Vol No. 74 Issue No. 6 June 2026 ISSN: 0004-5772

Journal of
The Association of Physicians of India



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Article
Hydatid Cyst of Right Atrium

Editor-in-Chief: **Prof. Dr. Nandini Chatterjee**

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

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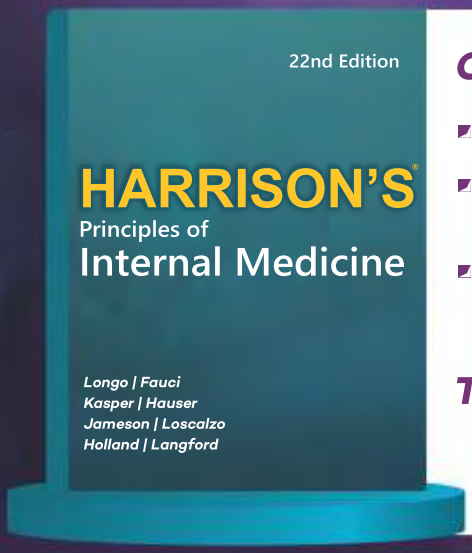
Composition: Each film coated tablet contains:BisoprololFumarate IP2.5mg/5mgTelmisartan Ip40mg **Indications:** The fixed dose combination of Bisoprololfumarate and Telmisartan tablets is indicated for the treatment of stage 1 and stage 2 hypertension. **Dosage & Administration:** The recommended dose 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 Bisoprololfumarate and Telmisartan tablets is contraindicated in hypersensitivity to Bisoprolol and Telmisartan or to any of the excipients in the formulation. **Bisoprolol:** cardiogenic shock,AV block of second or third degree, symptomatic bradycardia and hypotension. **Telmisartan:** Second and third trimesters of pregnancy, Biliary obstructive disorders, severe hepatic impairment, The concomitant use of Telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2) **Warning & Precautions:** Bisoprolol-Especially in patients with ischaemic heart disease the cessation of therapy with Bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition. There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with coronary heart disease.Bisoprolol must be used with caution in bronchospasm, diabetes mellitus, AV block of first degree, Prinzmetal's angina, Peripheral arterial occlusive disease. **Telmisartan** is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since Telmisartan is mostly eliminated with the bile.Volume- and/or sodium-depleted patients: Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. **Drug Interactions:** Bisoprolol-Combination not recommended-Verapamiil, Diltiazem, Methyldopa,Lidocaine. Combinations to be used with caution- Amlodipine,Amiodarone 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, Aliskiren. **Special Populations: Pregnancy:** Bisoprolol is not recommended during pregnancy unless clearly necessary and breast-feeding.**Telmisartan**-Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started. Telmisartan is not recommended inbreast-feeding. **Hepatic or Renal impairment:Bisoprolol -** In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment isnormally 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 isrecommended. **Adverse Reactions:Bisoprolol-** Most common adverse reactions includeheadache 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.

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References: 1. Heinemann L et al. Journal of diabetes science and technology. 2023 Nov;17(6):1649-61. | 2. Ozempic® CDSCO approved package insert version dated 23 Oct 2025.

Abbreviated prescribing information (and not full package insert)
Generic Name: Semaglutide Injection 0.25 mg (r-DNA Origin), solution for injection in pre-filled pen, Semaglutide Injection 0.5 mg (r-DNA Origin), solution for injection in pre-filled pen, Semaglutide Injection 1 mg (r-DNA Origin), solution for injection in pre-filled pen **Brand Name:** Ozempic® **Presentation:** Ozempic® is available in 0.25 mg, 0.5 mg and 1 mg. **Indication:** Semaglutide injection is indicated as; an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, 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 eGFR decline, end-stage kidney disease and cardiovascular death in adults with type 2 diabetes mellitus and chronic kidney disease. **Description:** Ozempic® is a clear and colorless or almost colorless solution for injection in a pre-filled pen. **Posology:** The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks, the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. **Method of administration:** Subcutaneous use. Ozempic® is administered once weekly at any time of the day, with or without meals. It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It should not be administered intravenously or intramuscularly. If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (>72 hours). Patients should be advised to read the instructions for use included in the package leaflet carefully before administering Ozempic®. **Special Population:** No dose adjustment is required based on age. No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited. No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. The safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients, with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function. Increased risk of residual gastric content due to delayed gastric emptying should be considered prior to performing procedures with general anaesthesia or deep sedation. Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. 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 sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide. In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. **Use in special populations (Fertility, pregnancy and lactation):** Women of child-bearing potential are recommended to use contraception when treated with semaglutide. There are limited data regarding the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life. Semaglutide should not be used during breast-feeding. The effect of semaglutide on fertility in humans is unknown. **Drug Interaction:** Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. Paracetamol: Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardized meal test. No clinically relevant effect on paracetamol was observed with semaglutide. No dose adjustment of paracetamol is necessary when administered with semaglutide. Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree, when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Atorvastatin: Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Digoxin: Semaglutide did not change the overall exposure or Cmax of digoxin following a single dose of digoxin (0.5 mg). Metformin: Semaglutide did not change the overall exposure or Cmax of metformin following dosing of 500 mg twice daily over 3.5 days. Warfarin: Semaglutide did not change the overall exposure or Cmax of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. **Effects on ability to drive and use machines:** Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable effects:** In 8 phase 3a trials, 4792 patients were exposed to semaglutide up to 1 mg. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration. **Overdose:** Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications. There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. **Shelf-life:** Before first use: 36 months. After first opening: 6 weeks. Store below 30 °C or in a refrigerator (2 °C–8 °C). **Storage:** Store in a refrigerator (2 °C–8 °C). Keep away from the cooling element. Do not freeze. Keep the pen cap on in order to protect from light.
Disclaimer: The abbreviated package insert is updated from the CDSCO approved package insert (File No. BE/OIMP/25/000251 dated 19 Sep 2025 and subsequent approval vide File No. I-ONA-1101/13/2025-eoffice dated 23 Oct 2025).

