percent of patients were male, while 35% were female. Comorbidities and risk factors were present in 84% of the patients; diabetes mellitus accounted for 41% of these, followed by hypertension (36%), smoking (34%), and other conditions. The majority of patients had a chief complaint of fever (99%), followed by shortness of breath (97%), cough with or without expectoration (61%), and altered sensorium (23%). A qSOFA score of 3 was observed in 52% of patients, and a qSOFA score of 2 was observed in 48% of patients.

### Blood and/or Sputum Culture Findings

Blood and/or sputum cultures were positive in 41% of patients and sterile in 59% of patients. The most frequently isolated pathogens included *Klebsiella pneumoniae* and *Escherichia coli*. As illustrated in Figure 1, other isolated organisms were *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*

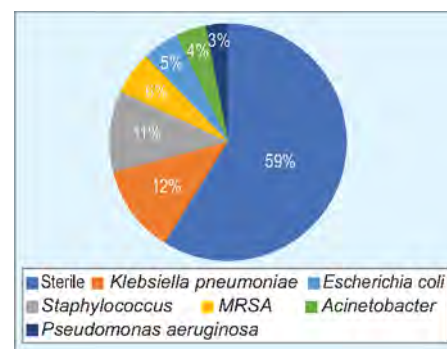


Fig. 1: Pie chart showing findings on blood and/or sputum culture of all patients

(MRSA), *Acinetobacter*, and *Pseudomonas aeruginosa*.

The whole study population was split into two groups: First, based on blood/sputum culture findings, that is, the diagnostic group; and second, based on clinical outcome, that is, the prognostic group. Under the diagnostic group, two subgroups were formed, namely, culture-proven and culture-sterile, which included 41 and 59% of patients, respectively. Under the prognostic group, two subgroups were formed, that is, survivors and nonsurvivors, which included 75 and 25% of patients, respectively. Regarding clinical profile and culture results, there were statistically insignificant differences between the subgroups of both the diagnostic and prognostic groups.

### Presepsin

The normal range of the Human Presepsin ELISA Kit derived in our study was 17.58–93.94 ng/L [mean  $\pm 2$  standard deviations (SD)]. Among all 100 patients, the values (in ng/L) ranged from 112.82 to 595.51, with a mean (SD) of 207.71 (102.01).

The two subgroups of the diagnostic group ( $p < 0.001$ ) and prognostic group ( $p = 0.017$ ) differed significantly in terms of presepsin, with the culture-proven and nonsurvivor subgroups having the highest mean presepsin values, respectively (Table 1).

### Prediction Analysis

With an area under the receiver operating characteristic curve (AUROC) of 0.995, presepsin (ng/L) had a very high ability to predict culture positivity [95% confidence interval (CI): 0.989–1]. At  $p < 0.001$ , it was statistically significant. It predicted positive culture with 100% sensitivity, 100% negative predictive value (NPV), 96% diagnostic accuracy, 93% specificity, and 91.1% positive predictive value (PPV) at a cutoff of presepsin  $\geq 176.71$  ng/L (Fig. 2).

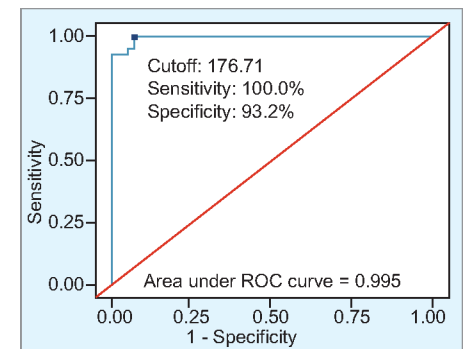
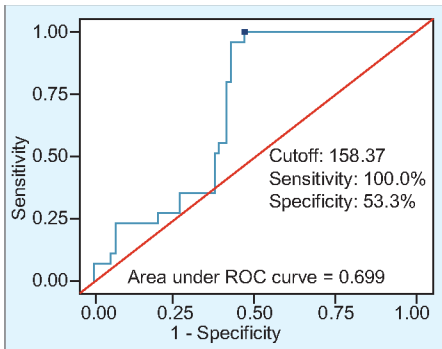
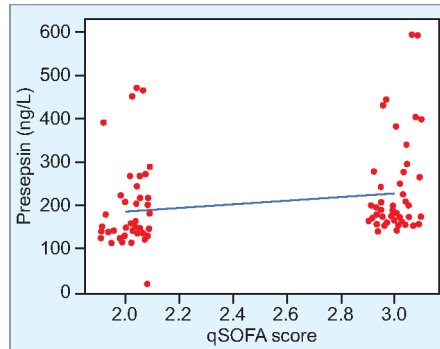


Fig. 2: ROC curve analysis showing diagnostic performance of Presepsin (ng/L) in predicting culture positivity



**Fig. 3:** ROC curve analysis showing diagnostic performance of Presepsin (ng/L) in predicting mortality



**Fig. 4:** Correlation between qSOFA Score and Presepsin (ng/L)

**Table 1:** Comparison of subgroups of Diagnostic and Prognostic groups in terms of Presepsin and their *p*-value

Group	Subgroup	Mean (SD) of presepsin	<i>p</i> -value
Diagnostic	Culture proven	291.67 (113.94)	<0.001
	Culture sterile	149.36 (19.03)	
Prognostic	Survivors	193.77 (85.57)	0.017
	Non-survivors	249.52 (133.85)	

The AUROC for presepsin (ng/L) predicting mortality was 0.699 (95% CI: 0.596–0.802), thus demonstrating poor diagnostic performance. It was statistically significant ( $p = 0.017$ ). It predicted mortality with 100% sensitivity, 100% NPV, 65% diagnostic accuracy, 53% specificity, and 41.7% PPV at a cutoff of presepsin  $\geq 158.37$  ng/L (Fig. 3).

### Correlation of Presepsin with Quick Sequential Organ Failure Assessment Score Using the Correlation Coefficient (*r*)

A moderate positive correlation between qSOFA score and presepsin (ng/L) was detected, which was statistically significant ( $\rho = 0.37, p < 0.001$ ), as shown in Figure 4.

## DISCUSSION

Sepsis is a potentially fatal condition that presents itself in a variety of clinical manifestations, making it difficult to detect and treat. The primary cause of sepsis is CAP, which results in significant mortality and morbidity.<sup>7</sup> Higher risk is noted in the elderly population because of the presence of comorbidities and atypical presentation.<sup>17</sup>

To optimize therapy and avoid subsequent consequences, early detection of sepsis is crucial. Scoring criteria, such as the qSOFA score, hematological measures, and different biomarkers, have been proposed as a result of the quest for early identification and treatment of sepsis, and these tools all contribute to more efficient management.

Presepsin is an emerging biomarker of sepsis, and its importance in the early detection of sepsis cannot be underestimated.<sup>18</sup>

The recently identified sepsis biomarker presepsin is derived from the glycoprotein CD14, which exists on the surface of macrophages and monocytes.

In its primary role, it acts as a high-affinity receptor for lipopolysaccharides (LPS), which are essentially released from the outer wall of gram-negative bacteria. There are two types of CD14: soluble CD14 (sCD14) and membrane-bound CD14 (mCD14). In healthy individuals, sCD14 levels in the blood are usually rather low. It is the LPS-CD14 complex that is released into the bloodstream when mCD14 separates from the cell membrane to generate sCD14, which aids in immune regulation. Proteases cleave sCD14 under inflammatory circumstances to produce presepsin, or soluble CD14 subtype (sCD14-ST), a 64-amino-acid N-terminal fragment. Presepsin's physiological function mostly involves the phagocytosis of bacteria and the lysosomal cleavage of different microorganisms. Presepsin levels in the blood rise in response to a microbial infection. Within 2 hours of infection, levels begin to climb and peak within 3 hours.<sup>18,19</sup>

In our study, the mean presepsin level at admission among all CAP patients was found to be 207.71 ng/L. Presepsin levels were significantly higher in the culture-proven subgroup ( $p < 0.001$ ) than in the culture-sterile subgroup. Our study suggested that, at admission, presepsin  $\geq 176.71$  ng/L significantly predicts culture positivity, that is, bacteremia. Higher presepsin levels were substantially

related to bacteremia, which is in accordance with research by Romualdo et al. and Imai et al.<sup>20,21</sup> Those who did not survive also had higher presepsin levels ( $p = 0.017$ ) than those who survived. Our study suggested that, at admission, presepsin  $\geq 158.37$  ng/L significantly predicts mortality. This is consistent with research conducted by Liu et al.; higher levels of presepsin significantly predicted mortality.<sup>22</sup>

The association between qSOFA score and presepsin was moderately positive and statistically significant ( $\rho = 0.37, p < 0.001$ ). This is consistent with research conducted by Ozkan et al.<sup>23</sup> This correlation signifies that higher levels of presepsin and a higher qSOFA score are indicators of mortality risk.

## CONCLUSION

This research concludes that presepsin is an important tool for detecting sepsis in elderly CAP patients. Greater presepsin concentrations at admission can accurately predict bacteremia and mortality risk, thereby assisting in risk stratification and prompt care. The current study's limited sample size constituted a major limitation. Thus, further investigation is required to evaluate the function of presepsin.

## ORCID

Shreya Sharma <https://orcid.org/0009-0000-1131-1734>

Anita Tahlan <https://orcid.org/0000-0003-4148-8121>

Monica Gupta <https://orcid.org/0000-0002-3992-1013>

Nidhi Singla <https://orcid.org/0000-0001-7108-8861>

## REFERENCES

- Mandell LA, Niederman MS. Pneumonia. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, editors. *Harrison's Principles of Internal Medicine*. 21st ed. New York: McGraw-Hill; 2022. pp. 1009–1020.
- Husain AN. The lung. In: Kumar V, Abbas AK, Aster JC, editors. *Robbins and Cotran Pathologic Basis of Disease*. 10th ed. Philadelphia (PA): Elsevier Health Sciences; 2020. pp. 705–714.
- Gu X, Zhou F, Wang Y, et al. Respiratory viral sepsis: epidemiology, pathophysiology, diagnosis and treatment. *Eur Respir Rev* 2020;26:1–12.
- Para RA, Fomda BA, Jan RA, et al. Microbial etiology in hospitalized North Indian adults with community-acquired pneumonia. *Lung India* 2018;35:108–115.
- Prasad P, Bhat S. Clinicomicrobiological study of community-acquired pneumonia. *Lung India* 2017;34:491–492.
- Brant EB, Seymour CW, Angus DC. Sepsis and septic shock. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, editors. *Harrison's Principles of Internal Medicine*. 21st ed. New York: McGraw-Hill; 2022. pp. 2241–2249.
- Quinton LJ, Walkey AJ, Mizgerd JP. Integrative physiology of pneumonia. *Physiol Rev* 2018;98:1417–1464.

8. Huang M, Cai S, Su J. The pathogenesis of sepsis and potential therapeutic targets. *Int J Mol Sci* 2019;20:1–31.
9. Baig MA, Sheikh S, Hussain E, et al. Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic shock patients in the emergency department of a low middle income country. *Turk J Emerg Med* 2018;18:148–151.
10. Galliera E, Massaccesi L, de Vecchi E, et al. Clinical application of presepsin as diagnostic biomarker of infection: overview and updates. *Clin Chem Lab Med* 2019;58:11–17.
11. Opota O, Croxatto A, Prod'hom G, et al. Blood culture-based diagnosis of bacteraemia: state of the art. *Clin Microbiol Infect* 2015;21:313–322.
12. Saukkoriipi A, Palmu AA, Jokinen J. Culture of all sputum samples irrespective of quality adds value to the diagnosis of pneumococcal community-acquired pneumonia in the elderly. *Eur J Clin Microbiol Infect Dis* 2019;38:1249–1254.
13. Ceccato A, Torres A. Sepsis and community-acquired pneumonia. *Ann Res Hosp* 2018;2:1–8.
14. Fleming C, Brouwer R, Lindemans J, et al. Validation of the body fluid module on the new Sysmex XN-1000 for counting blood cells in cerebrospinal fluid and other body fluids. *Clin Chem Lab Med* 2012;50:1791–1798.
15. Cerutti H, Muzzi C, Leoncini R, et al. Erythrocyte sedimentation rate measurement by VES Matic Cube 80 in relation to inflammation plasma proteins. *J Clin Lab Anal* 2011;25:198–202.
16. Farag SM, Nasr RA, El Sheikh NG, et al. Presepsin as a predictive indicator of severity in coronavirus disease-2019 (COVID-19). *Nov Res Microbiol J* 2021;5:1325–1337.
17. Fung HB, Monteagudo-Chu MO. Community-acquired pneumonia in the elderly. *Am J Geriatr Pharmacother* 2010;8:47–62.
18. Kim MH, Choi JH. An update on sepsis biomarkers. *Infect Chemother* 2020;52:1–18.
19. Pizzolato E, Ulla M, Galluzzo C, et al. Role of presepsin for the evaluation of sepsis in the emergency department. *Clin Chem Lab Med* 2014;52:1395–1400.
20. Romualdo LG, Torrella PE, González MV, et al. Diagnostic accuracy of presepsin (soluble CD14 subtype) for prediction of bacteremia in patients with systemic inflammatory response syndrome in the emergency department. *Clin Biochem* 2014;47:505–508.
21. Imai Y, Taniguchi K, Iida R, et al. Diagnostic accuracy of presepsin in predicting bacteraemia in elderly patients admitted to the emergency department: prospective study in Japan. *BMJ Open* 2019;9:1–4.
22. Liu B, Chen YX, Yin Q, et al. Diagnostic value and prognostic evaluation of presepsin for sepsis in an emergency department. *Crit Care* 2013;17:1–12.
23. Ozkan S, Kahveci U, Hur I, et al. Prognostic importance of serum presepsin level in pneumonia focal sepsis and its relationship with other biomarkers and clinical severity scores. *Saudi Med J* 2021;42:994–1001.

# Cardiac Magnetic Resonance Imaging Study on Cardiovascular Involvement >60 Days Post COVID-19 Recovery



Nihar Mehta<sup>1\*</sup>, Tanushree Somir Banerjee<sup>2</sup>, Chandresh O Karnavat<sup>3</sup>, Rajesh M Parikh<sup>4</sup>, Ritu Kashikar<sup>5</sup>, Shraddha Sinhasan<sup>6</sup>, Shruti Tandan-Pardasani<sup>7</sup>, Susheel Bindroo<sup>8</sup>, Anand Bhabhor<sup>9</sup>, Indraneil Raut<sup>10</sup>, Nimish Shah<sup>11</sup>, Shrinivas B Desai<sup>12</sup>, Munira Kapadia<sup>13</sup>, Maherra Desai<sup>14</sup>, Aarshee Kapoor<sup>15</sup>

Received: 01 March 2026; Accepted: 08 May 2026

## ABSTRACT

**Context:** This study evaluates individuals who have recovered from coronavirus disease 2019 (COVID-19) for cardiac manifestations at least 60 days postrecovery, using cardiac magnetic resonance (CMR) imaging. Native T1, native T2, and late gadolinium enhancement (LGE) were used as parameters to detect potential cardiac pathologies.

**Aim:** To study the incidence and nature of cardiac manifestations in long COVID using CMR.

**Study design:** Prospective observational study.

**Methods:** A total of 54 COVID-19-recovered patients and 50 healthy matched controls (age- and sex-based) underwent CMR using a 3 T scanner. Pathologies were assessed through native T1 and T2 mapping and LGE imaging. Data analysis was conducted using SPSS version 23.

**Results:** Only 1 patient (1.85%) showed midmyocardial LGE in the basal and midinferior segments, along with raised native T1 and T2 values. The remaining 53 recovered patients (98.15%) revealed no LGE or elevated T1/T2 values compared to controls. Native T1 and T2 values did not significantly differ between the post-COVID participants and healthy controls. Mild concentric hypertrophy was observed in six patients, which appeared incidental and unrelated to COVID-19. None of the patients exhibited elevated troponin T levels.

**Conclusion:** In this study, CMR imaging did not find a significant increase in cardiac manifestations that may be attributed to long COVID in patients who had recovered from COVID-19 compared with uninfected controls. We believe the incidence of cardiovascular comorbidities related to long COVID syndrome is much lower in the Indian population than reported in Western literature. These findings are reassuring and may help alleviate concerns among the Indian population regarding long-term cardiovascular involvement of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

*Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1609*

## INTRODUCTION

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has infected millions of people all over the world, leading to significant morbidity and mortality. It is well established that COVID-19 is a multisystem disease, having pulmonary and extrapulmonary manifestations and adverse effects on the cardiovascular system.<sup>1</sup> Several studies have shown that COVID-19 significantly impacts cardiac function during the acute phase, with approximately 20–30% of patients affected.<sup>2,3</sup> Multiple mechanisms have been proposed, including direct myocardial infection by SARS-CoV-2 via angiotensin-converting enzyme 2 (ACE2) receptors, hemodynamic stress secondary to respiratory failure, systemic cytokine activation, and stress-induced cardiomyopathy.<sup>4–7</sup>

Evidence regarding post-COVID-19 cardiac manifestations has been conflicting,

with the prevalence of COVID-19-related cardiac pathologies varying between 1.4 and 58–78%.<sup>8–10</sup> Another aspect is the occurrence of “long COVID” syndrome. According to the Department of Health and Human Services (HHS), in association with the Centers for Disease Control and Prevention (CDC), “long COVID” refers to symptoms, signs, and conditions that persist for 4 weeks or more after SARS-CoV-2 infection. These symptoms may be multisystemic and can have a relapsing-remitting presentation. Some commonly reported cardiac problems of long COVID include chest pain, electrocardiogram (ECG) changes, postural tachycardia, new-onset arrhythmias, and conditions such as postinfectious perimyocarditis with subsequent ventricular failure, arterial wall inflammation, or microthrombosis.<sup>11</sup>

Cardiac magnetic resonance (CMR) is the benchmark for noninvasive cardiovascular imaging and is essential in characterizing myocardial tissue, quantifying volumes, and detailing the structural and dynamic functions

of the heart.<sup>9</sup> Myocardial mapping, which includes T1 and T2 mapping, is valuable in visualizing and quantifying focal or diffuse pathologies of the myocardium.<sup>10</sup> T1 values can help identify fibrosis, lipid accumulation, amyloid deposits, and iron overload,<sup>12</sup> while T2 values assist in detecting myocarditis, edema due to infarction, and other inflammatory pathologies, as well as intramyocardial hemorrhage.<sup>13,14</sup> Late gadolinium enhancement (LGE) helps differentiate viable from nonviable myocardium and is used to detect myocardial infarction and scarring. LGE occurs approximately 10–20 minutes after administering gadolinium-based contrast and results from regional differences in myocardial uptake and washout within the extracellular space, seen in conditions like myocardial injury, edema, necrosis, and fibrosis.<sup>15</sup>

Several studies evaluating the cardiac manifestations of COVID-19 have utilized CMR imaging. Given the variations in the prevalence of cardiac manifestations and to assess the incidence of cardiac involvement in the Indian population, we conducted this study to understand the long-term cardiovascular involvement of COVID-19 beyond 60 days after recovery from the infection.

<sup>1</sup>Consultant, Department of Cardiology; <sup>2,3,5,6</sup>Consultant, Department of Radiology;

<sup>4</sup>Honorary Consultant Psychiatrist & Neuropsychiatrist, Director, Medical Research, Department of Psychiatry/ Medical Research;

<sup>7</sup>Academic and Research Coordinator, Consultant, Department of Critical Care; <sup>8</sup>Head, Department of Interventional Pulmonology; <sup>9,10</sup>Additional Director, Critical Care, Department of Critical Care; <sup>11</sup>Consultant, Department of Respiratory Medicine; <sup>12</sup>Director of Imaging and Interventional Radiology, Department of Radiology; <sup>13,14</sup>Consultant, Department of Psychology; <sup>15</sup>Research Coordinator, Department of Cardiology, Jaslok Hospital & Research Centre, Mumbai, Maharashtra, India;

\*Corresponding Author

**How to cite this article:** Mehta N, Banerjee TS, Karnavat CO, et al. Cardiac Magnetic Resonance Imaging Study on Cardiovascular Involvement >60 Days Post COVID-19 Recovery. *J Assoc Physicians India* 2026;74(7):32–37.

**METHODS**

**Study Design and Participants**

This prospective observational study included patients with SARS-CoV-2 infection confirmed by a positive reverse transcription–polymerase chain reaction (RT-PCR) or rapid antigen test at least 60 days before enrollment. The study was conducted during the first and second waves of COVID-19, which included infections with the Delta variant. All patients were asymptomatic postrecovery and reported no cardiovascular issues related to their illness.

**Inclusion Criteria**

- Confirmed diagnosis of SARS-CoV-2 infection.
- Recovered from COVID-19 with at least 60 days postpositive test result.
- Signed informed consent to participate in the study.

**Exclusion Criteria**

- Preexisting cardiac disease, including dilated cardiomyopathy, myocarditis, severe valvular heart disease, infective endocarditis, recent acute coronary syndrome (within the last 3 months), hypertrophic or restrictive cardiomyopathy.
- Current alcohol or substance abuse.
- History of cardiotoxic chemotherapy.
- Active malignancies.
- Chronic kidney disease/end-stage renal disease [creatinine >1.5 mg/dL or

glomerular filtration rate (GFR) <50 mg/dL] or on chronic dialysis.

- Contraindications to magnetic resonance imaging (MRI) scanning.
- Pregnancy (negative pregnancy test required before enrollment for women of childbearing potential).
- Allergy to contrast agents used in MRI.
- Patients not confirmed as infected with SARS-CoV-2 by a positive rapid antigen test or RT-PCR, regardless of high-resolution computed tomography (HRCT) findings.
- Unwillingness to participate.

The study results were evaluated against age- and sex-matched adult controls not taking cardiac drugs and with normal cardiac function and volumes and no myocardial scarring (healthy controls; *n* = 50).

**Cardiac Magnetic Resonance Scanning Protocol**

Cardiac magnetic resonance was performed using a 3 T Philips Ingenia scanner with standardized protocols. For T1 mapping, apical, mid, and basal short-axis Modified Look-Locker (MOLLI) images were attained during breath-hold in expiration. T2 mapping was performed with mGRASE sequences in apical, basal, and mid short-axis slices. LGE images were acquired 10 minutes after administration of 0.2 mmol/kg body weight of gadobutrol (Gadovist; Bayer).

Cardiac function and volumes were quantified using artificial intelligence–based automated contour detection, with manual adjustments applied when necessary. T1 and T2 relaxation times were quantified in apical, mid, and basal slices using motion-corrected images. LGE interpretation was categorized as myocardial or pericardial.

Figure 1 shows representative images of native T1 and T2 mapping in apical, basal, and mid slices.

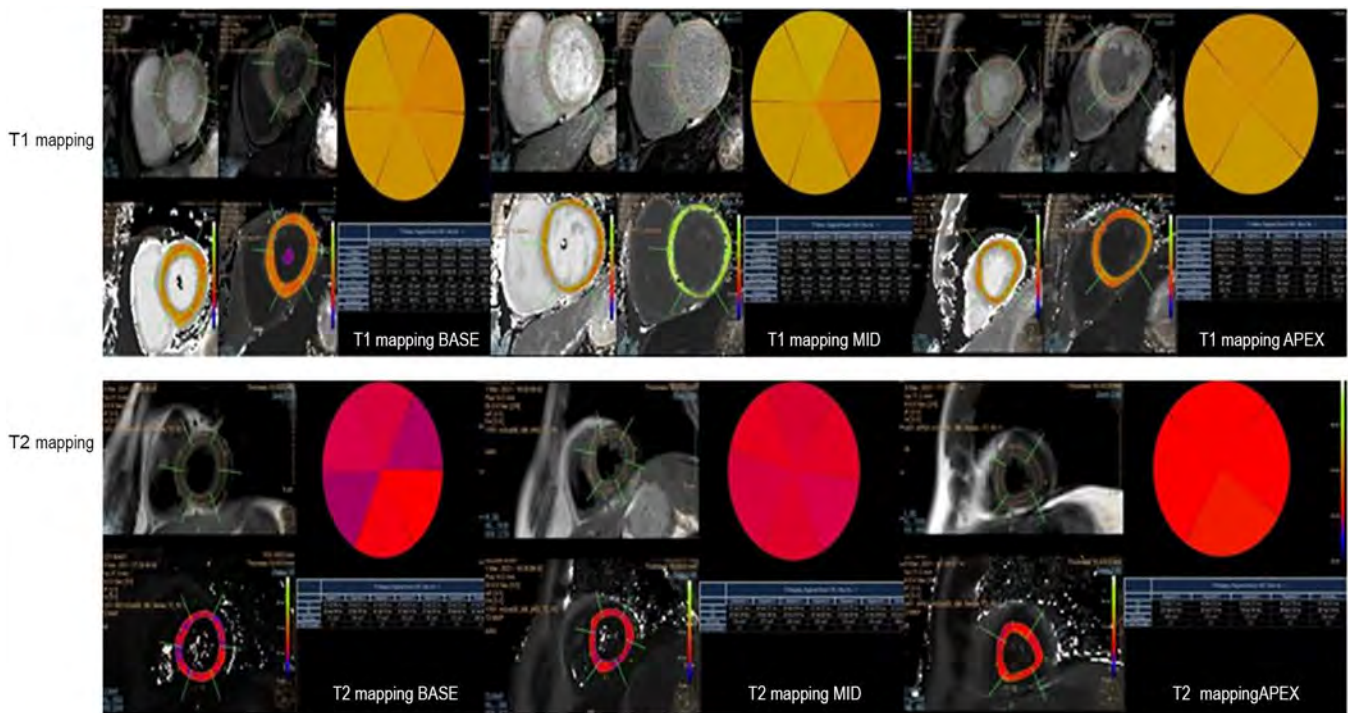
**Statistical Analysis**

Data were entered and organized in Microsoft Excel. All statistical analyses were conducted using SPSS software, version 23 (IBM Corp., Armonk, NY, USA). Continuous variables are summarized as mean ± standard deviation or as median and interquartile range (IQR), as appropriate, while categorical variables are reported as frequencies and percentages.

For two-group comparisons of continuous data, an independent-samples *t*-test was performed. Linear relationships between two continuous variables were evaluated using Pearson’s correlation coefficient for normally distributed data and Spearman’s rank correlation coefficient for nonnormally distributed data. A *p*-value < 0.05 was considered indicative of statistical significance.

**Ethical Statement**

The study protocol adhered to the Declaration of Helsinki. The protocol was approved by the



Representative images of Native T1 and T2 mapping in base, mid and apex.

**Fig. 1:** Representative T1 and T2 mapping in healthy controls

hospital's Institutional Ethics Committee before study initiation. Written informed consent was obtained from all participants. No harm was intended for the subjects. Prior to obtaining consent, the advantages and potential risks of participating in the study were discussed with the patients. Participants were not subjected to any additional costs due to the study.

**RESULTS**

**Population Characteristics**

A total of 62 recovered COVID-19 patients who completed at least 60 days after the positive COVID-19 test were recruited for the study and underwent CMR. Of these, eight patients were excluded; seven were excluded due to poor breath-hold, and one was excluded due to extensive motion artifacts caused by patient movement. The study population consisted of 54 patients who had recovered from COVID-19 and 50 healthy control participants.

**Table 1:** Distribution of the cases in terms of age (years) and gender

Age (years)	
Mean (SD)	46.35
Median (IQR)	45.5
Range	23–81
Gender	
Male	38 (70.4%)
Female	16 (29.6%)

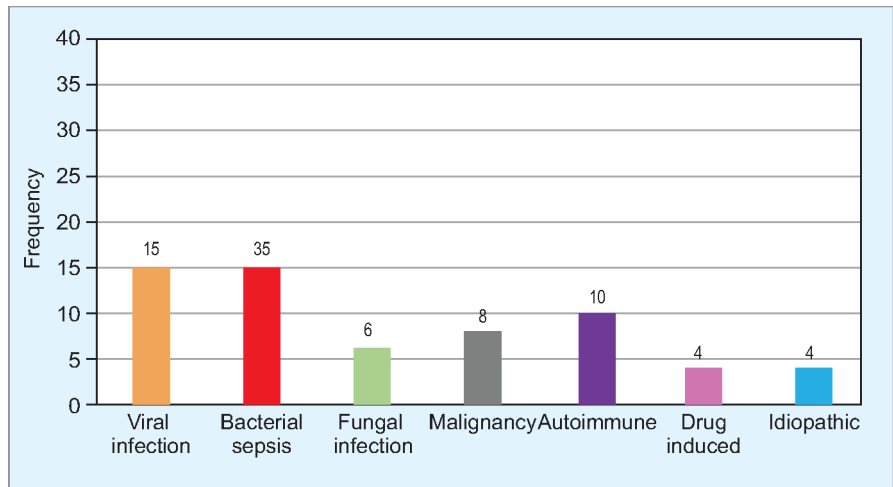
The demographic and clinical features of the patients who had recovered from COVID-19 are summarized in Table 1 and Figure 2. The COVID-19-recovered participants had a mean age of 46.35 ± 12.30 years, and 38 of them (70.4%) were male. None of the patients had documented elevated troponin T levels.

**Native T1 Values**

As summarized in Table 2, the mean native T1 values at the base, mid, and apex in COVID-19-recovered patients were 1258.81 ± 18.00, 1262.95 ± 21.03, and 1285.07 ± 30.54 ms, respectively. Among the control group patients, the mean T1 values were 1255.08 ± 39.90, 1260.91 ± 47.97, and

1293.88 ± 49.95 ms at the base, mid, and apex, respectively. Among the recovered and control individuals, the average native T1 values were 1267.99 ± 19.07 and 1269.96 ± 37.90 ms, respectively. In myocardial T1 relaxation times at the base, mid, apex, or in the average values, no statistical difference was found between the study patients and controls (W = 1425.000, p = 0.628).

Figure 3 shows the association between cases and controls with respect to native T1 values at the base, mid, apex, and average values. Elevated T1 values were noted in one patient, specifically in the midinferior segment (as compared to the highest values seen among controls).



**Fig. 2:** Age and gender demographics of study participants

**Table 2:** CMR imaging T1 and T2 values amongst post COVID-19-infected patients and controls

Variable	Group	Mean (SD)	Median (IQR)	Min–Max	Test statistic (t/W)	p-value
T1: Base average	Case	1258.81 (18.00)	1257.58 (1248.67–1270.33)	1219.17–1313.67	t = 0.606	0.546
	Control	1255.08 (39.90)	1253.2 (1242.82–1266.53)	1162.3–1281		
T1: Mid average	Case	1262.95 (21.03)	1260.5 (1245.83–1277.17)	1226.83–1334	W = 1592.000	0.116
	Control	1260.91 (47.97)	1252.5 (1235.6–1271.58)	1141.5–1314		
T1: Apex average	Case	1285.07 (30.54)	1280.75 (1260.69–1305.62)	1222.5–1337.5	W = 1248.000	0.509
	Control	1293.88 (49.95)	1287.5 (1264.08–1316.28)	1189.5–1413		
T1: Average	Case	1267.99 (19.07)	1264.81 (1252.14–1282.91)	1230.81–1312	W = 1425.000	0.628
	Control	1269.96 (37.90)	1262.9 (1243.53–1283.19)	1182.83–1379.97		
T2: Base average	Case	45.81 (1.29)	46.11 (44.81–46.81)	43.12–58.28	t = -0.551	0.584
	Control	46.05 (2.81)	45.8 (44.4–47.1)	38.8–54.1		
T2: Mid average	Case	45.97 (1.21)	45.9 (45.36–46.59)	42.74–56.1	t = -0.189	0.851
	Control	46.04 (2.24)	46.3 (44.52–47.7)	40.4–49.4		
T2: Apex average	Case	47.86 (2.17)	48.35 (46.04–49.53)	42.58–51.42	t = -4.571	<0.001*
	Control	49.98 (2.53)	50.2 (48.65–51.58)	43.3–55.4		
T2: Average	Case	46.43 (0.98)	46.54 (45.66–47.14)	44.15–48.18	t = -3.137	0.002*
	Control	47.21 (1.47)	47.37 (46.1–48.25)	44.07–50.5		

\*The T2 values among the controls were found to be higher than those in the cases; however, this finding is clinically irrelevant; t, t-test; W, Wilcoxon–Mann–Whitney U test

**Table 3:** CMR imaging LGE

LGE	Post COVID-19 patients	Healthy controls
Myocardial enhancement	1	0
Pericardial enhancement	0	0

recovered and control individuals, the average native T2 values were  $46.43 \pm 0.98$  and  $47.21 \pm 1.47$  ms, respectively. No statistically significant difference was identified between the recovered patients and controls in myocardial T2 relaxation times at the base, mid, apex, or average values. Additionally, T2 values were not elevated in cases compared to controls.

Figure 4 illustrates the association between cases and controls with respect to native T2 values at the base, mid, apex, and average values. Elevated T2 values were observed in one patient, specifically in the midinferior segment (as shown in Figure 5). No patient had myocardial hemorrhage on the scan.

**Late Gadolinium Enhancement**

LGE was noted in 1 patient as midmyocardial enhancement (as shown in Table 3 and Figure 5). In the midinferior segment, midmyocardial enhancement and raised native T1 and T2 values were noted. The patient with midmyocardial enhancement, however, did not show decreased left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), or raised troponin levels.

**Left Ventricular Ejection Fraction Analysis**

Mean (SD) of LVEF (%) was 67.41 (4.17). The median (IQR) of LVEF (%) was 67.00 (64–70.75). The LVEF (%) ranged from 60–78 (Table 4).

The distribution showed minimal skewness (0.12), indicating that it was normally distributed. The kurtosis value of  $-0.68$  was consistent with a normal distribution. A nonsignificant Shapiro–Wilk test ( $p = 0.396$ ) also suggested normally distributed data. There appeared to be only one mode/peak in the data, confirming that the data were unimodal, as represented in Figure 6.

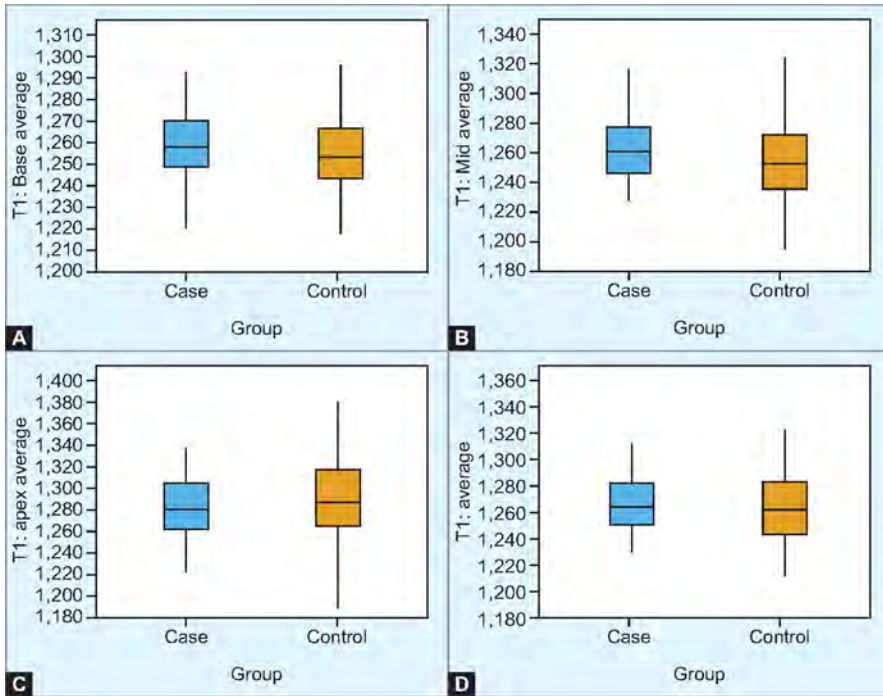
**Right Ventricular Ejection Fraction Analysis**

The mean (SD) of RVEF (%) was 52.28 (4.23). The median (IQR) of RVEF (%) was 52.00 (49–55). The RVEF (%) ranged from 45–62 (Table 5).

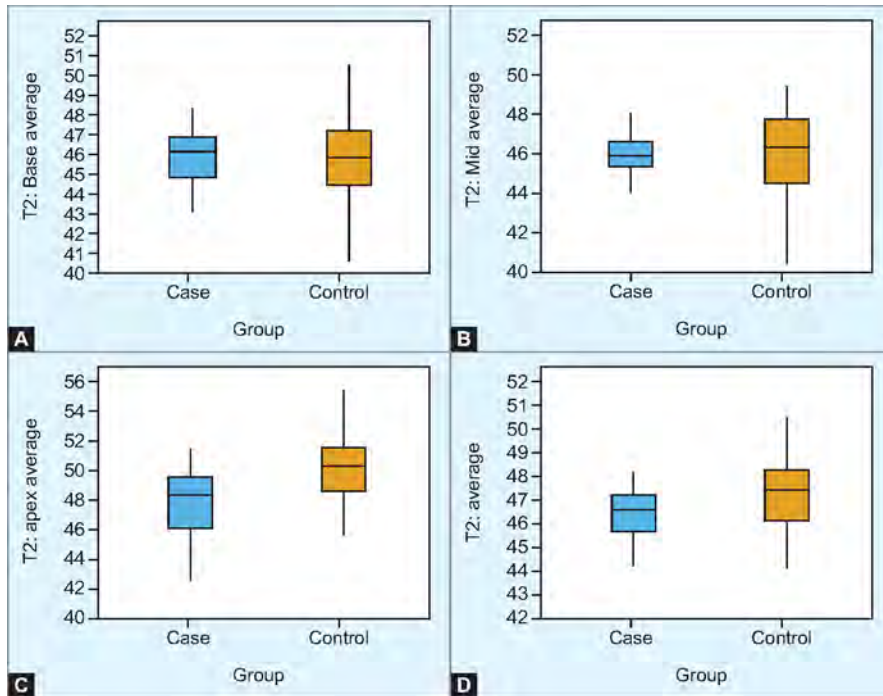
The distribution showed minimal skewness (0.27), indicating that it was normally distributed. The kurtosis value of  $-0.89$  was consistent with a normal distribution. A nonsignificant Shapiro–Wilk test ( $p = 0.141$ ) also suggested normally distributed data. There appeared to be only one mode/peak in the data, confirming that the data were unimodal, as represented in Figure 7.

**Morphological Analysis**

Six patients were found to have mild concentric hypertrophy. This appears to be an incidental finding with no obvious relation to COVID-19.



**Figs 3A to D:** Distribution of T1 values in the base, mid, apex, and T1 average in cases and controls



**Figs 4A to D:** Distribution of T2 values in the base, mid, apex, and T2 average in cases and controls

**Native T2 Values**

As shown in Table 2 the mean native T2 values at the base, mid, and apex in the COVID-19-recovered patients were  $45.81 \pm 1.29$ ,  $45.97 \pm$

$1.21$ , and  $47.86 \pm 2.17$  ms, respectively. Among controls, the mean T2 values were  $46.05 \pm 2.81$ ,  $46.04 \pm 2.24$ , and  $49.98 \pm 2.53$  ms at the base, mid, and apex, respectively. Among the

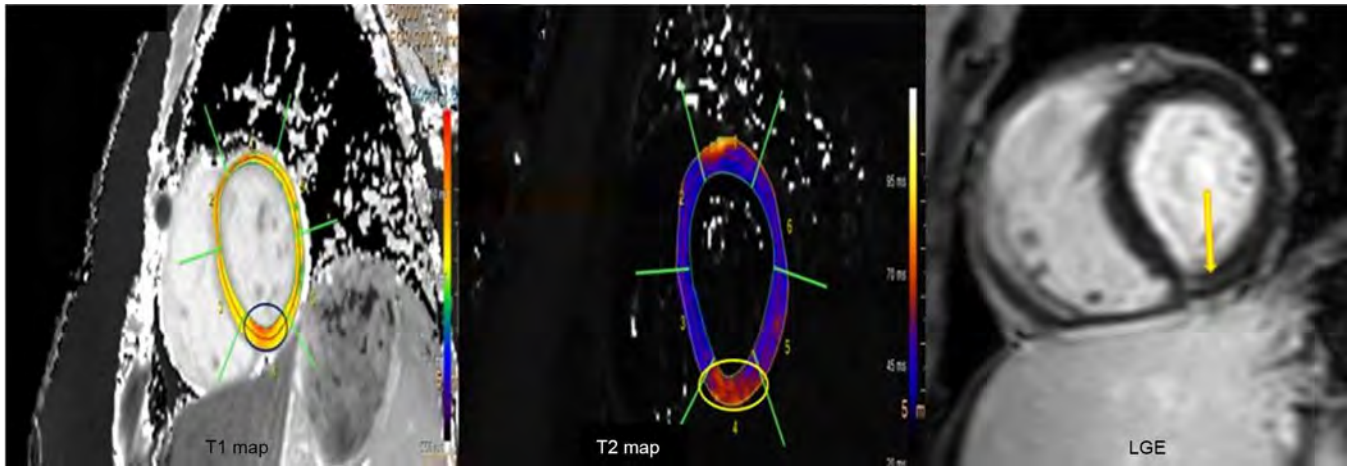


Fig. 5: Elevated midmyocardial T1 and T2 values and LGE in the basal inferior and mid inferior locations

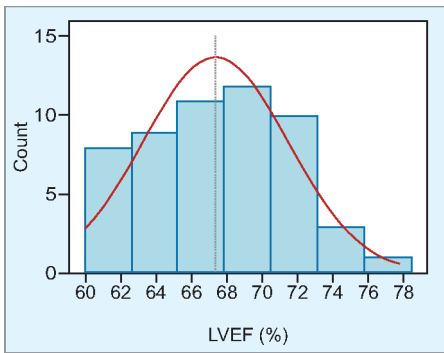


Fig. 6: Distribution of left ventricular ejection fraction (LVEF)

Table 4: Distribution of the participants in terms of LVEF (%)

LVEF (%)	
Mean (SD)	67.41 (4.17)
Median (IQR)	67 (64–70.75)
Range	60–78

Table 5: Distribution of the participants in terms of RVEF (%)

RVEF (%)	
Mean (SD)	52.28 (4.23)
Median (IQR)	52 (49–55)
Range	45–62

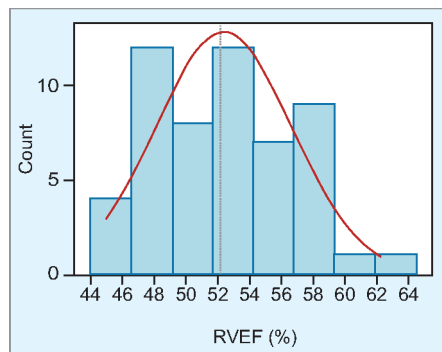


Fig. 7: Distribution of right ventricular ejection fraction (RVEF)

Patient scans included CMR imaging, with parameters such as native T1 and T2 values, LGE, left ventricular ejection fraction (LVEF), and right ventricular ejection fraction (RVEF) being studied. The primary objective was to identify myocarditis, pericarditis, and heart failure due to long COVID syndrome. In our study, myocarditis and pericarditis were rare, with only one patient (1.85%) demonstrating myocarditis (raised native T1 and T2 values and LGE) among 54 patients. Six patients had mild concentric hypertrophy, but this appeared to be incidental, with no clear clinical relationship to COVID-19.