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

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Published and Edited by
Prof. Dr. Nandini Chatterjee, on behalf of **The Association of Physicians of India**, Journal of The Association of Physicians of India, Unit No. 3301, Prestige Turf Tower 'D', Shakti Mill Lane, Off. Dr. E. Moses Road, Near Mahalaxmi Station (West), Mumbai-400 011.
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JAPI: Its Journey towards the Platinum Peak

Nandini Chatterjee*

The Journal of the Association of Physicians of India, the erstwhile "MEDICINE", has come a long way since its inception on a busy morning in 1952. The association had been founded in 1944 by a band of visionaries who felt that physicians needed a platform for academic exchange and enrichment. It took another eight years to conceptualize and bring out the Journal of API, then named simply "MEDICINE". It was a treatise that would be the mouthpiece of the physicians of India, the medium of dissemination of new information, research, and the wisdom of the times.

The Past[1,2]

The first editor was Prof. SS Misra, from King George Medical College, Lucknow. As the lore goes, Prof. Misra had requested Dr JC Patel, then the Secretary of API, to donate funds to run this journal. The whole fund that belonged to the association–a total of. ₹ 1000/- was utilized to launch their dream "A Journal of their own".

Initially, it was a quarterly journal, and Prof Mishra envisioned it to publish "original articles, along with reports on clinicopathological conferences, extracts from current modern literature, and association notes"—his exact words as he penned down his thoughts in his first editorial.

However, the publication was discontinued after three issues due to a lack of funds. The Journal rose from the ashes in 1955 when it was resurrected by Dr George Coelho from Bombay. He was appointed the second editor of The Journal that now had a new name, "Journal of the Association of Physicians of India," JAPI.

Dr Coelho, the then superintendent of Bai Jerbai Wadia Hospital, the first children's hospital in India, steered the Journal from 1955 to 1971 with able dexterity, converting it to a monthly journal eventually from 1961.

The journal got indexed in SCOPUS in 1961 and thereafter in PUBMED in 1965, both during the editorship of Dr Coelho.

The Present

The journal continued to flourish from less than 500 pages per year to the current average of more than 1200 a year. Side by side, from printing monthly 3,000 copies in 1982, the copy numbers have multiplied exponentially, trying to cater to the ever-expanding member pool, touching 26,000 in the current year.

The Journal receives over 600 manuscripts annually, and it is a veritable challenge to publish them in a stipulated time. Taking into account the piling backlog of articles, online supplement publication had been started from 2025.

Professor SS Misra belonged to Lucknow. He was the only editor in the past to hail from outside of Mumbai, as all successive editors operated from the head office of API at Mumbai, where subsequently dedicated staff for JAPI have been employed.

The most historic fallout of the COVID pandemic was the development of the internet revolution. The lockdown had forced people to remain indoors. But the world had to go on. Hence, the online versions of books, newspapers, movies, and television serials. So why would journals be far behind?

Thus, from January 2026, the 13th editor of JAPI took over from West Bengal. The daily operation of JAPI is now a combined dedicated effort of the Mumbai-based staff, the Bengal-based Editor, the editorial committee, and reviewers from all over the nation connected through the ethereal waves of modern technology.

The Future

JAPI has expanded not only in volume but also in stature and prestige. However, medical science is progressing at an explosive speed with the advent of artificial intelligence. The journal has to keep up and reinvent itself to flourish and shine.

The article turnover needs to build up, shortening processing time with prompt reviews and decisions. We should aim for better reach of the journal, a more inclusive author profile, and publication of articles enriched in scientific rigor and variety.

Now in June 2026, we are at the threshold of the platinum jubilee of JAPI, its morale soaring high and resolve ironclad to excel in the academic stratosphere! All we need is the goodwill, support, and insights of API members in its journey forward.

Reference

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How to cite this article: Chatterjee N. JAPI: Its Journey towards the Platinum Peak. J Assoc Physicians India 2026;74(6):11.

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ORIGINAL ARTICLE

Hypothyroidism in Nonalcoholic Fatty Liver Disease

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Received: 27 May 2025; *Accepted:* 30 March 2026

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease with increasing global prevalence. Thyroid dysfunction, particularly hypothyroidism, has been implicated in its pathogenesis and progression.

Objectives: To evaluate the prevalence and pattern of hypothyroidism in NAFLD patients and assess its association with hepatic steatosis and fibrosis severity using imaging and noninvasive fibrosis scoring systems.

Materials and methods: This cross-sectional observational study was conducted on 158 adult NAFLD patients at a tertiary care hospital in northern India over 1 year. Patients with significant alcohol intake or other chronic liver diseases were excluded. Hepatic steatosis and fibrosis were assessed by ultrasonography and transient elastography, respectively. Fibrosis severity was categorized using FibroScan and the FIB-4 index. Thyroid function was evaluated by serum TSH, FT3, and FT4. Statistical analysis included intergroup comparisons and correlation assessments using SPSS v26, with $p < 0.05$ considered significant.

Results: Among 158 NAFLD patients, 41.14% were hypothyroid. The prevalence of hypothyroidism increased with disease severity: 71.43% in fibrotic NASH and 44.44% in cirrhosis (FibroScan-based). A dose-response trend was observed between steatosis grade and hypothyroidism, reaching 80% in grade 3 steatosis. FT4 showed a significant positive correlation with liver stiffness ($r = 0.432$, $p < 0.001$). Additional associations included positive correlations of liver stiffness with urea and INR, and negative correlations with serum protein, fasting glucose, and LDL. Overall, hypothyroidism emerged as a significant cofactor in NAFLD pathogenesis and fibrosis progression.