None of the patients exhibited abnormal left or right ventricular ejection fractions suggestive of heart failure.

As mentioned previously, several studies have reported varied results pertaining to the cardiovascular effects of SARS-CoV-2 infection. Puntmann et al.<sup>10</sup> studied 100 individuals who recovered from COVID-19, with a gap of 64–92 days between COVID-19 diagnosis and CMR analysis, and found that 78 patients (78%) had abnormal CMR findings. They reported that 73% had raised native T1 values, 60% had raised T2 values, 32% had myocardial LGE, and 22% had pericardial enhancement.

They concluded that a substantial proportion of people with recent SARS-CoV-2 infection exhibited cardiac involvement, highlighting the need for investigation into long COVID cardiac consequences. Similarly, Huang et al.<sup>9</sup> found that 15 patients (58%) out of a cohort of 26 patients recovered from SARS-CoV-2 had abnormal findings on CMR, including myocardial edema, cardiac fibrosis, as well as impairment of right ventricular function.

Xie et al.<sup>16</sup> used national healthcare databases from the US Department of Veterans Affairs to study 1,53,760 individuals with COVID-19, along with control cohorts, to assess the risks and burden of cardiovascular outcomes at 1 year. They demonstrated that after the first 30 days of infection, individuals had an increased risk of cardiovascular complications, including ischemic and nonischemic heart disease, heart failure, cerebrovascular disorders, arrhythmias, pericarditis, myocarditis, as well as thromboembolic disease. Another retrospective double-cohort study consisting of symptomatic and asymptomatic COVID-19-infected patients and uninfected people concluded that both symptomatic and asymptomatic patients were at an increased risk of late cardiovascular outcomes.<sup>17</sup>

A pathological study during autopsy on COVID-19 patients' hearts identified myocyte necrosis as being caused most commonly by microthrombi, suggesting antithrombotic strategies may mitigate COVID-19's cardiac effects.<sup>18</sup> Another literature review summarized several possible mechanisms of myocardial injury following SARS-CoV-2 infection.<sup>19</sup>

Similar to our study, several others have reported that COVID-19 is not associated with an increase in the incidence of cardiovascular involvement. Breitbart et al.<sup>20</sup> found that only one patient (2%) had myocarditis and eight patients (14%)

## DISCUSSION

Cardiovascular involvement due to COVID-19 infection has been reported worldwide, with prevalence rates ranging from 1.4 to 58–78%.<sup>1–3</sup> Most studies have been dedicated to findings during the acute phase of the illness, with less research on the cardiac consequences of "long COVID." This study aimed to assess potential cardiac pathologies after 60 days of recovery from COVID-19 in individuals without preexisting cardiovascular comorbidities.

had suspicious CMR findings out of 56 post-COVID-19 infection patients. They hypothesized that myocarditis in post-COVID-19 patients was infrequent and that, among the eight patients with suspicious CMR findings, myocarditis was unlikely because left ventricular function was preserved. Tuvali et al.<sup>21</sup> analyzed data from 1,96,992 patients, with findings of myocarditis in 9 cases and pericarditis in 11 cases among COVID-19-recovered patients, with no significant difference in incidence compared to controls. Starekova et al.<sup>8</sup> reported similar results, finding myocarditis in only two (1.4%) out of 145 athletes recovering from COVID-19. Kotecha et al.<sup>22</sup> found no significant difference in the proportion of LGE or T1 and T2 abnormalities between case and control subjects. Another study found no differences in cardiac function, structure, tissue characterization, or biomarkers between COVID-19-seropositive and seronegative healthcare workers.<sup>23</sup>

Large variability in the incidence of cardiac manifestations post-COVID-19 infection is observed. Possible reasons for this variability include:

- Inconsistent use of the 2018 Lake Louise criteria for interpreting CMR findings (as noted by Breitbart et al.<sup>20</sup>).
- Preexisting cardiac disease confounding CMR findings, which our study sought to exclude.
- Raised native T2 values, which are not specific to myocarditis and may occur in other cardiac pathologies.
- Lack of controls with other viral infections.

### Limitations

This investigation was carried out at one center, with a relatively small cohort, and did not include control groups with other viral infections.

### CONCLUSION

In our study of 54 patients who had COVID-19 infection and were at least 60 days from the infection, LGE (myocarditis) was noted in only 1 patient (1.85%), who also had raised native T1 and T2 values. The remaining 53 patients (98.15%) showed no LGE or increase

in native T1 and T2 values compared to controls. Overall, our study suggests that there is no statistically significant increase in cardiac manifestations in patients who have recovered from COVID-19 compared to uninfected controls. We believe the frequency of cardiovascular comorbidities related to long COVID syndrome is much lower in the Indian population than reported in Western literature. These findings are reassuring and may help alleviate concerns among the Indian population regarding the long-term cardiovascular effects of COVID-19 infection.

### DATA AVAILABILITY

Available on reasonable request.

### FUNDING

The research was funded by Jaslok Hospital and Research Centre, Mumbai, where the research was carried out, and an approximate fund of Rupees 18,78,240 was contributed by the institute (62 patients underwent the study, of which eight were excluded, and 50 healthy controls were included).

### ORCID

Tanushree Somir Banerjee  <https://orcid.org/0009-0009-2692-3464>

### REFERENCES

1. Johnson KD, Harris C, Cain JK, et al. Pulmonary and extra-pulmonary clinical manifestations of COVID-19. *Front Med (Lausanne)* 2020;7:526.
2. Bavishi C, Bonow RO, Trivedi V, et al. Acute myocardial injury in patients hospitalized with COVID-19 infection: a review. *Prog Cardiovasc Dis* 2020.
3. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020.
4. Akhmerov A, Marban E. COVID-19 and the heart. *Circ Res* 2020;126:1443–1455.
5. Madjid M, Safavi-Naeini P, Solomon SD, et al. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol* 2020.
6. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. *Circulation* 2020;141:1648–1655.
7. Cheng R, Leedy D. COVID-19 and acute myocardial injury: the heart of the matter or an innocent bystander? *Heart* 2020.
8. Starekova J, Bluemke DA, Bradham WS, et al. Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019

with cardiac magnetic resonance imaging. *JAMA Cardiol* 2021.

9. Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-19 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging* 2020;13:2330–2339.
10. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1265–1273.
11. Gyöngyösi M, Alcaide P, Asselbergs FW, et al. Long COVID and the cardiovascular system—elucidating causes and cellular mechanisms in order to develop targeted diagnostic and therapeutic strategies: a joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial and Pericardial Diseases. *Cardiovasc Res* 2023;119(2):336–356.
12. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance—2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. *J Cardiovasc Magn Reson* 2020;22:19.
13. Captur G, Manisty C, Moon JC. Cardiac MRI evaluation of myocardial disease. *Heart* 2016;102(18):1429–1435.
14. Roller FC, Harth S, Schneider C, et al. T1, T2 mapping and extracellular volume fraction (ECV): application, value, and further perspectives in myocardial inflammation and cardiomyopathies. *Rofo* 2015;187(9):760–770.
15. Zia MI, Ghugre NR, Connelly KA, et al. Characterizing myocardial edema and hemorrhage using quantitative T2 and T2\* mapping at multiple time intervals post ST-segment elevation myocardial infarction. *Circ Cardiovasc Imaging* 2012;5(5):566–572.
16. Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;28:583–590.
17. Tereshchenko LG, Bishop A, Fisher-Campbell N, et al. Risk of cardiovascular events after COVID-19: a double-cohort study. *medRxiv* 2021.
18. Pellegrini D, Kawakami R, Guagliumi G, et al. Microthrombi as a major cause of cardiac injury in COVID-19: a pathologic study. *Circulation* 2021;143:1031–1042.
19. Rali AS, Ranka S, Shah Z, et al. Mechanisms of myocardial injury in coronavirus disease 2019. *Cardiac Fail Rev* 2020;6:e15.
20. Breitbart P, Koch A, Schmidt M, et al. Clinical and cardiac magnetic resonance findings in post-COVID patients referred for suspected myocarditis. *Clin Res Cardiol* 2021;110:1832–1840.
21. Tuvali O, Tshori S, Derazne E, et al. The incidence of myocarditis and pericarditis in post COVID-19 unvaccinated patients—a large population-based study. *J Clin Med* 2022;11(8):2219.
22. Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021;42(19):1866–1878.
23. Joy G, Artico J, Kurdi H, et al. Prospective case-control study of cardiovascular abnormalities 6 months following mild COVID-19 in healthcare workers. *J Am Coll Cardiol Img* 2021;14(11):2155–2166.

# Clinical Presentations of Different Types of Nodopathies

Laxmi Khanna<sup>1\*</sup>, Ish Anand<sup>2</sup>, Praveen Kumar<sup>3</sup>, Mandaville Gourie-Devi<sup>4</sup>

Received: 28 March 2026; Accepted: 08 May 2026



## ABSTRACT

**Background and objectives:** Nodoparanodopathies are subtypes of inflammatory polyneuropathies that differ in clinical presentation, duration, and response to intravenous immunoglobulins. Antineurofascin antibodies are detected by cell-based assays from serum or cerebrospinal fluid. The aim of our study was to describe the clinical presentation, electrophysiology, antibody assay, and response to treatment in different types of nodopathies.

**Methods:** During the last 1 year, we came across three patients with neurofascin 140/186 positivity and one patient with neurofascin 155 antibody positivity. The clinical features, electrophysiology, treatment response, and outcome were studied after obtaining informed consent from the patients.

**Results:** Both groups improved with treatment; however, patients with neurofascin 140/186 positivity were older, with proximal weakness and a good response to intravenous immunoglobulins, while the patient with neurofascin 155 positivity was younger, with cranial and respiratory involvement, gait ataxia, high cerebrospinal fluid protein, a prolonged clinical course, and an inadequate response to intravenous immunoglobulins. The interesting observation made was that both groups of patients had varying conduction blocks without temporal dispersion on nerve conduction studies, which reversed rapidly with treatment.

**Conclusion:** The spectrum of illness, electrophysiology, and treatment varied widely in affected patients. Ultimately, the outcome depended on one's clinical acumen, antibody levels, and prompt treatment, as illustrated in the patients mentioned. This patient series was small, but the results were illustrative of the complexities of the disorder and the necessity for testing for nodopathies in patients with atypical clinical presentations, a prolonged clinical course, or conduction blocks in nerve conduction studies.

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1604

388 ng/mL (normal: 0–366 ng/mL), respectively. Nerve conduction studies revealed motor demyelinating polyneuropathy with conduction block in the left radial nerve at the spiral groove, and sensory nerve conduction studies were normal in the upper and lower limbs. Electromyography revealed active denervation with neurogenic changes, more prominent in the distal and proximal muscles of all four limbs. Magnetic resonance imaging (MRI) of the cervical spine was normal. Sural nerve biopsy revealed a reduction in myelinated fibers with axonal loss. He was treated with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days with ongoing physiotherapy. 10 days later, motor power was 4/5 in all four limbs with normal deep tendon reflexes. In 1 month, he recovered from his illness and returned to work with no motor weakness. Repeat nerve conduction studies revealed normal motor and sensory conduction.

## INTRODUCTION

Nodopathies are a fascinating group of disorders involving the nodes of Ranvier. The nodes of Ranvier play a crucial role in the rapid conduction of electrical impulses in myelinated nerves. In 3% of cases of chronic inflammatory demyelinating polyradiculoneuropathy, antibodies expressed against nodal or paranodal axoglial proteins, such as neurofascin 155 immunoglobulin G4 (IgG4), neurofascin 140/186 immunoglobulin G3 (IgG3), contactin 1, or contactin-associated protein 1, lead to axolemmal dysfunction and impaired saltatory conduction with a reversible conduction block. Thus, nodopathies are variants of chronic inflammatory polyneuropathy but differ in their clinical course, electrophysiology, and response to treatment. The spectrum of nodopathies depends on the type and levels of antibodies, as illustrated in the case reports mentioned below.

## CASE DESCRIPTION

### Patient 1

A 52-year-old right-handed man, a nonsmoker, presented with a history of weakness of both hands of 6 months'

duration. He had trouble with fine motor movements, such as buttoning clothes and opening bottle caps. Two months later, there was weakness of both feet with bilateral foot drop. There were no muscle cramps, fasciculations, or stiffness. There was no history of exposure to heavy metals or toxins. On examination, there were no neurocutaneous markers or visible fasciculations. Higher mental functions and cranial nerve examination were normal. There was hypotonia of all four limbs with bilateral foot drop and wasting of the intrinsic muscles of the hands and feet. By the MRC grading, power in the wrist and finger dorsiflexors was 3/5, elbow flexors and extensors were 4/5, dorsiflexors and plantar flexors of the feet were 2/5, and knee flexors and extensors were 4/5. Superficial reflexes were present, and deep tendon reflexes were absent. There was no sensory loss, cerebellar signs, or thickened peripheral nerves. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal, and vasculitic markers, collagen markers, antiganglioside antibodies, and the myeloma panel were negative. Neurofascin 140 and 186 antibodies were elevated at 320 ng/mL (normal: 0–233 ng/mL) and

### Patient 2

A 44-year-old right-handed woman complained of pain and paresthesias with walking difficulty of 1 year's duration. She experienced a burning sensation in the hands with weakness of hand grip 6 months later. There was slowly progressive walking difficulty, loss of balance, and bilateral foot drop. Higher mental functions and cranial nerve examination were normal. Power was 4/5 in the upper limbs and 3/5 in the lower limbs by MRC grading, with hypotonia, areflexia, and bilateral flexor plantar reflexes. There was no sensory loss, cerebellar signs, thickened and palpable nerves, or neurocutaneous markers. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal, and vasculitic and collagen markers were negative. Autoimmune antibody profiling revealed

<sup>1</sup>Consultant, Department of Neurophysiology;

<sup>2</sup>Department of Neurology; <sup>3</sup>Consultant, Department of Pediatric Neurology; <sup>4</sup>Senior Consultant, Department of Neurophysiology, Sir Ganga Ram Hospital, Delhi, India;

\*Corresponding Author

**How to cite this article:** Khanna L, Anand I, Kumar P, *et al.* Clinical Presentations of Different Types of Nodopathies. *J Assoc Physicians India* 2026;74(7):38–41.

elevated levels of neurofascin 140 and 186 antibodies at 280 ng/mL (normal: 0–233 ng/mL) and 366 ng/mL (normal: 0–366 ng/mL), respectively. An immunoglobulin A (IgA) lambda band was seen in the beta region on serum protein electrophoresis, with restriction in the gamma region corresponding to IgA without excess kappa or lambda light chains on immunofixation electrophoresis. Bone marrow biopsy was cellular with trilineage hematopoiesis, 7% plasma cells, and dysmegakaryopoiesis. Nerve conduction studies revealed demyelinating motor polyradiculoneuropathy affecting the bilateral lower limbs, with conduction block in the tibial nerves at the popliteal fossa and prolonged F-wave latencies in both lower limbs. MRI of the whole spine showed contrast enhancement in the cauda equina. There was a fluorodeoxyglucose (FDG)-avid osteosclerotic lesion in the D5 vertebra on whole-body positron emission tomography-computed tomography (PET-CT) scan. Treatment was started with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days, followed by intravenous steroids at 250 gm/day for the next 5 days. She received simultaneous treatment for POEMS syndrome with lenalidomide 20 mg daily, followed by daratumumab injection. Six months later, serum protein electrophoresis revealed no monoclonal band. However, pain, paresthesias, and weakness continued with recurrent foot drop. On examination, there was areflexia, MRC grade 3/5 power in the upper limbs, 2/5 power in the right lower limb, and 1/5 power in the left lower limb. Repeat nerve conduction studies revealed a demyelinating motor polyradiculoneuropathy involving both upper and lower limbs without conduction block. Treatment was resumed with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days, followed by intravenous methylprednisolone 1 gm daily for 5 days. The patient received low-dose radiation to the D5 vertebral body and cauda equina. However, despite medication, there was no relief of symptoms; hence, intravenous rituximab was administered, following which motor power improved in all four limbs.

### Patient 3

A 42-year-old right-handed woman presented with numbness and weakness of the left hand with a fine tremor of 1 year's duration. Six months later, there was numbness and paresthesias of the right hand with weakness. Later, there was weakness of both lower limbs with tripping of the feet while walking.

Higher mental functions and cranial nerves were normal. There were no fasciculations or muscle wasting. Power was MRC grade 4/5 in the proximal muscles and 3/5 in the distal muscles of the upper and lower limbs, with impairment of touch and pain sensation in a glove-and-stocking distribution. Deep tendon reflexes were diminished, with bilateral flexor plantar responses. There were no cutaneous markers or thickened peripheral nerves. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal, and vasculitic markers, collagen markers, antiganglioside antibodies, and serum immunofixation electrophoresis were negative. Neurofascin 140 levels were 279 ng/mL (normal: 0–233 ng/mL), and neurofascin 186 levels were 489 ng/mL (normal: 0–366 ng/mL). Nerve conduction studies revealed a distal sensorimotor polyneuropathy involving all four limbs. Sural nerve biopsy revealed loss of myelinated fibers with axonopathy. MRI of the brachial plexus showed increased signal along the brachial plexus and dorsal root ganglia. She responded to treatment with intravenous immunoglobulin at 0.4 gm/kg/day, intravenous methylprednisolone 1 gm daily for 5 days, and physiotherapy.

### Patient 4

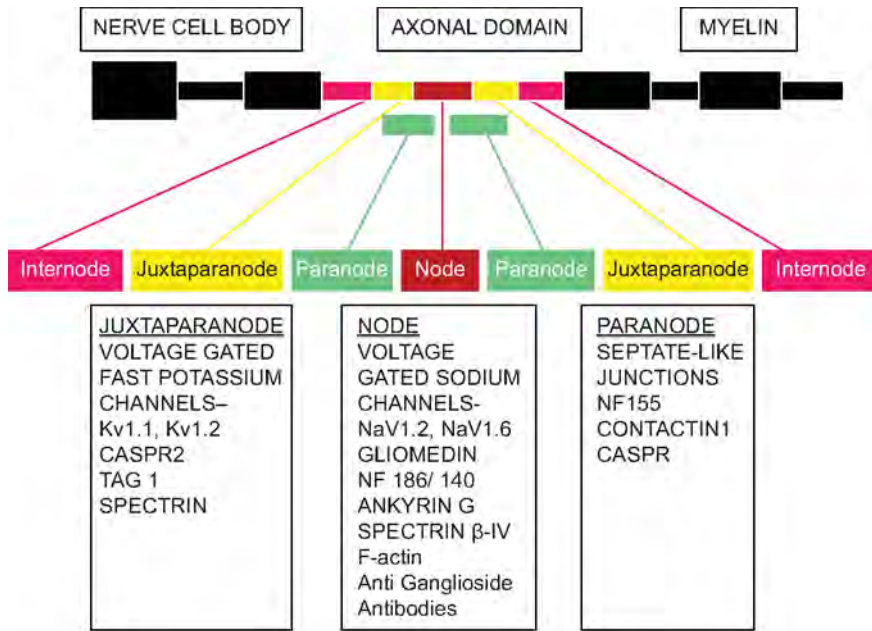
A 15-year-old right-handed boy, who had recovered from acute inflammatory polyneuropathy 1 year earlier, developed recurrent flaccid quadriparesis. Nerve conduction studies done previously revealed prolonged distal latencies, normal compound muscle action potential (CMAP) amplitudes, reduced conduction velocities with conduction block of the bilateral tibial and left peroneal nerves, persistence of F waves in the lower limbs, and normal conduction in the bilateral upper limbs. He recovered motor power after 2 months following treatment with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days and physiotherapy. During the present admission, there was MRC grade 3/5 power in all four limbs, neck and trunk weakness, and reduced respiratory excursions requiring ventilation. However, his illness progressed rapidly to bilateral total ophthalmoplegia, bulbar weakness, hypotonia, and areflexia. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal except for elevated protein levels, and vasculitic markers, collagen markers, antiganglioside antibodies including GM1 ganglioside and GQ1b, and the myeloma panel were negative. Neurofascin 155 antibodies were 129 ng/mL (normal: 0–232 ng/mL), and

repeat nerve conduction studies revealed sensorimotor axonal polyneuropathy. As he had a low Glasgow Coma Scale (GCS) score of E1M1VET, autonomic dysfunction, total ophthalmoplegia, absent brainstem reflexes, and flaccid areflexic quadriparesis, plasmapheresis and supportive treatment were started immediately, followed by intravenous immunoglobulin at 0.4 gm/kg/day for 5 days and intravenous methylprednisolone 1 gm daily for 5 days. Repeat autoimmune antibody profiling revealed decreasing levels of neurofascin 155 antibodies at 25 ng/mL (normal: 0–232 ng/mL). By 1 month, there was recovery of eye movements. With ongoing physiotherapy and occupational therapy, he made a slow recovery and was discharged from the hospital with mild gait ataxia 3 months later.

## DISCUSSION

Nodo-paranodopathies are the clinical continuum of acute or chronic immune-mediated polyneuropathies with varied presentations and positive neurofascin antibodies, as described above. Nerve conduction reports vary between reversible conduction failure and secondary axonal degeneration.<sup>1</sup>

This paper focuses on four patients with neurofascin antibody-induced polyneuropathies, of whom the first three patients were neurofascin 140/186 positive and the last patient was neurofascin 155 antibody positive. Patients with neurofascin 140/186 antibodies presented with progressive limb weakness causing limitation of daily activities. The first two patients had demyelinating motor neuropathy of all four limbs with reversible conduction block and no temporal dispersion, while the third patient had sensorimotor axonal polyneuropathy. Neurofascin 140/186 antibodies caused detachment of paranodal myelin, lengthening of nodes, disequilibrium of sodium ions, and depolarization.<sup>2</sup> This resulted in an immune-mediated attack on the nodes of Ranvier with disruption of sodium channels, causing conduction failure that reversed with therapy (Fig. 1).<sup>3</sup> Uncini coined the term nodo-paranodopathies in 2013 for diseases of the nodes of Ranvier presenting as demyelinating or axonal polyneuropathies.<sup>3</sup> Notturmo et al. reported that 62% of patients with multifocal motor neuropathy harbored anti-NF186 antibodies, while in 10%, anti-GM1 ganglioside antibodies were negative, as was observed in the first patient.<sup>4</sup> Vallat et al. described a case similar to the second patient, presenting with motor weakness, areflexia, a



**Fig. 1:** Schematic illustration showing the structure of a myelinated neuron and the different subdivisions of the axonal domain: the node of Ranvier, the paranode, the juxtaparanode, and the internode. Receptors and antibodies at the node, paranode, juxtaparanode, and internode

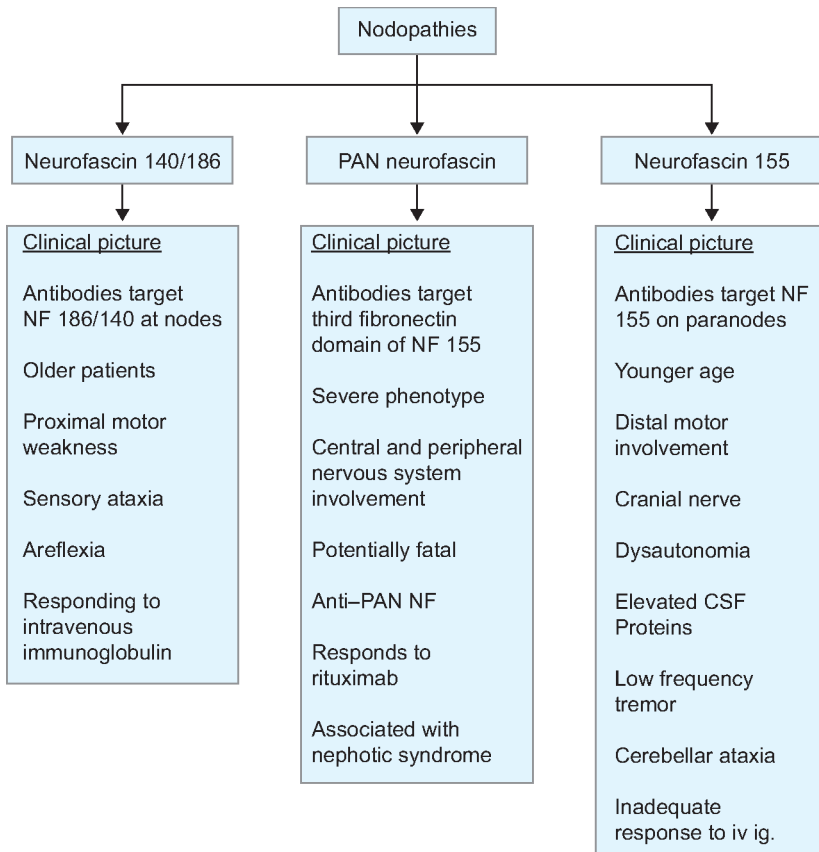
On the other hand, anti-NF155 autoimmune nodopathies differed in the clinical spectrum, as illustrated in the last case. In a case series of 40 patients with neurofascin 155 antibodies described by Aguilar et al., patients presented with distal weakness, tremor, and ataxia at a young age.<sup>6</sup> There was associated cranial nerve and respiratory involvement, elevated protein in cerebrospinal fluid, and an inadequate response to intravenous immunoglobulins.<sup>7,8</sup> Quinot et al. highlighted the occurrence of cranial nerve palsies, autonomic dysfunction, brainstem and respiratory impairment in neurofascin 155 autoimmune nodopathy, similar to the patient described.<sup>9</sup>

The juxtaparanode harbors voltage-gated fast potassium channels that prevent propagation of nodal currents to the internode (Fig. 1).<sup>10,11</sup> Caspr2 and transient axonal glycoprotein at the juxtaparanode link neurofascin 155 isoforms to septate-like junctions on the axolemma (Fig. 1).<sup>12,13</sup> Potassium channels enable repolarization of the neuronal membrane and generation of action potentials.<sup>14</sup> IgG4 antibodies react with paranodal glial neurofascin 155, resulting in malfunctioning of sodium-potassium pumps and reversible conduction failure with conduction blocks in the absence of temporal dispersion, which respond to treatment.<sup>15</sup> The clinical continuum of the different nodopathies is well illustrated through the four cases mentioned above (Fig. 2).

**CONCLUSION**

Our understanding of immune neuropathies has expanded beyond the realm of peripheral nerves to involve conduction at nodes and paranodes. The clinical manifestations caused by these antibodies are diverse and require a high index of suspicion for diagnosis. Thus, the above-mentioned cases stand apart from peripheral neuropathies because of their prolonged clinical course, reversible conduction blocks, central and peripheral nervous system involvement, and inadequate response to conventional therapy.

The lessons learned were that autoimmune nodopathies comprised 3% of inflammatory polyneuropathy cases. Neurofascin 140/186 nodopathies occurred in older patients with proximal motor weakness and areflexia, responding to intravenous immunoglobulins, steroids, and plasma exchange. In contrast, neurofascin 155 nodopathies occurred in young people with distal weakness, cranial nerve palsies, elevated cerebrospinal fluid protein levels, tremors, and ataxia, which responded to intravenous rituximab treatment. Pan-neurofascin nodopathies presented



**Fig. 2:** Schematic illustration of the three different types of nodopathies

low-grade IgA-lambda myeloma, neurofascin 140/186 positivity, and conduction block without temporal dispersion.<sup>5</sup> Secondary axonal degeneration was consequent to

complement-mediated damage at the nodes of Ranvier, proteolytic cleavage of neurofilaments, mitochondrial damage, and Wallerian degeneration.<sup>5</sup>

with central and peripheral nervous system involvement, a higher mortality rate, and a good response to rituximab treatment. This article aims to enhance clinician awareness about the diverse presentations of these rare disorders.

### Limitations of the Study

The number of cases was small, and further studies need to be conducted to validate our results. Nerve biopsies were performed in only two of four patients.

### PATIENT CONSENT

Informed consent was obtained from the patients for publication of their case reports.

### AUTHOR CONTRIBUTIONS

All authors contributed equally to the clinical cases, writing, drafting, and preparation of the manuscript.

### ORCID

Laxmi Khanna  <https://orcid.org/0000-0001-7756-2392>

### REFERENCES

1. Devaux JJ, Odaka M, Yuki N. Nodal proteins are target antigens in Guillain–Barre syndrome. *J Peripher Nerv Syst* 2012;17:62–71.
2. Uncini A, Kuwabara S. Nodopathies of the peripheral nerve: an emerging concept. *J Neurol Neurosurg Psychiatry* 2015;86:1186–1195.
3. Uncini A. Autoimmune nodo-paranodopathies 10 years later: clinical features, pathophysiology and treatment. *J Peripher Nerv Syst* 2023;28(Suppl 3):S23–S35.
4. Notturmo F, Febo TD, Yuki N, et al. Autoantibodies and gliomedin in multifocal motor neuropathy. *J Neuroimmunol* 2014;276:207–212.
5. Vallat JM, Mathis S, Magy L, et al. Subacute nodopathy with conduction blocks and anti-neurofascin 140/186 antibodies: an ultrastructural study. *Brain* 2018;141:1–4.
6. Martin-Aguilar L, Lieixa C, Pascual-Goni E, et al. Clinical and laboratory features in anti-NF 155 autoimmune nodopathy. *Neurol Neuroimmunol Neuroinflamm* 2022;9:1–9.
7. Zhang L, Zhang Y, Li R, et al. Anti neurofascin 155 antibody mediated a distinct phenotype of chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol* 2024;271:4991–5002.
8. Khadilkar SV, Kamat S, Patel R. Nodoparanodopathies: concepts, clinical implications, and management. *Ann Indian Acad Neurol* 2022;25(6):1001–1008.
9. Quinot V, Rostasy K, Hoftberger R. Antibody mediated nodo and paranodopathies. *J Clin Med* 2024;5721:1–26.
10. Fehmi J, Scherer SS, Willison HJ, et al. Nodes, paranodes and neuropathies. *J Neurol Neurosurg Psychiatry* 2018;89:61–71.
11. Querol L, Dalakas M. The discovery of autoimmune nodopathies and the impact of Ig4 antibodies in autoimmune neurology. *Neurol Neuroimmunol Neuroinflamm* 2025;12:e200365.
12. Johnson CB, Fehmi J, Rinaldi S. The immunology and neuropathology of autoimmune nodopathies. *J Neuroimmunol* 2025;406:578665.
13. Delmont E, Manso C, Querol L, et al. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain* 2017;140:1851–1858.
14. Vural A, Doppler K, Meini E. Autoantibodies against the Node of Ranvier in seropositive chronic inflammatory polyneuropathy: diagnostic, pathogenic and therapeutic relevance. *Front Immunol* 2018;9(1029):1–14.
15. Pascual-Goni E, Caballero-Avila M, Querol Luis: antibodies in autoimmune neuropathies. *Neurology* 2024;103:e209725, 1–10.

# Association of Hemoglobin–Albumin–Lymphocyte–Platelet Count (HALP) Score and Type 2 Diabetes Retinopathy



Vijay Kumar<sup>1\*</sup>, Kadiri Gururaj<sup>2</sup>, Pratibha Modi<sup>3</sup>, Sanjeev Kumar<sup>4</sup>, Anil Balivada<sup>5</sup>, Amit Raj<sup>6</sup>

Received: 25 February 2026; Accepted: 22 May 2026

## ABSTRACT

**Introduction:** Diabetic retinopathy (DR) represents a frequent microvascular consequence of type 2 diabetes mellitus (T2DM). Both inflammatory activity and nutritional status influence its development. The hemoglobin–albumin–lymphocyte–platelet (HALP) index is a composite marker that reflects these factors and has been explored in several diseases. This study assessed its association with the occurrence and severity of DR.

**Materials and methods:** We carried out a cross-sectional analysis of 150 individuals with T2DM (equal male–female distribution, mean age 58.9 ± 10.9 years). Retinal changes were graded through fundus examination. Laboratory values for calculating the HALP index were obtained. Statistical analysis included t-tests, Mann–Whitney U tests, and receiver operating characteristic (ROC) curves.

**Results:** DR was found in 43.4% of patients, predominantly in the moderate stage. The mean HALP index was 34.3 ± 36.6. Differences in HALP values between the DR and non-DR groups were not statistically significant ( $p = 0.249$ ), although lower scores tended to appear in DR. ROC analysis showed modest discriminatory power (AUC 0.555 for DR; 0.599 for moderate–severe DR). Hemoglobin was significantly higher among those with moderate–severe DR ( $p = 0.006$ ).

**Conclusion:** Although the HALP index did not independently predict DR, its downward trend in advanced stages suggests potential as part of a multifactorial risk assessment. Owing to its affordability and simplicity, the HALP index may complement existing tools for identifying patients at higher risk of vision-threatening DR.

*Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1605*

## INTRODUCTION

Diabetic retinopathy (DR) remains one of the most common microvascular complications of diabetes and is a major cause of visual disability worldwide.<sup>1</sup> Its occurrence is strongly related to disease duration, with up to three-quarters of patients eventually showing retinal involvement.<sup>1,2</sup> DR is classified into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is initially asymptomatic, presenting with microaneurysms and hemorrhages, while PDR is marked by neovascularization and carries a high risk of severe vision loss.<sup>3</sup>

Multiple factors—poor glycemic control, hypertension, dyslipidemia, and chronic hyperglycemia—contribute to diabetic eye disease progression.<sup>4</sup> Persistent hyperglycemia promotes oxidative stress, endothelial dysfunction, and accumulation of advanced glycation end products, which together compromise the blood-retinal barrier.<sup>5</sup> This environment leads to ischemia and stimulates the release of vascular endothelial growth factor (VEGF), driving pathological neovascularization.<sup>3</sup>

Inflammation also plays a central role in DR. Elevated cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha

(TNF- $\alpha$ ) are commonly observed in affected patients,<sup>6,7</sup> while leukocyte adhesion and oxidative stress further aggravate vascular occlusion and ischemia.<sup>5</sup> Platelets contribute by releasing inflammatory mediators and forming aggregates with leukocytes, worsening microvascular damage.<sup>8–10</sup>

Nutritional status also influences DR. Low albumin levels indicate both malnutrition and systemic inflammation and are linked to retinal edema and poorer outcomes.<sup>11–13</sup> Anemia, common in diabetic patients with kidney disease, exacerbates retinal hypoxia and accelerates VEGF-driven damage.<sup>14,15</sup> These factors highlight the importance of integrating nutritional and inflammatory markers in DR-related research.

## Hemoglobin–Albumin–Lymphocyte–Platelet Score: Concept, Calculation, Existing Evidences and Its Clinical Applications in Various Diseases

The hemoglobin–albumin–lymphocyte–platelet (HALP) index is a recently proposed composite biomarker designed to capture both nutritional reserve and inflammatory burden. It is calculated as:

$$\text{HALP score} = (\text{hemoglobin} \times \text{albumin} \times \text{lymphocytes}) / \text{platelets}$$

A low HALP value suggests poor nutritional status together with heightened inflammation, both of which are linked to unfavorable outcomes in various clinical conditions.<sup>16</sup> Initially developed in oncology research, it has since been applied to cardiovascular disease, acute heart failure, and ischemic stroke, where lower scores were associated with worse survival and functional recovery.<sup>6,17–19</sup>

The HALP score as a diagnostic and prognostic marker has been explored in several clinical scenarios. In hepatocellular carcinoma, a lower HALP score has been associated with poor prognosis, correlating with tumor aggressiveness and lower survival rates.<sup>17</sup> Similarly, in acute heart failure, studies have shown that the HALP score can predict short-term mortality, reflecting the combined impact of inflammation and malnutrition on cardiovascular outcomes.<sup>19</sup> In ischemic stroke, a low HALP score has been linked to worse neurological outcomes and higher mortality.<sup>6</sup>

These studies collectively suggest that the HALP score serves as an effective prognostic marker by encapsulating the interplay between systemic inflammation and nutritional status. Given the shared pathophysiological mechanisms, namely inflammation and nutritional imbalance, the HALP score may hold potential as a diagnostic and prognostic marker in DR.

Given that DR shares pathophysiological pathways with these disorders, particularly chronic inflammation and malnutrition, the HALP index may have utility in ophthalmic settings. Preliminary data suggest that patients with reduced HALP are more likely

<sup>1</sup>Additional Professor; <sup>2,3</sup>Resident; <sup>4</sup>Assistant Professor; <sup>5</sup>Junior Resident, Department of General Medicine; <sup>6</sup>Professor, Department of Ophthalmology, All India Institute of Medical Sciences, Patna, Bihar, India; \*Corresponding Author

**How to cite this article:** Kumar V, Gururaj K, Modi P, et al. Association of Hemoglobin–Albumin–Lymphocyte–Platelet Count (HALP) Score and Type 2 Diabetes Retinopathy. *J Assoc Physicians India* 2026;74(7):42–48.

to show advanced DR.<sup>16</sup> One proposed mechanism is that a low HALP score reflects an elevated inflammatory state and suboptimal nutritional status, both of which can accelerate microvascular damage in the retina. However, the evidence is not yet conclusive, and further research is needed to establish the HALP score's reliability as a biomarker for the diagnosis and severity assessment of DR.

A variety of inflammatory biomarkers have been evaluated for their association with DR. Markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and the neutrophil-to-lymphocyte ratio (NLR) have shown promise in reflecting the inflammatory milieu of diabetic patients.<sup>6,7</sup> In contrast, nutritional markers such as albumin and hemoglobin, while traditionally used to assess nutritional status, have also been linked to DR severity.<sup>12-15</sup>

The HALP score is unique because it consolidates these parameters into a single index, providing a more holistic measure of the patient's systemic state. While individual markers offer insight into specific aspects of inflammation or nutrition, the HALP score may capture the synergistic effect of these factors on retinal health. The integration of these markers into a single score simplifies clinical decision-making and could potentially facilitate early intervention in patients at high risk for DR progression.

The prevalence and progression of DR vary among different populations because of genetic, environmental, and socioeconomic factors. In Western populations, the focus has often been on the roles of glycemic control and hypertension in DR development.<sup>2</sup> However, in Asian populations, including India, additional factors such as malnutrition and differential inflammatory responses have been highlighted.<sup>4</sup>

Several studies have suggested that nutritional deficiencies and inflammatory conditions may be more pronounced in regions with limited health care resources, potentially exacerbating the risk and progression of DR.<sup>13</sup> In this context, the HALP score, reflecting both nutritional and inflammatory status, may offer a more sensitive indicator of DR risk in these populations. Moreover, the relative simplicity and cost-effectiveness of the HALP score make it an attractive option for large-scale screening in resource-constrained settings.

**Role of Lifestyle and Comorbidities in Diabetic Retinopathy**

Lifestyle factors, including diet, physical activity, and smoking, significantly impact both inflammatory and nutritional status. A diet deficient in antioxidants and essential nutrients can contribute to malnutrition

and exacerbate inflammation, thereby increasing the risk of DR.<sup>6,13</sup> Smoking, in particular, has been associated with elevated inflammatory markers and a higher risk of vascular complications in diabetic patients.<sup>20</sup>

Comorbid conditions, especially cardiovascular disease and chronic kidney disease, further complicate the relationship between diabetes and DR. These conditions are themselves associated with chronic inflammation and nutritional deficits, and they may amplify the deleterious effects of diabetes on retinal vessels. The HALP score, by reflecting these systemic changes, may also serve as an indicator of overall vascular health, linking DR to broader cardiovascular risks.<sup>18,19</sup>

**Potential Mechanisms Linking Hemoglobin–Albumin–Lymphocyte–Platelet Score Components to Diabetic Retinopathy**

The individual components of the HALP score have distinct roles in the pathophysiology of DR:

**Hemoglobin:** Anemia, frequently observed in diabetic patients, may exacerbate retinal hypoxia. Hypoxia is a potent inducer of VEGF and neovascularization, thereby contributing to the progression of DR.<sup>14,15</sup>

**Albumin:** Low albumin levels, reflecting malnutrition and elevated inflammation,

may compromise antioxidant defense mechanisms. Hypoalbuminemia has been linked to increased vascular permeability and edema in the retina.<sup>11,12</sup>

**Lymphocytes:** As key components of the immune system, lymphocytes help modulate inflammation. Reduced lymphocyte counts may indicate immunosuppression and chronic inflammation, both of which can contribute to retinal microvascular damage.<sup>20,21</sup>

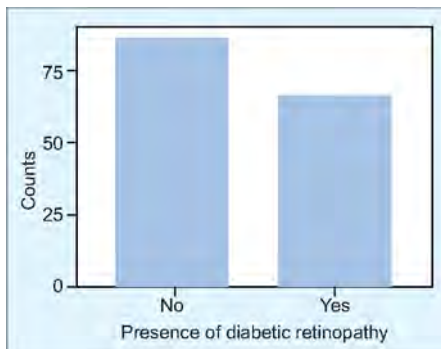
**Platelets:** Platelets are not only essential for clotting but also play an active role in inflammation. Elevated platelet counts, or dysregulated platelet function, can lead to microthrombus formation and vascular occlusion, thereby worsening retinal ischemia.<sup>8-10</sup>

Collectively, the interaction among these components may create a milieu conducive to the development and progression of DR. A low HALP score, indicating poor nutritional status and heightened inflammation, could thus serve as a surrogate marker for increased DR risk and severity.

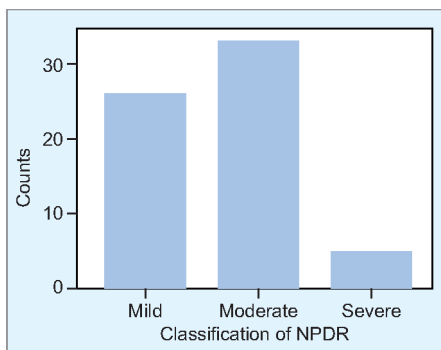
**MATERIALS AND METHODS**

**Study Design**

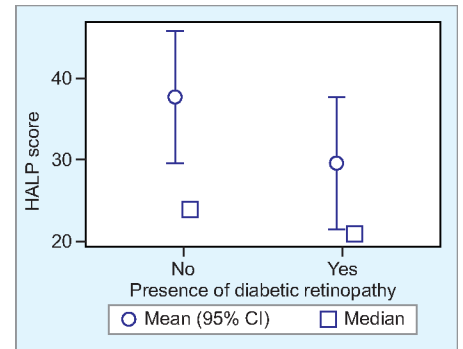
A cross-sectional analysis was conducted on 150 patients with type 2 diabetes mellitus (T2DM).



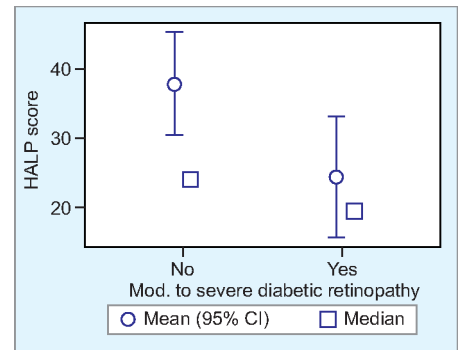
**Fig. 1:** Presence of diabetic retinopathy among study population



**Fig. 2:** Classification of non proliferative diabetic retinopathy



**Fig. 3:** Comparison of HALP score in patients with and without diabetic retinopathy



**Fig. 4:** Comparison of HALP score in patients with and without moderate to severe Diabetic retinopathy

**Participant Profile**

The sample included 75 males and 75 females, with a mean age of 58.9 years, representing a typical at-risk population for DR.

**Data Collection**

Clinical and demographic data were collected alongside laboratory measurements required to calculate the HALP score.

**Data Analysis**

Statistical tests, including Student’s *t*-tests, Mann–Whitney *U* tests, and receiver operating characteristic (ROC) curve analysis, were applied to evaluate differences between the DR and non-DR groups and to assess the HALP score’s discriminative power.

**Diabetic Retinopathy Assessment**

All participants underwent fundus examination, with grading into mild, moderate, or severe nonproliferative diabetic retinopathy (NPDR).

**Statistical Analysis**

Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] and compared using an independent *t*-test or Mann–Whitney *U* test. Categorical variables were compared using the Chi-squared test. ROC analysis assessed diagnostic performance. *p* < 0.05 was considered statistically significant.

**Ethical Approval**

Approved by the Institutional Ethics Committee; informed consent was obtained from all participants.

**RESULTS**

Out of the total study population, there were 75 males (50.0%) and 75 females (50.0%), indicating an equal gender distribution. The cumulative percentage shows that males accounted for the first 50.0% of the sample, and the inclusion of females completed the total 100% representation, as shown in Table 1. This balanced proportion minimizes

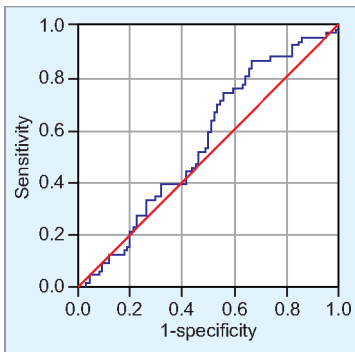
gender-related selection bias and allows for gender-based subgroup analysis, if required.

Among the study participants, 86 individuals (56.6%) did not have DR, while 66 individuals (43.4%) were diagnosed with DR. The cumulative percentage indicates that the absence of retinopathy accounted for over half of the sample (56.6%), with the inclusion of those affected bringing the total to 100%. This distribution highlights that nearly two-fifths of the study population had DR, underscoring the clinical relevance of screening and early detection in diabetic patients, as shown in Table 2.

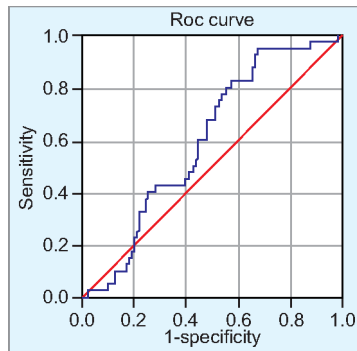
Among participants diagnosed with nonproliferative diabetic retinopathy (NPDR), 26 individuals (40.6%) had mild NPDR, 33 individuals (51.6%) had moderate NPDR, and five individuals (7.8%) had severe NPDR. The cumulative percentage shows that mild and moderate NPDR together accounted for 92.2% of cases, while severe NPDR constituted the smallest proportion (7.8%), as shown in Table 3. This distribution indicates that moderate NPDR was the most prevalent stage in the study population.

The study population had a mean age of 58.9 years (SD = 10.9), a median age of 58 years, and an IQR of 16.5 years, with age distribution approximating normality (Shapiro–Wilk *p* = 0.417). The mean hemoglobin level was 101 gm/L (SD = 70.5; IQR = 37.0), with a median of 92.5 gm/L, showing a nonnormal distribution (*p* < 0.001). Serum albumin was normally distributed (mean 32.0 gm/L, SD = 5.89; IQR = 8.18; median 32.2 gm/L; *p* = 0.379). Lymphocyte count (mean  $1.80 \times 10^9/L$ , SD = 1.36; IQR = 1.21; median  $1.39 \times 10^9/L$ ; *p* < 0.001), platelet count (mean  $209 \times 10^9/L$ , SD = 114; IQR = 111; median  $179 \times 10^9/L$ ; *p* < 0.001), and HALP score (mean 34.3, SD = 36.6; IQR = 24.6; median 22.8; *p* < 0.001) all demonstrated significant skewness, as shown in Table 4. Thus, while age and serum albumin followed a normal distribution, hemoglobin, lymphocyte count, platelet count, and HALP score were nonnormally distributed, informing the use of parametric or nonparametric statistical tests in further analyses.

Comparison of laboratory parameters between groups revealed that hemoglobin levels showed no significant difference by the independent-samples *t*-test (*p* = 0.944; mean difference = –0.81 gm/L), whereas the Mann–Whitney *U* test detected a significant difference (*p* = 0.006), with a median difference of approximately 10 gm/L, highlighting the impact of nonnormal distribution. Serum albumin levels showed no significant difference between groups on either the *t*-test (*p* = 0.956) or the Mann–Whitney *U* test (*p* = 0.950). Similarly, lymphocyte counts (*t*-test *p* = 0.321;



**Fig. 5:** ROC curve for HALP score in predicting occurrence of diabetic retinopathy (AUC -0.555)



**Fig. 6:** ROC curve for HALP score in predicting moderate to severe diabetic retinopathy (AUC-0.599)

**Table 1:** Distribution of gender among study participants

Frequencies of gender			
Gender	Counts	% of total	Cumulative %
Male	75	50.0%	50.0%
Female	75	50.0%	100.0%

**Table 2:** Presence of DR among study participants

Presence of DR	Counts	% of total	Cumulative %
No	86	56.6%	56.6%
Yes	66	43.4%	100.0%

**Table 3:** Classification of nonproliferative diabetic retinopathy (NPDR)

Classification of NPDR	Counts	% of total	Cumulative %
Mild	26	40.6%	40.6%
Moderate	33	51.6%	92.2%
Severe	5	7.8%	100.0%

**Table 4:** Descriptive statistics of study variables

	Age (years)	Hb (gm/L)	Albumin (gm/L)	Lymphocyte count (cells × 10 <sup>9</sup> /L)	Platelet count (cells × 10 <sup>9</sup> /L)	HALP score
Mean	58.9	101	32.0	1.80	209	34.3
Median	58	92.5	32.2	1.39	179	22.8
Standard deviation	10.9	70.5	5.89	1.36	114	36.6
IQR	16.5	37.0	8.18	1.21	111	24.6
Shapiro–Wilk <i>p</i>	0.417	<0.001	0.379	<0.001	<0.001	<0.001

**Table 5:** Comparison of study variables between groups

		Statistic	<i>p</i>	Mean difference
Hb	Student’s <i>t</i>	−0.0700	0.944	−0.8101
	Mann–Whitney <i>U</i>	2,095	0.006	10.0000
Albumin	Student’s <i>t</i>	0.0556	0.956	0.0540
	Mann–Whitney <i>U</i>	2,755	0.950	0.0999
Lymphocyte count	Student’s <i>t</i>	0.9964	0.321	0.2227
	Mann–Whitney <i>U</i>	2,626	0.503	0.0929
Platelet count	Student’s <i>t</i>	0.2463	0.806	4.5994
	Mann–Whitney <i>U</i>	2,680	0.558	−8.0001
HALP score	Student’s <i>t</i>	1.3571	0.177	8.1442
	Mann–Whitney <i>U</i>	2,467	0.249	3.1580

**Table 6:** Comparison of study variables by presence of DR

	Presence of DR	Mean	Median	SD
Hb	No	100.52	99.50	23.75
	Yes	101.33	87.00	103.90
Albumin	No	32.05	31.20	6.47
	Yes	31.99	32.55	5.10
Lymphocyte count	No	1.90	1.44	1.54
	Yes	1.67	1.33	1.09
Platelet count	No	211.37	173.50	127.14
	Yes	206.77	186.00	94.34
HALP score	No	37.85	23.64	38.40
	Yes	29.70	20.41	33.88

**Table 7:** Comparison of study variables by presence of moderate to severe DR

	Moderate to severe DR	Mean	Median	SD
Hb	No	98.70	95.50	22.92
	Yes	106.97	82.50	132.945
Albumin	No	32.17	32.05	6.23
	Yes	31.62	32.20	4.853
Lymphocyte count	No	1.93	1.49	1.48
	Yes	1.43	1.18	0.894
Platelet count	No	213.46	178.50	123.17
	Yes	197.95	179.00	81.987
HALP score	No	37.83	24.37	38.77
	Yes	24.47	19.50	27.914

Mann–Whitney *U* test *p* = 0.503), platelet counts (*t*-test *p* = 0.806; Mann–Whitney *U* test *p* = 0.558), and HALP score (*t*-test *p* = 0.177; Mann–Whitney *U* test *p* = 0.249) did not differ significantly between groups, as shown in Table 5. Overall, only hemoglobin demonstrated a significant

intergroup difference when evaluated with a nonparametric test, suggesting that skewed data distribution may have obscured differences in parametric testing.

Participants without DR had a mean hemoglobin level of 100.52 gm/L (median

99.50; SD = 23.75), whereas those with DR had a mean of 101.33 gm/L (median 87.00; SD = 103.90), reflecting substantial variability in the DR group. Serum albumin levels were nearly identical between groups (32.05 gm/L without DR vs 31.99 gm/L with DR), with minimal median difference. Lymphocyte counts were slightly higher in the no-DR group (1.90 × 10<sup>9</sup>/L) compared to the DR group (1.67 × 10<sup>9</sup>/L). Similarly, platelet counts were marginally higher in participants without DR (211.37 × 10<sup>9</sup>/L) versus those with DR (206.77 × 10<sup>9</sup>/L), with comparable medians. Notably, the HALP score was higher among participants without DR (mean 37.85) than among those with DR (mean 29.70), suggesting a potential link between lower HALP scores and the presence of DR, as shown in Table 6. Overall, these descriptive findings indicate that reduced lymphocyte counts, platelet counts, and HALP scores may be associated with DR, warranting further confirmation through formal statistical testing.

Participants without moderate-to-severe DR had a mean hemoglobin level of 98.70 gm/L (median 95.50; SD = 22.92), whereas those with moderate-to-severe DR had a higher mean of 106.97 gm/L (median 82.50; SD = 132.95), reflecting marked variability in the latter group. Serum albumin levels were comparable between groups (32.17 vs 31.62 gm/L). Lymphocyte counts were higher in the no-DR group (1.93 × 10<sup>9</sup>/L) compared to the moderate-to-severe DR group (1.43 × 10<sup>9</sup>/L), suggesting a trend toward lymphopenia with increasing DR severity. Platelet counts were also slightly higher in the no-DR group (213.46 × 10<sup>9</sup>/L) compared to the moderate-to-severe DR group (197.95 × 10<sup>9</sup>/L). The HALP score was notably greater among participants without moderate-to-severe DR (mean 37.83) than among those with moderate-to-severe DR (mean 24.47), indicating a potential association between lower HALP scores and greater DR severity, as shown in Table 7. Overall, these descriptive trends suggest that reduced lymphocyte counts, platelet counts, and HALP scores may be linked to the progression of DR, although statistical validation is needed to establish significance.

**Table 8:** ROC curve analysis of HALP score for presence of DR

Area under the curve				
Test result variable(s): HALP score and presence of DR				
Area	Standard error <sup>a</sup>	Asymptotic significance <sup>b</sup>	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.555	0.047	0.248	0.463	0.647

<sup>a</sup>Under the nonparametric assumption; <sup>b</sup>Null hypothesis: true area = 0.5

**Table 9:** ROC curve analysis of HALP score for predicting moderate to severe DR

Area under the curve				
Test result variable(s): HALP score and moderate to severe DR				
Area	Standard error <sup>a</sup>	Asymptotic significance <sup>b</sup>	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.599	0.048	0.065	0.505	0.692

<sup>a</sup>Under the nonparametric assumption; <sup>b</sup>Null hypothesis: true area = 0.5

The area under the ROC curve (AUC) for the HALP score in predicting the presence of DR was 0.555 (SE = 0.047; 95% CI: 0.463–0.647), which was not statistically significant ( $p = 0.248$ ), as shown in Table 8. This indicates that the HALP score had only a slightly better-than-chance ability to discriminate between participants with and without DR, and the result was not statistically significant.

The area under the ROC curve (AUC) for the HALP score in predicting moderate-to-severe DR was 0.599 (SE = 0.048; 95% CI: 0.505–0.692), with a  $p$ -value of 0.065, as shown in Table 9. Although the AUC indicates a modest discriminatory ability, the result did not reach statistical significance at the 0.05 threshold, suggesting that while the HALP score may have some predictive value for more advanced stages of DR, its performance in this study was limited.

## DISCUSSION

The study comprised 150 patients with equal gender distribution (75 males and 75 females) and a mean age of  $58.9 \pm 10.9$  years. This demographic profile aligns with existing epidemiological data indicating that middle-aged and older adults are predominantly affected by DR.<sup>1,22,23</sup> Given the established link between prolonged diabetes duration and microvascular complications, our sample represents a typical at-risk population.

DR was present in 43.4% of participants, with 40.6% having mild nonproliferative diabetic retinopathy (NPDR), 51.6% moderate NPDR, and 7.8% severe NPDR. The proportion of moderate-to-severe DR cases (26.3%) is consistent with prior studies, which suggest that approximately 75% of long-term diabetes patients develop some form of DR.<sup>1,2,22</sup> These findings reinforce the necessity for early

detection strategies, as progression from mild to severe NPDR is well documented in DR pathogenesis.<sup>3</sup> The distribution of DR severity also provides an opportunity to evaluate how biochemical markers, such as the HALP score, correlate with disease progression.

The HALP score, calculated as  $HGB \times ALB \times LYM / PLT$ , exhibited significant variability, with a mean of  $34.3 \pm 36.6$ , and exhibited a nonnormal distribution (Shapiro–Wilk test,  $p < 0.001$ ). This heterogeneity reflects the diverse metabolic and inflammatory states among patients with T2DM.<sup>16</sup> Although hemoglobin levels showed no significant difference between the DR and non-DR groups ( $p = 0.944$ ), they were significantly elevated in patients with moderate-to-severe DR compared to those with milder forms ( $p = 0.007$ , Mann–Whitney  $U$  test). Previous studies have linked altered hemoglobin levels with DR severity, suggesting that elevated hemoglobin may reflect a compensatory response to chronic retinal hypoxia.<sup>14</sup>

Albumin, lymphocyte count, and platelet count did not differ significantly between the DR and non-DR groups. However, the HALP score demonstrated a trend toward lower values in more severe DR, although this did not achieve statistical significance ( $p = 0.065$ ). ROC analysis showed an area under the curve (AUC) of 0.555 ( $p = 0.248$ ) for overall DR detection but increased to 0.599 ( $p = 0.065$ ) for moderate-to-severe DR. While these AUC values indicate limited discriminative power, they suggest that the HALP score might be more relevant for identifying advanced DR stages.

The HALP score integrates parameters linked to inflammation and nutritional status. Albumin, known for its anti-inflammatory properties, has been associated with retinal vascular permeability, making it a relevant

biomarker for DR severity.<sup>11,12</sup> Studies have also demonstrated that low serum albumin correlates with higher DR risk, further supporting its inclusion in composite indices.<sup>13</sup>

Lymphocyte count, reflective of immune function, plays a role in chronic inflammation, which is a key driver of DR pathogenesis.<sup>20,21</sup> Platelets, beyond their role in hemostasis, contribute to inflammatory cascades and microvascular dysfunction, exacerbating ischemic damage in the retina.<sup>8–10</sup> Given that the HALP score captures these parameters collectively, its association with DR severity aligns with research on inflammatory and nutritional markers in diabetic complications.

Although the HALP score alone did not emerge as a strong predictor of DR presence, its association with moderate-to-severe DR suggests a potential role in risk stratification. The relatively low AUC for overall DR detection (0.555) indicates limited predictive power in isolation; however, the trend seen in moderate-to-severe DR (AUC = 0.599) suggests possible clinical relevance when combined with other risk factors such as glycemic control and blood pressure.<sup>6,17–19</sup>

The observed increase in hemoglobin levels in moderate-to-severe DR cases can be interpreted in light of retinal hypoxia and compensatory mechanisms.<sup>5</sup> Elevated hemoglobin may lead to increased blood viscosity and vascular compromise, contributing to DR progression. This interplay underscores the multifactorial nature of DR, highlighting the need for composite indices such as the HALP score rather than reliance on single biomarkers.

Our findings align with existing research that has explored individual HALP score components in DR and other inflammatory conditions. Previous studies have reported that reduced albumin levels and altered

hemoglobin concentrations correlate with DR progression.<sup>12-15</sup> Moreover, research on HALP in cardiovascular and metabolic diseases suggests that it may serve as a prognostic indicator in conditions involving chronic inflammation and nutritional deficits.<sup>6,17-20</sup>

Although previous studies have highlighted the HALP score's prognostic value across various conditions such as acute ischemic stroke and cancer, its role in DR remains underexplored. The current study contributes to this growing body of evidence by demonstrating that, although the HALP score is not a strong independent predictor of DR presence, its association with disease severity warrants further investigation.

The results align with prior studies linking decreased albumin levels and altered hemoglobin concentrations with DR progression. The integrated approach of using the HALP score is supported by research emphasizing the prognostic value of composite biomarkers in diseases involving both inflammatory and nutritional imbalances. Although the HALP score was not a statistically robust independent predictor in this study, its potential to identify more severe DR cases merits further investigation.

Several biological mechanisms may underpin the relationship between a low HALP score and the severity of DR. First, a low hemoglobin level can result in retinal hypoxia, which is a well-known stimulus for the overproduction of VEGF, thereby promoting neovascularization and worsening DR.<sup>14</sup> Second, hypoalbuminemia, often indicative of both malnutrition and a heightened inflammatory state, can impair blood-retina barrier integrity, resulting in edema and exudation. Third, a decreased lymphocyte count may reflect an impaired immune response, resulting in persistent low-grade inflammation that further damages the retinal microvasculature. Finally, platelets are known to be involved in inflammatory processes and may contribute to microvascular occlusion when their function is altered.<sup>8-10</sup> Taken together, these findings indicate that the HALP score effectively reflects key nutritional and inflammatory parameters that contribute to the development and progression of DR.

## SUMMARY

This study examined the relationship between the HALP score and DR in individuals with T2DM. Findings revealed that, although the HALP score did not significantly distinguish between DR and non-DR patients overall, trends were observed that suggest its potential utility in identifying patients with moderate-

to-severe DR. Specifically, although the HALP score's area under the ROC curve (AUC) for predicting the presence of DR was only 0.555 ( $p = 0.248$ ), its AUC for moderate-to-severe DR was 0.599 ( $p = 0.065$ ), indicating that the score may have better discriminative power for more advanced disease stages. Additionally, hemoglobin levels were significantly elevated in the moderate-to-severe DR subgroup, further highlighting the complex interplay between nutritional status and DR severity.

The findings of our study are in line with previous research that has emphasized the role of inflammatory and nutritional markers in the progression of DR. Several studies have identified lower levels of albumin and hemoglobin as being associated with more severe forms of DR.<sup>12</sup> Our observation that a lower HALP score trends toward an association with moderate-to-severe DR supports the hypothesis that systemic inflammation and malnutrition are key contributors to retinal microvascular damage.

While the overall HALP score did not significantly distinguish between the DR and non-DR groups, this could be attributed to the multifactorial nature of DR, where other variables such as glycemic control, duration of diabetes, and blood pressure may play critical roles. The relatively modest AUC values suggest that the HALP score, when used in isolation, may not be sufficient as a stand-alone diagnostic tool. However, it could be highly valuable as part of a composite panel of biomarkers for DR risk stratification, particularly in resource-limited settings where more expensive tests are not feasible.

## CONCLUSION

The potential clinical implications of our findings are significant. Given the simplicity and cost-effectiveness of calculating the HALP score using routinely available laboratory parameters, it may serve as a practical tool for early DR screening and risk stratification, especially in primary care and resource-limited environments. Integrating the HALP score into routine diabetic assessments could allow clinicians to identify patients at higher risk of progressing to moderate or severe DR, thereby facilitating timely referrals for ophthalmologic evaluation and intervention.

Moreover, the HALP score could be particularly useful when combined with other clinical parameters such as glycemic control [glycated hemoglobin (HbA1c)], blood pressure, and lipid profiles. Such an integrative approach would provide a more comprehensive risk assessment model, ultimately aiding in the prevention of DR-related complications.

## RECOMMENDATIONS

### Enhance Risk Stratification

Integrate the HALP score with established DR risk factors (e.g., HbA1c, diabetes duration, and blood pressure) to develop a comprehensive risk prediction model for early identification of high-risk patients.

### Conduct Longitudinal Analyses

Implement prospective studies to assess whether variations in the HALP score over time predict the progression of DR, thereby validating its prognostic utility.

### Broaden the Scope of Biomarker Evaluation

Investigate the role of the HALP score in other diabetes-related microvascular complications, such as nephropathy and neuropathy, to determine its overall applicability as a systemic biomarker.

### Assess the Impact of Targeted Interventions

Explore whether interventions aimed at improving nutritional and inflammatory status (e.g., optimizing albumin and hemoglobin levels) can favorably modify the HALP score and potentially slow the progression of DR.

## FUTURE DIRECTIONS

While the HALP score alone may not be sufficient for DR screening, the observed trends suggest its potential role in a multifactorial risk assessment framework. Future studies should explore longitudinal associations between changes in the HALP score and DR progression. Additionally, integrating HALP with other biomarkers may improve predictive accuracy and support early intervention strategies in clinical practice. Expanding research in this area could provide cost-effective methods for enhancing DR risk stratification and guiding patient management.

Future research should focus on validating the HALP score as part of a composite risk model for DR. Longitudinal studies could assess whether changes in the HALP score over time correlate with DR progression or regression, providing insight into its utility for monitoring disease course. Additionally, exploring the integration of the HALP score with other emerging biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), or the neutrophil-to-lymphocyte ratio (NLR), may enhance its predictive power. A multicenter approach, particularly involving diverse populations, would also

help determine the generalizability of the findings.

This thesis explores the association between the HALP score and the severity of DR in individuals with T2DM. Recognizing the burden of DR as a major microvascular complication of diabetes, the study was motivated by the need to identify accessible composite biomarkers that reflect both inflammatory and nutritional status, thereby aiding in early detection and risk stratification.

### Limitations

**Cross-sectional design:** Limits the ability to establish causal relationships between the HALP score and DR progression.

**Sample size and diversity:** The relatively small and geographically restricted sample may reduce the generalizability of the findings.

**Biomarker variability:** The nonnormal distribution and inherent variability of the HALP score components could affect the robustness of the statistical analysis.

**Confounding factors:** Potential confounders such as comorbidities, medication use, and lifestyle factors were not fully controlled, which might influence the observed associations.

### ACKNOWLEDGMENTS

We acknowledge the contribution and support of all the patients and their relatives, and all the residents of the departments of medicine and ophthalmology.

### ORCID

Vijay Kumar  <https://orcid.org/0000-0001-6042-7784>

Anil Balivada  <https://orcid.org/0009-0007-0565-650X>

### REFERENCES

1. Fung TH, Patel B, Wilmot EG, et al. Diabetic retinopathy for the non-ophthalmologist. *Clin Med* 2022;22(2):112–116.
2. Tan TE, Wong TY. Diabetic retinopathy: looking forward to 2030. *Front Endocrinol* 2023;13:1077669.
3. Wang W, Lo ACY. Diabetic retinopathy: pathophysiology and treatments. *Int J Mol Sci* 2018;19(6):1816.
4. Teo ZL, Tham YC, Yu M, et al. Do we have enough ophthalmologists to manage vision-threatening diabetic retinopathy? A global perspective. *Eye* 2020;34(7):1255–1261.
5. Al-Kharashi AS. Role of oxidative stress, inflammation, hypoxia and angiogenesis in the development of diabetic retinopathy. *Saudi J Ophthalmol* 2018;32(4):318–323.
6. Tian M, Li Y, Wang X, et al. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score is associated with poor outcome of acute ischemic stroke. *Front Neurol* 2020;11:610318.
7. Wang S, Pan X, Jia B, et al. Exploring the correlation between the Systemic Immune Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), and Type 2 diabetic retinopathy. *Diabetes Metab Syndr Obes* 2023;16:3827–3836.
8. Rossaint J, Margraf A, Zarbock A. Role of platelets in leukocyte recruitment and resolution of inflammation. *Front Immunol* 2018;9:2712.
9. Gros A, Ollivier V, Ho-Tin-Noé B. Platelets in inflammation: regulation of leukocyte activities and vascular repair. *Front Immunol* 2014;5:678.
10. Thomas MR, Storey RF. The role of platelets in inflammation. *Thromb Haemost* 2015;114(3):449–458.
11. Zheng Y, Zhu Y, Liu X, et al. The screening of albumin as a key serum component in preventing release of neutrophil extracellular traps by selectively inhibiting mitochondrial ROS generation. *Can J Physiol Pharmacol* 2021;99(4):427–438.
12. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *JPEN J Parenter Enteral Nutr* 2019;43(2):181–193.
13. Wang GX, Fang ZB, Li JT, et al. The correlation between serum albumin and diabetic retinopathy among people with type 2 diabetes mellitus: NHANES 2011–2020. *PLoS One* 2022;17(6):e0270019.
14. Bahar A, Kashi Z, Ahmadzadeh Amiri A, et al. Association between diabetic retinopathy and hemoglobin level. *Casp J Intern Med* 2013;4:759.
15. Feng R, Tian Z, Mao R, et al. Gut microbiome-generated phenylacetylglutamine from dietary protein is associated with Crohn's disease and exacerbates colitis in a mouse model possibly via platelet activation. *J Crohns Colitis* 2023;17(11):1833–1846.
16. Farag CM, Antar R, Akosman S, et al. What is hemoglobin, albumin, lymphocyte, platelet (HALP) score? A comprehensive literature review of HALP's prognostic ability in different cancer types. *Oncotarget* 2023;14:153.
17. Zhou J, Yang D. Prognostic significance of Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) score in hepatocellular carcinoma. *J Hepatocell Carcinoma* 2023;10:821–831.
18. Alshuweishi Y, Basudan AM, Alfaifi M, et al. Association of the HALP score with dyslipidemia: a large, nationwide retrospective study. *Medicina (Kaunas)* 2023;59(11):2002.
19. Kocaoglu S, Atlati T. The efficiency of the HALP score and the modified HALP score in predicting mortality in patients with acute heart failure presenting to the emergency department. *J Coll Physicians Surg Pak* 2023;32(6):706.
20. Abu Bakar MH, Hairunisa N, Zaman Huri H. Reduced mitochondrial DNA content in lymphocytes is associated with insulin resistance and inflammation in patients with impaired fasting glucose. *Clin Exp Med* 2018;18(3):373–382.
21. Xu H, Chen Y, Li Y, et al. Mitochondrial apoptosis of lymphocyte is induced in type 2 diabetes. *Chin Med J (Engl)* 2014;127(2):213–217.
22. Modjtahedi BS, Wu J, Luong TQ, et al. Severity of diabetic retinopathy and the risk of future cerebrovascular disease, cardiovascular disease, and all-cause mortality. *Ophthalmology* 2021;128(8):1169–1179.
23. Lin KY, Hsieh WH, Lin YB, et al. Update in the epidemiology, risk factors, screening, and treatment of diabetic retinopathy. *J Diabetes Investig* 2021;12(8):1322–1325.



# Clinicopathological Features and Outcomes of Metastatic Colorectal Cancers Treated at a Tertiary Care Hospital: A Bidirectional Observational Study

Hema Sireesha Natti<sup>1</sup>, Vishesh Gumdal<sup>2\*</sup>, Deepak Koppaka<sup>3</sup>, Swapna Nuguri<sup>4</sup>, Sanjana Reddy Potu<sup>5</sup>, Rudra Sanjeev Rudra<sup>6</sup>, Rajeena Moulasa Jaffer<sup>7</sup>

Received: 15 May 2026; Accepted: 25 May 2026

## ABSTRACT

**Background:** Metastatic colorectal cancer (mCRC) remains a major contributor to cancer-related mortality worldwide. Real-world data from low- and middle-income countries remain limited.

**Materials and methods:** This bidirectional observational study included 60 patients with histologically confirmed mCRC treated at a tertiary care center between January 2019 and December 2025. Demographic, clinicopathological, molecular, treatment, and survival data were analyzed. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Cox proportional hazards regression was used to identify prognostic factors.

**Results:** The median age was 48.5 years, and 63.3% of patients were male. Extensive metastatic disease was present in 96.7% of patients. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations were detected in 20.7% of patients, whereas microsatellite instability-high (MSI-high) status was identified in one patient. Median PFS and OS were 10.6 and 22.3 months, respectively. On multivariable analysis, peritoneal metastasis independently predicted inferior PFS [hazard ratio (HR) 4.45, 95% confidence interval (CI) 2.16–9.19;  $p < 0.001$ ] and OS (HR 2.83, 95% CI 1.13–7.07;  $p = 0.026$ ). Poorly differentiated histology independently predicted worse OS (HR 3.05, 95% CI 1.03–9.06;  $p = 0.045$ ).

**Conclusion:** This study highlights the substantial burden of advanced disease in Indian patients with colorectal cancer. Peritoneal metastasis and poor differentiation were associated with adverse outcomes. Improved early detection and wider access to targeted therapies may improve survival outcomes in resource-limited settings.

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1616

## INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies worldwide and a major cause of cancer-related mortality, with many patients presenting with or eventually developing metastatic disease.<sup>1</sup> Despite advances in surgery and systemic therapy, metastatic colorectal cancer (mCRC) continues to have poor survival outcomes. While the AJCC TNM staging system remains standard for prognostication, survival differences within the same stage suggest that tumor biology also plays a significant role. Consequently, clinicopathological factors and molecular alterations such as NRAS, KRAS, BRAF mutations, and mismatch repair deficiency have emerged as important prognostic and predictive markers in mCRC.<sup>2</sup>

Molecular profiling has transformed treatment strategies in metastatic disease, particularly with the use of anti-EGFR therapy and immune checkpoint inhibitors (ICI) in selected patients. However, real-world data regarding clinicopathological profile, molecular characteristics, treatment patterns, and outcomes of mCRC from India and other

low- and middle-income countries (LMICs) remain limited. Therefore, this bidirectional observational study was undertaken to evaluate the demographic profile, clinicopathological features, molecular characteristics, treatment patterns, and survival outcomes of patients with mCRC treated at a tertiary care center, and to identify prognostic factors associated with clinical outcomes in routine practice.

## MATERIALS AND METHODS

This bidirectional observational study was conducted at a tertiary care hospital in India after obtaining approval from the institutional ethics committee ESICMC/SNR/IEC-S0400/06–2024 and informed consent. The current trial is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary File S1). Adult patients aged  $\geq 18$  years with an ECOG performance status of 2 or below who received at least 1 cycle of systemic therapy for histologically confirmed CRC and radiologically and/or pathologically confirmed metastatic disease were included.

Individuals were excluded from the study if they presented with synchronous secondary malignancies, lacked critical data, or were lost to follow-up (LTFU) immediately following diagnosis. The sample size was calculated using the single population proportion formula, assuming a metastatic colorectal cancer prevalence of 22%, 95% confidence interval, and 10% precision, yielding a minimum sample size of 60 patients. All eligible patients during the study period were included in the analysis.

## Objectives

The primary objective of this study is to ascertain the overall survival (OS) of patients with mCRC. Secondary objectives include determining progression-free survival (PFS), evaluating clinicopathological characteristics and molecular profile patterns, documenting the treatment protocols employed (including first-line, maintenance, and second-line therapies in accordance with NCCN/ESMO guidelines), and examining the association of clinicopathological and molecular factors with treatment outcomes (PFS and OS) and chemotherapy-related toxicity profiles.

## Statistical Analysis

Data were collected on patient demographic variables, including age, sex, socioeconomic status, ECOG status, primary tumor site (right colon from cecum to right 2/3rd of transverse colon, the left colon from splenic flexure,

<sup>1</sup>Senior Resident; <sup>2</sup>Head; <sup>3</sup>Associate Professor, Department of Medical Oncology; <sup>4</sup>Associate Professor, Department of Pathology; <sup>5–7</sup>Senior Resident, Department of Medical Oncology, ESIC Medical College and Hospital, Hyderabad, Telangana, India; \*Corresponding Author

**How to cite this article:** Natti HS, Gumdal V, Koppaka D, et al. Clinicopathological Features and Outcomes of Metastatic Colorectal Cancers Treated at a Tertiary Care Hospital: A Bidirectional Observational Study. *J Assoc Physicians India* 2026;74(7):49–54.

descending colon and sigmoid colon and rectum including rectosigmoid junction and rectum), comorbidities, histological subtype, tumor grade, molecular markers (KRAS, NRAS, MSI by IHC) and characteristics of metastatic disease (such as the number and location of metastatic sites, oligometastatic versus extensive metastatic patterns, and radiological tumor burden). Additionally, treatment details were documented, including first-line (CAPOX, FOLFOX, FOLFIRI), targeted therapies (bevacizumab, cetuximab, panitumumab), maintenance therapy, subsequent lines of treatment, and chemotherapy toxicity using CTCAE version 5.0.

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), based on distribution assessed using the Shapiro–Wilk test. Categorical variables were summarized as frequencies and percentages. OS was defined as the time from the diagnosis to death from any cause or last follow-up. PFS was defined as the time from the diagnosis to documented radiological progression or death, whichever occurred first. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

Univariable analysis was performed to evaluate the association between clinicopathological variables and survival outcomes. Variables with a *p*-value < 0.10 on univariable analysis were included in multivariable analysis using Cox proportional hazards regression to identify independent prognostic factors. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. A significance level of 5% (*p* < 0.05) was considered statistically significant. The statistical analysis was conducted using Jamovi.

## RESULTS

In this bidirectional observational study, a total of 60 patients with mCRC were included. Three patients with ECOG PS > 2 and one patient with second synchronous malignancy were excluded (Fig. 1A).

The baseline characteristics of the included patients are given in Table 1. Synchronous metastases were more frequent than metachronous metastases across all primary tumor sites.

In this study, two patients with oligometastatic CRC and ECOG PS 2 underwent curative-intent surgery postinduction chemotherapy. One received 8 CAPOX cycles with bevacizumab, followed by right hemicolectomy and complete hepatic metastatectomy, with no residual disease, and is under follow-up. The second, after 6 CAPOX cycles with bevacizumab, had subtotal colectomy plus wide hepatic metastatectomy but experienced disease progression after 19.8 months and started on CAPIRI with bevacizumab.

Among 58 patients receiving first-line chemotherapy, 7 were LTFU, and 42 had disease progression. 7 died before progression, 4 from organ failure and 3 from unknown causes. At analysis, 2 remained on treatment without progression.

In the first-line setting, the commonly administered regimens are given in Figure 1B.

Out of 42 patients with disease progression, 38 received second-line therapy. The most common regimen was CAPIRI plus bevacizumab (47.4%; *n* = 18), followed by FOLFIRI plus bevacizumab (18.4%; *n* = 7) and FOLFIRI plus cetuximab (10.5%; *n* = 4). Other regimens were CAPOX plus bevacizumab (7.9%; *n* = 3), CAPIRI alone (2.6%; *n* = 1), FOLFOX plus bevacizumab (2.6%; *n* = 1), and CAPIRI plus

cetuximab (2.6%; *n* = 1). Nivolumab was given to one patient (2.6%). Tegafur monotherapy was administered to 2 patients (5.3%) with poor ECOG PS, unfit for combination chemotherapy.

Disease progression following second-line therapy was observed in 7 patients who proceeded to receive third-line treatment. Among these, 2 patients died due to progressive disease, and 2 patients were LTFU. The remaining three patients continued on treatment at the time of analysis with regorafenib.

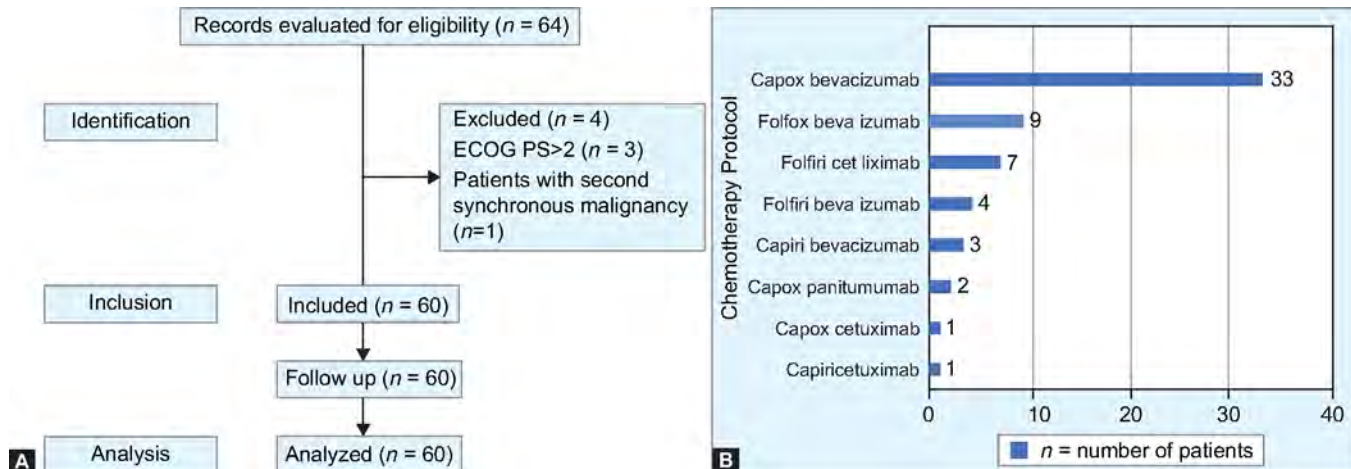
Microsatellite instability-high status through IHC was seen in one patient, who received first-line treatment with FOLFIRI combined with cetuximab for 6 cycles. Upon progression, nivolumab was given as a single agent in the second line for 2 cycles. Unfortunately, the patient died due to a nondisease-related cause (accident).

## SURVIVAL OUTCOMES

### Overall Survival

The estimated mOS for the entire cohort was 22.3 months (95% CI: 19.4–NE) (Fig. 2A) with a median follow-up duration of 22.2 months, and the factors affecting OS were NRLN, peritoneal metastasis, and grade (Fig. 2B and Table 2).