Conclusion: This study demonstrates a strong association between hypothyroidism and both hepatic steatosis and fibrosis in NAFLD. Routine thyroid function screening is recommended in NAFLD patients, particularly those with metabolic syndrome or suspected fibrosis. Early detection and treatment of hypothyroidism may provide therapeutic benefits in slowing or reversing NAFLD progression.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1502

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major public health concern characterized by excessive triglyceride deposition in hepatocytes among individuals consuming minimal or no alcohol. Its diagnosis is based on imaging or histology in the absence of secondary causes such as alcohol abuse, medications, or genetic liver disorders.[1] Globally, NAFLD affects 20–30% of adults and is considered the hepatic component of metabolic syndrome.[1,2] In patients with type 2 diabetes mellitus, prevalence may reach 70%, highlighting its close association with insulin resistance and cardiometabolic disturbances.[2] The disease spectrum ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma.[3] Although early stages are often asymptomatic, advanced fibrosis increases the risk of severe liver-related outcomes. Recent advances in noninvasive diagnostics, including transient elastography and scoring indices such as FIB-4, have improved fibrosis assessment and reduced reliance on biopsy.[4]

Hypothyroidism, defined as reduced thyroid hormone production or action, is increasingly recognized as a contributor to NAFLD. Globally, iodine deficiency remains the most common cause, though autoimmune thyroiditis predominates in iodine-sufficient regions.[5,6] Its clinical features are often nonspecific, and diagnosis is established biochemically with elevated TSH and reduced FT4.[7] Thyroid hormones regulate lipid metabolism and mitochondrial function, and their deficiency promotes hepatic lipid accumulation, impaired β-oxidation, and oxidative stress.[8,9] Furthermore, TSH receptors expressed on hepatocytes may directly stimulate lipid synthesis.[10]

Epidemiological data and meta-analyses have shown that both overt and subclinical hypothyroidism increase the risk of NAFLD and are associated with more severe fibrosis.[11] Certain cohorts report NAFLD, particularly among patients with histologically confirmed NASH prevalence as high as 46% in hypothyroid patients.[12,13] Emerging therapeutic studies suggest levothyroxine replacement may reduce hepatic steatosis and improve metabolic parameters.[14]

In this context, the present study was designed to evaluate the association between hypothyroidism and NAFLD in an Indian population. The objectives included assessing the prevalence of thyroid dysfunction in NAFLD patients, determining its distribution across different stages of liver disease, and exploring correlations between thyroid hormone levels and fibrosis severity. Through this analysis, we aimed to better understand the endocrine-metabolic interface underlying NAFLD and to highlight the relevance of routine thyroid function screening in this population.

Materials and Methods

This was a cross-sectional observational study conducted over 1 year in the Department of Medicine in collaboration with the Department of Medical Gastroenterology at a tertiary care hospital in northern India. Ethical approval was obtained from the Institutional Ethics Committee (IEC) prior to study initiation, and informed written consent was taken from all participants.

Study Population

Adult male and female patients above 18 years of age diagnosed with NAFLD were

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How to cite this article: Chaudhary SC, Singh P, Usman K, *et al.* Hypothyroidism in Nonalcoholic Fatty Liver Disease. J Assoc Physicians India 2026;74(6):12–15.

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included. The diagnosis of NAFLD was based on abdominal ultrasonography (USG) showing hepatic steatosis, defined as:

- Increased echogenicity of the liver compared with the renal cortex.
- Blurring of intrahepatic vessel walls.
- Posterior beam attenuation.

Inclusion Criteria

- Patients with ultrasonographic evidence of fatty liver.
- Both diabetic and non-diabetic patients.
- Adults willing to provide written informed consent.

Exclusion Criteria

- History of significant alcohol consumption (>11–15 gm/day in females, >2 drinks/day in males for ≥10 years).
- Pregnant women.
- Patients with hepatitis B or C infection (confirmed by viral markers).
- Autoimmune hepatitis or metabolic liver diseases (e.g., Wilson's disease, hemochromatosis) confirmed by serology.
- Renal impairment (acute or chronic kidney disease).
- Critically ill patients or those with multi-organ dysfunction.

Sample Size

The required sample size was calculated as 158 based on an assumed hypothyroidism prevalence of 12% among NAFLD patients, with a 95% confidence interval and 5% absolute error, using the formula:

$$n = Z^2 \times P(1-P)/d^2$$

where $Z = 1.96$, $P = 0.12$, and $d = 0.05$.

Table 1: Ultrasonographic findings of study population

Parameter	*Count (n = 158)*	*Percentage (100%)*
Ultrasound findings		
Grade 1 fatty liver	41	25.95
Grade 2 fatty liver	15	9.40
Grade 3 fatty liver	7	4.44
Hepatomegaly	95	60.12

Investigations and Data Collection

All patients underwent a detailed clinical history and physical examination. Laboratory tests included complete blood count, liver function tests, fasting and postprandial blood glucose, HbA1c, serum protein, albumin, lipid profile, urea, creatinine, electrolytes, PT/INR, and thyroid function tests (TSH, FT3, FT4). Viral markers, autoimmune profiles, and relevant tests for Wilson's disease and hemochromatosis were performed to exclude secondary causes of liver disease.

Imaging

Ultrasonography was used for grading fatty liver and hepatomegaly.

Transient elastography (FibroScan, Echosens, France) measured liver stiffness (in kilopascals) and controlled attenuation parameter (CAP) for steatosis, using the median of 10 valid readings. Fibrosis stages were categorized as:

- NAFL: <7 kPa
- Early NASH (F0–F1): 7–9.9 kPa
- Fibrotic NASH (F2–F3): 10–14.9 kPa
- NASH Cirrhosis (F4): ≥15 kPa

Noninvasive Scoring

The FIB-4 index was calculated as: FIB-4 = Age × AST/platelet count × √ALT.

Scores were interpreted as:

- <1.45: Stage 0–1 fibrosis
- 1.45–3.25: Stage 2–3 fibrosis
- >3.25: Stage 4–6 fibrosis

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS v26. Continuous variables were expressed as mean ± SD or median with interquartile range. Categorical variables were expressed as percentages. Intergroup comparisons were performed using Student's *t*-test or Chi-square test, where applicable. Correlations were tested using Pearson's or Spearman's coefficients. Chi-square test was applied to assess the association of thyroid status (hypothyroid vs euthyroid) with NAFLD severity across steatosis grades (ultrasound) and fibrosis stages (FibroScan, FIB-4). A p-value < 0.05 was considered statistically significant.

Results

This study included 158 NAFLD patients, predominantly middle-aged, with a male predominance. The majority (31.65%) were in the 21–40 year group, followed by 41–60 years (31.01%) and ≥61 years (32.27%).

Ultrasonographic Findings

Grade 1 steatosis was the most frequent, followed by grade 2 and grade 3. Hepatomegaly was seen in 60.12% of participants (Table 1).

FibroScan Staging

Nearly half (47.47%) had early NASH (F0–F1), while 8.86% and 11.39% were classified as fibrotic NASH (F2–F3) and NASH cirrhosis (F4), respectively. About one-third (32.28%) were in the NAFL stage (Table 2). FIB-4 scoring further showed that 63.29% had minimal fibrosis, whereas 27.84% and 8.80% were in stages 2–3 and 4–6, respectively (Table 3).

Cross-comparison of USG Grade with FibroScan Stage

Among the 63 patients who were graded for steatosis on USG, advanced steatosis grades were significantly associated with higher fibrosis stages (χ^2 test, $p < 0.05$). In grade 3 steatosis, 50% were in fibrotic or cirrhotic categories, compared to only 7.3% in grade 1 (Table 4).

Table 2: FibroScan staging

Parameter	*Count (n = 158)*	*Percentage (100%)*
NAFL	51	32.28
Early NASH (F0–F1)	75	47.47
Fibrotic NASH (F2–F3)	14	8.86
NASH cirrhosis (F4)	18	11.39

Table 3: FIB-4 staging

Parameter	*Count (n = 158)*	*Percentage (100%)*
Stage 0–1 (<1.45)	100	63.29
Stage 2–3 (1.45–3.25)	44	27.84
Stage 4–6 (>3.25)	14	8.80

Table 4: Fatty liver grade (USG) vs NAFLD stage (FibroScan)

USG fatty liver grade	*NAFL (n, %)*	*Early NASH (n, %)*	*Fibrotic NASH (n, %)*	*NASH Cirrhosis (n, %)*
Grade 1 ($n = 41$)	25 (60.98%)	13 (31.71%)	2 (4.88%)	1 (2.44%)
Grade 2 ($n = 12$)	6 (50.00%)	4 (33.33%)	1 (8.33%)	1 (8.33%)
Grade 3 ($n = 10$)	2 (20.00%)	3 (30.00%)	3 (30.00%)	2 (20.00%)
Total ($n = 63$)	33 (52.38%)	20 (31.75%)	6 (9.52%)	4 (6.35%)

Thyroid Function

Of the total cohort, 41.14% were hypothyroid, 55.70% euthyroid, and 3.16% hyperthyroid (Table 5). The prevalence of hypothyroidism increased with NAFLD severity on both ultrasound and FibroScan. On ultrasound, hypothyroidism was observed in 53.66% of grade 1, 75% of grade 2, and 80% of grade 3 patients. Similarly, prevalence rose from 33.33% in NAFL to 71.43% in fibrotic NASH, while 44.44% of cirrhosis patients were hypothyroid (Table 6). Chi-square analysis showed no statistically significant association between hypothyroidism and both steatosis grade and fibrosis stage ($p < 0.05$).

Table 5: Thyroid status in NAFLD

Parameter	*Count (n = 158)*	*Percentage (100%)*
Euthyroid	88	55.70
Hyperthyroid	5	3.16
Hypothyroid	65	41.14

Biochemical and Metabolic Profile

Patients showed mild anemia, slightly reduced protein/albumin, borderline dyslipidemia, and impaired glucose regulation. Correlation analysis revealed:

- Positive associations of FibroScan stiffness with FT4 (0.432, $p < 0.001$), serum urea, and INR.
- Negative associations with serum protein, fasting glucose, and LDL cholesterol (Table 7).
- Other parameters, including hemoglobin, platelets, albumin, SGOT, SGPT, TSH, and FT3, did not correlate significantly with liver stiffness.