NRLN involvement was significantly associated with worse OS. On univariable analysis, NRLN metastases were associated with increased risk of death (HR 9.30, 95% CI 1.19–72.51; *p* = 0.033), although this was not retained on multivariable analysis (HR 6.68, 95% CI 0.72–61.95; *p* = 0.095). mOS was 21.7 months (95% CI 18.4–NE) in patients with NRLN metastases, while median OS was not reached in those without involvement. Peritoneal metastasis was significantly associated with inferior OS,



**Figs 1A and B:** (A) Study construction flowchart according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines; (B) chemotherapy protocol 1 regimen

**Table 1:** Characteristics of the included variables

Variables	Value
Age (years), median (range)	48.5 (22–78)
Sex, <i>n</i> (%)	
Female	22 (36.7)
Male	38 (63.3)
Marital status, <i>n</i> (%)	
Married	60 (100)
Comorbidities, <i>n</i> (%)	
Present	22 (36.7)
Absent	38 (63.3)
ECOG performance status, <i>n</i> (%)	
0	9 (15.0)
1	10 (6.7)
2	41 (68.3)
Smoker/alcoholic, <i>n</i> (%)	
Smoker	5 (8.3)
Alcoholic	10 (16.7)
Both	12 (20.0)
Site, <i>n</i> (%)	
Left	22 (36.7)
Right	22 (36.7)
Rectum	16 (26.6)
Metastatic sites, <i>n</i> (%)	
Nonregional lymph node	54 (90.0)
Peritoneal	33 (55.0)
Liver	52 (86.7)
Lung	20 (33.3)
Bone	2 (3.3)
Brain	2 (3.3)
Ovary	3 (5.0)
Metastatic patterns, <i>n</i> (%)	
Oligometastatic	2 (3.3)
Extensive	58 (96.7)
Metastatic types, <i>n</i> (%)	
Synchronous	37 (61.7)
Metachronous	23 (38.3)
Grade, <i>n</i> (%)	
Well-differentiated	18 (30.0)
Moderately differentiated	28 (46.7)
Poorly differentiated	14 (23.3)
Histology, <i>n</i> (%)	
Adenocarcinoma NOS	58 (96.7)
Mucinous adenocarcinoma	2 (3.3)
MSI, <i>n</i> (%)	
High	1 (1.7)
Stable	59 (98.3)
KRAS, <i>n</i> (%)	
Mutated	12 (20.7)
Wild	46 (79.3)
NRAS, <i>n</i> (%)	
Mutated	1 (1.7)
Wild	57 (98.3)
BRAF, <i>n</i> (%)	
Wild	58 (100)

with mOS of 19.4 months compared to not reached in those without peritoneal involvement. It remained significant on both univariable and multivariable analysis. Poorly differentiated tumors showed a trend toward worse OS, whereas well-differentiated tumors were associated with significantly lower mortality risk. On multivariable analysis, poorly differentiated tumors remained an independent adverse prognostic factor, while well-differentiated histology retained significant survival benefit.

**Progression-Free Survival**

The estimated mPFS for the entire cohort was 10.6 months (95% CI: 8.47–14.3) (Fig. 2C), and the factors affecting PFS were NRLN, peritoneal metastasis, grade, and KRAS (Fig. 2D and Table 3).

NRLN involvement was significantly associated with worse PFS, with a higher risk of progression on both univariable and multivariable analysis. Patients without NRLN had longer mPFS (19.55 months, 95% CI 14.97–NR) compared to those with involvement (9.97 months, 95% CI 8.13–13.2). Peritoneal metastasis was associated with increased risk of progression on both univariable and multivariable analysis. Patients with peritoneal metastasis had markedly shorter mPFS compared to those without (7.97 months, 95% CI 7.03–10.6 vs. 14.87 months, 95% CI 11.37–19.5). Univariable analysis showed well-differentiated tumors had lower progression risk; poorly differentiated had a non-significant increased risk. Multivariable analysis found neither tumor type had independent prognostic significance for PFS, though well-differentiated showed a trend toward improved outcomes. KRAS wild-type showed a non-significant trend toward improved PFS on univariable analysis, which was not retained on multivariable analysis. mPFS was 8.47 months in KRAS-mutated versus 11.37 months in wild-type.

**Toxicity Patterns**

Forty-five patients received oxaliplatin-based regimens, and 15 received irinotecan-based regimens. Diarrhea was the most common toxicity, followed by neutropenia, HFS, thrombocytopenia, and neuropathy (Table 4).

**DISCUSSION**

This bidirectional observational study provides important real-world insights into the clinicopathological profile, molecular characteristics, treatment patterns, and outcomes of mCRC in a tertiary care setting in India. The median age at diagnosis in our cohort (48.5 years) was notably lower than that

reported in Western populations, supporting emerging evidence of an increasing burden of EOCC in LMICs.<sup>2,3</sup> Male predominance was observed, consistent with global epidemiological trends.<sup>1</sup> The low prevalence of family history suggests predominance of sporadic disease, although hereditary syndromes may be underrecognized because of limited genetic testing availability.<sup>4</sup>

Most patients have extensive metastatic disease, while only a small proportion have oligometastatic disease, reflecting delayed diagnosis and limited screening uptake. Synchronous metastases were common, further emphasizing advanced presentation at diagnosis. The liver was the most frequent metastatic site, consistent with established dissemination patterns in CRC.<sup>5,6</sup> However, the prevalence of peritoneal metastasis (55%) was considerably higher than that

reported in Western literature, where rates are generally around 20–30%.<sup>5</sup> This may reflect advanced disease burden, referral bias associated with a tertiary care center, or differences in staging practices. Similarly, the high frequency of NRLN metastasis may be related to extensive PET-based detection and radiological interpretation criteria. Bone and brain metastases relatively uncommon, in line with previously reported dissemination patterns. Only two patients were eligible for curative-intent surgery, highlighting the limited opportunity for potentially curative interventions in routine practice.

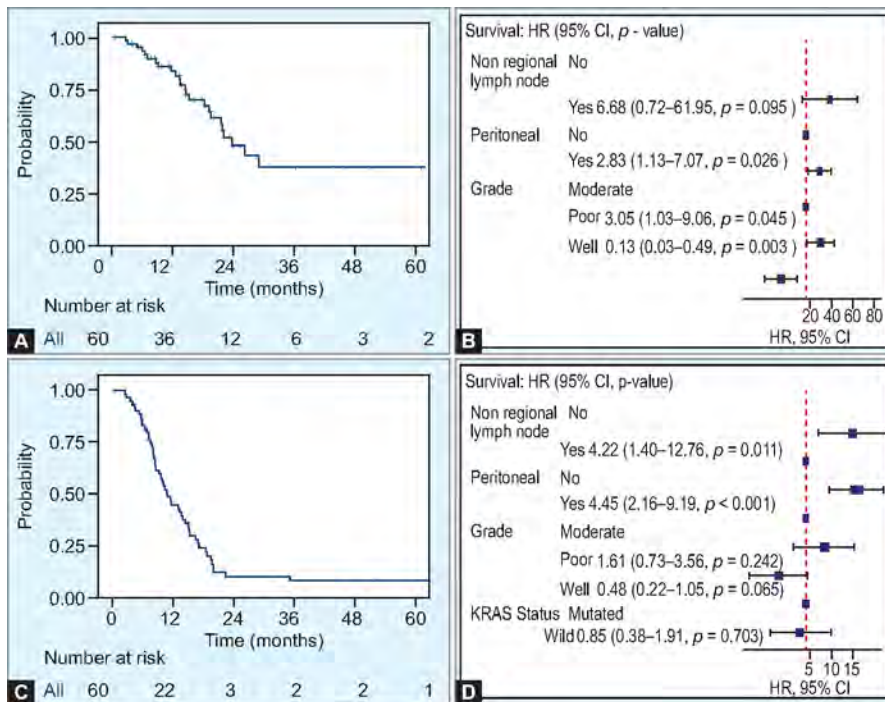
Moderately differentiated adenocarcinoma constituted the majority, comparable to previous studies.<sup>7</sup> The prevalence of KRAS mutations was lower than globally reported frequencies, while NRAS mutations were infrequent and no BRAF

mutations were identified.<sup>8</sup> MSI-high tumors were also uncommon compared with Western datasets.<sup>9</sup> These differences may reflect population-specific molecular heterogeneity and limited sample size.

CAPOX plus bevacizumab was the most commonly used first-line regimen, consistent with NCCN and ESMO recommendations.<sup>10,11</sup> Second-line treatment commonly involved irinotecan-based regimens following oxaliplatin exposure.<sup>12</sup> However, considerable heterogeneity existed in chemotherapy backbones. Limited access to anti-EGFR therapy and immunotherapy was largely influenced by institutional procurement systems and drug availability, reflecting real-world treatment challenges in resource-constrained settings.

The mPFS (10.6 months) and mOS (22.3 months) observed in our study were broadly comparable to other Indian real-world studies, although somewhat lower than outcomes reported in clinical trials where OS often exceeds 30 months.<sup>13–15</sup> This discrepancy likely reflects advanced disease burden at presentation, restricted access to targeted therapies, treatment interruptions, and substantial LTFU. Peritoneal metastasis emerged as an independent adverse prognostic factor for both PFS and OS, consistent with prior studies demonstrating poorer outcomes in patients with peritoneal dissemination.<sup>16,17</sup> NRLN metastasis was also associated with inferior PFS, although these findings should be interpreted cautiously given the unusually high prevalence of nodal disease in our cohort.<sup>18</sup> Poorly differentiated tumors were associated with inferior OS, consistent with previous reports linking poor differentiation to aggressive tumor biology.<sup>19</sup>

Although KRAS wild-type showed a trend toward improved PFS, statistical significance was not maintained on multivariable analysis, possibly due to limited sample size, treatment heterogeneity, and restricted anti-EGFR use.<sup>20,21</sup>



**Figs 2A to D:** (A) Overall survival (OS) of the entire cohort; (B) factors affecting OS; (C) progression-free survival (PFS) of the entire cohort; (D) factors affecting PFS

**Table 2:** Multivariable analysis of different prognostic factors for OS

Variable	n (%)	HR (univariable)	HR (multivariable)
<b>NRLN</b>			
No	6 (10.0)	–	–
Yes	54 (90.0)	9.30 (1.19–72.51, <i>p</i> = 0.033)	6.68 (0.72–61.95, <i>p</i> = 0.095)
<b>Peritoneal</b>			
No	27 (45.0)	–	–
Yes	33 (55.0)	2.99 (1.29–6.94, <i>p</i> = 0.011)	2.83 (1.13–7.07, <i>p</i> = 0.026)
<b>Grade</b>			
Moderate	28 (46.7)	–	–
Poor	14 (23.3)	2.68 (0.96–7.45, <i>p</i> = 0.059)	3.05 (1.03–9.06, <i>p</i> = 0.045)
Well	18 (30.0)	0.13 (0.04–0.42, <i>p</i> = 0.001)	0.13 (0.03–0.49, <i>p</i> = 0.003)

**Table 3:** Multivariable analysis of different prognostic factors for PFS

Variable	n (%)	HR (univariable)	HR (multivariable)
NRLN			
No	6 (10.3)	–	–
Yes	52 (89.7)	4.11 (1.44–11.77, <i>p</i> = 0.008)	4.22 (1.40–12.76, <i>p</i> = 0.011)
Peritoneal			
No	25 (43.1)	–	–
Yes	33 (56.9)	3.72 (1.96–7.05, <i>p</i> < 0.001)	4.45 (2.16–9.19, <i>p</i> < 0.001)
Grade			
Moderate	28 (48.3)	–	–
Poor	14 (24.1)	1.57 (0.75–3.28, <i>p</i> = 0.230)	1.61 (0.73–3.56, <i>p</i> = 0.242)
Well	16 (27.6)	0.40 (0.20–0.80, <i>p</i> = 0.009)	0.48 (0.22–1.05, <i>p</i> = 0.065)
KRAS status			
Mutated	12 (20.7)	–	–
Wild	46 (79.3)	0.52 (0.24–1.12, <i>p</i> = 0.095)	0.85 (0.38–1.91, <i>p</i> = 0.703)

**Table 4:** First-line chemotherapy toxicity

Toxicity	Oxaliplatin-based (n = 45), n (%)	Irinotecan-based (n = 15), n (%)	Total (n = 60), n (%)
Diarrhea (grade 1–2)	12 (26.7)	6 (40.0)	18 (30.0)
Diarrhea (grade ≥ 3)	4 (8.9)	2 (13.3)	6 (10.0)
Neutropenia (grade 1–2)	11 (24.4)	5 (33.3)	16 (26.6)
Neutropenia (grade ≥ 3)	3 (6.6)	1 (6.7)	4 (6.6)
Thrombocytopenia (any grade)	9 (20.0)	2 (13.3)	11 (18.3)
Peripheral neuropathy (grade 1–2)	8 (17.7)	2 (13.3)	10 (16.6)
Peripheral neuropathy (grade ≥ 3)	2 (4.4)	0 (0.0)	2 (3.3)
Hand–foot syndrome (grade 1–2)	14 (31.1)	2 (13.3)	16 (26.6)
Hand–foot syndrome (grade ≥ 3)	3 (6.7)	0 (0.0)	3 (31.7)

A major practical challenge in this study was substantial LTFU, particularly in later treatment lines, reflecting real-world issues such as financial constraints, travel burden, and inadequate structured follow-up systems. Toxicity patterns were generally consistent with established evidence, with irinotecan-based regimens associated with greater gastrointestinal and hematological toxicity and oxaliplatin associated with neuropathy; however, most toxicities were manageable, supporting the feasibility of combination chemotherapy in this setting.

Overall, this study highlights the high burden of advanced disease at presentation, the need for improved screening and early detection strategies, and the impact of limited access to precision oncology therapies in real-world Indian practice. Strengthening molecular diagnostic infrastructure, improving access to targeted therapies, and developing robust patient follow-up systems may help improve outcomes in mCRC.

This study provides valuable real-world evidence from a routine tertiary care setting, reflecting the practical challenges encountered in everyday oncology practice, including variability in patient characteristics, treatment access, and follow-up. A major strength of the study was the comprehensive

evaluation of both clinicopathological and molecular factors, including primary tumor site, metastatic pattern, RAS/BRAF mutation status, MSI status, and treatment details, which enabled a broader understanding of disease behavior and outcomes in mCRC. Furthermore, the use of multivariable analysis strengthened the reliability and clinical relevance of the findings by adjusting for potential confounders and identifying independent prognostic factors influencing PFS and OS. However, several limitations should be considered while interpreting the results. As a single-center retrospective study conducted at a tertiary care institution, the findings may not be fully generalizable to broader populations because of variations in referral patterns, patient demographics, and institutional practices. In addition, heterogeneity in treatment regimens, targeted therapy use, and sequencing strategies could have influenced outcomes, while a significant proportion of patients LTFU may have affected survival analysis and long-term outcome assessment.

### CONCLUSION

In conclusion, this study provides real-world evidence on mCRC from a tertiary care setting

in India, demonstrating that outcomes are influenced by metastatic burden, tumor biology, and access to therapy. While survival outcomes are broadly consistent with other LMIC data, differences from clinical trial results highlight the impact of real-world constraints. Strengthening early detection and expanding availability of targeted therapies are critical steps toward improving outcomes in this population.

### SUPPLEMENTARY MATERIAL

Supplementary file (STROBE Checklist) is available online at the journal website.

### REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74(3):229–263.
2. Stintzing S, Stremtizer S, Sebio A, et al. Predictive and prognostic markers in the treatment of metastatic colorectal cancer (mCRC): personalized medicine at work. *Hematol Oncol Clin North Am* 2015;29(1):43–60.
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71(3):209–249.
4. Patel SG, Karlitz JJ, Yen T, et al. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors,

- prevention, and early detection. *Lancet Gastroenterol Hepatol* 2022;7(3):262–274.
5. Lawler T, Parlato L, Warren Andersen S. The histological and molecular characteristics of early-onset colorectal cancer: a systematic review and meta-analysis. *Front Oncol* 2024;14:1349572.
  6. Riihimäki M, Hemminki A, Sundquist J, et al. Patterns of metastasis in colon and rectal cancer. *Sci Rep* 2016;6(1):29765.
  7. van der Geest LGM, Lam-Boer J, Koopman M, et al. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis* 2015;32(5):457–465.
  8. Sharma V, Sharma A, Raina V, et al. Metastatic colorectal cancer: real life experience from an Indian tertiary care center. *BMC Cancer* 2021;21(1):630.
  9. Levin-Sparenberg E, Bylsma LC, Lowe K, et al. A systematic literature review and meta-analysis describing the prevalence of KRAS, NRAS, and BRAF gene mutations in metastatic colorectal cancer. *Gastroenterology Res* 2020;13(5):184–198.
  10. Martini G, Dienstmann R, Ros J, et al. Molecular subtypes and the evolution of treatment management in metastatic colorectal cancer. *Ther Adv Med Oncol* 2020;12:1758835920936089.
  11. Benson AB, Venook AP, Adam M, et al. Colon cancer, version 3.2024, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2024;22(2D):e240029.
  12. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34(1):10–32.
  13. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27(8):1386–1422.
  14. Patil PS, Saklani A, Gambhire P, et al. Colorectal cancer in India: an audit from a tertiary center in a low prevalence area. *Indian J Surg Oncol* 2017;8(4):484–490.
  15. Ramaswamy A, Babu V, Kothari R, et al. Treatment of metastatic colorectal cancers in resource-constrained low- and middle-income countries (LMICs) scenario—outcomes, practice patterns, and commentary on treatment costs. *South Asian J Cancer* 2022;11(4):293–298.
  16. Yokoi R, Tajima JY, Fukada M, et al. Optimizing treatment strategy for oligometastases/oligo-recurrence of colorectal cancer. *Cancers (Basel)* 2023;16(1):142.
  17. Tonello M, Cenzi C, Pizzolato E, et al. Systemic chemotherapy in colorectal peritoneal metastases treated with cytoreductive surgery: systematic review and meta-analysis. *Cancers* 2024;16(6).
  18. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of North Central Cancer Treatment Group Phase III trials N9741 and N9841. *J Clin Oncol* 2012;30(3):263–267.
  19. Guren MG, Kørner H, Pfeffer F, et al. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993–2010. *Acta Oncol* 2015;54(10):1714–1722.
  20. Huh JW, Lee WY, Shin JK, et al. A novel histologic grading system based on lymphovascular invasion, perineural invasion, and tumor budding in colorectal cancer. *J Cancer Res Clin Oncol* 2019;145(2):471–477.
  21. Yaeger R, Chatila WK, Lipsyc MD, et al. Clinical sequencing defines the genomic landscape of metastatic colorectal cancer. *Cancer Cell* 2018;33(1):125–136.

In T2DM with Comorbidities,

Tri Simplified Care

With

**UDAPA-Trio**

Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 500 mg XR

**UDAPA-Trio Forte**

Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 1000 mg XR



# 1. Aardvark Mar Jan 2020

**Abridged Prescribing Information**

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

In T2DM Across Continuum,

Choose the Leader

**Glycomet®-GP**  
Metformin Hydrochloride 500/850/1000 mg SR + Glimpepride 0.5/1/2/3/4 mg

**Glycomet®-GP 0.5**  
Metformin Hydrochloride 500 mg SR + Glimpepride 0.5 mg

**Glycomet®-GP 1**  
Metformin Hydrochloride 500 mg SR + Glimpepride 1 mg

**Glycomet®-GP 2**  
Metformin Hydrochloride 500 mg SR + Glimpepride 2 mg

**Glycomet®-GP 2/850**  
Metformin Hydrochloride 850 mg SR + Glimpepride 2 mg

**Glycomet®-GP 3/850**  
Metformin Hydrochloride 850 mg SR + Glimpepride 3 mg

**Glycomet®-GP 3 FORTE**  
Metformin Hydrochloride 1000 mg SR + Glimpepride 3 mg

**Glycomet®-GP 4 FORTE**  
Metformin Hydrochloride 1000 mg SR + Glimpepride 4 mg

**Glycomet®-GP 0.5 FORTE**  
Metformin Hydrochloride 1000 mg SR + Glimpepride 0.5 mg

**Glycomet®-GP 1 FORTE**  
Metformin Hydrochloride 1000 mg SR + Glimpepride 1 mg

**Glycomet®-GP 2 FORTE**  
Metformin Hydrochloride 1000 mg SR + Glimpepride 2 mg



**Abridged Prescribing Information**

Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets Indication: For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycaemic control. Dosage and Administration: The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed. Adverse Reactions: For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur; allergic reactions or pseudo allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in Vit B12 absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesaemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders. Warnings and Precautions: For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly. Contraindications: Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma). Severe renal failure (GFR<30ml/min). In pregnant women: In lactating women: Acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents); acute or chronic disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock); hepatic insufficiency; acute alcohol intoxication; alcoholism. Use in a special population: Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. Additional information is available on request. Last updated: 24th March 2020

\* In case of any adverse events, kindly contact: pv@usv.in For the use of registered medical practitioner, hospital or laboratory. \*



Your reliable healthcare partner

**USV Private Limited**

Arvind Vithal Gandhi Chowk, B. S. D. Marg, Govandi, Mumbai - 400 088. | Tel: 91-22-2556 4048 | Fax: 91-22-2558 4025 | www.usvindia.com



**The Complete Metabolic Care**

**UDAPA**

Dapagliflozin 5mg & 10mg

**UDAPA-Pro**

Dapagliflozin 10mg + Pioglitazone HCl 15mg

**UDAPA GOLD**

Metformin HCl 500/1000mg (ER) + Glimepiride 1/2mg + Dapagliflozin 10mg

 **Glycomet<sup>®</sup> Trio**

Glimepiride 1mg/2mg + Metformin HCl 500mg/1000mg (SR) + Voglibose 0.2mg



Your reliable healthcare partner

In T2DM Patients with Comorbidities,

Choose the  
**Right Triple,**

# Jalra®-Trio

Vildagliptin 100mg SR + Dapagliflozin 10mg + Metformin 500mg SR

**Control + Protect + Stabilize**

Also Available

**Jalra®-Trio Forte**

Vildagliptin 100mg SR + Dapagliflozin 10mg + Metformin 1000mg SR

In young people with uncontrolled T2DM / HbA1c >8%

Rx

# Glycomet®-GP STAR

Glimepiride 1/2 mg + Metformin 500/1000 mg + Sitagliptin 50 mg

**START STRONG to Build Metabolic Memory**

Start with

**Glycomet®-GP STAR 1**

Glimepiride 1 mg + Metformin 500mg + Sitagliptin 50 mg

**Glycomet®-GP STAR 2**

Glimepiride 2 mg + Metformin 500mg + Sitagliptin 50 mg

Uptitrate to

**Glycomet®-GP STAR 1/1000**

Glimepiride 1 mg + Metformin 1000 mg + Sitagliptin 50 mg

**Glycomet®-GP STAR 2/1000**

Glimepiride 2 mg + Metformin 1000 mg + Sitagliptin 50 mg



Scan the QR Code for AbPI

1. For the use of Registered Medical Practitioner or a Hospital or a Laboratory only | 2. For AE reporting, contact [pv@usv.in](mailto:pv@usv.in)



Your reliable healthcare partner



In T2DM patients uncontrolled on SU-MET and post GLP-1 RA

# UDAPA-S

Dapagliflozin 10 mg + Sitagliptin 100 mg Tablets

**SMART ESSENTIAL**  **FOR BETTER RISK REDUCTION\***

In T2DM management

Add/ Initiate with

# UDAPA-M XR



Dapagliflozin 5mg/10mg + Metformin Extended Release Tablets 500mg/1000mg

**Start Early**  **Stay Protected**



OD Dosing advantage<sup>1</sup>



Ease of Identification<sup>1</sup>



Enhanced Convenience<sup>1</sup>



Improved Adherence<sup>1</sup>



Elderly Friendly<sup>1</sup>

## Patient Centric Packaging



References:

1. 2025 Selvan et al. Cureus 17(10): e95473. DOI 10.7759/cureus.95473

#Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-57.

\*Data on file

USV Private Limited

Arvind Vithal Gandhi Chowk, B.S.D. Marg, Govandi East, Mumbai-400088  
Tel.: 91-22-2556 4048 Fax: 91-22-2558 4025 www.usvindia.com





Your reliable healthcare partner

# EMPOWER PEOPLE AFFECTED BY TYPE 2 DIABETES WITH OBESITY\* THROUGH THE **CIRCLE OF CARE**



Semaglutide Injection 0.25 mg/0.5 mg/1.0 mg

# usema

Powering change  
*responsibly*



From the **Leaders**  
in **Diabetes Care**



>**6 decades** of  
uncompromised **quality**



Highest **global quality**  
standards fully  
made in India



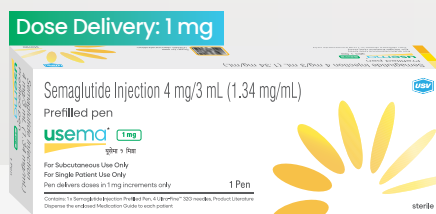
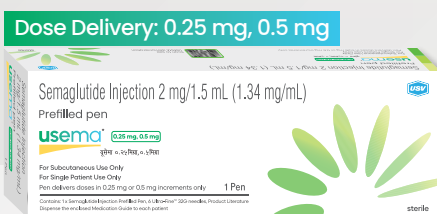
**Finger print** like structural  
and functional **similarity**  
as compared to Innovator



API to finished product  
**manufacturing and quality**  
control under one roof



Guaranteed complete  
**cold chain care**



\*Clinically proven efficacy and safety in people with T2DM with obesity.  
(Sorli C, et al. Lancet Diab Endocrinol. 2017;5(4):251-260.)

# Pregnancy Outcomes in Patients with Tuberculosis: A Systematic Review and Meta-analysis

Hemlata Sharma<sup>1\*</sup>, Swati Garg<sup>2</sup>, Saurabh Sharma<sup>3</sup>, Urvashi Sharma<sup>4</sup>, Ashok Kumar<sup>5</sup>

Received: 07 February 2026; Accepted: 21 April 2026



## ABSTRACT

**Background and objectives:** Tuberculosis (TB) is an important global health problem, especially for pregnant women, a vulnerable group. This systematic review and meta-analysis was conducted in this group to obtain cumulative results in a collective effort toward the World Health Organization (WHO) End TB Strategy.

**Methodology:** The databases Ovid MEDLINE, Embase, PubMed, ScienceDirect, Scopus, and Cochrane Central Register of Controlled Trials were searched for the last 10 years till 14<sup>th</sup> January 2025. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this analysis. Pregnancy outcomes in terms of maternal complications and perinatal complications, including observed mortality, were considered for analysis.

**Results:** A total of 9,873 records were identified through database searching, and 15 studies, including 3,045 pregnant women with TB, were selected for final analysis. The pooled mean maternal age was 27.6 years, and more than half of TB cases were diagnosed antenatally. Among pregnancy-related complications, fetal growth restriction, pregnancy-induced hypertension, oligohydramnios, and gestational diabetes were seen in 19, 15, 11, and 10% of cases, respectively. Low birth weight, preterm birth, small for age, and low Apgar score (<7) had pooled prevalences of 30, 22, 20, and 13%, respectively. Maternal mortality and neonatal mortality showed pooled prevalences of 0.05 [95% confidence interval (CI): 0.03–0.08] and 5% (95% CI: 3–8%), respectively. Low to moderate heterogeneity was found among observations.

**Interpretation and conclusion:** This systematic review and meta-analysis showed continued maternal and perinatal adverse outcomes in pregnant women with TB even in the current era, highlighting the need to optimize healthcare.

*Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1608*

## INTRODUCTION

Tuberculosis (TB) has probably returned as the world's leading cause of mortality from a single infectious agent, replacing COVID-19.<sup>1</sup> Approximately 10.8 million people globally fell ill with TB in the year 2023, which corresponds to an incidence of 134 cases per 1,00,000 population.<sup>1</sup> The South-East Asia, Africa, and Western Pacific regions of the World Health Organization (WHO) reported the maximum number of TB cases in the year 2023, contributing 45, 24, and 17% of cases, respectively, with lower numbers from the Eastern Mediterranean, the Americas, and Europe, reporting 8.6, 3.2, and 2.1% of cases, respectively.<sup>1</sup> Approximately 1.25 million people were estimated to have died from TB in the year 2023, with almost one-third of deaths (1,61,000 people) occurring among people with human immunodeficiency virus (HIV)-TB coinfection.<sup>1</sup> The incidence rates and the number of mortalities due to TB showed reductions of 8.3 and 23%, respectively, over 9 years, between the years 2015 and 2023. Despite this positive trend, the reductions were substantially lower than the target reductions of 50 and 75% for the incidence rates and the number of mortalities due to

TB, respectively, by the year 2025, a milestone set by the WHO End TB Strategy.<sup>1</sup>

As per the National Tuberculosis Prevalence Survey of 2019–2021, an estimated 312 per 1,00,000 people have TB in India, representing approximately 25% of the global TB burden.<sup>2</sup>

The immunological and endocrine changes during pregnancy affect antituberculosis immunity and influence the specific course of the disease during pregnancy.<sup>3</sup> Evidence regarding the exact incidence of TB during pregnancy and the postpartum period is currently limited. However, globally, around 2,00,000 women are diagnosed with TB during pregnancy and the postpartum period annually, according to estimates presented at an annual global conference on TB and lung diseases in the year 2019, with contributions of 75 and 25% from each period, respectively.<sup>4</sup> The majority of women belonged to the African and South-East Asia regions of the WHO.<sup>4</sup> In a systematic review by Morton et al., the risk ratio for the incidence of TB during pregnancy was reported as 1.4, and that for the postpartum period was reported as 1.9.<sup>4</sup>

TB during pregnancy is associated with adverse maternal and perinatal outcomes,

which can lead to maternal mortality in 6–15% of cases and pose a high risk to the newborns of women with TB.<sup>5–7</sup>

A number of studies have shown variable pregnancy outcomes in patients with TB across the globe. Our systematic review and meta-analysis included studies from the last 10 years to obtain cumulative results in patients with this globally important health problem among the vulnerable pregnant population in the current scenario, in a collective effort toward the WHO End TB Strategy.

## METHODOLOGY

Study protocol of this systematic review was registered with PROSPERO with ID No. CRD420251040280.

Databases—Embase, PubMed, Ovid MEDLINE, ScienceDirect, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus—were searched for the last 10 years till 14<sup>th</sup> January 2025. After searching the electronic databases, further hand-searching was conducted from the reference lists of selected studies to identify any other eligible studies.

Studies published in English only were selected, but there were no geographical restrictions. The keywords and search terms, such as TB, TB infection, pregnancy outcomes, maternal outcomes, perinatal outcomes, and neonatal outcomes, were used for reviewing the literature. Preferred Reporting

<sup>1</sup>Assistant Professor, Department of Obstetrics and Gynecology, Mahatma Gandhi University of Medical Sciences and Technology; <sup>2</sup>Professor, Department of Obstetrics and Gynecology, Mahatma Gandhi Medical College and Hospital;

<sup>3</sup>Assistant Professor, Department of Pathology, Pandit Naval Kishor Sharma Medical College and Hospital; <sup>4</sup>Professor, Department of Obstetrics and Gynecology, Mahatma Gandhi Medical College and Hospital; <sup>5</sup>Statistician Cum Assistant Professor, Department of Community Medicine, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India; \*Corresponding Author

**How to cite this article:** Sharma H, Garg S, Sharma S, et al. Pregnancy Outcomes in Patients with Tuberculosis: A Systematic Review and Meta-analysis. *J Assoc Physicians India* 2026;74(7):60–65.

Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this analysis. Pregnancy outcomes in terms of maternal complications and perinatal complications, including observed mortality, were considered for analysis.

### Study Inclusion Criteria

Original research publications, case-control, cohort, and cross-sectional studies published in peer-reviewed journals, and randomized controlled trials having a minimum sample size of 10 cases or more were included.

Pregnant women affected with TB, diagnosed by any method [clinical, interferon-gamma release assay (IGRA), or microbiologically confirmed], irrespective of their diagnosis pre-pregnancy or during pregnancy, were selected as the population of study interest. All cases of pregnancy with TB, irrespective of the site of TB (either pulmonary or extrapulmonary), were included.

### Study Exclusion Criteria

Studies without an abstract, without full text available, case reports, case series, studies with the wrong study design (research question not answered), conference abstracts/papers, and letters to the editor were excluded.

Studies recruiting pregnant women with human immunodeficiency virus (HIV)-coinfected populations exclusively or studies conducted exclusively on infertile populations/*in vitro* fertilization (IVF) pregnancies were excluded.

### Data Collection

The results from each database were extracted and entered into the appropriate standardized form. Screening of the titles and abstracts of the extracted studies was conducted independently by two reviewers, the first two authors (author 1 and 2), after removing duplicates. After applying the inclusion/exclusion criteria and reviewing the abstracts, the full texts of the retrieved articles were reviewed. A third reviewer (author 4) resolved the discrepancies. This study did not enroll any patients.

### Quality Assessment of the Included Studies

The quality of the included studies was assessed using the Newcastle–Ottawa Scale.<sup>8</sup> Risk of selection bias, comparability of study groups, and risk of outcome bias were assessed. The prespecified criteria were selected, and two independent reviewers (author 1 and 2) allocated stars based on those criteria. A high risk of bias was deemed present when studies scored one star for selection bias risk or ascertainment of outcome bias risk, or zero stars for any of the three domains,

whereas a low risk of bias was deemed present when studies scored four stars for selection bias risk, two stars for comparability, and three stars for ascertainment of outcome bias risk. A medium risk of bias was considered when studies had intermediate star ratings. Studies scoring three to four stars were included in the analysis.

### Data Extraction and Analysis

Information related to study characteristics, participant demographics, TB diagnosis details, and reported maternal and perinatal outcomes was extracted. The extracted data for comparison were compiled by two independent reviewers (author 1 and 2). The pooled incidence of adverse pregnancy outcomes was calculated. The effect size and anticipated heterogeneity were calculated between studies using a random-effects model. The  $I^2$  test was used to assess heterogeneity between studies ( $I^2$  40–60%: suggestive of moderate heterogeneity, 50–90%: substantial heterogeneity, and 75–100%: considerable heterogeneity). IBM SPSS 29.0.2.020.12 statistical software was used for statistical analyses.<sup>9</sup>

## RESULTS

### Characteristics of Included Studies

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in this analysis. Figure 1 shows the flow diagram of PRISMA. A total of 9,873 records were identified through database screening, and 15 studies were selected for final analysis.<sup>10–24</sup>

These studies included 3,045 pregnant women with TB, irrespective of whether their diagnosis was made pre-pregnancy or during pregnancy. Twelve studies were from Asian countries—seven from India, two from China, and one each from Israel, Malaysia, and Pakistan<sup>10–20,22</sup>—and three were from America,<sup>21,23,24</sup> showing the burden of TB in certain geographical areas. Clinical or radiological findings alone or in combination, supported by microbiological and/or histological confirmation, were used for the diagnosis of active TB.

Table 1 presents a comprehensive meta-analysis summarizing maternal characteristics, the timing of TB diagnosis, and the site of TB, along with pooled estimates derived from multiple studies. The pooled mean maternal age, based on 10 studies, was 27.6 years (95% CI: 25.9–29.2).<sup>10–16,18,20,21</sup> Five studies reported the socioeconomic status of pregnant women with TB, showing a pooled proportion of 0.62 (95% CI: 0.54–0.69) in women of low socioeconomic status across variable geographical areas.<sup>15–18,21</sup> Twenty-eight percent (95% CI: 0.21–0.35) of cases had a diagnosis of TB before pregnancy; however, more than half of TB cases were diagnosed antenatally, with a pooled proportion of 0.54 (95% CI: 0.45–0.62), while postpartum diagnosis of TB accounted for 18% of cases reported in 10 studies.<sup>10–13,15–19,22</sup> A pooled proportion of 0.71 (95% CI: 0.64–0.77) was noted for pulmonary TB and 0.29 (95% CI: 0.23–0.36) for extrapulmonary TB in 11 studies.<sup>10–13,15–18,20,22,23</sup> Moderate to substantial heterogeneity was found among maternal characteristics, timing of diagnosis, and site of

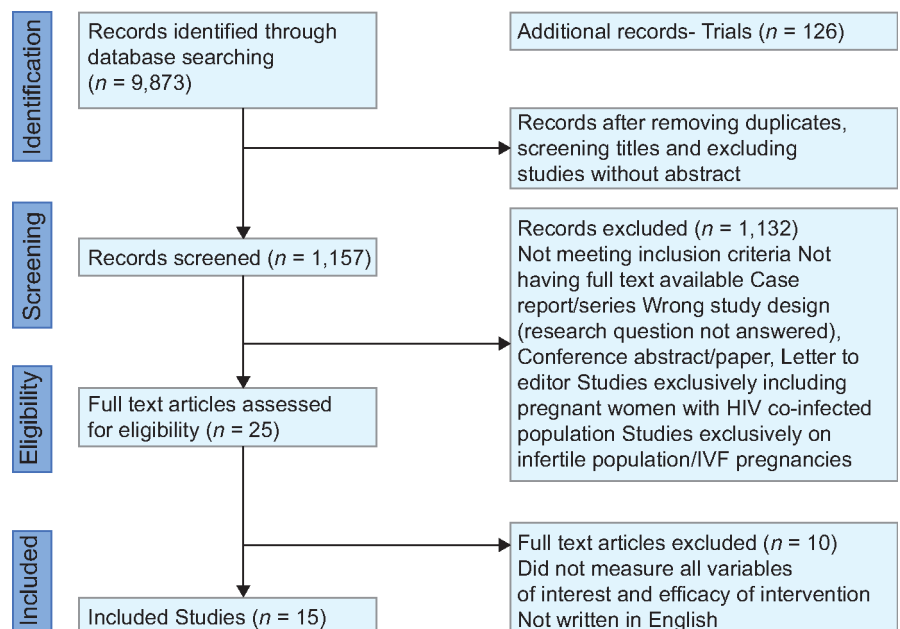


Fig. 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram: Identification and selection of relevant articles

TB, suggesting reasonable consistency among the included studies.

Table 2 presents a comprehensive meta-analysis of pregnancy complications and mode of delivery in pregnant women with TB. Among pregnancy-related complications, the most frequent observations were fetal growth restriction, pregnancy-induced hypertension, oligohydramnios, and gestational diabetes, occurring in 19% (95% CI: 0.13–0.26; five

studies),<sup>10,12,18,19,24</sup> 15% (95% CI: 0.10–0.21; five studies),<sup>10,11,14,18,24</sup> 11% (95% CI: 0.07–0.17; three studies),<sup>10,11,18</sup> and 10% of cases (95% CI: 0.06–0.15; five studies),<sup>11,14,18,21,24</sup> respectively. A low to moderate level of heterogeneity ( $I^2 = 33$ –43%) was observed.