Table 6: Distribution of hypothyroidism across the NAFLD spectrum

Parameter	*Count*	*Percentage (100%)*
Hypothyroidism by USG grade		
Grade 1 fatty liver	22	53.66
Grade 2 fatty liver	9	75.00
Grade 3 fatty liver	8	80.00
Hypothyroidism by FibroScan		
NAFL	17	33.33
Early NASH (F0–F1)	30	40.00
Fibrotic NASH (F2–F3)	10	71.43
NASH Cirrhosis (F4)	8	44.44
Chi-square = 4.26; $p = 0.234$		
Hypothyroidism by FIB-4		
Stage 0–1	34	34.00
Stage 2–3	26	59.09
Stage 4–6	5	35.71

Table 7: Biochemical and metabolic profile of study population and correlation with liver fibrosis (FibroScan)

Parameter	*Mean ± SD*	*r (correlation coefficient)*	*p-value*
Hemoglobin (gm/dL)	9.99 ± 2.19	0.011	0.892
TLC (cells/mm^3)	9066.33 ± 11075.71	0.002	0.982
Platelets (lakh/mm^3)	2.18 ± 1.59	0.084	0.294
Serum Protein (gm/dL)	6.25 ± 0.74	−0.245	0.002
Albumin (gm/dL)	3.53 ± 2.71	−0.033	0.679
Sodium (mEq/L)	133.12 ± 14.91	−0.064	0.58
Potassium (mEq/L)	3.92 ± 2.18	0.215	0.049
Urea (mg/dL)	37.29 ± 22.77	0.263	0.001
Creatinine (mg/dL)	1.08 ± 0.96	0.082	0.308
SGOT (U/L)	57.50 ± 46.29	0.006	0.942
SGPT (U/L)	49.45 ± 62.48	−0.016	0.844
PT (sec)	13.38 ± 3.34	0.131	0.100
INR	1.17 ± 0.35	0.237	0.003
Fasting blood sugar (mg/dL)	108.59 ± 25.42	−0.223	0.005
Postprandial sugar (mg/dL)	145.39 ± 32.14	−0.061	0.445
HbA1c (%)	6.11 ± 1.64	−0.115	0.149
Cholesterol (mg/dL)	160.19 ± 53.78	−0.026	0.749
Triglycerides (mg/dL)	159.98 ± 90.94	0.105	0.191
HDL (mg/dL)	49.62 ± 25.12	0.096	0.233
LDL (mg/dL)	83.37 ± 39.89	−0.170	0.032

Discussion

The prevalence of hypothyroidism in our cohort was 41.14%, which increased with advancing disease stage, reaching 80% in grade 3 steatosis and 71.43% in fibrotic NASH. These findings support the concept that thyroid dysfunction may play a direct role in disease progression rather than being a coincidental comorbidity, consistent with earlier reports by Guo et al.[8]

The demographic profile of middle-aged predominance and male excess was in line with other metabolic syndrome studies, as noted by Lee et al.[2] Our data also confirmed that ultrasonography, despite its limitations, remains a useful first-line tool for fatty liver detection, while FibroScan provides more accurate staging, as emphasized by Loomba et al.[4] The concordance of higher ultrasound grades with advanced fibrosis on elastography in our study reinforces the practical utility of combining imaging modalities for NAFLD risk stratification.

The prevalence of hypothyroidism in our NAFLD patients was higher than that reported in some international cohorts. A recent population-based study by Almomani et al. demonstrated a significantly higher prevalence of hypothyroidism (22.4%) in NAFLD and suggested that thyroid hormone replacement may positively influence disease course.[15] Biopsy-based evidence from D'Ambrosio et al. demonstrated a prevalence to be around 21% and that abnormal thyroid function is closely related to histological severity of NAFLD.[16] Importantly, a study by Parikh et al. reported a prevalence of 16.8% of hypothyroidism in NAFLD patients in western India.[17] These observations are supported by the systematic review by Eshraghian and Jahromi, which comprehensively summarized earlier studies and concluded that thyroid dysfunction consistently increases the risk and severity of NAFLD and found the prevalence of hypothyroidism to be around 15.2–36.3%.[18] This variation may reflect differences in iodine sufficiency, autoimmunity burden,

and population-level metabolic risks. Taken together, these findings strengthen the argument that hypothyroidism contributes to NAFLD progression rather than representing a coincidental comorbidity.

Biochemical findings in our patients further reinforced the metabolic-liver-thyroid axis. The positive correlation of liver stiffness with FT4 may indicate altered hormone metabolism in chronic liver disease, while the absence of significant correlation with TSH suggests possible nonthyroidal illness effects. These findings are consistent with earlier studies showing that conventional thyroid markers may not always capture the dynamic interplay of thyroid and liver function.[11] Additionally, negative associations of fibrosis with serum protein, fasting glucose, and LDL cholesterol underline the complex interactions of hepatic synthetic function, insulin resistance, and lipid handling, as also observed in recent Indian cohorts, such as Parikh et al.[17]

From a mechanistic standpoint, thyroid hormone deficiency is known to impair β-oxidation, enhance intrahepatic lipid accumulation, and promote oxidative stress, inflammation, and fibrogenesis.[9,10] Clinical evidence, including levothyroxine intervention studies, suggests that thyroid hormone replacement may ameliorate hepatic steatosis and improve metabolic parameters.[14] These data support the possibility of thyroid-targeted interventions as adjuncts in NAFLD management.

This study was limited by its single-center design and modest sample size, which may restrict generalizability. Its cross-sectional nature prevented establishing causality between hypothyroidism and NAFLD progression. Although FibroScan and FIB-4 scoring are validated tools, the absence of histopathology could have influenced staging accuracy. Confounding effects of altered thyroid hormone metabolism in advanced liver disease and unmeasured factors such as diet, physical activity, and iodine status could not be fully accounted for.

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ORIGINAL ARTICLE

Role of Expanded A-DROP Score in Predicting 14-day Mortality in Patients with Community-acquired Pneumonia: A Prospective Observational Study from a Tertiary Care Center in North India

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Received: 04 November 2025; *Accepted:* 06 March 2026

Abstract

Background: Community-acquired pneumonia (CAP) carries substantial mortality. Common scoring tools such as CURB-65, A-DROP, and PSI have limitations. The expanded A-DROP incorporates clinical and biochemical markers, showing promise and requires validation in Indian settings.