Seven percent of women had spontaneous abortion (95% CI: 0.05–0.10; five studies), while 24% underwent induced abortion (95% CI: 0.17–0.31; five studies).<sup>13,15,16,18,19</sup> The pooled

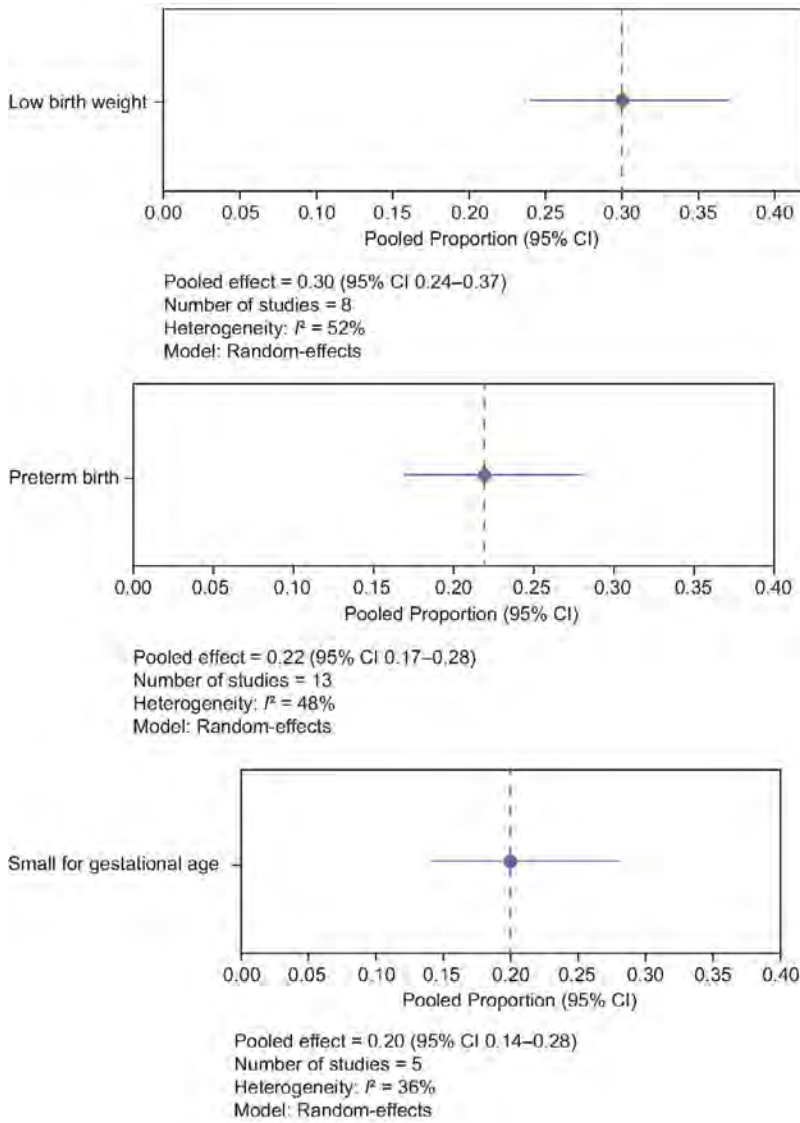
prevalence of normal vaginal delivery was 64% (95% CI: 56–71%; 10 studies), while 36% (95% CI: 29–44%; 10 studies) underwent lower-segment cesarean section (LSCS).<sup>10–16,18,19,24</sup> The heterogeneity was moderate ( $I^2 = 44%$ ), suggesting acceptable variability across studies. Maternal mortality was reported in 10 studies and showed a pooled prevalence of 0.05 (95% CI: 0.03–0.08) with low heterogeneity ( $I^2 = 31%$ ).<sup>10,11,13–18,20,24</sup>

**Table 1:** Comprehensive meta-analysis of maternal characteristics, timings of diagnosis, and site of TB in studies

Category	Outcome	Included studies (author, year)	No. of studies	Pooled effect (95% CI)	$I^2$ (%)
Maternal characteristics	Mean maternal age (years)	Chopra, 2016; Sade, 2020; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Wang, 2018; LaCourse, 2016	10	27.6 (25.9–29.2)	42
	Low socioeconomic status	Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Ullah, 2024; LaCourse, 2016	5	0.62 (0.54–0.69)	58
Timing of TB diagnosis	Prepregnancy	Chopra, 2016; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Sengupta, 2018; Ullah, 2024; Zainudin, 2024	10	0.28 (0.21–0.35)	46
	During pregnancy	Chopra, 2016; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Sengupta, 2018; Ullah, 2024; Zainudin, 2024	10	0.54 (0.45–0.62)	52
	Postpartum	Chopra, 2016; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Sengupta, 2018; Ullah, 2024; Zainudin, 2024	10	0.18 (0.12–0.25)	39
Site of TB	Pulmonary TB	Chopra, 2016; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Wang, 2018; Ullah, 2024; Zainudin, 2024; Garry, 2024	11	0.71 (0.64–0.77)	49
	Extrapulmonary TB	Chopra, 2016; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Wang, 2018; Ullah, 2024; Zainudin, 2024; Garry, 2024	11	0.29 (0.23–0.36)	49

**Table 2:** Comprehensive meta-analysis of pregnancy complications and mode of delivery in pregnant women with TB in studies

Category	Outcome	Included studies (author, year)	No. of studies	Pooled effect (95% CI)	$I^2$ (%)
Pregnancy complications	Fetal growth restriction	Chopra, 2016; Yadav, 2022; Buddhewar, 2022; Sengupta, 2018; El-Messidi, 2016	5	0.19 (0.13–0.26)	43
	Pregnancy-induced hypertension	Chopra, 2016; Sade, 2020; Yadav, 2019; Buddhewar, 2022; El-Messidi, 2016	5	0.15 (0.10–0.21)	38
	Oligohydramnios	Chopra, 2016; Yadav, 2019; Buddhewar, 2022	3	0.11 (0.07–0.17)	33
	Gestational diabetes mellitus	Sade, 2020; Yadav, 2019; Buddhewar, 2022; LaCourse, 2016; El-Messidi, 2016	5	0.10 (0.06–0.15)	31
Maternal mortality	Maternal death	Chopra, 2016; Sade, 2020; Wen, 2024; Yadav, 2019; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Wang, 2018; Ullah, 2024; El-Messidi, 2016	10	0.05 (0.03–0.08)	31
Mode of delivery	Normal vaginal delivery	Chopra, 2016; Sade, 2020; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Sengupta, 2018; El-Messidi, 2016	10	0.64 (0.56–0.71)	44
	LSCS	Chopra, 2016; Sade, 2020; Wen, 2024; Yadav, 2019; Yadav, 2022; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Sengupta, 2018; El-Messidi, 2016	10	0.36 (0.29–0.44)	44



**Fig. 2:** Forest plot analysis using a random-effects model for low birth weight, preterm birth, and small for gestational age

**Table 3:** Comprehensive meta-analysis of birth outcomes in pregnant women with TB in studies

Category	Outcome	Included studies (author, year)	No. of studies	Pooled effect (95% CI)	$I^2$ (%)
Birth outcomes	Low birth weight	Sade, 2020; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Ullah, 2024; LaCourse, 2016; Zainudin, 2024; Garry, 2024	8	0.30 (0.24–0.37)	52
	Preterm birth	Chopra, 2016; Sade, 2020; Wen, 2024; Yadav, 2019; Lewis, 2021; Tushar, 2024; Buddhewar, 2022; Sengupta, 2018; Ullah, 2024; LaCourse, 2016; Zainudin, 2024; Garry, 2024; El-Messidi, 2016	13	0.22 (0.17–0.28)	48
	Stillbirth	Seema Chopra 2016; Vikash Yadav 2019; Vikash Yadav 2022; Amita S. Buddhewar 2022; Zurina Zainudin 2024; Amira El-Messidi 2016	6	0.06 (0.04–0.10)	34
	APGAR <7	Chopra, 2016; Sade, 2020; Wen, 2024; Yadav, 2019; Yadav, 2022; Zainudin, 2024	6	0.13 (0.09–0.19)	37
	SGA	Yadav, 2019; Wang, 2018; LaCourse, 2016; Zainudin, 2024; Garry, 2024	5	0.20 (0.14–0.28)	36
	Neonatal TB	Yadav, 2019; Sengupta, 2018; Ullah, 2024	3	0.03 (0.01–0.06)	21
	Neonatal death	Sade, 2020; Wen, 2024; Yadav, 2019; Buddhewar, 2022; Sengupta, 2018; Ullah, 2024; Zainudin, 2024	7	0.05 (0.03–0.08)	30

Table 3 presents a comprehensive meta-analysis of birth outcomes in pregnant women with TB in the included studies. The most frequent birth outcomes were low birth weight, preterm birth, small for gestational age (SGA), and low Apgar score (<7), with pooled prevalences of 30% (95% CI: 24–37%; eight studies),<sup>14–18,21–23</sup> 22% (95% CI: 17–28%; 13 studies),<sup>10,11,13–19,21–24</sup> 20% (95% CI: 14–28%; five studies),<sup>11,20–23</sup> and 13% (95% CI: 9–19%; six studies),<sup>10–14,22</sup> respectively. Neonatal TB was reported in three studies, showing a pooled prevalence of 0.03 (95% CI: 0.01–0.06).<sup>11,17,19</sup> The pooled prevalence of stillbirth and neonatal death was 6% (95% CI: 4–10%; six studies)<sup>10–12,18,22,24</sup> and 5% (95% CI: 3–8%; seven studies),<sup>11,13,14,17–19,22</sup> respectively. A low to moderate level of heterogeneity ( $I^2 = 30–52\%$ ) was observed.

Figures 2 to 4 depict the forest plot analysis of the pooled effect sizes with 95% confidence intervals (CI) for major pregnancy and perinatal complications in relation to TB during pregnancy. In Figure 2, most studies show effect sizes on the same side of the null line, suggesting an overall increased risk of low birth weight (LBW), preterm birth (PTB), and SGA. The combined effect estimate in Figure 3 suggests a higher risk of stillbirth and neonatal mortality, while the wide confidence intervals in some studies reflect variability and uncertainty. In Figure 4, the summary estimate indicates an increased risk of maternal mortality. The spread of confidence intervals suggests moderate heterogeneity, emphasizing the need for cautious interpretation of the pooled results.

## DISCUSSION

This systematic review and meta-analysis was conducted to obtain cumulative results

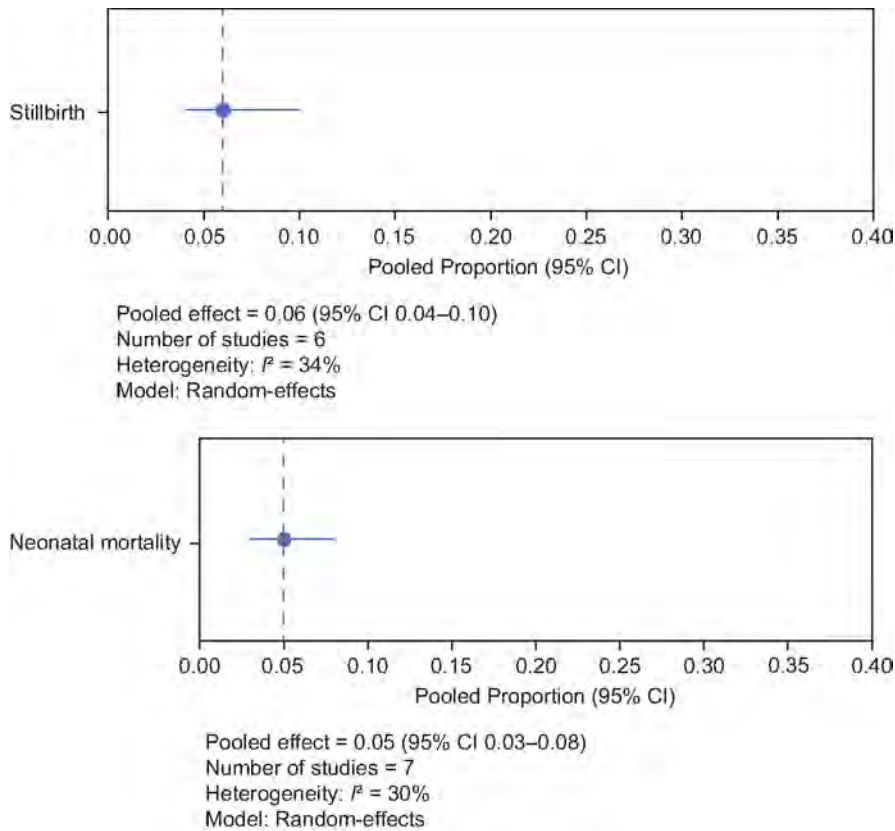


Fig. 3: Forest plot analysis using a random-effects model for stillbirth and neonatal mortality

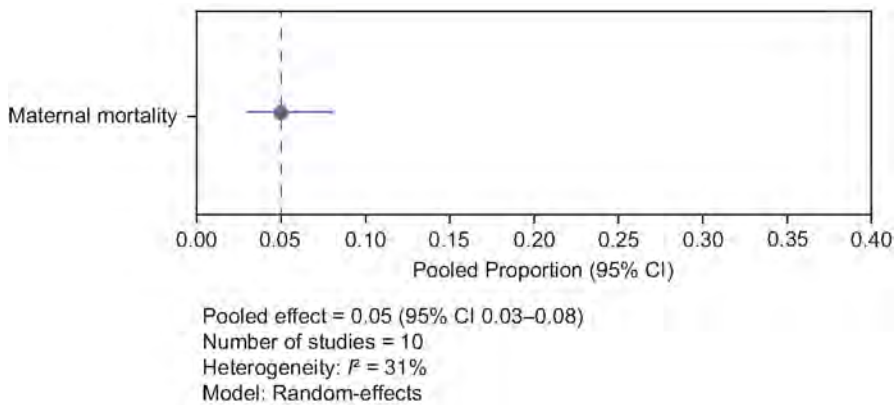


Fig. 4: Forest plot analysis using a random-effects model for maternal mortality

in pregnant patients with TB. Moderate to substantial heterogeneity was found among maternal characteristics, timing of diagnosis, and site of TB, suggesting reasonable consistency among the included studies. A low to moderate level of heterogeneity ( $I^2 = 33\text{--}43\%$ ) was observed for pregnancy-related complications and birth outcomes. The mode of delivery showed moderate heterogeneity ( $I^2 = 44\%$ ), suggesting acceptable variability across studies. Both maternal and neonatal mortality showed low heterogeneity ( $I^2 = 30\text{--}31\%$ ). Despite the variable heterogeneity, the direction of effect remained positive across all studies, supporting a consistent benefit or relationship.

Sobhy et al.<sup>25</sup> performed a systematic review and meta-analysis of studies from inception through December 2015, in which 13 studies were included and 3,384 pregnant women with active TB and 1,19,448 pregnant women without TB were compared. Pregnant women with active TB were found to have higher odds of maternal morbidity, cesarean delivery, anemia, low birth weight, preterm birth, birth asphyxia, and perinatal death [odds ratio (OR): 2.8, 2.1, 3.9, 1.7, 1.7, 4.6, and 4.2, respectively].<sup>25</sup>

### Strengths and Limitations

Our study followed the PRISMA reporting guidelines. The study protocol of this

systematic review was registered with PROSPERO. By applying strict exclusion criteria [such as excluding studies recruiting pregnant women with exclusively human immunodeficiency virus (HIV)-coinfected populations or studies conducted exclusively on infertile populations/*in vitro* fertilization (IVF) pregnancies], the majority of confounding factors were removed from the analysis, thereby strengthening the study results. Studies with a minimum sample size of 10 cases or more were included to enable the selection of studies across variable geographical areas so that the results of this meta-analysis could be applicable worldwide in critical appraisal.

Inclusion of studies was limited to articles published in English only, which likely excluded important findings reported in other languages. The meta-analysis revealed low to moderate heterogeneity among the included studies, which may require further exploration through subgroup analysis or meta-regression to identify the source of heterogeneity.

## INTERPRETATION AND CONCLUSION

Among the maternal characteristics analyzed, mean maternal age showed a stronger and more significant association with the outcome, while low socioeconomic status demonstrated a comparatively smaller effect. TB diagnosed during pregnancy was associated with the greatest adverse effect, followed by prepregnancy diagnosis, while postpartum diagnosis showed the least association, as demonstrated by the highest pooled effect size observed during pregnancy. This highlights the critical impact of TB occurring during pregnancy on maternal and perinatal outcomes, emphasizing the importance of early detection and management.

The pooled effect size for pulmonary TB was high, indicating a strong and statistically significant association with adverse maternal and perinatal outcomes compared with extrapulmonary TB. This highlights that the disease burden and severity associated with pulmonary involvement may contribute more significantly to unfavorable maternal and neonatal outcomes.

Among pregnancy complications, fetal growth restriction showed the strongest association among the listed complications, followed by pregnancy-induced hypertension and oligohydramnios, while gestational diabetes showed the weakest association. This highlights the predominance of placental and vascular complications in TB-affected pregnancies.

Most women delivered vaginally, although cesarean section rates were considerable.

Among birth outcomes, low birth weight and preterm birth were the most common adverse outcomes, while stillbirth and neonatal death occurred less frequently but remain clinically significant concerns.

This systematic review and meta-analysis suggested adverse maternal and perinatal outcomes in pregnant women with TB even in the current era of the 21st century, since the first diagnosed case in 1882.

## ORCID

Hemlata Sharma  <https://orcid.org/0000-0003-4919-9121>

Swati Garg  <https://orcid.org/0000-0002-1519-8166>

Urvashi Sharma  <https://orcid.org/0009-0003-5743-6112>

Ashok Kumar  <https://orcid.org/0009-0009-1724-4881>

## REFERENCES

- World Health Organization. Global Tuberculosis Report 2024. World Health Organization; 2024.
- Indian Council of Medical Research (ICMR). National TB prevalence survey India 2019-2021.
- Starshinova A, Churilov LP, Kudryavtsev I, et al. Immune-neuroendocrine reactivity and features of tuberculosis in pregnancy. *Front Med (Lausanne)* 2025;12:1503402.
- Morton AJ, Roddy Mitchell A, Melville RE, et al. Mycobacterium tuberculosis infection in pregnancy: a systematic review. *PLOS Glob Public Health* 2024;4(11):e0003578.
- WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022.
- Maugans C, Loveday M, Hlangu S, et al. Best practices for the care of pregnant people living with TB. *Int J Tuberc Lung Dis* 2023;27:357–366.
- Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clin Infect Dis* 2012;55:1532–1549.
- Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [www.ohri.ca/programs/clinical\_epidemiology/oxford.asp].
- IBM SPSS Statistics 29.0.2.0. <https://www.ibm.com/support/pages/node/7091371>
- Chopra S, Siwatch S, Aggarwal N, et al. Pregnancy outcomes in women with tuberculosis: a 10-year experience from an Indian tertiary care hospital. *Trop Doct* 2017;47(2):104–109.
- Yadav V, Sharma JB, Kachhawa G, et al. Obstetrical and perinatal outcome in pregnant women with extrapulmonary tuberculosis. *Indian J Tuberc* 2019;66(1):158–162.
- Yadav V, Sharma JB, Kriplani A, et al. Obstetrics outcome in pulmonary tuberculosis. *Indian J Tuberc* 2022;69(3):305–310.
- Wen J, He JQ. Clinical characteristics and pregnancy outcomes in pregnant women with TB: a retrospective cohort study. *Ann Med* 2024;56(1):2401108.
- Sade S, Wainstock T, Sheiner E, et al. Perinatal outcome and long-term infectious morbidity of offspring born to women with known tuberculosis. *J Clin Med* 2020;9(9):2768.
- Lewis PF, Budhewar AS, Bavdekar NB. Fetomaternal outcome of pregnant women infected with tuberculosis: an analytical study. *J South Asian Feder Obst Gynae* 2021;13(4):197–201.
- Tushar, Singh Ralawata A, Singh S. Tuberculosis. Patients with pregnancy and their fetomaternal outcome: an analytical study. *Int J Pharm Clin Res* 2024;16(7):1491–1496.
- Ullah I, Hassan N, Mumtaz HN, et al. Impact of tuberculosis on fetomaternal outcomes in postnatal cases, Dir Lower, Khyber Pakhtunkhwa, Pakistan. *Afr J Biomed Res* 2024;27:3338–3346.
- Buddhewar AS, Anand MN, Anand NP, et al. Comparative study of maternal and fetal outcome of tuberculosis in pregnancy in tertiary care centre. *Int J Reprod Contracept Obstet Gynecol* 2022;11:1483–1490.
- Sengupta M, Dasgupta A, Santra D, et al. Clinical manifestations and challenges in management of tuberculosis in pregnancy in a rural setting in Eastern India. *J South Asian Feder Obst Gynae* 2018;10(1):15–22.
- Wang K, Ren D, Qiu Z, et al. Clinical analysis of pregnancy complicated with miliary tuberculosis. *Ann Med* 2022;54(1):71–79.
- LaCourse SM, Greene SA, Dawson-Hahn EE, et al. Risk of adverse infant outcomes associated with maternal tuberculosis in a low burden setting: a population-based retrospective cohort study. *Infect Dis Obstet Gynecol* 2016;2016:6413713.
- Zainudin Z, Nunis M, Abdulla A, et al. Adverse neonatal outcome associated with maternal tuberculosis in a public tertiary centre: a retrospective cohort study. *Med J Malaysia* 2024;79:337–341.
- Garay-Aguilar NV, Reynoso-Rosales LR, Llamovilcherrez AP, et al. Tuberculosis in pregnancy and adverse neonatal outcomes in two Peruvian hospitals. *Eur J Obstet Gynecol Reprod Biol X* 2024;22:100304.
- El-Messidi A, Czuzoj-Shulman MN, Spence AR, et al. Medical and obstetric outcomes among pregnant women with tuberculosis: a population-based study of 7.8 million births. *Am J Obstet Gynecol* 2016;215(6):797.e1–797.e6.
- Sobhy S, Babiker ZOE, Zamora J, et al. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. *BJOG* 2016.

Your Magnificent Choice



for a

**MEGA** Life



# ME-MEGA™

Calcium Citrate Malate 1100 mg (eq. to el. calcium 250 mg) + Magnesium Hydroxide 180 mg  
(eq. to el. Magnesium 75 mg) + Zinc Sulphate Monohydrate 13.72 mg (eq. to el. Zinc 5 mg) +  
Vitamin D<sub>3</sub> 2000 IU + Methylcobalamin 1500 mcg + L-Methyl Folate Calcium 1 mg + Pyridoxal-5-Phosphate 20 mg

In

Neuromuscular Weakness | Diabetic Peripheral Neuropathy | Post Stroke Recovery  
Osteoporosis/Osteopenia | For Better Outcomes in Pregnancy

Also Available

## ME-12 OD®

Mecobalamin 1500 mcg (E.R.) + Pyridoxine HCl 20 mg + Folic Acid 5 mg Tablets

## ME-D3™

Methylcobalamin 1500 mcg + Alpha Lipoic Acid 100 mg + Vitamin D<sub>3</sub> 1000 IU + Pyridoxine Hydrochloride 3 mg + Folic Acid 1.5 mg Tablets



# From Clinic to Community: A Public Health Framework for Metabolic Dysfunction-associated Steatotic Liver Disease Prevention in India

Shambo Samrat Samajdar<sup>1</sup>\*, Sanjay Bandyopadhyay<sup>2</sup>, Shashank R Joshi<sup>3</sup>

Received: 14 July 2025; Accepted: 06 November 2025

## ABSTRACT

**Background:** India is witnessing a rapid rise in metabolic dysfunction-associated steatotic liver disease (MASLD), driven by the country's expanding population with obesity, type 2 diabetes (T2D), and other metabolic comorbidities. Despite this growing burden, structured liver disease screening is absent from routine noncommunicable disease (NCD) services at the primary care level.

**Problem:** A majority of MASLD diagnoses in India occur only after progression to advanced fibrosis or cirrhosis, even among individuals regularly engaged with healthcare systems for diabetes or hypertension. Primary health centers (PHCs) and community health centers (CHCs) currently lack standardized protocols for liver risk stratification, leading to critical missed opportunities for early intervention.

**Approach:** This article outlines a scalable, systems-integrated model for community-based liver care, piloted at the All India Institute of Medical Sciences (AIIMS), Rishikesh. The model incorporates noninvasive fibrosis scoring tools (FIB-4, APRI), selective deployment of nurse-led FibroScan services, maternal hepatitis B virus screening, lifestyle modification strategies, and digital follow-up systems—seamlessly embedded within existing maternal health and NCD platforms.

**Insights:** A real-world vignette from an urban diabetes outreach program in Kolkata illustrates the diagnostic gap: a high-risk patient remained undiagnosed for MASLD despite multiple healthcare encounters. International experiences, such as the Gwent model in Wales, further reinforce the feasibility of decentralized hepatology through community triage, nurse-led services, and simplified biochemical tools.

**Conclusion:** India stands at a pivotal moment in redefining hepatology as a preventive, public health-oriented discipline. By embedding liver screening within existing NCD frameworks, leveraging task-sharing, and mobilizing digital infrastructure and public-private partnerships, India can develop a replicable model for early MASLD detection and intervention. This community hepatology framework—if scaled nationally—has the potential to position India as a global leader in MASLD prevention for low- and middle-income countries.

*Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1511*

## INTRODUCTION: THE MASLD EPIDEMIC IN INDIA

India, home to more than 130 million individuals living with obesity, type 2 diabetes (T2D), or both, is confronting an accelerating epidemic of metabolic liver disease.<sup>1–3</sup> Historically, liver-related mortality in the region was driven by viral hepatitis. However, this paradigm is rapidly shifting. Metabolic dysfunction-associated steatotic liver disease (MASLD) has now emerged as the leading cause of chronic liver disease globally, and India is poised to bear a disproportionate share of this burden.<sup>3</sup>

Despite this shift, MASLD frequently goes unrecognized until the onset of advanced fibrosis or cirrhosis. Alarming, this often occurs despite multiple interactions with the healthcare system for coexisting metabolic conditions. The lack of systematic liver risk assessment at the level of primary health

centers (PHCs) and community health centers (CHCs) represents a critical missed opportunity.

This emerging crisis reflects more than just an epidemiological transition. It underscores a failure to integrate hepatology into India's broader noncommunicable disease (NCD) control strategy, where diabetes, hypertension, and cardiovascular risks are prioritized, but liver health is conspicuously absent.

## REAL-WORLD ILLUSTRATION: MISSED MASLD DETECTION IN ROUTINE CARE

A real-world case from North Kolkata underscores persistent gaps in the early detection of metabolic dysfunction-associated steatotic liver disease (MASLD) within India's primary care system. A 44-year-old woman, residing in an underserved

urban locality and living with T2D for nearly a decade, presented repeatedly to healthcare facilities over a 3-year period with symptoms including fatigue and dyspepsia. Despite at least seven clinical visits to different providers, no liver-related investigations were initiated during this time.

Her diagnosis of advanced liver fibrosis (F3–F4) occurred only when she participated in a mobile diabetes outreach initiative that incorporated point-of-care liver stiffness assessment via FibroScan. Until this point, liver risk had not been addressed—despite her longstanding T2D, a well-established risk factor for MASLD.

This scenario is not isolated. Multiple studies have documented the underdiagnosis of MASLD in patients with T2D, particularly within fragmented care systems lacking structured screening algorithms. One recent global consensus emphasized that 50–70% of individuals with T2D have concurrent MASLD, yet the majority remain undiagnosed in standard NCD programs due to the absence of embedded fibrosis risk stratification protocols.<sup>4</sup>

Following her diagnosis, the patient was linked to specialist care and enrolled in a multidisciplinary lifestyle counseling program—an outcome contingent on the community initiative, not standard clinical care.

This case illustrates the need for urgent integration of MASLD screening into routine diabetes and hypertension pathways. Without such alignment, high-risk individuals

<sup>1</sup>Assistant Professor, Department of Clinical Pharmacology, JMN Medical College and Hospital, Nadia; <sup>2</sup>Senior Consultant, Department of Gastroenterology, ILS Hospital, Dumdum, Kolkata, West Bengal; <sup>3</sup>Consultant, Department of Endocrinology, Joshi Clinic, Mumbai, Maharashtra, India; \*Corresponding Author

**How to cite this article:** Samajdar SS, Bandyopadhyay S, Joshi SR. From Clinic to Community: A Public Health Framework for Metabolic Dysfunction-associated Steatotic Liver Disease Prevention in India. *J Assoc Physicians India* 2026;74(7):67–69.

continue to fall through the cracks—resulting in missed opportunities for early intervention and disproportionate escalation of healthcare costs and liver-related morbidity.

## OPERATIONALIZING PREVENTIVE HEPATOLOGY: THE AIIMS RISHIKESH MODEL

In response to India's rising MASLD burden and the absence of structured liver care integration within primary health services, the All India Institute of Medical Sciences (AIIMS) Rishikesh has conceptualized and implemented a Preventive Hepatology framework within its Department of Community and Family Medicine.<sup>5</sup> This initiative represents one of the country's first systematic efforts to decentralize liver disease prevention using public health infrastructure.

The model encompasses several key operational elements:

- **Noninvasive risk stratification:** Liver fibrosis risk is evaluated using widely validated, low-cost, noninvasive tools—such as FIB-4 and APRI—embedded into clinical workflows at antenatal care (ANC) and noncommunicable disease (NCD) clinics.
- **Point-of-care technology deployment:** Vibration-controlled transient elastography (FibroScan) is selectively deployed in peripheral clinics and community health initiatives, enabling early-stage fibrosis detection without tertiary referral.
- **Task-shifting to interdisciplinary teams:** Screening and counseling are led by trained nursing staff and supported by a team of physiotherapists, public health practitioners, and dietitians—demonstrating scalable models of task delegation in resource-limited settings.
- **Maternal hepatitis B screening and immunoprophylaxis:** The program includes universal maternal HBV testing and administration of timely birth-dose vaccination, aligned with WHO's hepatitis elimination goals.
- **Lifestyle and digital integration:** Patients at risk receive structured lifestyle modification counseling and digital follow-up through a mobile-enabled tracking system, designed to promote continuity of care and remote monitoring.

Although formal program evaluation is ongoing, this model has shown early feasibility and system alignment, particularly within India's National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS). By embedding

liver health into existing maternal and metabolic services, AIIMS Rishikesh offers a replicable template for other institutions and states.

Notably, the framework aligns with international guidelines from the World Health Organization (WHO) and the British Society of Gastroenterology (BSG), both of which recommend integrating early liver disease risk stratification into primary care settings.<sup>6,7</sup> Similarly, the American Association for the Study of Liver Diseases (AASLD) emphasizes noninvasive diagnostics, behavioral interventions, and multidisciplinary delivery as core principles of MASLD care across diverse health systems.<sup>8</sup>

This program underscores the viability of a community-centric liver care model in low- and middle-income countries (LMICs)—offering a scalable, evidence-informed strategy to address the metabolic liver disease epidemic.<sup>5</sup> Figure 1 illustrates the core components of India's community-based MASLD prevention framework, highlighting risk stratification, nurse-led diagnostics, maternal screening, digital follow-up, and integration into existing NCD programs.

### Toward Integrated, Equitable Hepatology Services

India's National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) presents a timely and strategic opportunity to incorporate liver disease screening into the country's broader NCD infrastructure.<sup>9</sup> Given the shared metabolic etiology of MASLD with type 2 diabetes, hypertension, and obesity, a unified public health strategy is both operationally feasible and economically prudent.

A forward-looking, community-anchored framework for MASLD prevention and control should include the following components:

- **Workforce enablement:** Strengthen the capacity of frontline workers—Accredited Social Health Activists (ASHAs) and Auxiliary Nurse Midwives (ANMs)—to identify at-risk individuals using simplified, community-appropriate criteria (e.g., elevated BMI, waist circumference, or coexisting T2D/hypertension).
- **Integrated risk stratification:** Embed validated liver risk algorithms (e.g., FIB-4, APRI, AST: ALT ratios) into routine workflows at primary health centers (PHCs) and community health centers (CHCs)—alongside established NCD screening and follow-up protocols.
- **Digital surveillance infrastructure:** Establish longitudinal liver health

registries to enable individual-level tracking, fibrosis risk stratification, and system-wide referral coordination. This also facilitates real-time program monitoring and research.

- **Multisectoral resource mobilization:** Leverage corporate social responsibility (CSR) funding, nongovernmental organization (NGO) engagement, and public-private partnerships to expand access to key diagnostics—such as portable FibroScan units and serological tests (HBV/HCV)—as well as to support awareness campaigns in high-burden regions.

Importantly, this approach calls for a paradigm shift in hepatology practice. The discipline must move beyond its traditional confines within tertiary-care, hospital-centric systems and embed itself horizontally across the public health continuum. For MASLD—a disease that evolves silently and intersects deeply with metabolic and social determinants—prevention must begin at the community level, not at the stage of irreversible liver injury.

By aligning hepatology with India's robust NCD framework, the country has the opportunity not only to improve early detection and intervention, but also to establish a scalable model for low- and middle-income countries (LMICs) navigating similar epidemiologic transitions.

### POLICY AND PROFESSIONAL REORIENTATION

The rapid emergence of metabolic dysfunction-associated steatotic liver disease (MASLD) as the predominant cause of chronic liver disease—both globally and in India—marks a critical inflection point for the discipline of hepatology. The prevailing model, which confines liver care largely to tertiary-care settings, is increasingly insufficient in addressing a condition that is silent, progressive, and fundamentally metabolic in origin.

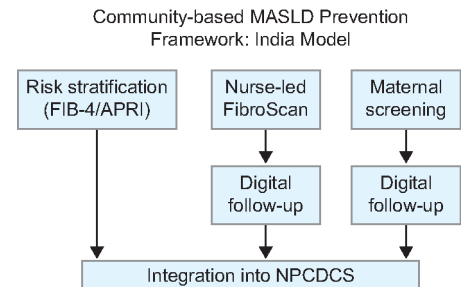


Fig. 1: Community-based MASLD prevention framework: India model

To deliver equitable, preventive, and system-wide liver care, hepatology must evolve from a specialist-centric, hospital-based domain into a public health-integrated specialty, embedded across levels of care. This transformation is supported by recent expert consensus from Indian endocrinologists and hepatologists, which emphasizes early screening, primary-level fibrosis risk stratification, and multidisciplinary community-based management of MASLD in individuals with type 2 diabetes.<sup>4</sup>

To institutionalize this reorientation, three strategic policy and training reforms are urgently required:

- *Formal recognition of preventive hepatology as a subspecialty:* A dedicated subspecialty in preventive hepatology, under the umbrella of the National Health Mission (NHM) and NPCDCS, would provide the necessary institutional scaffolding for integrating liver health into national health priorities. This recognition would:
  - Enable structured curricula emphasizing decentralized liver care, including population-based screening and risk stratification;
  - Facilitate targeted programmatic funding and infrastructure allocation for MASLD prevention;
  - Encourage a new cadre of hepatologists trained in community-facing and preventive frameworks.
- This aligns with the Indian MASLD Consensus recommendations, which advocate for proactive identification of MASLD among individuals with diabetes and other metabolic risks.<sup>4</sup>
- *Incentivized engagement of hepatologists in primary care and NCD platforms:* Bringing hepatology expertise closer to underserved populations requires system-level incentives that embed hepatologists within primary health centers (PHCs), community health centers (CHCs), and Ayushman Bharat Health and Wellness Centers. Mechanisms may include:
  - Institutional mandates require medical colleges and academic hospitals to participate in district-level hepatology outreach.
  - Telementoring programs (e.g., ECHO model) to link hepatology specialists with rural providers.
  - Integration of hepatology into NCD clinic workflows, supported by simplified screening tools and referral algorithms.

- Such engagement would support earlier MASLD detection, slow fibrosis progression, and reduce tertiary-care dependence—echoing both Indian and international MASLD management frameworks.
- *Embedding public health competency in hepatology training:* As hepatology expands its scope to intersect with NCD control, fellowship programs must evolve to equip future hepatologists with the tools for population health impact. Core competencies should include:
  - Epidemiology, screening program design, and burden estimation.
  - Health systems and implementation science, with a focus on cost-effective, scalable interventions.
  - Behavioral and lifestyle medicine, including motivational interviewing and community engagement.

This transition aligns with ongoing reforms by the National Medical Commission (NMC) to integrate public health, communication, and systems-based practice into specialty training pathways, ensuring that emerging hepatologists can lead prevention strategies in both clinical and community domains.

In sum, reimagining hepatology through a policy-aligned, professionally reoriented, and publicly engaged lens is not only timely—it is essential. Without this shift, hepatology risks remaining reactive and exclusionary, intervening only after irreversible disease progression. Conversely, a preventive, integrated approach will enable India to build a liver care model that is scalable, inclusive, and globally relevant.

## CONCLUSION: TOWARD GLOBAL LEADERSHIP IN MASLD PREVENTION

In the era of metabolic dysfunction-associated steatotic liver disease (MASLD), hepatology must undergo a paradigmatic shift—from a reactive, tertiary-based specialty to a proactive, community-integrated discipline. With more than 130 million Indians living with obesity or type 2 diabetes, the country sits at the epicenter of a rising tide of metabolic liver disease.

Fortunately, India's robust public health infrastructure—including the National Health Mission (NHM), Ayushman Bharat Health and Wellness Centers, and the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke

(NPCDCS)—offers a unique opportunity to mainstream liver care into population-level strategies. Embedding MASLD risk stratification into routine NCD workflows, leveraging task-sharing models, and expanding digital health tools can collectively shift the diagnostic curve toward early detection and intervention.

This transformation is not only clinically urgent but also ethically essential. The integration of liver health within primary care reflects a commitment to health equity—ensuring that the benefits of early MASLD detection are not confined to urban tertiary hospitals but reach the underserved millions most at risk.

With strategic investments—through CSR funding, international partnerships (e.g., World Bank), and alignment with NHM budgetary priorities—India is positioned to lead by example. This community-based framework offers a replicable template for other low- and middle-income countries (LMICs) navigating similar epidemiological transitions.

With the right systems in place, India can pioneer a globally relevant model for MASLD prevention—grounded in community health and equity. The time to act is now.

## ORCID

Shambo Samrat Samajdar  <https://orcid.org/0000-0002-9199-0905>  
 Shashank R Joshi  <https://orcid.org/0000-0003-2741-5022>

## REFERENCES

1. Magliano DJ, Boyko EJ. IDF Diabetes Atlas 10th edition. Brussels: International Diabetes Federation; 2021.
2. World Obesity Federation. World Obesity Atlas 2023. London: World Obesity Federation; 2023.
3. International Institute for Population Sciences (IIPS) and ICF. National Family Health Survey (NFHS-4), India, 2015–16. Mumbai, India. Mumbai: IIPS; 2017.
4. Zargar AH, Bhansali A, Majumdar A, et al. Management of metabolic dysfunction-associated steatotic liver disease (MASLD): an expert consensus statement from Indian diabetologists' perspective. *Diabetes Obes Metab* 2025;27(Suppl 4):3–20.
5. Bhadoria AS, Saxena G, Pandey P, et al. Preventive hepatology at AIIMS Rishikesh: Delivering comprehensive and integrated care for liver diseases in Northern state of India. *J Family Med Prim Care* 2024;13(1):28–35.
6. World Health Organization. Guidelines on hepatitis B and C testing. Geneva: WHO; 2017.
7. Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut* 2018;67(1):6–19.
8. Rinella ME, Lazarus JV, Ratzliff V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;78(6):1966–1986.
9. Thakur JS, Paika R, Singh S. Burden of noncommunicable diseases and implementation challenges of National NCD Programs in India. *Med J Armed Forces India* 2020;76(3):261–267.

# Continuous Glucose Monitoring—Purposes, Benefits, and Problems: A Review of the Indian Scenario



Anushtha Kushwaha<sup>1\*</sup>, Aarti Niveditha Kodirekkala<sup>2</sup>, Aruna Saharawat<sup>3</sup>, Rashi Jaiswal<sup>4</sup>

Received: 08 January 2024; Accepted: 04 March 2026

## ABSTRACT

One of the global epicenters of the diabetes mellitus pandemic is India. Over the past 40 years, there has been a sharp rise in the prevalence of diabetes mellitus in India due to rapid socioeconomic development, demographic shifts, and increasing susceptibility in the Indian population. Diabetes affects 74.2 million individuals in India, which places a significant strain on the country's economy and healthcare system. A patient's diet, lifestyle, medication, and glucose monitoring must all be customized for optimal diabetes control. The rates of glucose monitoring in India are abysmal. Most of the monitoring methods currently in use are based on single-point-in-time readings, which may not be totally indicative of the state of diabetes control. This presents problems. With advancements in technology, the new monitoring tool—continuous glucose monitoring (CGM)—provides visibility into the glycemic profile 24 × 7 with user-friendly reports that provide information much beyond glycated hemoglobin (HbA1c) and self-monitoring of blood glucose. This device also detects the time spent in range by the individual with diabetes. This review article discusses CGM in terms of its purposes, technologies, accuracy, clinical indications, benefits, and problems associated with it.

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1615

## INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic noncommunicable disease that has attained an epidemic proportions worldwide. Diabetes is primarily caused by genetic factors, immune disorders, and other influences impacting the human body. These elements cause insulin resistance and a decline in islet function, which throws off glucose homeostasis. The manifestation of this imbalance is seen as a failure in glucose metabolism and the presence of hyperglycemia.<sup>1</sup> Diabetes is classified into two main types: type 1 and type 2. Diabetes type 1 is caused by a scarcity of insulin secretion in the pancreas. Type 2 DM, however, primarily occurs when patients experience a reduction in insulin sensitivity and an increase in insulin resistance, leading to ineffective insulin use.<sup>2</sup> More than 415 million persons in the world had diabetes mellitus in 2015; by 2040, that figure is expected to rise to 642 million.<sup>1</sup> As per the Indian Council of Medical Research–India Diabetes (ICMR INDIAB) study published in 2023, the prevalence of diabetes is 10.1 crores. The Indian Council of Medical Research (ICMR) in 1971 initiated the first multicenter study on diabetes mellitus. The prevalence of the disease was found to be 2.1% in the urban areas and 1.5% in the rural areas.<sup>3</sup>

Research on diabetes mellitus and its complications has expanded in tandem with the disease's rising incidence in India. There are several different types of diabetes

technology, including continuous glucose monitoring (CGM) and insulin pumps. Insulin pumps have made insulin delivery more convenient, while CGM has replaced finger pricks in diabetes management. In this review, we discuss the complications of diabetes mellitus in India, focusing on the purpose, technology, accuracy, indications, and outcomes of CGM.

## NEED FOR GLUCOSE MONITORING

Diabetes has a natural progression to end-stage complications. Thus, maintaining good glycemic control is critical in the management of diabetes, especially in its initial stages, as this leads to what is known as a “good glycemic legacy.” Good control is associated with a reduction in both macro- and microvascular complications of diabetes. Diabetes control is assessed by several monitoring techniques, i.e., self-monitoring of blood glucose (SMBG) and laboratory tests, including hemoglobin A1c (HbA1c) and fasting and postprandial blood glucose levels. Unfortunately, monitoring is not given the importance it deserves within the diabetes management domain.<sup>4</sup>

The gold standard in diabetes management is glycated hemoglobin (HbA1c), which indicates the average blood glucose level over a span of 2–3 months. Although it offers a great measure of long-term control, it lacks any information about the daily aspects. Glucose levels

can fluctuate. In addition, research has shown that individuals with identical levels of HbA1c may experience varying levels of fluctuating glucose. Laboratory tests such as fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) are commonly prescribed, but they solely indicate the glucose levels for that particular day. In a country such as India, where people traditionally consume high-carbohydrate meals three times a day, the sporadic information provided by FPG and PPG does not accurately reflect the actual state of diabetes control. The introduction of continuous glucose monitoring brought about a significant advancement in glucose monitoring in this scenario (Table 1).<sup>5</sup>

**Table 1:** Differences between CGM and IGM<sup>7</sup>

Continuous glucose monitoring	Intermittent glucose monitoring
Provides multiple glucose levels of fair accuracy	Measures discrete glucose levels extremely accurately
Trends in glucose levels do have this predictive capability	Current blood glucose levels do not indicate future glucose levels
Too much data is generated to study all data points	Studying each measured blood glucose value throughout various time periods is simple
Blood glucose monitoring does not require effort to operate	Blood glucose monitoring requires effort to operate

IGM, intermittent glucose monitoring

<sup>1</sup>MDS, Department of Public Health Dentistry;

<sup>2</sup>MDS, Department of Oral and Maxillofacial Pathology; <sup>3</sup>BDS, Treble Aesthetics; <sup>4</sup>MDS, Department of Oral Medicine and Radiology, Greater Noida, Uttar Pradesh, India;

\*Corresponding Author

**How to cite this article:** Kushwaha A, Kodirekkala AN, Saharawat A, et al. Continuous Glucose Monitoring—Purposes, Benefits, and Problems: A Review of the Indian Scenario. *J Assoc Physicians India* 2026;74(7):70–72.