Materials and methods: This prospective observational study at a North Indian tertiary center (March 2024–June 2025) included 80 adults with CAP. Expanded A-DROP scores were calculated within 24 hours of admission, and patients were followed for ICU admission, in-hospital, and 14-day postdischarge mortality. Analyses used ANOVA, Chi-square, logistic regression, and receiver operating characteristic (ROC) curves ($p < 0.05$).

Results: Of 80 patients, 22 (27.5%) died within 14 days. Mortality was 1/23 (4.3%) in group I (0–2), 2/22 (9.1%) in group II (3–4), and 19/35 (54.3%) in group III (≥5) ($p < 0.001$). ICU admission rose with severity: 1/23 (4.3%), 8/22 (36.4%), and 25/35 (71.4%) ($p < 0.001$). Mean (SD) hospital stay increased: 4.0 (0.9), 7.0 (1.1), and 9.0 (1.3) days ($p < 0.0001$), with positive correlation to score ($\rho = 0.53$, $p < 0.000001$). ROC analysis gave an AUC of 0.871 (95% CI: 0.783–0.958). A score ≥5 predicted mortality with 86.2% sensitivity and 72.4% specificity. Multivariate regression identified Expanded A-DROP as the only independent predictor (OR 3.07, $p < 0.001$).

Conclusion: Expanded A-DROP demonstrated strong predictive power for short-term mortality, ICU requirement, and hospital stay in CAP. It is a simple, clinically relevant, and effective tool for early triage, especially in resource-limited settings.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1516

Introduction

Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality globally, especially among the elderly and those with comorbidities.[1] Despite advances in antimicrobial therapy and supportive care, CAP continues to impose a significant burden on healthcare systems—particularly in low- and middle-income countries such as India, where the first 2 weeks of hospitalization are critical due to heightened mortality risk.[2,3]

In India, factors such as high population density, air pollution, undernutrition, limited rural healthcare access, and a high prevalence of diabetes, COPD, and tuberculosis amplify the burden of CAP.[4] Lower respiratory tract infections rank among the top causes of infectious disease-related deaths and disability-adjusted life years (DALYs) lost in the country.[5] Seasonal variation, low adult vaccination coverage, and antibiotic misuse further complicate disease control and management.[6,7] Many hospitalized patients progress to respiratory failure or sepsis, contributing to high early mortality rates.[8]

Several clinical prediction tools are used to assess CAP severity and guide triage decisions, such as the pneumonia severity index (PSI), CURB-65, and the A-DROP score, developed by the Japanese Respiratory Society for Asian populations.[9–15] The Expanded A-DROP score is a modified version of A-DROP that incorporates additional risk factors: malignancy, heart rate ≥100/min, serum albumin ≤3.09 gm/dL, serum lactate >1.7 mmol/L, and NT-proBNP >500 pg/mL,[12] in addition to the original five parameters (age, dehydration, respiratory status, orientation, and blood pressure). Each component scores 1 point, yielding a total of 0–10. Based on the cumulative score, patients are stratified into three categories:

- Score 0–2: Low risk
- Score 3–4: Intermediate risk
- Score ≥5: High risk

Initial retrospective studies by Ahn et al. in 2018 demonstrated that the Expanded A-DROP score had better predictive accuracy for mortality in CAP than conventional tools. In a large-scale study involving 1,574 hospitalized CAP patients, Ahn JH et al. reported significantly higher AUC values for the Expanded A-DROP score (0.835) compared to CURB-65 (0.779) and PSI (0.790), supporting its superior discriminative ability.[12] Studies that had come before and after this also supported the inclusion of biomarkers such as NT-proBNP, lactate, and albumin in CAP prognostication.[16–19] However, limitations of these studies include regional and demographic homogeneity, retrospective design in earlier studies, and a lack of focus on short-term (14-day) mortality relevant for early triage decisions.

Given the high early mortality associated with CAP and the evolving need for more robust and locally applicable prognostic tools, this study seeks to evaluate the utility of the Expanded A-DROP score in predicting 14-day mortality among hospitalized patients with community-acquired pneumonia. By doing so, it aims to contribute to improved clinical decision-making and patient outcomes in routine medical practice.

Materials and Methods

Study Design and Setting

A prospective observational study was conducted in the Department of Internal Medicine at a tertiary care center in North India. The study spanned 16 months, from

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How to cite this article: Prakash R, Sinha N, Goyal P. Role of Expanded A-DROP Score in Predicting 14-day Mortality in Patients with Community-acquired Pneumonia: A Prospective Observational Study from a Tertiary Care Center in North India. J Assoc Physicians India 2026;74(6):16–21.

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March 1, 2024, to June 30, 2025, with the last patient enrolled on June 15, 2025.

Ethical Clearance

Approval was obtained from the Institutional Ethics Committee on February 5, 2024. Written informed consent was taken from all participants or their legal guardians.

Eligibility Criteria

Patients aged 18 years or older, admitted with clinical and radiological evidence of community-acquired pneumonia (CAP), were included. CAP was defined by the presence of symptoms such as cough, fever, dyspnea, or pleuritic chest pain along with new pulmonary infiltrates on imaging, acquired outside the hospital or within 48 hours of admission.

Exclusion criteria included hospital-acquired or ventilator-associated pneumonia, active pulmonary tuberculosis or fungal infections, or refusal to consent.

Data Collection

Demographic details, presenting complaints, comorbidities, and vital parameters were recorded at admission. Laboratory investigations included complete blood count, renal and liver function tests, electrolytes, arterial blood gas, serum lactate, albumin, and NT-proBNP levels. Radiographic findings were documented based on the chest X-ray.

Scoring Systems

The Expanded A-DROP score was calculated for each patient using 10 parameters: age (≥70 years for males, ≥75 years for females), blood urea nitrogen (BUN) ≥21 mg/dL, SpO_2 ≤90% or PaO_2 ≤60 mm Hg, confusion, systolic BP ≤90 mm Hg, heart rate ≥100/min, serum albumin ≤3.09 gm/dL, lactate >1.7 mmol/L, NT-proBNP >500 pg/mL, and presence of malignancy. One point was given per criterion (maximum score: 10). Patients were categorized into three risk groups:

- Low risk (0–2).
- Moderate risk (3–4).
- High risk (≥5).

Outcome Measure

The primary outcome was 14-day all-cause mortality. In-hospital patients were followed daily, and those discharged before day 14 were contacted telephonically to verify survival status. Secondary outcomes were duration of hospital stay, need for ICU admission, and in-hospital mortality.

Statistical Analysis

Analysis was performed using IBM SPSS v28.0. Categorical variables were presented as frequencies and percentages. Intergroup comparisons were made using Chi-square or Fisher's exact test. Group comparisons among A-DROP categories for the primary and secondary outcomes were analyzed using one-way ANOVA. Univariate regression was performed to find individual significant contributors to 14-day mortality, and multivariate regression analysis was done to remove all confounding factors.

Receiver operating characteristic (ROC) curves were plotted to assess the predictive accuracy of Expanded A-DROP scores for 14-day mortality. A p-value < 0.05 was considered statistically significant.

Results

Demographics

A total of 80 patients with community-acquired pneumonia (CAP), as defined by clinical criteria, were enrolled after obtaining informed written consent. The mean age of the study population was 62.1 (11.9) years, with a median age of 63.5 years (range: 33–85 years). The maximum number of participants (36.3%) was within the age group of 56–65 years (Table 1). Of the 80 participants, 41 (51.3%) were female, and 39 (48.8%) were male.

Clinical Characteristics

The most common presenting complaint was shortness of breath in 53 patients (66.2%), followed by cough with or without expectoration in 51 (63.7%) and fever in

Table 1: Baseline sociodemographic and clinical characteristics of the study population

Characteristic	*Mean (SD)/median (IQR)*
Age (years)	62.08 (11.9)/63.5 (15)
Age group	Number of participants (%)
35–45 years	11 (13.75%)
46–55 years	10 (12.5%)
56–65 years	29 (36.25%)
66–75 years	18 (22.5%)
76–85 years	12 (15%)
Gender	
Male	41 (51.25%)
Comorbidities	
Smoking exposure (active/passive)	23 (28.7%)
Diabetes mellitus	30 (37.5%)
History of hospitalization/IV antibiotic use in the past 90 days	29 (36.2%)
Chronic obstructive pulmonary disease	19 (23.7%)
Immunosuppression	5 (6.2%)
Hypertension	28 (35%)
Coronary artery disease	9 (11.2%)
Chronic kidney disease	12 (15%)
Chronic liver disease	1 (1.2%)
Hypothyroidism	4 (5%)
Malignancy	6 (7.5%)
Symptoms at presentation	
Shortness of breath	53 (66.2%)
Cough	51 (63.75%)
Fever	43 (53.7%)
Chest pain	12 (15%)
Anxiety	10 (12.5%)
Altered sensorium	20 (25%)
Vital parameter	Mean (SD)
Pulse rate (bpm)	105 (17)
Systolic BP (mm Hg)	120 (32)
Diastolic BP (mm Hg)	73 (18)
Respiratory rate (breaths/min)	23 (6)
Room-air oxygen saturation (%)	86 (9)

43 (53.7%). Other symptoms included pleuritic chest pain in 12 (15.0%) and a sense of restlessness ("ghabraahaat") in 10 (12.5%). Altered sensorium was documented in 20 patients (25.0%).

On examination, tachycardia (pulse >100/min) was present in 47 patients (58.8%). The mean SpO_2 on room air was 86 (9)% (median 87, range 60–99). The mean respiratory rate was 23 (6) breaths/min (median 22, range 12–36). Hypotension (SBP < 90 mm Hg) was observed in 11 patients (13.8%).

Comorbidities and Risk Factors

Among the 80 participants, the most common comorbidities were type 2 diabetes mellitus (30, 37.5%), hypertension (28, 35.0%), and COPD (19, 23.7%), followed by chronic kidney disease (12, 15.0%) and coronary artery disease (9, 11.2%). Malignancy was present in six patients (7.5%), hypothyroidism in four (5.0%), and chronic liver disease in one (1.2%). A history of hospital admission or intravenous antibiotic use within 90 days was reported in 29 patients (36.2%). Exposure to cigarette smoke occurred in 23 patients (28.7%), including six passive smokers. Immunosuppression was noted in five patients (6.2%), including one with HIV and four on long-term immunosuppressive therapy. Two patients had prior COVID-19 infection, and one had a previous CAP episode.

Laboratory Findings

The laboratory profile reflected the heterogeneity and severity of CAP (Table 2).