## CONTINUOUS GLUCOSE MONITORING: PURPOSES

The commercial availability of CGM began in 2000. It provides information unattainable by intermittent capillary blood glucose, including instantaneous real-time display of glucose levels and rate of change of glucose, alerts and alarms for actual or impending hypo- and hyperglycemia, “24/7” coverage, and the ability to characterize glycemic variability. CGM has the capability of informing, educating, motivating, and alerting people with diabetes. CGM is medically indicated for patients with frequent, severe, or nocturnal hypoglycemia, especially in the presence of hypoglycemia unawareness.<sup>6</sup> Continuous glucose readings that supply trend information can help identify and prevent unwanted periods of hypo- and hyperglycemia.

## CONTINUOUS GLUCOSE MONITORING: TECHNOLOGY

The CGMs that are now on the market monitor blood glucose either noninvasively

**Table 2:** Differences between the two types on CGM<sup>5</sup>

Parameters	Professional CGM	Personal CGM
Owned by	Healthcare professionals	Patients him/herself or caregivers
Real-time readings	No	Yes
Analysis	CGM data analyzed by healthcare professionals	Patients can take decisions according to hypo/hyperglycemia
Advantages	It gives a clear picture of the most probable behavior of blood glucose and outliers	Increases TIR
	Helps HCPs and patients to discuss intervention areas through diet and lifestyle	Shows daily variability of glucose levels. Reduction in HbA1c, hospitalization, and work absenteeism
	Allows detection of unknown hypoglycemia	Provides a detailed view of day-to-day glucose readings that help patients

HbA1c, glycosylated hemoglobin

by delivering electromagnetic radiation via the skin to the body’s blood vessels or minimally invasively by continuously measuring interstitial fluid (ISF). To establish a connection between a sensor and ISF, different technological approaches can be employed. These methods involve either implanting a sensor under the skin (such as in the abdominal wall or arm) to directly measure ISF in its natural location, or utilizing techniques that disrupt the skin barrier to gather the fluid and transfer it to an external sensor.

In the United States, the US Food and Drug Administration has granted approval for five CGM devices, while in Europe, these devices have obtained the CE mark for utilization. The Continuous Glucose Monitoring System-Gold (CGMS-Gold) from Medtronic MiniMed, located in Northridge, CA, is one of the devices included in this collection. Another device is the GlucoWatch G2 Biographer (GW2B) from Cygnus in Redwood City, CA. Medtronic MiniMed also offers the Guardian Glucose Monitoring System. Lastly, there is GlucoDay from a currently unspecified location. Menarini Diagnostics is based in Florence, Italy, and Pendra (Pendragon Medical) is located in Zurich, Switzerland. The FreeStyle Navigator Continuous Glucose Monitor, produced by Abbott Laboratories in Alameda, CA, is the sixth monitor to undergo FDA premarket approval.<sup>7</sup>

Continuous glucose monitors can be classified into professional and personal CGMs. See Table 2 for differences enumerated between these two CGM types. As the name suggests, a professional CGM is meant for use by the treating healthcare professionals (HCPs), and it provides a set of reports that can be downloaded for discussion between the HCP and the patient. In contrast, the personal version is designed to be a personal device specifically for patients, enabling them to monitor their own glucose levels. There are two versions of CGM available in India: one for HCPs and the other for patients to monitor their diabetes control.<sup>5</sup>

## Real-time Continuous Glucose Monitoring

The real-time continuous glucose monitoring (RT-CGM) is a compact, hassle-free system that avoids finger pricks and provides 288 glucose readings in a single day. There is a 20-minute delay in the glucose concentrations in the interstitial fluid compared to the glucose concentrations in the blood. RT-CGM is immensely advantageous and the preferred method for detecting nocturnal or unidentified hypoglycemia and glycemic variability (GV). The range of RT readings offered extends from 5 to 6 days up to 10–14 days. The incidence

of hyperglycemia can be reduced by using RT-CGM. The mean absolute relative difference (a measure of the accuracy of the CGM systems) of the latest device is extremely low, showing its precision and accuracy.<sup>8,9</sup> It is now universally agreed that maintaining a time in range (TIR) of at least 70% (i.e., blood glucose is under control for 70% of the time in a day—which represents good glucose control for 16.8 hours within 24 hours) would effectively prevent the complications of diabetes. TIR has a direct correlation to HbA1c in both type 1 diabetes (T1DM) and type 2 diabetes (T2DM). Every 10% increase in TIR brings a ~0.5% reduction in HbA1c in T2DM and a ~0.8% reduction in HbA1c in T1DM and T2DM. In various published studies, the use of TIR is effective at improving diabetes outcomes through the benefits offered.<sup>10</sup>

## CONTINUOUS GLUCOSE MONITORING: CLINICAL INDICATIONS

Continuous monitoring of blood glucose is necessary in various situations that demand specific and detailed information. These situations include adjusting therapy to manage diabetes effectively, evaluating the effectiveness of a diabetes treatment through trials, determining the influence of lifestyle changes on glycemic control, monitoring conditions that require strict control without risking low blood sugar levels (such as gestational diabetes, pediatric diabetes, or patients in the intensive care unit), identifying and preventing hypoglycemia during sleep or in cases of hypoglycemia unawareness, and diagnosing and managing postprandial hypoglycemia. Continuous blood glucose monitoring is mostly used to support therapeutic modifications aimed at enhancing control. Specific therapeutic adjustments include changing from regular to a synthetic ultra-short-acting insulin analog at mealtime, changing from NPH to synthetic ultra-long-acting insulin once or twice per day, varying the insulin bolus amount given at mealtime and varying the basal insulin rate, modifying the insulin to glucose adjustment algorithm for premeal hyperglycemia, as well as the way that intermittent hypoglycemia or hyperglycemia are treated, changing the insulin-to-carbohydrate ratio at mealtime, changing the method for counting carbohydrates, changing the carbohydrate composition of the diet, changing the discount in short-acting insulin dosage for exercise, changing the nighttime regimen because of the dawn phenomenon, modifying the desired preprandial or postprandial blood glucose levels, or prior to recommending

psychological counseling for a patient in order to enhance treatment regimen adherence.<sup>7</sup>

## CONTINUOUS GLUCOSE MONITORING: LIMITATIONS

One major problem is their lack of accuracy for each single data point compared with the accuracy of simultaneous intermittent blood glucose measurements. CGMs are generally the least accurate in the hypoglycemic range.<sup>11</sup> As CGM sensors detect the glucose level in interstitial fluid rather than in the blood, there are concerns about the lag time resulting in differential readings between the two media. However, this slight delay does not diminish the usefulness of the device. It is crucial to remember that it is currently not possible to stick a sensor into a blood vessel periodically to get blood glucose readings, as it could lead to serious clot formation.<sup>12</sup>

The following are some of the challenges of CGM use:

- Requires patients to insert sensors every 10–14 days, which requires both adequate dexterity and cognitive function.
- Visual impairment may make it difficult for patients to view their CGM data.
- Hearing impairment may make it difficult for patients to detect alarms/alerts when they occur.
- Perceptions of data overload may cause or increase patient anxiety.
- Frequent alarms/alerts can cause “alarm/alert fatigue.” This may cause patients to ignore their alarms/alerts or discontinue CGM use.
- Requires patients or their caregivers to learn how to accurately interpret and appropriately respond to the CGM data.
- It may involve significant out-of-pocket expenses or copays, depending on insurance coverage.<sup>13</sup>
- It reduces hypoglycemia.
- Improves HbA1c.
- The need for fingerstick testing is reduced or eliminated.
- Long-term exposure to midrange glycemia may prove to be more beneficial in preventing complications than experiencing numerous upward hyperglycemic spikes and downward hypoglycemic spikes. This is because it reduces glycemic variability.<sup>7</sup>
- Provides audible alarms/alerts for current and impending hyperglycemia and hypoglycemia.
- Provides downloadable reports that facilitate data interpretation and patient learning.

- Provides features that share data and allow caregivers to view patients’ glycemic status in real-time.
- Rather than relying on a single data point such as HbA1c or fructosamine, continuous glucose monitoring provides valuable information about the time spent in normal, low, and high glucose ranges.
- In addition, continuous glucose monitoring presents the opportunity to express the average blood glucose level in innovative ways. Treatment can cause a rapid shift in the average blood glucose level.<sup>13</sup>

## CONCLUSION

Diabetes is a long-term condition that significantly adds to sickness and death rates. In India, the management of diabetes is disappointingly inadequate, as only one-third of individuals with diabetes are able to reach the desired HbA1c level of less than 7%. As a result, the burden caused by both macro- and microvascular complications remains substantial. Thus, it is imperative to prioritize maintaining optimal glycemic control in all individuals diagnosed with diabetes. The use of innovative technologies such as CGM with real-time readings can aid in enhancing metabolic control, minimizing hypoglycemic episodes, and elevating the overall quality of life. CGM, in the long run, may contribute to minimizing the occurrence of chronic diabetes complications and potentially even lower the rates of morbidity and mortality associated with the condition, resulting in reduced expenses in the healthcare sector. These measures would, in turn, enhance the quality of life for diabetes patients in India. Further investigation is required to accurately record these findings among diabetic patients in India.<sup>5</sup> CGM has several advantages over intermittent glucose monitoring, especially in situations where glycemic patterns are not well understood. With intermittent blood glucose monitoring, one cannot access the information pertaining to the direction, magnitude, duration, frequency, and underlying causes of fluctuations in blood glucose levels, as provided by continuous glucose monitoring. CGMs have proven to be useful when it comes to adjusting therapy or documenting the state of physiology that requires retrospective patterns. A real-time CGM is an abundant resource when one requires simultaneous monitoring of both the absolute level and trend patterns of glycemia.<sup>7</sup>

In today’s era of information overload, it seems highly probable that continuous glucose monitors (CGMs) will soon become

a standard tool for managing diabetes. They will initially cater to individuals struggling to control their diabetes, eventually extending their benefits to the majority of diabetes patients. With the continuous advancement of minimally invasive and non-invasive monitoring methods, diabetic patients will increasingly incorporate this technology into their regular routines. In the 21st century, data printouts emerging from CGMs will serve as a valuable tool for navigating diabetes management more effectively.

## ACKNOWLEDGMENTS

Nil.

## SOURCE OF SUPPORT

Nil.

## CONFLICT OF INTEREST

None.

## REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 7th ed. Brussels: International Diabetes Federation; 2015. pp. 1–140.
2. Tang L, Chang SJ, Chen CJ, et al. Non-invasive blood glucose monitoring technology: a review. *Sensors* 2020;20(23):6925.
3. Ahuja MMS. Epidemiological studies on diabetes mellitus in India. In: Ahuja MMS (ed). *Epidemiology of Diabetes in Developing Countries*. New Delhi: Interprint; 1979. pp. 29–38.
4. Russell-Minda E, Jutai J, Speechley M, et al. Health technologies for monitoring and managing diabetes: a systematic review. *J Diabetes Sci Technol* 2009;3(6):1460–1471.
5. Mohan V, Unnikrishnan R, Mithal A. Continuous glucose monitoring with real-time readings. *Int J Diabetes Technol* 2022;1(4):3–7.
6. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther* 2016;18(2):3–13.
7. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care* 2005;28(5):1231–1239.
8. Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technol Ther* 2009;11(1):6–11.
9. Brynes AE, Adamson J, Dornhorst A, et al. The beneficial effect of a diet with low glycaemic index on 24 h glucose profiles in healthy young people as assessed by continuous glucose monitoring. *Br J Nutr* 2005;9(3):179–182.
10. Kesvadev J, Shankar A, Krishnan G. Is time-independent of A1c? A study in Asian Indian population. *Diabetes* 2020;6(9):880.
11. Klonoff DC. The need for separate performance goals for glucose sensors in the hypoglycemic, normoglycemic, and hyperglycemic ranges. *Diabetes Care* 2004;27(3):834–836.
12. Steil GM, Rebrin K, Hariri F, et al. Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia. *Diabetologia* 2005;48(9):1833–1840.
13. Munshi NM. Continuous glucose monitoring use in older adults for optimal diabetes management. *Diabetes Technol Ther* 2023;25(3):S56–S64.



# Navigating Bone Health in Epilepsy—A Detailed Review of Anticonvulsant-induced Osteomalacia: Its Mechanisms and Therapeutic Strategies

Sundar Sri MK<sup>1</sup>, Karthickeyan Krishnan<sup>2,\*</sup>

Received: 11 December 2025; Accepted: 06 February 2026

## ABSTRACT

Anticonvulsants are the drugs given for managing epilepsy and some other types of neurological disorders; however, their long-term use is increasingly suspected of causing adverse skeletal outcomes, including osteomalacia. Osteomalacia is a condition marked by defective mineralization of bone, leading to bone softening, bone pain, muscle weakness, and predisposition to fractures. The disruption of vitamin D metabolism, impaired calcium absorption, and altered bone turnover are mechanisms attributed to several commonly used anticonvulsants, especially enzyme-inducing agents such as phenytoin, carbamazepine, and phenobarbital, in contributing to osteomalacia. Hence, this review aims to provide detailed information about the pathophysiology, clinical manifestations, diagnosis, and treatment of anticonvulsant-induced osteomalacia. The review places further emphasis on the importance of regular monitoring of bone health in individuals receiving long-term antiepileptic treatment, supplementation, lifestyle interventions, and interprofessional care. A proper understanding of this preventable complication will certainly help healthcare providers to minimize the impact in these patients and improve outcomes.

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1597

## INTRODUCTION

Epilepsy can be a chronic neurological disorder characterized by seizures that recur unprovoked due to abnormal electrical activity in the brain. It affects an estimated 50 million people worldwide, being among the most commonly encountered neurological disorders. The burden of epilepsy is especially felt in shops where diagnosis and treatment cannot be afforded in low- and middle-income countries. Long-term control of seizures is colloquially achieved by the use of anticonvulsant medicines, which, in fact, are the mainstay of therapy.<sup>1</sup>

The anticonvulsant or antiepileptic drug (AED) class contains a wide array of agents including phenytoin, carbamazepine, valproate, phenobarbital, and the newer types such as levetiracetam and lamotrigine. These medications have truly been a blessing in the lives of people living with epilepsy. Long-term use of a drug can cause numerous side effects, one of them affecting bone metabolism. There is emerging evidence in the literature that with prolonged use, some AEDs may cause vitamin D deficiency, hypocalcemia, and consequently arrested bone mineralization, eventually resulting in metabolic bone diseases such as osteomalacia, as shown in Table 1.<sup>4</sup>

Osteomalacia is an endocrine skeletal disorder in adults in which bones soften

because of defective mineralization of osteoid matrix mainly due to vitamin D deficiency with phosphate or calcium metabolism abnormalities. Clinicians find evident bone pain, muscle weakness, and easy fractures in patients. In the setting of anticonvulsant therapy, osteomalacia results from a change in vitamin D metabolism, poor calcium absorption, and impaired bone turnover.

As greater awareness grows around bone health issues with long-term anticonvulsant use, an understanding of the mechanisms of osteomalacia, risk factors for it, and prevention will become more important. This is a review to gather present knowledge on this relevant clinical entity, shedding light on the difficult aspects of diagnosing and managing the disorder. Thereby, enhanced awareness can promote better screening and preventive measures by healthcare providers, hence improving long-term safety under anticonvulsant care.<sup>5,6</sup>

## OVERVIEW OF ANTICONVULSANT CLASSES

Anticonvulsant drugs are thought to begin their career in the therapeutic field with the onset of action: first, older, or generation, depending upon the classification system, and then, second and third generation. The traditional anticonvulsants still cannot be superseded from their respective uses,

ranging over the seizure types. These are the drugs of phenytoin, phenobarbital, carbamazepine, and valproate (Table 2). Although the drugs have been in clinical use for many decades and are still active in numerous seizure types, they have been recognized for their numerous side effects, including effects on bone metabolism and vitamin D deficiency triggered by enzyme induction. Drug burdens include complex pharmacokinetics and numerous drug interactions requiring careful monitoring.<sup>8</sup>

New generation anticonvulsants, such as levetiracetam, lamotrigine, topiramate, oxcarbazepine, and many others, were developed to improve control of seizures with fewer side effects and best tolerability possible (Table 2). They largely have better pharmacokinetic profiles, less interaction potential with other drugs, and some do not induce or inhibit liver enzymes; thus, they avoid certain side effects like bone disease.<sup>9</sup>

## MECHANISMS OF SEIZURE CONTROL

Seizures are caused when there occurs an abnormal, excessive synchronous activity of neurons within the brain. Various mechanisms are used by anticonvulsants to overmodulate neuronal excitability:

- *Enhancement of inhibitory neurotransmission:* Many anticonvulsants act by potentiating gamma-aminobutyric acid (GABA) neurotransmission. For instance, drugs such as phenobarbital and benzo-

<sup>1</sup>Assistant Professor; <sup>2</sup>Professor and Head, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technological and Advanced Studies, Chennai, Tamil Nadu, India; \*Corresponding Author

**How to cite this article:** Sundar Sri MK, Krishnan K. Navigating Bone Health in Epilepsy—A Detailed Review of Anticonvulsant-induced Osteomalacia: Its Mechanisms and Therapeutic Strategies. *J Assoc Physicians India* 2026;74(7):73–79.

**Table 1:** Risk factors

Risk factor	Description
Long-term anticonvulsant use	Long-term use (ranging from months to years) of enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine, phenobarbital) interferes with vitamin D metabolism
Type of anticonvulsant	Usage of enzyme-inducing AEDs tends to increase vitamin D catabolism, whereas the nonenzyme inducers usually have less detrimental effects on bone
Vitamin D deficiency	Pre-existing low vitamin D levels due to inadequate sunlight exposure, poor diet, or malabsorption syndromes
Poor nutritional status	Deficiency in calcium, phosphate, or protein intake can diminish bone mineralization
Limited sunlight exposure	UV-B radiation deficiency lowers the synthesis capacity of vitamin D in the skin
Age	Those who are very old or very young are at an increased risk of bone disorders because their bone density and vitamin D status are impaired naturally
Gender	Women are vulnerable, especially postmenopausal ones, due to hormonal changes that influence bone metabolism
Coexisting medical conditions	Conditions such as chronic kidney disease, malabsorption syndromes (e.g., celiac disease), or liver disease may worsen vitamin D metabolism and bone health
Reduced mobility	Physical inactivity or immobility lessens mechanical stimulation of bone, therefore promoting bone loss
Concurrent medications	Concurrent use of other drugs disruptive to bone metabolism (i.e., glucocorticoids, heparin) only thickens the plot of risk of vitamin D deficiency <sup>2,3</sup>

**Table 2:** Commonly prescribed anticonvulsant drugs associated with osteomalacia

Drug name	Classification	Enzyme induction	Impact on bone health
Phenytoin	Hydantoin	Strong inducer of CYP450	Accelerates vitamin D catabolism: vitamin D deficiency, hypocalcemia, secondary hyperparathyroidism, osteomalacia
Carbamazepine	Dibenzazepine derivative	Strong inducer of CYP450	Similar to phenytoin, reduces vitamin D levels: impaired bone mineralization and increased fracture risk
Phenobarbital	Barbiturate	Strong inducer of CYP450	Increases vitamin D metabolism: osteomalacia and bone demineralization
Valproate	Fatty acid derivative	Weak or no enzyme induction	Less commonly linked; may cause bone loss by indirect mechanisms
Lamotrigine	Phenyltriazine derivative	No significant induction	Minimal impact on vitamin D metabolism and bone health
Levetiracetam	Pyrrolidone derivative	No significant induction	Minimal evidence of bone metabolism disruption
Topiramate	Sulfamate	Weak inducer	Potential mild effects on bone; data limited <sup>7</sup>

diazepines augment GABAergic activity that inhibits neuronal firing.

- **Inhibition of excitatory neurotransmission:** Several anticonvulsants diminish the activity of excitatory neurotransmitters, such as glutamate, thus averting the spread of seizures.
- **Modulation of ion channels:** Sodium and calcium ion channels are essential for the generation and propagation of electrical impulses in neurons. Phenytoin, carbamazepine, and lamotrigine block voltage-gated sodium channels, thereby stabilizing neuronal membranes and preventing repetitive firing. Other drugs may block T-type calcium channels, thereby reducing excitability.

By these diverse mechanisms, anticonvulsants restore the excitatory-inhibitory balance in the CNS and control seizures.<sup>10,11</sup>

**Hepatic Enzyme Induction vs Noninduction**

The liver microsomal cytochrome P450 enzymes CYP3A4 and CYP2C9 remain

a principal set of enzymatic mediators which are induced during the use of anticonvulsants.

- With enzyme-induced drugs such as phenytoin, carbamazepine, and phenobarbital, the induction results in a thousand-fold increase in the activity of liver enzymes metabolizing a variety of compounds, including vitamin D, by accelerating the metabolism of vitamin D metabolites, thus diminishing the serum levels of active vitamin D. Decrease in active vitamin D concentration leads to vitamin D deficiency, lowering the calcium absorption in the gut and consequently causing secondary hyperparathyroidism and bone resorption that may result in osteomalacia.<sup>12</sup>
- Nonenzyme-inducing anticonvulsants such as levetiracetam, lamotrigine, and valproate do not alter liver enzyme activity to any extent; hence, they may not interfere with vitamin D metabolism and bone health to a great extent. Long-term treatment is an important consideration for this distinction, especially for those at risk of bone disease.<sup>13</sup>

**Overview of Osteomalacia**

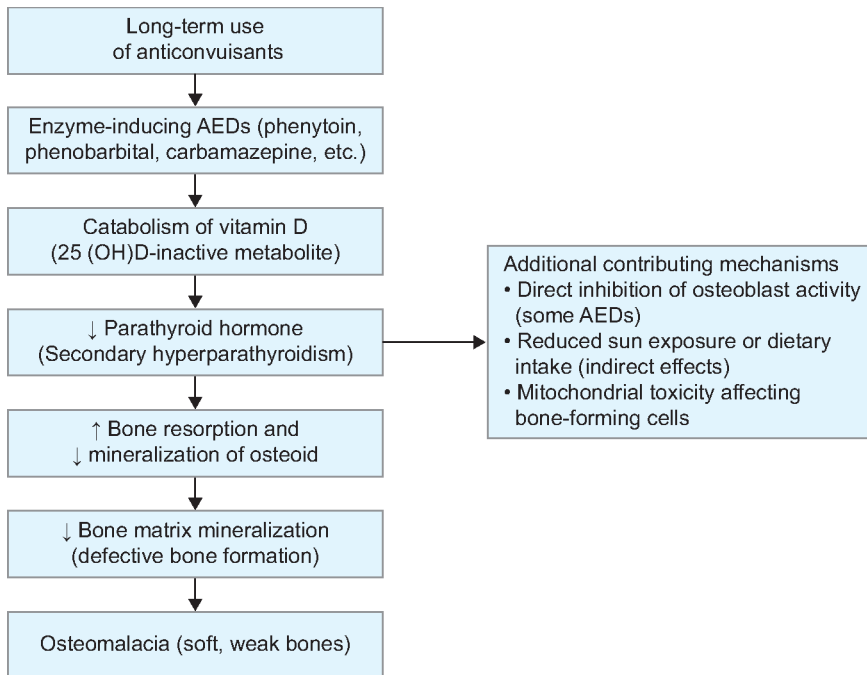
Osteomalacia is the softening of bone due to improper bone mineralization in adults, usually caused by a deficient amount of calcium, phosphate, or vitamin D in the blood. An important difference between osteoporosis and osteomalacia is that with the former there is a decrease in the intrinsic matrix of the bone while with the latter, the matrix is intact. Osteomalacia can cause pain in the bones, weakness in the muscles, and susceptibility to fracture (Table 3). In children, the condition is called rickets. Osteomalacia can be caused by dietary deficiencies, malabsorption, renal forms of tubular acidosis, or drug-induced forms, mainly arising from the administration of anticonvulsants that interfere with vitamin D metabolism.<sup>15</sup>

**PATHOPHYSIOLOGY**

The major aspect in osteomalacia is the impairment of mineralization of the osteoid (newly formed unmineralized bone matrix) secondary to any deficiency or dysfunction of

**Table 3:** Clinical features

Clinical feature	Description
Bone pain and tenderness	Diffuse dull pain, aching in the lower back, pelvis, hips, and legs; increases with activity
Muscle weakness	Proximal muscle weakness, mainly affecting the pelvic and shoulder girdles, rendering standing or climbing stairs difficult
Skeletal deformities	Bone softening leads to deformities such as bowed legs (genu varum/valgum), pelvic deformities, and spinal curvatures (kyphosis)
Fractures	With minimal trauma, there is an increased risk of insufficiency fracture in looser zones; common sites include ribs, femoral neck, and pubic rami
Neuromuscular symptoms	Hypocalcemic cramps and tetany and paresthesias caused by increased neuromuscular excitability
General symptoms	Fatigue, malaise, and reduced ability to perform daily activities <sup>14</sup>



**Fig. 1:** Pathogenesis of anticonvulsant-induced osteomalacia

vitamins D, calcium, or phosphate. Vitamin D is the central player since it promotes the intestinal absorption of calcium and phosphate and the mineralization of bone. Deficiency states in which calcium absorption is decreased result in hypocalcemia and consequent stimulation of the parathyroid glands to release parathyroid hormone (PTH). PTH in turn causes increased bone resorption as well as phosphate wasting by the kidneys, thereby exacerbating the mineral disorder. Accumulation of unmineralized osteoid with the development of soft and weak bones is characteristic of osteomalacia.<sup>5</sup>

**Mechanism of Anticonvulsant-induced Osteomalacia**

Osteomalacia is strongly associated with long-term use of enzyme-inducing anticonvulsants such as phenytoin, carbamazepine, and phenobarbital. These drugs induce the hepatic cytochrome P450 enzymes, increasing the hepatic catabolism of vitamin D to inactive metabolites. The lack of active vitamin D reduces

intestinal calcium and phosphate absorption, hypocalcemia, secondary hyperparathyroidism, and bone resorption. These changes lead to poorly mineralized bones, which has been called osteomalacia. Another possible direct inhibitory effect by some anticonvulsants may be on osteoblast function. Decreased sun exposure and poor nutrition during chronic therapy further add to the risk of developing bone disease as depicted in Figure 1.<sup>16</sup>

**Induction of Hepatic Cytochrome P450 Enzymes**

Anticonvulsants such as phenytoin, carbamazepine, phenobarbital, and primidone are the most potent inducers of hepatic cytochrome P450 enzymes and in particular the CYP3A4 isoenzyme. These enzymes are the metabolizers of a large number of substances, including vitamin D. During the induction process, the hydroxylation of vitamin D metabolites into their inactive forms is accelerated.

Consequently, there is a marked reduction in the serum levels of 25-hydroxyvitamin D [25(OH)D], the major circulating storage form, and 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], the active hormone vital for calcium homeostasis. Vitamin D becomes less biologically active in the regulation of calcium and phosphate due to this depletion. This is especially dangerous with chronically sustained anticonvulsant treatment, where the persistent enzyme induction maintains the deficit in vitamin D metabolites, thereby predisposing to subsequent metabolic derangements affecting bone.<sup>17</sup>

**Vitamin D Deficiency and Impaired Calcium Absorption**

The role of vitamin D is essential in allowing intestinal absorption of calcium, a mineral important for population-level bone mineralization. By increased metabolism, there is a diminution in the level of active vitamin D, which results in the reduced synthesis of calcium-binding proteins in the intestinal epithelium. In consequence, calcium absorption declines from the gastrointestinal tract, giving rise to hypocalcemia or low serum calcium levels. To compensate for this insufficiency, PTH secretion is stimulated, a condition termed secondary hyperparathyroidism. PTH tries to restore serum calcium at the expense of bone integrity by pulling calcium from the skeleton and promoting its reabsorption in the kidney. The process of pulling calcium from the skeleton dries out the porous city bones and, together with the inadequate mineral supply, weakens bones and increases the propensity of patients for osteomalacia.<sup>18</sup>

**Secondary Hyperparathyroidism and Bone Resorption**

The hypocalcemia induced by chronic vitamin D deficiency leads to secondary hyperparathyroidism, with PTH increase profoundly impacting bone and mineral metabolism. The enhanced osteoclastic bone resorption caused by PTH promotes the

passage of calcium and phosphate into the blood. PTH also induces phosphaturia by impairing phosphate reabsorption at the renal proximal tubules so that plasma phosphate concentrations diminish. These two minerals are crucial in the formation of hydroxyapatite crystals that endow bone with hardness and strength. Therefore, lowering these two minerals in bones impairs the mineralization process of osteoid tissues, the unmineralized organic matrix produced by osteoblasts. Deficient mineralization becomes apparent on histology as osteoid accumulation and clinically as high osteoid and soft bones. The imbalance between excessive resorption of bones and insufficient mineralization contributes directly to the appearance of osteomalacia in cases undergoing long-term anticonvulsant therapy.<sup>19</sup>

#### *Direct Effects on Bone Cells*

Conversely, there may be a direct cellular toxicity exerted by anticonvulsants on bone cells, furthering bone deterioration. Osteoblasts, which form new bone tissue, include inhibited proliferation and diminished capacity in differentiation when exposed to certain anticonvulsants. Thus, inhibition decreases the ability to form and to mineralize the new bone matrix. From the other side, osteoclastic activity might increase, setting the scale to the remedy of bone loss. Such direct cellular impacts compound on the mineral deficit induced by modified Vitamin D metabolism. Although the exact molecular details remain to be probed, it is assumed that an anticonvulsant may interfere with intracellular signaling pathways and gene expression in bone cells, thereby enhancing diminished bone formation and accelerated resorption, culminating in softened and fragile bones.<sup>20</sup>

#### *Additional Contributory Factors*

Several other unsuspected common factors observed in patients undergoing long-term anticonvulsant therapy may eventually feed into the risk or even igniting a more severe osteomalacic condition. These include a decrease in exposure to sunlight—whether as a direct consequence of a lifestyle restriction or because of medication-induced photosensitivity, which interferes with vitamin D3 synthesis in the skin from UV-B radiation.

Nutritional deficiencies, such as in calcium, phosphate, or protein, inhibit normal bone mineralization directly. Lastly, some other interacting conditions, such as chronic kidney disease or liver disease, impair the hydroxylations necessary for vitamin D activation, adding onto the deficiency.

Other possible synergistic bone-evolving factors include treatments such as glucocorticoids and chemotherapeutics.

Conversely, increased immobility or a dysfunctional movement system decreases mechanical loading on the bones required to stimulate bone density and strength. The smiling of these factors with the idiopathic channel of anticonvulsant vitamin D deficiency and secondary hyperparathyroidism puts forth a multidimensional scheme of pathophysiology culminating in osteomalacia.<sup>21</sup>

## EPIDEMIOLOGY

Anticonvulsant-induced osteomalacia is a well-recognized decimen that flees recognition in most instances in patients under chronic AED administration. It is estimated from studies that as much as 50–80% of patients on enzyme-inducing anticonvulsants such as phenytoin, carbamazepine, and phenobarbital may show some signs of vitamin D deficiency and/or alterations in bone metabolism. The prevalence of osteomalacia is another story, being 5–40% in different accounts, depending on the population studied, exposure duration, and how it is being assessed.

For instance, it was found in one cohort study that 20–30% of chronic phenytoin users may develop biochemical or radiological evidence of osteomalacia in 1–5 years of treatment with the drug. Besides this, fracture risk has been calculated to be 2–6 times higher among patients receiving long-term AED treatment than in the general population, especially among older adults and postmenopausal women. Other magnitude factors include less vitamin D supplementation, malnutrition, poor atmospheric conditions for adequate sun exposure, among others. These substantially alarming figures have not been able to spur adequate emphasis on awareness and thus, on regular screening, and come diagnosis and treatment of bone disease in epileptic patients face uncalled-for delays.<sup>22</sup>

## DIAGNOSIS

### Clinical Evaluation

The diagnosis of anticonvulsant-induced osteomalacia begins with a complete clinical evaluation. There is commonly a past medical history of long-term use of anticonvulsants such as phenytoin, carbamazepine, or phenobarbital. Classically, patients present with diffuse bone pain, typically poorly localized, muscle weakness (predominantly in proximal muscles such as the thighs or shoulders), and impaired walking. Bone tenderness, skeletal deformities such as bowing of long bones, and abnormal gait can be elicited on examination. A careful drug history and review of symptoms will allow the clinician to raise suspicion of osteomalacia in such a patient.

## Biochemical Investigations

Laboratory testing is crucial in the diagnosis of osteomalacia. Serum calcium is low or low normal because of reduced absorption by the intestine. Serum phosphate is low because of renal phosphate wasting, either caused by secondary hyperparathyroidism or directly by drug effects. ALP, a marker of bone-forming activity, is elevated due to increased osteoblastic activity that attempts to mineralize osteoid. Vitamin D status is determined by measuring levels of 25-hydroxyvitamin D [25(OH)D], which is usually low due to increased breakdown by anticonvulsant medications. PTH is elevated, marking secondary hyperparathyroidism because of hypocalcemia. Urinary phosphate loss would support this diagnosis.<sup>23,24</sup>

## Radiological Evaluation

Radiographic imaging plays an essential role in diagnosing osteomalacia. X-ray films could reveal the characteristic features of Looser's zones or pseudofractures, appearing as transverse radiolucent lines at right angles to the cortex, usually located in the ribs, pelvis, or femoral neck. Other findings would be generalized osteopenia and thinning of the cortex. In the early stage of the disease, the X-rays may show nothing abnormal. Bone densitometry shows decreased bone mineral density but does not differentiate osteomalacia from osteoporosis. Bone scintigraphy can be used to detect areas of increased bone turnover and pseudofractures and hence may reveal more sensitive evidence of the disease.

## Histological Diagnosis

Histological confirmation through bone biopsy is required for the definite diagnosis of osteomalacia. Transiliac bone biopsies performed with double tetracycline labeling enable direct study and measurement of the mineralization lag time of the osteoid. An increase in the volume and thickness of unmineralized osteoid occurs, with any further mineral deposition being delayed in osteomalacia. Though invasive, bone biopsy is the gold standard distinction between osteomalacia and other metabolic bone diseases, especially when biochemical and radiological findings are inconclusive.<sup>25,26</sup>

## Differential Diagnosis

Apart from osteomalacia, many disorders cause bone pains with or without reduced bone density. The most common differential diagnosis is osteoporosis, which differs from osteomalacia in that the bone tissue mineralization remains normal in osteoporosis and generally does not have the biochemical abnormalities seen in osteomalacia. Renal osteodystrophy due

to chronic kidney disease may also present as osteomalacia, but the biochemical profile and clinical context differ. Other conditions such as hypophosphatasia or some inherited metabolic bone disorders should be considered when there are atypical features.

### Role of Monitoring in Anticonvulsant Users

Since osteomalacia is a risk, especially in persons on long-term anticonvulsant therapy, these patients grapple with the monitoring of their medical condition. Occasional monitoring of serum levels of calcium, phosphate, alkaline phosphatase, and vitamin D serves well to catch metabolic abnormalities at an early stage before their clinical manifestations arise. This should be accompanied by a clinical assessment for any complaints of bone pain or muscle weakness. Early detection allows treatment to commence, vitamin D and calcium supplementation being the most suitable means to avert the development of more severe forms of osteomalacia and fractures.<sup>27,28</sup>

## EVIDENCE FROM CLINICAL STUDIES AND CASE REPORTS

An association with osteomalacia has been reported by various clinical studies and case reports in the scenario of long-term administration of enzyme-inducing anticonvulsants. Discussions revolve around the signs and symptoms, diagnostic hallmarks, and the outcome of treated patients.

### Case Reports

- *Go Raya et al.* reported three adolescent cases were reported with carbamazepine and phenobarbital-induced osteomalacia. They exhibited the clinical features of bone pain, muscle weakness, and fractures. Radiological evidence showed Looser's zones and decreased bone densities. Biochemical tests evidenced osteomalacia with low serum calcium, low serum phosphorus, and raised alkaline phosphatase.<sup>29</sup>
- *Patil et al.* reported a 29-year-old woman on long-term phenytoin therapy developed osteomalacia characterized by bilateral hip pain and restricted movement. Biochemical investigations revealed vitamin D deficiency, secondary hyperparathyroidism, and elevated alkaline phosphatase levels. The patient's condition improved after discontinuation of phenytoin and initiation of vitamin D supplementation.<sup>30</sup>

### Clinical Studies

- *Moro-Alvarez et al.*: In the study of 30 epileptic patients on long-term

phenytoin therapy, it was seen that the prevalence of osteopenia was very high (56.6%) and osteoporosis was very low (3.3%). The bone mineral density was significantly decreased in the femur, and elevated bone turnover markers pointed to enhanced bone resorption.<sup>31</sup>

- *Cock studies* the review underscored that decreased bone mineral density culminating in osteomalacia and a greater risk of fractures is the long-term consequence of the enzyme-inducing anticonvulsants, namely, phenytoin, phenobarbital, and carbamazepine. Close monitoring of bone health, the review emphasized, should be conducted in patients treated with these medications.<sup>32</sup>

## Management and Prevention

### Vitamin D and Calcium Supplementation

Deficient vitamin D status is the core of anticonvulsant osteomalacia; thus, supplementation is critical. Usually, patients receive an initial high dose of vitamin D, followed by maintenance doses that are given on a daily basis to replenish and maintain vitamin D levels. Calcium requirements should also be met through diet or supplements so that calcium is readily available for bone mineralization. Serum levels of vitamin D, calcium, phosphate, and alkaline phosphatase should be monitored regularly to assess the response to therapy and promptly detect untoward effects. Such proper supplementation allows for the enhancement of bone health, alleviation of osteomalacic symptoms, and prevention of fractures.<sup>33</sup>

### Review and Adjustment of Anticonvulsant Therapy

Enzyme-inducing anticonvulsants promote the degradation of vitamin D and predispose to osteomalacia. When possible, pharmacists and physicians would do well to place their patients on a nonenzyme-inducing anticonvulsant, such as levetiracetam or lamotrigine, instead of an enzyme inducer with osteomalacia risks. Lessening the dose of the enzyme inducer may also reduce some of its effect on bone metabolism. Doses may therefore be reduced

with the risk of seizures balanced against the risk to bone health. This ultimately must be done under strict neurological supervision. Therapy should always remain focused on optimizing both neurological and skeletal outcomes.

### Bone Health Monitoring

Bone-related health status has to be regularly monitored for patients on long-term anticonvulsants. Dual-energy X-ray absorptiometry (DEXA) scans look into bone mineral density for the early detection of bone loss. Moreover, blood tests for vitamin D, calcium, phosphates and alkaline phosphatases are performed to follow up on the metabolic status. Thus, if detected early, interventions are possible to prevent fractures and progression to more severe osteomalacia. Depending on risk factors, the period between monitoring varies: duration of therapy, age, and so on.<sup>34,35</sup>

### Lifestyle Interventions

Lifestyle changes are important with regard to both the prevention and management of osteomalacia. Weight-bearing and resistance exercises help strengthen bones as well as help with balance, which in turn reduces the risk of a fracture. Moderate exposure to the sun helps in increasing the natural production of vitamin D. Patients should avoid smoking and excess alcohol consumption, as both of these adversely affect the health of the bone. This also helps to complement the medical treatment in strengthening the bones and improving the quality of life.

### Management of Established Osteomalacia

In cases of established osteomalacia, aggressive vitamin D and calcium therapy is necessary to reverse bone softening. Physical therapy can direct patients to work on muscle strength and coordination in an attempt to reduce bone pain and falls. Analgesics can provide symptomatic treatment. In osteoporotic cases, other drugs may be considered, such as bisphosphonates. Fractures must be treated at the earliest opportunity (Table 4). Close follow-up is

**Table 4:** Drugs used to manage osteomalacia

Drug/supplement	Purpose	Typical dosage
Vitamin D3 (cholecalciferol)	Correct vitamin D deficiency	50,000 IU weekly for 6–8 weeks, then 800–2000 IU daily maintenance
Vitamin D2 (ergocalciferol)	Alternative to vitamin D3	Similar dosing to vitamin D3
Calcium carbonate or citrate	Support bone mineralization	1000–1500 mg elemental calcium daily
Bisphosphonates (e.g., alendronate)	Treat coexisting osteoporosis	70 mg once weekly orally
Analgesics (e.g., NSAIDs) <sup>36</sup>	Manage bone pain	As needed

needed to ensure complete recovery and to prevent relapse.<sup>37</sup>

### Patient Education and Follow-up

Patient education is a necessity for the proper management and prevention of osteomalacia. Patients should be able to list the possibility of bone disease with anticonvulsants, which can relate to symptoms such as bone pain and muscle weakness, and understand that they should adhere strictly to vitamin D and calcium supplementation. Emphasis should also be placed on follow-up visits for biochemical monitoring and bone density testing. Patient education thus enables them to take part fully in their care, which leads to earlier detection and better outcomes.

### Role of Healthcare Professionals

Pharmacists are considered precious antedotes to prevent and manage adverse effects of anticonvulsant-induced osteomalacia. Initially, they inform the patient about the potential adverse bone-related effects of long-term antiepileptic treatment. They counsel patients to maintain adequate dietary calcium and vitamin D, engage in safe mud-washing sun exposure, and encourage physical activity to promote bone health. The pharmacist ensures that if supplementation is prescribed, the patient adheres to it; otherwise, in cases of deficiency, they may advise on OTC supplementation.

Early patient education can reduce the development of osteomalacia, especially in susceptible groups such as the elderly, women, and those on enzyme-inducing anticonvulsants.

In addition to education, pharmaceutical and medicinal monitoring and review by a pharmacist and other medical professionals are very important and should always be maintained. They can identify the need for periodic screening of bone health parameters, including serum calcium, vitamin D, and PTH. Once at-risk patients are identified, they can collaborate with physicians to change or modify treatment, e.g., replacing older enzyme-inducing anticonvulsants (such as phenytoin, phenobarbital) with newer ones that have minimal effects on bone metabolism. Regular review of medications will also allow for the recognition of polypharmacy alongside reducing any unnecessary exposure to drugs known for high osteomalacia potential.<sup>38</sup>

### Future Perspectives and Research Directions

Progress in understanding about anticonvulsant-induced osteomalacia has been made; however, there are still gaps

in concert with its pathophysiology, early diagnosis, and treatment. Research should be directed to the identification of the exact molecular pathways of a particular antiepileptic drug interfering with bone metabolism, especially in genetically susceptible subjects. Large-scale and long-term observational studies are needed to verify the cumulative effects of older and newer anticonvulsants on bone health in various populations. Detection and validation of early biomarkers of bone demineralization caused by AEDs would increase the efficiency of their screening and, therefore, preventive actions.

Furthermore, it is crucial to develop clinical guidelines to monitor bone health as a routine practice in patients who are on long-term anticonvulsant therapy. Work on the development of personalized medicine techniques, such as pharmacogenomic-based systems that can predict the susceptibility of an individual patient toward osteomalacia, should go hand-in-hand. Another priority toward integration would be to place clinical pharmacists within epilepsy care teams, thus providing comprehensive medication management, supplementation when needed, and patient education—interventions that will lead to a reduction in the incidence of this preventable complication.<sup>39</sup>

### CONCLUSION

Anticonvulsant-induced osteomalacia is a clinically important but frequently overlooked consequence of long-term AED therapy. Enzyme-inducing AEDs such as phenytoin, carbamazepine, and phenobarbital interfere with bone metabolism by speeding up the degradation of active vitamin D metabolites through induction of hepatic cytochrome P450 enzymes. This leads to decreased calcium absorption through the intestine, secondary hyperparathyroidism, and poor bone mineralization culminating in osteomalacia. On the clinical side, this manifestation is manifested by diffuse bone pain, muscle weakness, and fragility toward fractures in patients who have not been supplemented adequately with calcium as well as vitamin D.

Evidence from clinical studies and case reports backs the association of long-term therapy with anticonvulsants and reduction in bone mineral density or osteomalacia. Hence, bone health evaluation is infrequently done as a routine in patients on chronic AED therapy. Preventive measures of early screening, vitamin D and calcium supplementation, and repeated bone mineral density measurements should be strongly advocated, especially in the high-

risk groups. If at all possible, the nonenzyme-inducing types of AEDs should be used. Hence, the multidisciplinary team approach of neurologists, clinical pharmacists, and primary care providers is important for early diagnosis, prevention, and optimal treatment of the more awkward anticonvulsant-induced osteomalacia.

### ORCID

Sundar Sri MK  <https://orcid.org/0009-0009-8780-2252>

Karthickeyan Krishnan  <https://orcid.org/0000-0002-1709-730X>

### REFERENCES

- Manole AM, Sirbu CA, Mititelu MR, et al. State of the art and challenges in epilepsy—a narrative review. *J Pers Med* 2023;13(4):623.
- Bhan A, Rao AD, Rao DS. Osteomalacia as a result of vitamin D deficiency. *Endocrinol Metab Clin* 2010;39:321–331.
- Parfitt AM, Qiu S, Rao DS. The mineralization index: a new approach to the histomorphometric appraisal of osteomalacia. *Bone* 2004;35:320–325.
- French JA, Gazzola DM. New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety? *Ther Adv Drug Saf* 2011;2(4):141–158.
- Cianferotti L. Osteomalacia is not a single disease. *Int J Mol Sci* 2022;23(23):14896.
- Lee RH, Lyles KW, Colón-Emeric C. A review of the effect of anticonvulsant medications on bone mineral density and fracture risk. *Am J Geriatr Pharmacother* 2010;8(1):34–46.
- Tolman KG, Jubiz W, Sannella JJ, et al. Osteomalacia associated with anticonvulsant drug therapy in mentally retarded children. *Pediatrics* 1975;56(1):45–50.
- Löscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. *CNS Drugs* 2021;35(9):935–963.
- Hanaya R, Arita K. The new antiepileptic drugs: their neuropharmacology and clinical indications. *Neurol Med Chir (Tokyo)* 2016;56(5):205–220.
- Czapiński P, Błaszczak B, Czuczwar SJ. Mechanisms of action of antiepileptic drugs. *Curr Top Med Chem* 2005;5(1):3–14.
- Belete TM. Recent progress in the development of new antiepileptic drugs with novel targets. *Ann Neurosci* 2023;30(4):262–276.
- Hakkola J, Hukkanen J, Turpeinen M, et al. Inhibition and induction of CYP enzymes in humans: an update. *Arch Toxicol* 2020;94(11):3671–3722.
- Abou-Khalil BW. The far-reaching influence of hepatic enzyme-inducing antiepileptic drugs. *Epilepsy Curr* 2009;9(6):158–159.
- Rajeswari J, Balasubramanian K, Bhatia V, et al. Aetiology and clinical profile of osteomalacia in adolescent girls in northern India. *Natl Med J India* 2003;16:139–142.
- Arboleya L, Braña I, Pardo E, et al. Osteomalacia in adults: a practical insight for clinicians. *J Clin Med* 2023;12(7):2714.
- Dent CE, Richens A, Rowe DJ, et al. Osteomalacia with long-term anticonvulsant therapy in epilepsy. *Br Med J* 1970;4(5727):69–72.
- Hoikka V, Savolainen K, Alhava EM, et al. Osteomalacia in institutionalized epileptic patients on long term anticonvulsant therapy. *Acta Neurol Scand* 1981;64:122–131.
- Fan HC, Lee HS, Chang KP, et al. The impact of anti-epileptic drugs on growth and bone metabolism. *Int J Mol Sci* 2016;17(8):1242.

19. Christiansen C, Rødbro P, Tjellesen L. Pathophysiology behind anticonvulsant osteomalacia. *Acta Neurol Scand Suppl* 1983;94:21–28.
20. Dharmshaktu GS. Antiepileptic therapy, osteomalacia, and synchronous fractures: don't lose looser zones. *J Family Med Prim Care* 2017;6(1):167–168.
21. Pack AM. The association between antiepileptic drugs and bone disease. *Epilepsy Curr* 2003;3(3):91–95.
22. Christiansen C, Rødbro P, Lund M. Incidence of anticonvulsant osteomalacia and effect of vitamin D: controlled therapeutic trial. *Br Med J* 1973;4(5894):695–701.
23. Krause KH, Prager P, Schmidt-Gayk H, et al. Diagnostik der osteopathia antiepileptica im erwachsenenalter [Diagnosis of anticonvulsant osteomalacia in adults (author's transl)]. *Dtsch Med Wochenschr* 1977;102(51):1872–1877.
24. Palmer KT, Smith AE, Taylor BB. Anticonvulsant-induced osteomalacia. *Age Ageing* 1977;6(4):228–231.
25. Hahn TJ, Halstead LR. Anticonvulsant drug-induced osteomalacia: alterations in mineral metabolism and response to vitamin D3 administration. *Calcif Tissue Int* 1979;13–18.
26. Bhan A, Qiu S, Rao SD. Bone histomorphometry in the evaluation of osteomalacia. *Bone Rep* 2018;8:125–134.
27. Zhao Z, Chen W, Wang Y, et al. Comparative analysis of clinical and imaging features of osteomalacia and spondyloarthritis. *Front Med* 2021;8:680598.
28. Tomson T, Dahl ML, Kimland E. Therapeutic monitoring of antiepileptic drugs for epilepsy. *Cochrane Database Syst Rev* 2007;2007(1):CD002216.
29. Goraya JS, Gupta PN, Gupta RK, et al. Anticonvulsant induced osteomalacia. *Indian Pediatr* 2000;37(3):325–329.
30. Patil MM, Sahoo J, Kamalanathan S, et al. Phenytoin induced osteopathy: too common to be neglected. *J Clin Diagn Res* 2015;9(11):OD11–OD12.
31. Moro-Alvarez MJ, Diaz Curiel M, de la Piedra C, et al. Bone disease induced by phenytoin therapy: clinical and experimental study. *Eur Neurol* 2009;62(4):219–230.
32. Cock HR. Bone health in epilepsy. In: Rugg-Gunn FJ, Smalls JE (Eds). *From Channels to Commissioning: A Practical Guide to Epilepsy*, 15th edition. London: Epilepsy Society; 2015. pp. 1–14.
33. Nilsson OS, Lindholm TS, Elmstedt E, et al. Fracture incidence and bone disease in epileptics receiving long-term anticonvulsant drug treatment. *Arch Orthop Trauma Surg* 1986;105(3):146–149.
34. Cipriani C, Romagnoli E, Pepe J, et al. Long-term bioavailability after a single oral or intramuscular administration of 600,000 IU of ergocalciferol or cholecalciferol: implications for treatment and prophylaxis. *J Clin Endocrinol Metab* 2013;98(7):2709–2715.
35. Menninga N, Koukounas Y, Margolis A, et al. Effects of enzyme-inducing antiepileptic medication on vitamin D dosing in adult veterans with epilepsy. *Epilepsy Res* 2020;161:106287.
36. Drezner MK. Treatment of anticonvulsant drug-induced bone disease. *Epilepsy Behav* 2004;5 Suppl 2:S41–47.
37. Arora E, Singh H, Gupta YK. Impact of antiepileptic drugs on bone health: need for monitoring, treatment, and prevention strategies. *J Family Med Prim Care* 2016;5(2):248–253.
38. Valmadrid C, Voorhees C, Litt B, et al. Practice patterns of neurologists regarding bone and mineral effects of antiepileptic drug therapy. *Arch Neurol* 2001;58(9):1369–1374.
39. Feldkamp J, Becker A, Witte OW, et al. Long-term anticonvulsant therapy leads to low bone mineral density—evidence for direct drug effects of phenytoin and carbamazepine on human osteoblast-like cells. *Exp Clin Endocrinol Diabetes* 2000;108(1):37–43.

# Consultation Fees as a Barrier to Regular Follow-up

Rajesh Agrawal\*<sup>1</sup>

Received: 07 September 2025; Accepted: 10 October 2025



## ABSTRACT

Regular follow-up visits are essential for effective management and prevention of complications of chronic diseases like hypertension (HT), diabetes mellitus (DM), cardiovascular disease (CVD), and coronary artery disease (CAD), and many more, for continuity of care and improved patient outcomes including quality of life. However, consultation fees act as a significant barrier, particularly in low- and middle-income populations, where out-of-pocket expenses deter patients from adhering to follow-up schedules. This article explores how consultation fees influence patient behavior, reduce compliance with medical advice, and ultimately compromise the quality of care and life. A review of current literature highlights the financial challenges faced by patients and allows us to think about potential policy solutions, including subsidized follow-ups, bundled care models, and extended free follow-up windows. Addressing this financial constraint is critical for ensuring equitable access to ongoing care and improving long-term health outcomes. Well-planned research on this issue is required for long-term planning.

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1569

## INTRODUCTION

In India, consultation fees, though modest by global standards, act as a significant barrier to regular follow-up, particularly among financially compromised populations. Chronic conditions such as diabetes mellitus (DM), hypertension (HT), cardiovascular disease (CVD), cancers, thyroid disorders, and many other illnesses require regular monitoring and frequent consultations to achieve optimal outcomes. However, out-of-pocket expenses associated with each visit—like consultation fees, diagnostic workups, transportation, and loss of wages—may deter patients from adhering to scheduled follow-ups.

This issue is relevant to patients in India and other low- and middle-income countries (LMICs) with respect to trust and perception. This issue is unexplored or underexplored in clinical journals, but it is an important component of the long-term management of various chronic diseases such as DM, HT, and CVD. This is a big gap in management as well as literature. A review and its implications could be a first of its kind in the Indian context.

## DISCUSSION

The importance of frequent follow-ups cannot be ignored as they are the backbone of chronic disease management, medication adherence, monitoring of side effects, and timely therapeutic adjustments. Yet, we often encounter patients who do not return for follow-ups—not because they are not willing, but because they are unable to afford the financial burden of repeated consultation

fees and other expenses already mentioned, such as transportation, diagnostics, and loss of working hours for both the patient and the attending person.

In India, where a significant portion of healthcare expenditure is out-of-pocket, even modest consultation charges discourage patients from follow-ups. This is not only true for economically disadvantaged patients but also for financially stable patients who are suffering from multiple comorbidities requiring frequent follow-up, such as thyroid disorders, CVD, DM, HT, malignancies, and others.

We know the impact of missed follow-ups is not benign. We see patients coming after long gaps with deteriorations and complications such as uncontrolled sugars, exacerbated heart failure, and worsening asthma, which are entirely preventable complications. Each missed opportunity is a step backward, often leading to avoidable hospital admissions and even mortality.

Studies have shown that the discontinuity of care, due to any reason including cost, contributes to poor control, increased complications, and higher rates of emergency admissions. Patients often opt for self-medication, irregular medication, or visit only when symptoms worsen, leading to a reactive rather than preventive or proactive approach.

From the physician's perspective, missed follow-ups impede therapeutic monitoring and limit opportunities for timely intervention or patient education. This disconnect can also strain the doctor-patient relationship, and physicians are often blamed for lack of progress or no improvement despite inadequate patient engagement due to financial barriers.

To address this issue, there is a growing need to explore alternative models of care, such as subsidized follow-up visits, bundled payments, telemedicine for stable patients, or inclusion of regular outpatient care in insurance plans. A more nuanced understanding of the economic pressures faced by patients is essential for designing equitable and sustainable healthcare delivery models.

Consultation costs and irregular follow-ups are a hidden crisis in chronic disease management, and consultation fees rarely act in isolation; the cumulative burden of medical expenses, including diagnostics, transportation, medication, and lost wages, contributes to discontinuity of care.

A qualitative study among rural women with HT in India found that socioeconomic barriers for low adherence to antihypertensive medication are low awareness of HT and its complications, poor access to medical care and financial constraints. Out-of-pocket payments for consultation, medications, diagnostics, transportation, borrowing money, and lack of insurance were central to poor adherence and discontinuity of care.<sup>1</sup>

Research on glaucoma patients in South India highlighted that for about 44% of patients, cost is a key obstacle to appointments, and for 47%, distance, transportation, and lack of escorts are barriers to follow-ups.<sup>2</sup>

A study of 172 patients from a tertiary cancer care institute in a lower-middle-income setting revealed that financial distress and travel difficulties were among the main reasons for irregular follow-up. The average distance traveled was 143 ± 13.15 km. The most common reasons for loss of follow-up were lack of social support, financial constraints, difficulty commuting, and being too sick to come.<sup>3</sup>

Investigation into tuberculosis care in India captured firsthand physician insights that "Lack of money for transport and feeling

Consultant Diabetologist; CEO, DOT Clinic, Indore, State Secretary (MP State Chapter), RSSDI, Madhya Pradesh, India; \*Corresponding Author

**How to cite this article:** Agrawal R. Consultation Fees as a Barrier to Regular Follow-up. *J Assoc Physicians India* 2026;74(7):80–81.

well after 2 months of treatment is the reason for drop-out. Still, financial problems are the major issue.<sup>4</sup>

Broader research on user fees in LMICs demonstrated that eliminating consultation and diagnostic fees leads to substantially increased health service utilization. Systematic reanalysis noted that outpatient visits rose by 30–50% soon after the removal of user fees, with sustained increases over time.<sup>5</sup>

One review suggests that reducing or removing user fees increases the utilization of certain healthcare services. However, emerging evidence suggests that such a change may have unintended consequences on the utilization of preventive services and service quality. The review also found that increasing fees can have a negative impact on health services utilization, although some evidence suggests that when implemented with quality improvements, these interventions could be beneficial. Most of the studies included in the review had important methodological problems. More rigorous research is needed on this issue.<sup>6</sup>

One analysis based on a nationally representative health expenditure and utilization survey conducted in 2014 calculated the incidence and intensity of catastrophic health expenditure (CHE) based on households' out-of-pocket payments during a visit as a percentage of total household consumption expenditure. It shows that following the removal of user fees, the majority of patients

benefited from free care and a reduced likelihood of CHE. This analysis also concludes that despite the removal of fees at primary health care, CHE remains high among the poorest, and the cost of transportation is mainly responsible for limiting the protective effectiveness of user fee removal on CHE.<sup>7</sup>

## CONCLUSION

The importance of frequent follow-ups cannot be overlooked. Chronic conditions such as DM, HT, CVD, cancers, thyroid disorders, and many more require frequent consultations and monitoring to achieve optimal outcomes. They are the backbone of chronic disease management, medication adherence, monitoring of side effects, and timely therapeutic adjustments. Yet, patients do not return for follow-ups—not because they are not willing, but because they cannot afford the financial burden of repeated consultation fees and other expenses such as transportation, diagnostics, and loss of working hours for both the patient and the attending person.

In LMICs, including India, consultation fees, though modest by global standards, act as a significant barrier to regular follow-up, particularly among financially compromised populations.

We must find out other ways to reduce the burden of consultation fees along with other expenses such as telemedicine, prolonged follow-up interval for stable

patients, providing necessary devices such as glucometers in DM care, and rewarding patients for achieving their targets.

## ORCID

Rajesh Agrawal  <https://orcid.org/0009-0007-1237-210X>

## REFERENCES

1. Gupta S, Dharmija JP, Mohan I, et al. Qualitative study of barriers to adherence to antihypertensive medication among rural women in India. *Int J Hypertens* 2019;2019:5749648.
2. Killeen OJ, Pillai MR, Udayakumar B, et al. Understanding barriers to glaucoma treatment adherence among participants in South India. *Ophthalmic Epidemiol* 2020;27(3):200–208.
3. Sundriyal D, Kapoor M, Antil P, et al. Factors associated with default of treatment and follow-up among patients with cancer: a cross-sectional study from a lower-middle-income country. *JCO Glob Oncol* 2024;10:e2400411.
4. Shah HD, Chaudhary S, Desai B, et al. Exploring private sector perspectives on barriers and facilitators in availing tuberculosis care cascade services: a qualitative study from the Indian state. *BMC Prim Care* 2024;25(1):5.
5. Lagarde M, Palmer N. The impact of user fees on health service utilization in low- and middle-income countries: how strong is the evidence? *Bull World Health Organ*. 2008;86(11):839–848. DOI: 10.2471/blt.07.049197
6. Lagarde M, Palmer N. The impact of user fees on access to health services in low- and middle-income countries. *Cochrane Database Syst Rev* 2011;2011(4):CD009094.
7. Masiye F, Kaonga O, Kirigia JM. Does user fee removal policy provide financial protection from catastrophic health care payments? Evidence from Zambia. *PLoS One* 2016;11(1):e0146508.

# Curricular Integration of Point-of-care Ultrasound in Medical Education in India: An Immediate Need



Sushrut Ingawale<sup>1,\*</sup>, Vineet Upadhyaya<sup>2</sup>, Vineet Chandak<sup>3</sup>

Received: 24 December 2025; Accepted: 05 February 2026

## ABSTRACT

Point-of-care ultrasound (POCUS) has become an essential bedside imaging tool in modern medical practice, enabling rapid, real-time, and cost-effective assessment for cardiac, pulmonary, abdominal, and vascular conditions, as well as guidance for invasive procedures. Its value is well established in emergency and critical care settings, yet formal POCUS training is currently absent from the undergraduate as well as postgraduate medical curriculum in India. This gap persists despite the widespread applicability of POCUS across clinical disciplines and its proven role in improving diagnostic accuracy and patient safety. Major barriers to POCUS integration in Indian medical education include limited awareness among physicians, inadequate infrastructure and equipment, lack of trained faculty, curriculum deficiencies, and regulatory challenges. Additional constraints, such as limited time during clinical rounds and the absence of standardized quality assurance, further hinder adoption. This article highlights the urgent need for structured and uniform POCUS education within the competency-based medical education (CBME) framework. It proposes the "POCUS Megaphone Strategy," a comprehensive approach encompassing problem identification, curriculum and faculty development, trainee-focused training programs, infrastructural strengthening, and policy-level advocacy. Integrating standardized POCUS training under the National Medical Commission will equip future Indian physicians with essential bedside imaging skills and significantly enhance the quality and safety of patient care.

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1592

## INTRODUCTION

Point-of-care ultrasound (POCUS) has become an indispensable tool in modern medical practice, providing real-time, cost-effective imaging for cardiac, pulmonary, and abdominal assessments, as well as vascular access and guidance for invasive procedures.<sup>1,2</sup> Particularly in emergency settings, the utility of POCUS is demonstrated by protocols such as the extended focused assessment with sonography for trauma (eFAST). Despite its significant benefits, formal POCUS training is currently absent from the Indian medical curriculum.<sup>3</sup> There is an urgent need for structured and uniform formal POCUS education to equip medical students and residents with the necessary skills for its effective application in clinical practice.

## TOP BARRIERS TO POCUS TRAINING IN INDIAN MEDICAL EDUCATION

### Limited Awareness and Understanding

A substantial number of Indian doctors are not fully aware of the benefits and applications of POCUS due to the lack of formal training. A foundational level of competence and practice is essential before

a physician can independently use and interpret POCUS.<sup>1,3</sup>

### Infrastructure and Resource Constraints

The limited availability of POCUS machines in clinics and hospitals significantly hinders their widespread implementation. Although studies across the globe have identified a lack of handheld ultrasound devices as one of the top barriers, there are limited studies in the Indian context to estimate this burden.<sup>4</sup>

### Curriculum and Training Gaps

Nonavailability of trained personnel is a major hindrance to implementing POCUS.<sup>5,6</sup> Most studies across different countries have identified a lack of training and a lack of direct supervision as the top barriers.<sup>4</sup> An Indian study among neonatologists who had access to POCUS revealed that only 25% of them had undergone structured training.<sup>3</sup>

### Regulatory and Accreditation Challenges

The Pre-Conception and Pre-Natal Diagnostic Techniques (PCPNDT) Act, 1994, aimed at preventing female feticide, also poses a potential regulatory hurdle.<sup>5</sup> Despite its major role in preventing female feticide, compliance

with these stringent regulations may deter many family physicians from adopting POCUS in clinics.

### Other Barriers

As highlighted by Wong et al., lack of time to perform POCUS during rounds and lack of quality assurance processes necessitating an expert to confirm the findings were a few other barriers.<sup>4</sup>

## THE NEED FOR POCUS TRAINING IN INDIAN MEDICAL EDUCATION

Point-of-care ultrasound has widespread utility across clinics, emergency departments, and hospitalized patients, including those in critical care for various diagnostic and therapeutic purposes.<sup>1</sup> However, a resident survey revealed that its use is mainly adopted by learners for eFAST and vascular access.<sup>7</sup> Adopting POCUS for basic procedures such as paracentesis, thoracentesis, fluid taps, and central vascular access would advocate for patient safety by reducing complications. Furthermore, training in advanced examinations such as airway interpretation, renal ultrasound, IVC ultrasound, cardiac POCUS, and lung POCUS would enhance bedside management of critically ill patients. In the United States, the Accreditation Council for Graduate Medical Education (ACGME) mandates that emergency medicine programs

<sup>1</sup>PGY-3 Internal Medicine Resident, Department of Internal Medicine, Frank H Netter MD School of Medicine, Quinnipiac University, North Haven, Connecticut, USA; St. Vincent's Medical Center, Bridgeport, Connecticut, USA; <sup>2</sup>Junior Resident, Department of Radiodiagnosis and Interventional Radiology, All India Institute of Medical Sciences, New Delhi; <sup>3</sup>Medical Student, Department of General Medicine, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India; \*Corresponding Author

**How to cite this article:** Ingawale S, Upadhyaya V, Chandak V. Curricular Integration of Point-of-care Ultrasound in Medical Education in India: An Immediate Need. *J Assoc Physicians India* 2026;74(7):82–84.

complete a designated POCUS course, with established evaluation tools such as the Rapid Assessment of Competency in Echocardiography (RACE) and the Assessment of Competency in Thoracic Sonography (ACTS) to gauge proficiency.<sup>8</sup> It is the need of the hour to formalize POCUS education among medical trainees, both undergraduate and postgraduate, to ensure the highest level of patient care and safety.

### STRATEGIES TO INTEGRATE POCUS TRAINING

We propose the “POCUS Megaphone Strategy” (Fig. 1) as a comprehensive approach to enhance awareness, foster knowledge acquisition, shift attitudes, and integrate POCUS practices into clinical medicine.

The first step in addressing the issue is a comprehensive identification of the problem, which constitutes an ongoing process that is complemented by timely interventions. Subsequently, a series of interventions is implemented, categorized as follows: curriculum and faculty development, medical trainee-focused POCUS programs, and infrastructural adaptations. Analogous to the control mechanism of a megaphone switch, these interventions require reinforcement through policy-level support to ensure sustained effectiveness.

#### Identification of the Problem

Accurately identifying the gaps in POCUS knowledge, skills, and availability within the

clinical setting is a foundational step. This includes assessing current competency levels among healthcare providers, the availability of equipment, and existing barriers to POCUS adoption, such as limited training opportunities and a lack of standardized protocols. Through surveys, audits, and needs assessments, this diagnostic phase helps to pinpoint areas for improvement and guides the targeted design of interventions. By continually re-evaluating these factors, the program can adapt to emerging needs, ensuring that interventions remain relevant and effective.

#### Curriculum and Faculty Development

This involves integrating POCUS training into the medical curriculum, with modules tailored to different levels of clinical expertise. Faculty development programs are essential to train educators in POCUS techniques, ensuring consistency and quality in teaching. Continuous faculty workshops and certifications further enhance teaching capacity and keep instructors updated with evolving POCUS practices.

#### Medical Trainee-Focused POCUS Programs

Structured POCUS training programs are developed for medical trainees, incorporating didactic sessions, hands-on practice, and case-based learning. These programs include competency assessments to track progress and ensure skill proficiency. Mentorship and supervised clinical applications support trainees in translating

knowledge into practice within real-world clinical settings. Collaboration with healthcare institutions for resource sharing and seeking international partnerships for expertise and equipment support can enhance POCUS training.

#### Infrastructural Adaptations

Establishing dedicated ultrasound labs with high-quality machines, simulation stations, and handheld POCUS devices creates an environment conducive to immersive training. These resources facilitate diverse, hands-on experiences that are essential for mastering POCUS. Allocating designated spaces for POCUS workshops and providing access to digital resources for remote learning further support skill development and program accessibility.

#### Advocacy and Policy Change

Regulatory bodies should establish world-class POCUS accreditation standards to ensure providers are competent in standard views, recognizing anatomical features, artifacts, diagnostic findings, and understanding limitations. Clinical case-based assessments and peer evaluations should precede certification. Showcasing success stories from institutions that have implemented POCUS training can mitigate resistance.

### CONCLUSION

Point-of-care ultrasound is a versatile imaging modality with applications beyond the emergency department, including cardiology, pulmonology, obstetrics, gynecology, and gastroenterology. It is imperative to integrate

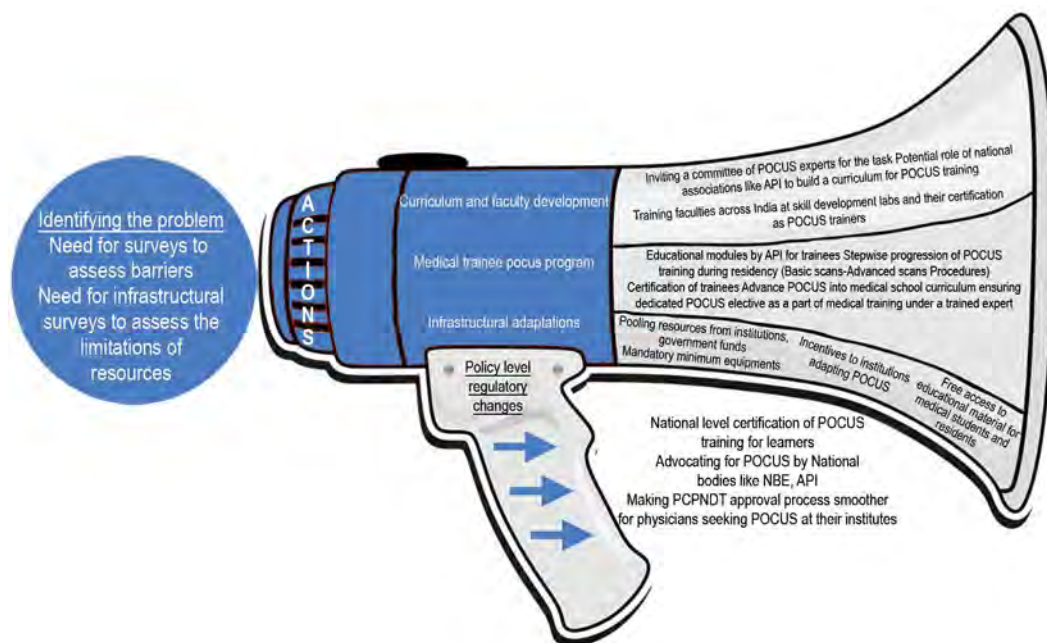


Fig. 1: The POCUS megaphone strategy for integrating point-of-care ultrasound into the medical curriculum

internationally recognized POCUS training into the CBME curriculum for medical students and residents, by the National Medical Commission (NMC) of India. This integration will ensure the future generation of doctors is proficient in POCUS, ultimately enhancing patient care across various medical fields.

## ORCID

Sushrut Ingawale  <https://orcid.org/0000-0002-6938-6672>

## REFERENCES

1. Díaz-Gómez JL, Mayo PH, Koenig SJ. Point-of-Care ultrasonography. *N Engl J Med* 2021;385(17):1593–1602. DOI: 10.1056/NEJMra1916062
2. Ingawale S, Hotchandani H, Upadhyaya V. POCUS: an emerging bedside tool. *Futuristic Trends Med Sci* 2024;3:139–155.
3. Rath C, Nagpal R, Suryawanshi P. Point-of-care ultrasound in neonatology in India: the way forward. *Indian Pediatr* 2023;60(5):351–357.
4. Wong J, Montague S, Wallace P, et al. Barriers to learning and using point-of-care ultrasound: a survey of practicing internists in six North American institutions. *Ultrasound J* 2020;12(1):19.
5. Deshpande S, Suryawanshi P, Sharma N, et al. Survey of point-of-care ultrasound uptake in Indian neonatal intensive care units: results and recommendations. *J Neonatol* 2019;33(1–4):13–21.
6. Kozyk M, Strubchevska K, Wasvary M, et al. S2140 A cross-sectional study assessing the prevalence of point-of-care abdominal ultrasound use among physicians. *Am J Gastroenterol* 2024;119(10S):S1528.
7. Thomas V, Abraham S, Balakrishnan J, et al. Point-of-care ultrasound training in Indian emergency medicine programs: a resident's perspective. *Int J Acad Med* 2017;3.
8. Ramgobin D, Gupta V, Mittal R, et al. POCUS in internal medicine curriculum: quest for the holy-grail of modern medicine. *J Community Hosp Intern Med Perspect* 2022;12(5):36–42.



It's not everyday, it's

# ONCE-WEEKLY **Awiqli**® insulin icodec injection 700 U/mL



## World's first once-weekly basal insulin<sup>1</sup>

CONVENIENCE

Reduces basal insulin injections from 7 to 1 per week<sup>2</sup>

EFFICACY

Superior HbA<sub>1c</sub> reduction and time in range vs. glargine U100<sup>\*3</sup>

SAFETY

More patients reach HbA<sub>1c</sub> <7% without hypoglycaemia<sup>†3</sup>



Most basal insulin injections require daily injections. Awiqli is the first once-weekly basal insulin. It is a long-acting insulin that provides a steady level of insulin over the course of a week. It is designed to be injected once a week, making it easier to manage your diabetes.

<sup>1</sup>First-in-class

<sup>2</sup>Based on a head-to-head comparison with glargine U100 in the pivotal 12-week, 500 mg trial.

<sup>3</sup>Based on a head-to-head comparison with glargine U100 in the pivotal 12-week, 500 mg trial. HbA<sub>1c</sub> reduction was significantly greater for Awiqli compared to glargine U100 in the overall population. Time in range was significantly greater for Awiqli compared to glargine U100 in the overall population.

<sup>†</sup>Based on a head-to-head comparison with glargine U100 in the pivotal 12-week, 500 mg trial. The percentage of patients reaching HbA<sub>1c</sub> <7% without hypoglycaemia was significantly greater for Awiqli compared to glargine U100 in the overall population.

For the use of any registered medical product or a hospital or a laboratory

**Generic Name:** Insulin icodec. **Trade Name:** Awiqli. **Manufacturer:** Novo Nordisk. **Formulation:** Awiqli is available in 700 U/mL and 100 U/mL presentations. **Indication:** Awiqli is indicated for the treatment of diabetes mellitus in adults. **Contraindications:** Awiqli is contraindicated in patients with severe hypoglycaemia. **Warnings:** Awiqli may cause hypoglycaemia. Patients should be monitored for hypoglycaemia. **Precautions:** Awiqli should be used with caution in patients with renal impairment. **Side Effects:** Common side effects include hypoglycaemia, injection site reactions, and allergic reactions. **Drug Interactions:** Awiqli may interact with other medications. **Storage:** Awiqli should be stored at 2-8°C. **Shelf Life:** Awiqli has a shelf life of 12 months. **After the opening of the package:** Awiqli should be used within 28 days. **Other information:** Awiqli is a registered trademark of Novo Nordisk. **References:** 1. [Novo Nordisk. Awiqli \(insulin icodec\) injection. Summary of Product Characteristics. 2023.](#) 2. [Novo Nordisk. Awiqli \(insulin icodec\) injection. Clinical Study Report. 2023.](#) 3. [Novo Nordisk. Awiqli \(insulin icodec\) injection. Clinical Study Report. 2023.](#)

INC6AW00054 | Last date of Review: 24 June, 2026

# Expanding the Spectrum: Isolated Acute Diencephalitis as the Initial Manifestation of Neuromyelitis Optica Spectrum Disorder



Jayaram Saibaba<sup>1\*</sup>, Pushkar Pazhani<sup>2</sup>, Vivek Venkataraman Iyer<sup>3</sup>

Received: 01 November 2025; Accepted: 24 November 2025

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1510

**D**iencephalic syndrome is a rare clinical variant of neuromyelitis optica spectrum disorder (NMOSD), observed in approximately 3.4% of presentations. Its hallmark features include endocrine and sleep-wake disturbances such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothermia, narcolepsy, daytime somnolence, and appetite dysregulation.<sup>1</sup> We report a case of NMOSD presenting as an isolated acute diencephalic syndrome, a rare and diagnostically challenging initial manifestation. This case underscores the importance of considering NMOSD even in the absence of typical optic neuritis or longitudinally extensive transverse myelitis.

A 27-year-old woman presented with a 3-week history of neuropsychiatric symptoms. Her illness began 1 month prior with a self-limited febrile episode. She subsequently developed right upper limb pain and paresthesia, followed by a complex diencephalic syndrome characterized by visual hallucinations, confabulation, significant recent memory deficits, excessive daytime sleepiness (10–14 hours/day), hyperphagia, hypothermia, and urinary frequency. She had no hiccups, vomiting, pruritus, blurred vision, pain on moving the

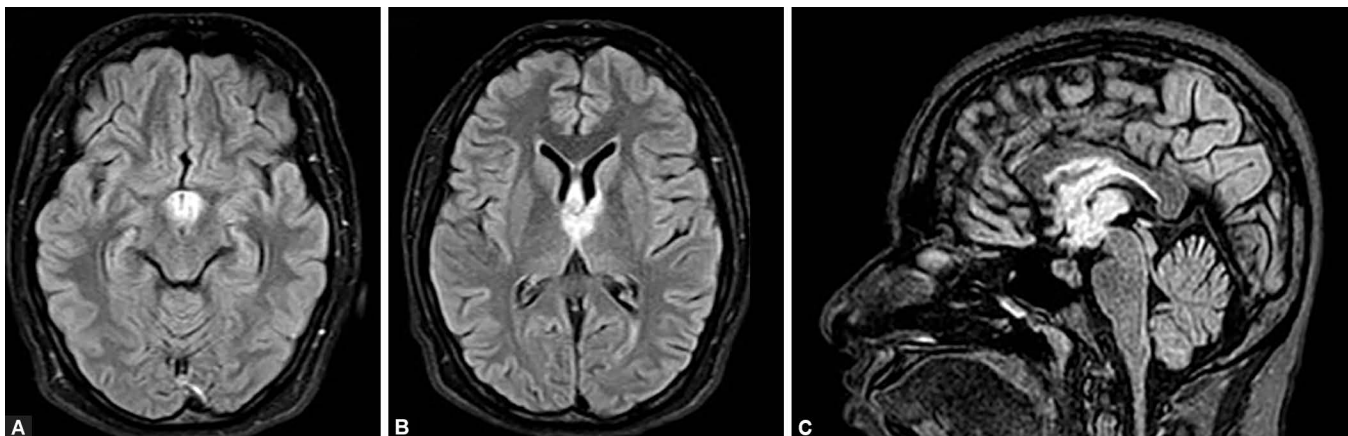
eyes, painful tonic spasms, sensory loss, and urinary retention. Examination revealed a drowsy but arousable patient with cognitive deficits [mini-mental state examination (MMSE) 24/30, frontal assessment battery (FAB) 14/18]. Cranial nerve, motor, sensory, and cerebellar examinations were normal. Basic hemogram and renal, liver, and thyroid function tests were normal. Viral markers were negative. Laboratory investigation identified profound hyponatremia (112 mEq/L) consistent with SIADH. She was treated at an outside hospital for SIADH, and sodium was corrected over 2 days. Magnetic resonance imaging (MRI) of the brain revealed striking T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities within the diencephalon, involving mammillary bodies, septum pellucidum, medial thalami, fornices, hypothalamus, and striatum (Figs 1A to C). Cerebrospinal fluid (CSF) analysis was unremarkable. Broad differentials included Wernicke encephalopathy, autoimmune encephalitis (anti-Ma2, IgLON5), neurosarcoidosis, neuro-Behçet's disease, infiltrative disorders, and central nervous system (CNS) neoplasms. Antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), autoimmune,

and paraneoplastic panel were negative. Visual evoked potentials were normal. Serum MOG and CSF oligoclonal bands were negative. Serum NMO tested strongly positive. The patient was treated with intravenous (IV) methylprednisolone (1 gm/day for 5 days), followed by five sessions of plasma exchange and an oral steroid taper. She was initiated on rituximab for relapse prevention. Her clinical course showed marked improvement in mentation, sleepiness, and hypothermia. A follow-up MRI 1 month later demonstrated significant resolution of the signal abnormalities.

Our patient, with exclusive symptomatic diencephalic involvement and positive anti-AQP4 antibodies, meets the 2015 NMOSD diagnostic criteria given by Wingerchuk et al.<sup>2</sup> While NMOSD is classically defined

<sup>1</sup>Assistant Professor, Department of Neurology, Mahatma Gandhi Medical College and Research Institute (MGMCRI), Puducherry; <sup>2</sup>Senior Resident and Fellow; <sup>3</sup>Joint Director and Senior Consultant, Department of Neurology, SRM Institute of Medical Sciences, Chennai, Tamil Nadu, India; \*Corresponding Author

**How to cite this article:** Saibaba J, Pazhani P, Iyer VV. Expanding the Spectrum: Isolated Acute Diencephalitis as the Initial Manifestation of Neuromyelitis Optica Spectrum Disorder. *J Assoc Physicians India* 2026;74(7):86–87.



**Figs 1A to C:** Magnetic resonance imaging of the brain, FLAIR sequence, axial sections (A and B), and sagittal section (C) showing hyperintensities in mammillary bodies, hypothalamus, septum pellucidum, and thalami

by optospinal involvement, atypical presentations are increasingly recognized. The diencephalic structures, rich in AQP4 channels, are a known target. Narcolepsy or hypersomnia from diencephalic periependymal lesions is a well-recognized, and sometimes presenting, feature of NMOSD.<sup>3</sup> In our patient, the profound hypersomnia suggests hypothalamic involvement, and CSF orexin level measurement, though not performed, would have been of interest to investigate this association. Similarly, the observed SIADH with hyponatremia has also been documented as an initial manifestation of the disease.

Similarly, Suzuki et al. reported a case with hypothermia, hypersomnia, and hyponatremia from a hypothalamic lesion as the initial sign of NMOSD.<sup>4</sup> It is important to distinguish NMOSD from other mimics like Wernicke encephalopathy, which also affects mammillary bodies but is typically associated with different clinical and radiological contexts. Peethambar et al. highlighted a similar case of a 19-year-old female

with SIADH, narcolepsy, bradycardia, and somnolence who presented as a diencephalic syndrome of NMOSD and improved with steroids.<sup>5</sup>

This case illustrates that an isolated acute diencephalic syndrome, especially with accompanying SIADH, can be the heralding presentation of NMOSD. Early serological testing for AQP4-IgG is crucial in such scenarios to enable prompt immunotherapy, which can significantly improve outcomes as demonstrated here.

### AUTHORS' CONTRIBUTIONS

Jayaram Saibaba, Pushkar Pazhani, and Vivek Venkataraman Iyer contributed equally to this work. All three authors were involved in the conception, organization, and execution of the research project, as well as the writing of the first draft of the manuscript and its subsequent review and critique.

### FUNDING

This study was not funded.

### CONFLICT OF INTEREST

None.

### ORCID

Jayaram Saibaba  <https://orcid.org/0009-0003-0736-5141>

### REFERENCES

1. Etemadifar M, Nouri H, Khorvash R, et al. Frequency of diencephalic syndrome in NMOSD. *Acta Neurol Belg* 2022;122(4):961–967.
2. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015;85(2):177–189.
3. Kume K, Deguchi K, Ikeda K, et al. Neuromyelitis optica spectrum disorder presenting with repeated hypersomnia due to involvement of the hypothalamus and hypothalamus-amygdala linkage. *Mult Scler J* 2015;21(7):960–962.
4. Suzuki K, Nakamura T, Hashimoto K, et al. Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: a case report and literature review. *Arch Neurol* 2012;69(10):1355–1359.
5. Peethambar GA, Shaikh J, Singh R, et al. May steroids wake you up! A rare case of diencephalic syndrome of neuromyelitis optica spectrum disorder. *Neurology* 2024;103(7 Suppl. 1):S106.

# When Febrile Seizures Are Not Benign: An Unusual Cause of Dyke–Davidoff–Masson Syndrome

Jashir Ahammed<sup>1</sup>\*, Syed Ahmed Zaki<sup>2\*</sup>, Kiran Kumar Reddy<sup>3</sup>

Received: 27 December 2025; Accepted: 05 March 2026



*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1588

A 14-year-old girl presented with a history of recurrent seizures over the past year, varying in type—generalized tonic-clonic and right-sided focal seizures involving both upper and lower limbs. Birth and family history were unremarkable, and early developmental milestones were appropriate. However, her academic performance declined over the past 2 years, eventually leading her to drop out of school. At 7 months of age, she had an upper respiratory tract infection followed by febrile status epilepticus lasting 20 minutes and requiring 5 days of hospitalization. Neuroimaging, cerebrospinal fluid analysis, and blood cultures were normal. There were no focal neurological deficits at discharge. Antiepileptic medications were discontinued after two seizure-free years. Current examination showed mild right-sided spasticity with increased deep tendon reflexes and an extensor plantar response. Magnetic resonance imaging (MRI) revealed left frontal sinus hypertrophy, left calvarial thickening, left cerebral atrophy, and right-sided crossed cerebellar atrophy, suggestive of Dyke–Davidoff–Masson syndrome (DDMS) (Fig. 1). Electroencephalography (EEG) revealed intermittent sharp waves and background slowing over the left

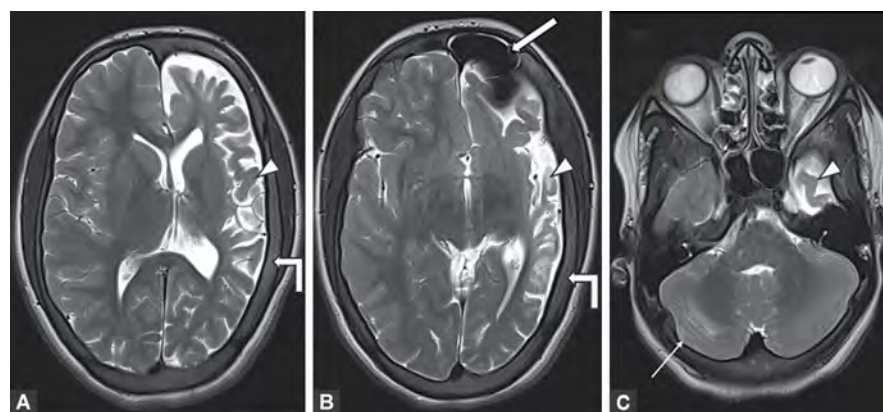
frontotemporal region. She was started on antiepileptic therapy, physiotherapy, and occupational and speech therapy.

Dyke–Davidoff–Masson syndrome is a rare neurological disorder characterized by cerebral hemiatrophy, hemiparesis, developmental delay, and seizures.<sup>1</sup> It can be congenital, often from intrauterine vascular insults, or acquired, secondary to perinatal trauma, infection, vascular events, or hemorrhage.<sup>1</sup> In the absence of antenatal, perinatal, or early developmental risk factors, the prolonged febrile seizure at 7 months represents the most likely neurological insult. Its temporal association with the characteristic neuroimaging findings supports a diagnosis of DDMS secondary to febrile status epilepticus. Febrile seizures are typically benign and self-limiting, with most children achieving complete neurological recovery. The association between febrile seizures and DDMS is rare and sparsely reported in the literature.<sup>2</sup> The proposed pathophysiological mechanism involves prolonged hypoxic-ischemic injury leading to reduced levels of brain-derived neurotrophic factors, impaired neuronal survival, and progressive cerebral atrophy.<sup>3</sup> Crossed cerebellar atrophy is an uncommon

feature in DDMS, typically observed in patients with longstanding, severe unilateral cerebral damage.<sup>4</sup> It results from disruption of the corticopontocerebellar pathways connecting the affected cerebral hemisphere and the contralateral cerebellum.<sup>4</sup> The presence of crossed cerebellar atrophy in our case suggests a chronic and progressive process rather than an acute insult alone. Our case is notable for several atypical features, including delayed clinical presentation in adolescence, crossed cerebellar atrophy, and an association with febrile status epilepticus. DDMS should be differentiated from conditions such as Sturge–Weber syndrome, basal ganglia germinoma, Silver–Russell syndrome, Fishman syndrome, linear nevus sebaceous syndrome, hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome, and Rasmussen encephalitis, based on clinical features and characteristic neuroimaging findings.<sup>1</sup> Prognosis is better if onset is after 2 years of age and seizures are well controlled. Hemispherectomy may be considered in selected patients with intractable epilepsy and hemiplegia. Long-term management requires a multidisciplinary approach, including antiepileptic therapy, physiotherapy, occupational therapy, speech therapy, and educational support.<sup>1–3</sup> Through this case, we highlight a rare presentation of DDMS following febrile status epilepticus and emphasize the need for long-term neurological follow-up.

## CONFLICT OF INTEREST

None.



**Figs 1A to C:** Axial T2-weighted MRI images: (A) Left cerebral atrophy (arrowhead) with ipsilateral calvarial thickening (bent arrow); (B) Left frontal sinus enlargement (thick arrow); (C) Contralateral cerebellar atrophy (thin arrow)

<sup>1</sup>Junior Resident; <sup>2</sup>Additional Professor, Department of Pediatrics; <sup>3</sup>Assistant Professor, Department of Radiodiagnosis, All India Institute of Medical Sciences, Hyderabad, Telangana, India; \*Corresponding Author

**How to cite this article:** Ahammed J, Zaki SA, Reddy KK. When Febrile Seizures Are Not Benign: An Unusual Cause of Dyke–Davidoff–Masson Syndrome. *J Assoc Physicians India* 2026;74(7):88–89.

## FINANCIAL DISCLOSURE

None.

## AUTHORS' CONTRIBUTION

Concept and design of study or acquisition of data or analysis and interpretation of data: SAZ, JA, KKR.

Drafting the article or revising it critically for important intellectual content: SAZ, JA, KKR.

Final approval of the version to be published: All authors approved the version of the manuscript to be published.

## ORCID

*Jashir Ahammed*  <https://orcid.org/0009-0008-0045-5191>

*Syed Ahmed Zaki*  <https://orcid.org/0000-0003-2652-4585>

*Kiran Kumar Reddy*  <https://orcid.org/0009-0008-1815-7192>

## REFERENCES

1. Behera MR, Patnaik S, Mohanty AK. Dyke–Davidoff–Masson syndrome. *J Neurosci Rural Pract* 2012;3:411–413.
2. Palani A, Periyanyagam A, James S, et al. Dyke–Davidoff–Masson syndrome - a dainty spectrum with a diligent diagnosis. *J Family Med Prim Care* 2024;13:4730–4733.
3. Sharma PK, Faizal A, Rubben Prabhu AL, et al. Dyke–Davidoff–Masson syndrome as a rare cause of cerebral hemiatrophy: insights from a case series. *Cureus* 2024;16:e54494.
4. Dilber B, Sahin S, Eyüboğlu I, et al. Two different manifestations of neonatal vascular injury: Dyke–Davidoff–Masson syndrome and crossed cerebellar atrophy. *J Stroke Cerebrovasc Dis* 2020;29:104600.

# Idiopathic Intracranial Hypertension Masquerading as Cerebral Venous Sinus Thrombosis: A Diagnostic Challenge



Nikhil Gupta<sup>1</sup>, Tanvi Batra<sup>2\*</sup>, Atul Kakar<sup>3</sup>, Ashima Abbott Chandra<sup>4</sup>

Received: 11 August 2025; Accepted: 24 March 2026

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1594

Idiopathic intracranial hypertension (IIH) is a syndrome identified by raised intracranial pressure (ICP), with absence of a mass lesion/hydrocephalus, typically affecting obese women of childbearing age.<sup>1</sup> It may present with similar symptoms such as headache, visual disturbances, and papilledema, making clinical differentiation challenging.<sup>1</sup> IIH primarily threatens vision, and treatment focuses on lowering ICP using medications like acetazolamide, serial lumbar punctures, or surgical interventions such as optic nerve sheath fenestration or CSF shunting in refractory cases.<sup>2</sup> Misdiagnosing IIH as CVST can lead to unnecessary anticoagulation, which may prove to be harmful for the patient.

A woman in her early 30s, from Noida, presented with a 15-day history of diplopia, floaters, and holocranial headache. Ophthalmologic evaluation revealed esotropia in the right eye and bilateral optic disk edema with hemorrhages (Fig. 1). The MRI brain was normal, while the MRI orbit showed cupping of the bilateral optic nerves—findings suggestive of bilateral papilledema. A lumbar puncture was done, which showed raised opening pressure. CSF biochemistry and cell counts were within normal limits. The patient also reported improvement in visual symptoms following the procedure. Given suspected cerebral

venous sinus thrombosis (CVST, the patient was started on low-molecular-weight heparin (dalteparin) and high-dose acetazolamide to reduce cerebrospinal fluid pressure. After 2 weeks, the patient presented to our hospital with persistent symptoms. Re-evaluation of laboratory tests, including a detailed history focusing on potential thrombosis risk factors,



**Fig. 2:** Contrast-enhanced magnetic resonance venography showing a hypoplastic left transverse sinus (red arrow) and patent right transverse sinus (yellow arrow), with no evidence of thrombus

was done. Physical and systemic examination were normal. A comprehensive thrombophilia panel was also sent, which was normal (Table 1). Fundus examination was done, which showed bilateral papilledema (Fig. 1). Repeat contrast-enhanced MR venography showed no evidence of CVST but revealed bilateral arachnoid granulations and hypoplastic left transverse sinus (Fig. 2). Repeat lumbar puncture demonstrated an opening pressure of 350 mm H<sub>2</sub>O with normal CSF biochemistry. Based on the above findings, she was diagnosed with idiopathic intracranial hypertension (IIH). Dalteparin was discontinued, and the patient was continued on high-dose acetazolamide with significant symptomatic improvement on follow-up. Follow-up visits included serial fundus examinations, which showed gradual resolution of papilledema in both eyes (Fig. 3), confirming clinical and therapeutic response.

## DISCUSSION

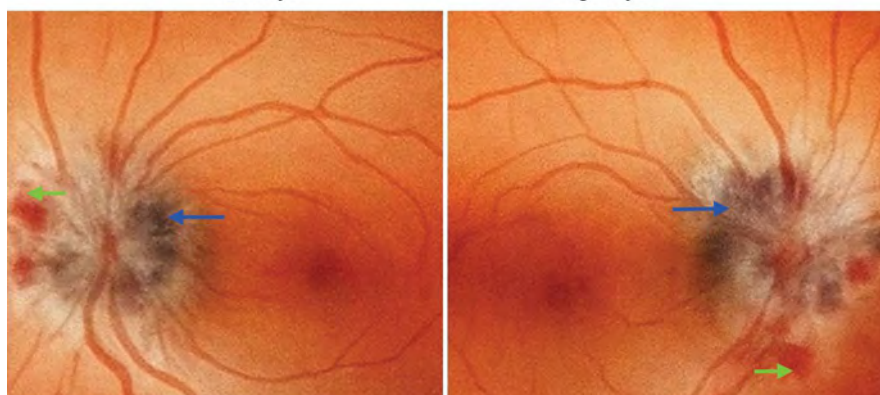
Idiopathic intracranial hypertension (IIH), formerly known as pseudotumor cerebri, is characterized by elevated intracranial pressure (ICP) in the absence of an intracranial mass, hydrocephalus, infection, or hypertensive encephalopathy.<sup>3</sup> In adults, standard ICP is generally 15 mm Hg, and values >25 cm H<sub>2</sub>O are considered elevated. IIH predominantly affects young, overweight women of childbearing age, with an annual incidence of 1–2 per 100,000 population, rising to 4–21 per 100,000 in obese females aged 15–44 years. Obesity is the most significant modifiable risk factor. Other associated factors include systemic conditions (e.g., Addison's disease, hypoparathyroidism), medications

<sup>1</sup>DNB Trainee; <sup>2</sup>Associate Consultant, Department of Internal Medicine; <sup>3</sup>Senior Consultant, Department of Medicine; <sup>4</sup>Consultant, Department of Ophthalmology, Sir Ganga Ram Hospital, Delhi, India; \*Corresponding Author

**How to cite this article:** Gupta N, Batra T, Kakar A, et al. Idiopathic Intracranial Hypertension Masquerading as Cerebral Venous Sinus Thrombosis: A Diagnostic Challenge. *J Assoc Physicians India* 2026;74(7):90–92.

Left eye

Right eye



**Fig. 1:** Fundus photographs of both eyes showing disk edema (blue arrow) and peripapillary hemorrhage (yellow arrow)

**Table 1:** Laboratory parameters

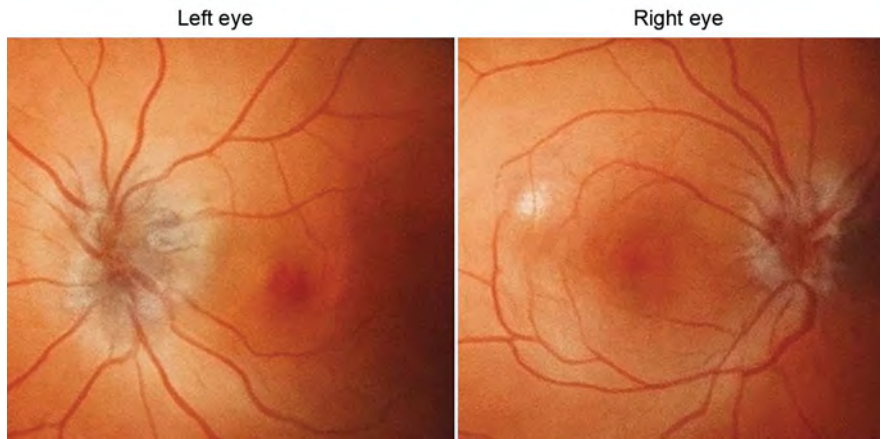
Parameter	Patient value	Reference range
Hemoglobin	10.0 gm/dL	13.5–17.5 gm/dL (male), 12.0–15.5 gm/dL (female)
Hematocrit (%)	31.6	41–53 (male), 36–46 (female)
Total leukocyte count	9250/μL	4,000–11,000/μL
Platelet count	359000/μL	150,000–450,000/μL
Differential leukocyte count (%)	75/20/4/1	Neutrophils 40–75, lymphocytes 20–45, monocytes 2–10, eosinophils 1–6
Total bilirubin	0.45 mg/dL	0.1–1.2 mg/dL
Direct bilirubin	0.35 mg/dL	0.0–0.3 mg/dL
Total protein	7.5 g/dL	6.0–8.3 g/dL
Serum albumin	4.2 g/dL	3.4–5.4 g/dL
AST	29 U/L	< 40 U/L
ALT	29 U/L	< 40 U/L
GGT	16 U/L	9–48 U/L
ALP	135 U/L	44–147 U/L
TSH	3.01 mIU/L	0.4–4.0 mIU/L
Free T3	3.44 pg/mL	2.0–4.4 pg/mL
Free T4	1.51 ng/dL	0.9–2.3 ng/dL
BUN	23 mg/dL	7–20 mg/dL
Creatinine	0.7 mg/dL	0.6–1.3 mg/dL
Na <sup>+</sup>	139 mEq/L	135–145 mEq/L
K <sup>+</sup>	4.23 mEq/L	3.5–5.0 mEq/L
Ca <sup>2+</sup>	9.2 mg/dL	8.5–10.5 mg/dL
Phosphorus	3.2 mg/dL	2.5–4.5 mg/dL
CSF opening pressure	350 mm H <sub>2</sub> O	100–250 mm H <sub>2</sub> O
Cell count	0 cells	0–5 cells/μL
Protein	22.2 mg/dL	15–45 mg/dL
Glucose	73.9 mg/dL	45–80 mg/dL
ADA	2.0 U/L	< 10 U/L (for TB screening)
TB PCR (Xpert MTB)	Not detected	Negative
CSF Gram stain	No organism seen	No organism seen
CSF AFB stain	Negative	Negative
ANA, ANCA	Negative	Negative
Protein C/protein S	Normal	Normal
Antithrombin III	105%	80–120%
Lupus anticoagulant/dRVVT	Negative	Negative
β2-GPI, ACA IgG/IgM	Negative	Negative
Homocysteine	7.23 μmol/L	4–15 μmol/L
Factor V Leiden mutation	Negative	Negative

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; TSH, thyroid-stimulating hormone; BUN, blood urea nitrogen; Na<sup>+</sup>, sodium; K<sup>+</sup>, potassium; Ca<sup>2+</sup>, calcium; CSF, cerebrospinal fluid; ADA, adenosine deaminase; TB, tuberculosis; PCR, polymerase chain reaction; MTB, Mycobacterium tuberculosis; AFB, acid-fast bacilli; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; dRVVT, dilute Russell viper venom time; β2-GPI, beta-2 glycoprotein I; ACA, anticardiolipin antibody; IgG, immunoglobulin G; IgM, immunoglobulin M

(e.g., tetracyclines, hypervitaminosis A), and more recently, abrupt cessation of GLP-1 receptor agonists such as semaglutide, which may result in rapid weight regain—a known risk factor for IIH development.<sup>4</sup> In this patient, clinical presentation with headache, visual floaters, diplopia, and bilateral papilledema with hemorrhages suggested raised ICP.<sup>5</sup> The initial noncontrast MRV, which falsely indicated cerebral venous sinus thrombosis (CVST), illustrates a frequent diagnostic pitfall. Flow-related artifacts and normal anatomical variants, such as hypoplastic sinuses or

prominent arachnoid granulations, can mimic thrombosis on imaging. This underscores the need for contrast-enhanced MRV, which remains the gold standard in differentiating true thrombus from anatomical variants.<sup>6</sup> The diagnostic confirmation of IIH in this case followed the modified Dandy criteria, which include: Symptoms of increased ICP pressure (e.g., headache, visual obscurations, papilledema), normal CNS examination (excluding VI nerve palsy), normal neuroimaging (excluding mass or hydrocephalus), raised opening pressure on lumbar puncture (>25 cm H<sub>2</sub>O) with normal

CSF parameters as well as alert and oriented mental status.<sup>7</sup> This patient's CSF opening pressure was significantly elevated (350 mm H<sub>2</sub>O), with normal cell count and biochemistry, aligning well with diagnostic criteria. The mainstay of medical treatment is acetazolamide, a carbonic anhydrase inhibitor that causes a reduction in production of CSF by its action at the choroid plexus.<sup>7</sup> As used in our case, it showed significant efficacy in improving both symptoms and fundoscopic findings. The patient showed marked improvement on serial fundus evaluations, confirming resolution



**Fig. 3:** Fundus photographs after 2 weeks of follow-up on acetazolamide therapy showing resolving disk edema

of papilledema. In refractory cases, options include topiramate and/or furosemide. Invasive interventions, such as CSF shunting or optic nerve sheath fenestration, may also prove to be helpful, especially when vision is threatened. Long-term care involves maintaining weight reduction and periodic vision monitoring to prevent relapse.

Idiopathic intracranial hypertension can mimic cerebral venous sinus thrombosis on imaging. High clinical suspicion, detailed

thrombophilia workup, CSF pressure analysis, and imaging with contrast MRV are crucial for accurate diagnosis. Ophthalmologic findings and symptom improvement after LP strongly support a diagnosis of IIH. Avoiding misdiagnosis prevents unnecessary anticoagulation and directs appropriate treatment.

#### PATIENT CONSENT STATEMENT

Participant's consent has been obtained.

#### ORCID

Nikhil Gupta  <https://orcid.org/0009-0007-4784-6184>

Tanvi Batra  <https://orcid.org/0009-0007-8215-5792>

#### REFERENCES

1. Saposnik G, Barinagarrementeria F, Brown RD Jr, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42(4):1158–1192.
2. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2013;81:1159–1165.
3. Mollan S, Davies B, Silver NC, et al. Idiopathic intracranial hypertension: consensus guidelines on management. *J Neurol Neurosurg Psychiatry* 2018;89:1088–1100.
4. Heckel B. Idiopathic intracranial hypertension after abrupt cessation of medication: a case report of abrupt glucagon-like peptide-1 (GLP-1) receptor agonist cessation and review of the literature. *Curr Pain Headache Rep* 2024;28:453–456.
5. Wall M. Idiopathic intracranial hypertension. *Neurol Clin* 2010;28:593–617.
6. Leach JL, Fortuna RB, Jones BV, et al. Imaging of cerebral venous thrombosis: Current techniques, spectrum of findings, and diagnostic pitfalls. *Radiographics* 2006;26 Suppl 1:S19–S41.
7. Ball AK, Clarke CE. Idiopathic intracranial hypertension. *Lancet Neurol*. 2006;5:433–442.

She doesn't just need reassurance  
**She needs the support she deserves...**



In PMS, PCOS

Rx **REVITAL<sup>®</sup>** **women**

12 Vitamins + 10 Minerals + 3% Natural Ginseng Extract

Her daily boost of energy and confidence



PMS: Premenstrual syndrome.  
PCOS: Polycystic ovary syndrome.  
For more information, please write to Sun Pharma, Sun House, CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai - 400063. Tel. No. : (+91 22) 4324 4324.

Validity : 21/4/2028 04-20260434 For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

# Imeglimin in Type 2 Diabetes Mellitus: Expert Opinions and Consensus in Indian Context



Jegan Duraiswamy<sup>1\*</sup>, Nitin Chintaman Gawari<sup>2</sup>, Tanvi Naik<sup>3</sup>, Teja Achyut Deshpande<sup>4</sup>

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1567

Dear Editor,

We read with interest the expert consensus by Seshadri et al. on imeglimin for the management of type 2 diabetes mellitus (T2DM). The article is timely and informative, particularly in view of the increasing complexity of diabetes management in India. The debate around the novel mechanism of imeglimin, which addresses both insulin resistance and mitochondrial dysfunction through mitochondrial routes, is well summarized and is in line with the increasing emphasis on preserving the function of the beta cell.<sup>1</sup>

Recommendations on the use of imeglimin in patients intolerant to metformin or as an add-on therapy are practical and relevant. Its favorable safety profile, in view of low risk of hypoglycemia and gastrointestinal adverse reactions, makes it favorable in multiple comorbid conditions in India.<sup>1,2</sup>

However, we would like to make a few comments:

- **Level of evidence classification:** Although the article categorizes recommendations at levels A, B, C, and E, it clearly omits level D, which typically includes nonanalytical studies (e.g., case reports or series of case reports). This could be useful, particularly given the anecdotal or observational nature of some of the allegations.
- **Lack of data on the Indian population:** Despite the focus on the Indian context, most of the cited studies, including TIMES 1–3 and others, were carried out in non-Indian populations, mainly in Japan.<sup>3,4</sup> Although expert consensus offers guidance, real-world data from Indian patients, such as

the INDI-TIMES study, remain limited and are insufficiently reflected in the Consensus Recommendation List (CRL).<sup>5</sup>

- **Dosage clarity:** The article gives due emphasis to the fact that the preferred dose is 1000 mg twice daily. However, several of the reference studies, including the Fouqueray et al. study, show that 1500 mg BID has higher efficacy in reducing glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) compared to 1000 mg BID.<sup>6</sup> The lack of detailed discussion on the potential confounders (e.g., tolerability, adverse effect profile, patient acceptability) associated with higher doses leaves an important gap in practical guidance.
- **Cost and availability considerations:** From a patient perspective, more comments on the cost-effectiveness of the medication would be valuable, particularly in rural India where affordability is often a key factor in adherence.

In conclusion, imeglimin is a promising agent with a novel mode of action and a safety profile that differentiates it from traditional oral agents. Specific data and more comprehensive long-term safety results in the Indian population are needed to support its widespread use in practice. The expert consensus provides a strong platform for advancing discussions and fostering further research on imeglimin in the Indian context.

## ORCID

Jegan Duraiswamy <https://orcid.org/0009-0007-8241-0351>

Nitin Chintaman Gawari <https://orcid.org/0009-0006-4241-8909>

Tanvi Naik <https://orcid.org/0009-0007-0155-9999>

## REFERENCES

1. Seshadri KG, Mohan V, Wangnoo SK, et al. Imeglimin in type 2 diabetes mellitus: expert opinions and consensus in Indian context. *J Assoc Physicians India* 2025;73(6):e15–e22.
2. Hallakou-Bozec S, Vial G, Kergoat M, et al. Mechanism of action of imeglimin: a novel therapeutic agent for type 2 diabetes. *Diabetes Obes Metab* 2021;23(3):664–673.
3. Dubourg J, Ueki K, Grouin JM, et al. Efficacy and safety of imeglimin in Japanese patients with type 2 diabetes: a 24-week phase 2b trial. *Diabetes Obes Metab* 2021;23(3):800–810.
4. Reilhac C, Dubourg J, Grouin JM, et al. TIMES 3: combination therapy with imeglimin and insulin in Japanese patients with T2DM. *Diabetes Ther* 2022;13(5):1211–1223.
5. Shaikh S, Sharma SK, Phatak S, et al. Real-world effectiveness of imeglimin in Indian T2DM patients: results from the INDI-TIMES study. *Diabetes Ther* 2025;16(4):645–661.
6. Fouqueray P, Pirags V, Diamant M, et al. The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with sitagliptin monotherapy. *Diabetes Obes Metab* 2014;37(7):1924–1930.

<sup>1</sup>Junior Resident; <sup>2</sup>Assistant Professor; <sup>3</sup>Junior Resident; <sup>4</sup>Associate Professor, Department of Pharmacology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India; \*Corresponding Author

**How to cite this article:** Duraiswamy J, Gawari NC, Naik T, Deshpande TA. Imeglimin in Type 2 Diabetes Mellitus: Expert Opinions and Consensus in Indian Context. *J Assoc Physicians India* 2026;74(7):94.

# Assessing the Impact of the District Residency Program on Pre- and Paraclinical Postgraduate Training in India



Nitin Chintaman Gawari<sup>1</sup>, Gampa Sarjanya<sup>2\*</sup>, Sujata Prakash Shingare<sup>3</sup>, Yasir Hassan<sup>4</sup>

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1564

## INTRODUCTION

Since 2023, the National Medical Commission's District Residency Program (DRP) has been placing postgraduate residents in district hospitals for 3 months, with the intention of strengthening primary healthcare and exposing young doctors to real-world community health challenges. The vision behind the program is admirable: to make future specialists more aware of ground-level healthcare issues while improving district-level services.<sup>1,2</sup>

However, applying the DRP uniformly across all specialties has created unintended consequences for those in the pre- and paraclinical disciplines. Unlike their clinical counterparts, these residents often find themselves in roles that do not align with their training. For many, the residency becomes less about academic growth and more about filling service gaps.

In districts where multiple medical colleges send their residents to the same hospital, the strain is even more apparent. The sudden influx of trainees overwhelms the system, stretching resources thin and limiting the capacity of clinicians to provide meaningful guidance. Instead of contributing to their academic development, pre- and paraclinical residents are often assigned routine clerical work or basic patient-care duties. This not only sidelines their professional growth but also erodes their sense of purpose.

Many residents report feeling harassed by administrative staff, while others struggle with language barriers when posted outside their home regions. For some, being thrust into patient-facing roles without adequate preparation adds yet another layer of stress, particularly since their early training rarely involves direct patient care.

In practice, what was designed as a transformative learning experience has, for pre- and paraclinical residents, sometimes become a source of frustration and professional stagnation.

## WHAT PRE- AND PARACLINICAL RESIDENTS OFTEN EXPERIENCE Feeling Disconnected from Learning

Residents in fields like anatomy, physiology, and microbiology often report that their time

in the DRP does not translate into meaningful academic growth. A study from Rajasthan highlighted that many felt the program failed to meet its teaching goals. Being away from their parent departments, they missed the mentorship, exposure, and subject-specific learning they had expected.<sup>1</sup>

## Struggling with Inadequate Infrastructure

District hospitals, while essential for community healthcare, are not always equipped to support specialized postgraduate education. Many residents point out the lack of diagnostic tools, laboratories, and advanced equipment. Without these resources, their ability to deepen subject knowledge or refine research skills becomes severely limited.

## Concerns About Safety

Personal safety remains a significant worry—especially among women residents. Long hours, inadequate facilities, and unfamiliar settings contribute to feelings of vulnerability, adding to the stress of the posting.

## Interrupted Academic Work

Being separated from their academic mentors also affects their research and exam preparation. Many residents find it difficult to continue thesis work or prepare for assessments in the absence of guidance and academic resources.<sup>3,4</sup>

## RECOMMENDATIONS

### Tailor the DRP to Each Specialty

A "one-size-fits-all" approach does not serve every discipline equally well. If the program is adapted to match the unique needs of each specialty, it can become far more effective. For pre- and paraclinical residents, alternative placements—such as research assignments, laboratory postings, or specialized project work—may provide more relevant and rewarding learning experiences.<sup>5</sup>

### Strengthen District Hospital Infrastructure

For the DRP to succeed, district hospitals need to be adequately equipped. This means creating

well-functioning laboratories, ensuring reliable access to diagnostic tools, and providing safe and sufficient housing for residents. Without these basics, the program risks falling short of its educational and service goals.<sup>6</sup>

## Foster Collaboration Between Key Stakeholders

Close cooperation among the National Medical Commission (NMC), the health department, and medical colleges is essential. With thoughtful planning and supportive policies, logistical hurdles can be addressed, allowing the program to better align with both healthcare delivery and postgraduate education.<sup>3,7</sup>

## Build Strong Feedback and Monitoring Systems

Continuous improvement depends on listening to the voices of those most affected. Regular monitoring, open channels for feedback, and routine reviews can help identify challenges early and ensure that residents' perspectives actively shape the evolution of the program.

## CONCLUSION

District Residency Program is a valuable initiative aimed at strengthening district healthcare and enriching postgraduate training. However, uniform implementation often disadvantages pre- and paraclinical residents due to limited infrastructure, safety issues, and academic disruption. Tailoring postings, improving facilities, fostering collaboration, and integrating resident feedback can transform the DRP into a balanced, meaningful, and truly impactful learning experience.

## ORCID

Nitin Chintaman Gawari  <https://orcid.org/0009-0006-4241-8909>

<sup>1,3</sup>Assistant Professor; <sup>2,4</sup>Junior Resident, Department of Pharmacology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India; \*Corresponding Author

**How to cite this article:** Gawari NC, Sarjanya G, Shingare SP, Hassan Y. Assessing the Impact of the District Residency Program on Pre- and Paraclinical Postgraduate Training in India. *J Assoc Physicians India* 2026;74(7):95–96.

Sujata Prakash Shingare  <https://orcid.org/0009-0002-5260-364X>

Yasir Hassan  <https://orcid.org/0009-0007-8917-9682>

## REFERENCE

1. Raj A, Singh S, Rathore M. Early evidence of implementation of District Residency Programme: experiences and challenges of residents in Rajasthan, India. *BMC Med Educ* 2024;24:493.
2. Why resident doctors are struggling with NMC's district residency programme. *Careers360*. Available from: <https://news.careers360.com/pg-medicine-college-resident-doctor-nmc-national-medical-commission-district-residency-osmania-nair-hospital> [Last accessed June, 2026].
3. Sindhu Abhivanth R, Madhukumar S. District Residency Program: exploration of the perceptions of postgraduates - a way ahead. *RGUHS J Med Sci* 2025;15:128–133.
4. Muthukumar A, Menon P, Shailaja M, et al. District Residency Program – students' perception. *Med JDr DY Patil Vidyapeeth* 2024;17(4):927–928.
5. Doddihal CR, Pattankar TP. District Residency Programme (DRP) for post-graduates: the community medicine perspective. *Natl J Community Med* 2024;15(8):697–698.
6. Sharda M. District Residency Program: an overview. *J Mod Med* 2024;2(2):47–49.
7. NMC's District Residency Programme worries Telangana medicos; implementation postponed to April 1. *EdexLive*. Available from: <https://www.edexlive.com/news/2023/mar/21/nmcs-district-residency-programme-worries-telangana-medicos-implementation-postponed-to-april-1-34375.html> [Last accessed June, 2026].

## A Conversation with ChatGPT about Pleural Effusion

Srinivas Sadanand Pai\*<sup>1</sup>

*Journal of The Association of Physicians of India* (2026); 10.59556/japi.74.1563

Dear Editor,

A conversation with ChatGPT (Chat Generative Pre-trained Transformer) about pleural effusion.

Artificial intelligence (AI) offers a complementary route in deciding about the prognosis, decision-making, estimating mortality rates, and the development of drugs related to pleural effusion. Wang et al. have come up with an AI model that can help differentiate between malignant pleural effusion (MPE) and benign pleural effusion (BPE).<sup>1</sup> The proposed mechanism is that AI looks at the computed tomography (CT) scan in small patches instead of one big picture. It also examines the image at different scales. In the above study, 362 new patient studies from a separate hospital were used to verify the generated AI model, which showed some degree of reliability.

One such AI language model is ChatGPT. It was developed by OpenAI in 2022. It can analyze uploaded pictures, give travel suggestions, help students understand difficult concepts, and much more. It uses processes like natural language processing (NLP) to respond like humans do.

Abnormal buildup of fluid in the pleural space is called pleural effusion. A small amount of pleural fluid is required to encourage smooth movement of the lungs during respiration. This balance, however, can be upset by a number of medical conditions, which results in an abnormal buildup of fluid. Nearly 1.5 million patients are affected by this condition annually.<sup>2</sup> Pleural effusion is a sign of higher rates of morbidity and mortality in some groups.<sup>3</sup> Hence, it is essential to know the cause of pleural effusion. The entire treatment revolves around the underlying cause of pleural effusion. However, there are challenges in treatment as it has diverse etiologies varying from heart failure to malignancy.

Particularly, one such topic of interest is differentiating BPE from MPE. Pleural nodules, circumferential pleural thickening, mediastinal pleural thickening, and parietal pleural thickening of >1 cm are examples of contrast-enhanced CT features in MPEs. The sensitivity of CT is not high in differentiating the two etiologies (18–53%).<sup>1</sup> Hence, it is important to look for an additional tool

that can help differentiate MPE from BPE with ease.

We asked ChatGPT some questions regarding pleural effusion and how to differentiate benign from MPE. The following was the response:

Question	Answer
1. What is pleural effusion?	Abnormal excess fluid in pleural space due to disrupted balance of fluid formation and absorption, causing lung compression and dyspnea
2. What are the types of pleural effusion?	Transudative (systemic pressure imbalance: CHF, cirrhosis, nephrotic) and exudative (local inflammation/malignancy: TB, cancer, pneumonia, PE). Special forms: chylous, hemorrhagic, empyema
3. How to distinguish transudative vs exudative pleural effusion?	Light's criteria: exudate if any: PF/serum protein >0.5; PF/serum LDH > 0.6; PF LDH > 2/3 upper normal serum limit
4. How to differentiate tubercular vs nontubercular pleural effusion?	TB: lymphocyte-predominant, ADA > 40 U/L, high protein (>3 gm/dL), ± low glucose, high LDH, pleural biopsy granulomas. Non-TB varies by cause (malignancy: cytology+; parapneumonic: neutrophils, very low pH/glucose)
5. How to differentiate benign vs malignant pleural effusion?	Malignant clues: positive cytology, bloodstained fluid, pH < 7.2, low glucose, high LDH, recurrent large effusion, nodular pleura on CT/US, trapped lung. Benign: resolves with underlying cause, cytology negative, no pleural thickening/nodules

As one can see, the answers to the questions about pleural effusion were fairly accurate. However, the use of AI in differentiating MPE from BPE should be taken with a grain of salt. There is something called overfitting phenomenon, where AI performs well on the data it learned from but fails when exposed to new patients or different clinical settings. Hence, it is important to add it up with clinical judgment as well as laboratory parameters.<sup>4</sup>

In a nutshell, AI has the potential to offer valuable assistance in looking for the probability of MPE by combining clinical and imaging modalities into meaningful risk predictions. Its use may help clinicians identify patients who have MPE. However, tissue confirmation remains the gold standard for establishing malignancy. AI-generated algorithms must therefore be viewed as triage tools that support rather than replace diagnostic pathways. For successful clinical translation, healthcare providers should possess a clear understanding of AI methodology, validation standards, and limitations. Multidisciplinary oversight will

ensure that AI strengthens clinical decision-making and improves patient care without introducing new risks.

## ORCID

Srinivas Sadanand Pai  <https://orcid.org/0009-0006-0469-3539>

## REFERENCES

1. Wang S, Tan X, Li P, et al. Differentiation of malignant from benign pleural effusions based on artificial intelligence. *Thorax*. 2023;78(4):376–382.
2. Walker SP, Morley AJ, Staddon L, et al. Nonmalignant pleural effusions: a prospective study of 356 consecutive unselected patients. *Chest* 2017;151(5):1099–1105.
3. Leung AN, Muller NL, Miller RR. CT in differential diagnosis of diffuse pleural disease. *AJR Am J Roentgenol* 1990;154(3):487–492.
4. Saguil A, Wyrick K, Hallgren J. Diagnostic approach to pleural effusion. *Am Fam Physician* 2014;90(2):99–104.

Assistant Professor, Department of Respiratory Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India; \*Corresponding Author

**How to cite this article:** Pai SS. A Conversation with ChatGPT about Pleural Effusion. *J Assoc Physicians India* 2026;74(7):97.



Choose the



# RIGINAL

That is widely available



**Huminsulin<sup>®</sup> 30/70**  
30% Regular and 70% NPH Human Insulin r-DNA origin

**Huminsulin<sup>®</sup> R**  
Human Regular Insulin r-DNA origin

**Huminsulin<sup>®</sup> N**  
Human NPH Insulin r-DNA origin

**Huminsulin<sup>®</sup> 50 50**  
50% Regular and 50% NPH Human Insulin r-DNA origin

For the use of Registered Medical Practitioners, Hospitals or Laboratory Only.



Together, bring  
more people under

Swachh  
**Arteries**  
Abhiyan

In India, approximately **4 out of 5**  
individuals suffer from Dyslipidemia\*

The **Turbo Power** range for **healthy arteries**

## Turbovas

(Rosuvastatin 5/10/20/40mg Tablets)

## Turbovas **F**

(Rosuvastatin 10mg + Micronized Fenofibrate 160mg Tablets)

## Turbovas **Gold**

(Rosuvastatin 10/20mg + Clopidogrel 75mg + Aspirin 75mg Capsules)

## Turbovas **CV**

(Rosuvastatin 10/20mg + Clopidogrel 75mg Capsules)

## Turbovas **EZ**

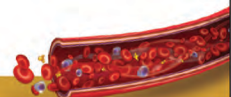
(Rosuvastatin 10/20mg + Ezetimibe 10mg Tablets)

## Turbovas **ASP**

(Rosuvastatin 10/20mg + Aspirin 75mg Capsules)



Micro Labs Ltd, Micro House, 4th Floor, Chandivali Farm Road,  
Near Kamani Oil Mills, Chandivali, Andheri (East), Mumbai 400072.  
Web: [www.microlabsltd.com](http://www.microlabsltd.com)



RNI NO. 11552/57  
Postal Reg. No. MCW/80/2021-2023  
MR/TECH/WPP-248/WEST/2021-23 licensed to post without prepayment  
Posted at Mumbai Patrika Channel Sorting Office, Mumbai 400 001 on 1st and 2nd of every month

In Fever & Pain,  
**Every Dose Delivers Trust!**

Rx

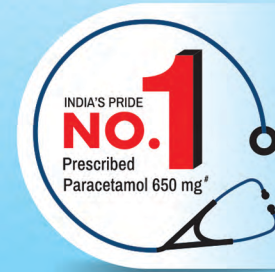
# Dolo-650

Paracetamol 650 mg Tablets

Extra Strength for Faster & Longer Action

AWARDED

Excellence in Pharma Technology & Innovation



POWERED BY



Engineered for fast disintegration  
with specialized disintegrant<sup>1</sup>  
"Sodium Starch Glycolate  
(SSG)"<sup>1</sup>



MICRO LABS  
LIMITED

1. Shah U et al. Pharm Dev Technol. 2002;7(3):345-59. | #IQVIA SSA MAT Mar'26.

IF UNDELIVERED PLEASE RETURN TO

Office: Unit No. 3301, Prestige Turf Tower 'D', Shakti Mill Lane,  
Off. Dr. E. Moses Road, Near Mahalaxmi Station (West), Mumbai-400 011.  
Mobile number: 7710020034/7710029211