Arterial blood gases indicated moderate hypoxemia, with a mean PaO_2 of 69.8 (30.5) mm Hg and a mean SaO_2 of 85.2%, the lowest being 47.9%. Serum lactate averaged 1.71 (0.84) mmol/L, reaching 4.7 mmol/L, while mean albumin was 3.27 (0.55) gm/dL, with hypoalbuminemia in 33.4% of patients. NT-proBNP levels were variable [mean 635 (384) pg/mL], exceeding 500 pg/mL in 62.5% of participants. Hematological parameters showed mean hemoglobin 11.3 (2.3) gm/dL (anemia 43.7%), total leukocyte count 12,667/mm^3 (leukocytosis 52.5%), and mean platelet count 2.58 (1.13) × 10^5/mm^3 (thrombocytopenia 16.2%). Renal dysfunction was common, with a mean urea of 58.6 (39) mg/dL, creatinine 1.51 (1.2) mg/dL, and 60% having BUN ≥21 mg/dL. Liver function tests showed only mild elevations.

Expanded A-DROP Score

The mean Expanded A-DROP score in the study population was 4.0 (2.0), with a median of 4 (range: 0–10). The interquartile range was 2–5, indicating that the majority of patients fell into the moderate-to-severe risk categories. The distribution of the study population into three different subgroups based on Expanded A-DROP scoring is given in Figure 1.

Outcomes by Expanded A-DROP Groups

Clinical outcomes demonstrated a clear worsening trend with higher Expanded A-DROP scores. Patients in the high-risk group (≥5) had significantly longer hospital stays, higher ICU admission rates, and greater in-hospital and 14-day mortality compared with those in the lower-score groups ($p < 0.001$ for all comparisons). The detailed distribution of outcomes across the three groups is presented in Table 3.

Predictors of 14-day Mortality

On univariate analysis, several clinical and laboratory parameters, including altered sensorium, tachycardia, hypotension, hypoxia, malignancy, elevated serum lactate, raised NT-proBNP, and higher Expanded A-DROP scores, were significantly associated with 14-day mortality (Tables 4 and 5).

On multivariate logistic regression, only the Expanded A-DROP score remained an independent predictor of 14-day mortality (OR 3.07, 95% CI 1.76–5.35, $p < 0.001$).

ROC Curve Analysis

The predictive performance of the Expanded A-DROP score incorporating NT-proBNP for

Table 2: Descriptive summary of laboratory parameters

Parameter	*Mean (SD)*	*Median (IQR)*	*Min–max*
Hemoglobin (gm/dL)	11.3 (2.3)	11.4 (10.1–12.6)	6.5–17.9
Total count (cells/mm^3)	12660 (7460)	11200 (8600–14200)	4400–54080
Platelet count (× 10^4 cells/mm^3)	2.58 (1.13)	2.45 (1.75–3.20)	0.40–5.70
Urea (mg/dL)	58 (39)	50 (34–74)	16–302
Creatinine (mg/dL)	1.5 (1.2)	1.1 (0.8–1.8)	0.3–8.2
BUN (mg/dL)	27 (18)	23 (16–34)	7–141
OT (IU/L)	77 (316)	35 (23–50)	7–2859
PT (IU/L)	51 (182)	18 (14–36)	3–1628
ALP (IU/L)	134 (117)	107 (74–142)	15–782
TB (mg/dL)	0.95 (0.60)	0.80 (0.50–1.26)	0.09–2.60
DB (mg/dL)	0.42 (0.40)	0.26 (0.10–0.60)	0.05–1.80
Serum lactate (mmol/L)	1.71 (0.84)	1.50 (1.10–2.10)	0.50–4.70
Serum albumin (gm/dL)	3.27 (0.55)	3.30 (2.98–3.60)	1.72–4.50
NT-proBNP (pg/mL)	635 (384)	659 (370–912)	6–1434

Cr, serum creatinine; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ALP, alkaline phosphatase; TB, total bilirubin; DB, direct bilirubin; NT-proBNP, N-terminal pro–B-type natriuretic peptide

Table 3: Comparison of clinical outcomes across expanded A-DROP score groups

Outcome	*Group I (0–2) n = 23*	*Group II (3–4) n = 22*	*Group III (≥5) n = 35*	*p-value*
Hospital stay (days), mean (SD)	4.0 (2.7)	7.3 (3.6)	9.5 (4.2)	< 0.0001
ICU admission, *n* (%)	1 (4.3%)	3 (13.6%)	25 (71.4%)	< 0.0001
In-hospital mortality, *n* (%)	0 (0%)	2 (9.1%)	16 (45.7%)	< 0.001
14-day mortality, *n* (%)	1 (4.3%)	2 (9.1%)	19 (54.3%)	< 0.001

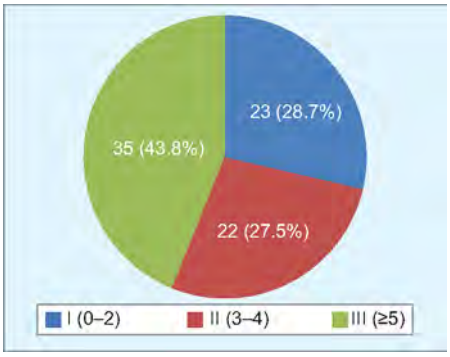


Fig. 1: Distribution of participants across Expanded A-DROP score groups

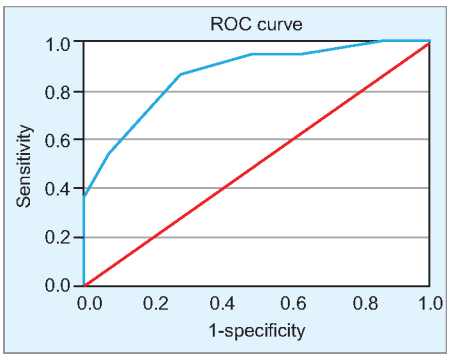


Fig. 2: ROC curve for Expanded A-DROP score

Table 4: Univariate analysis of quantitative demographic and laboratory parameters for 14-day mortality

Parameter	*Crude odds ratio [Exp(B)]*	*p-value*	*95% CI (lower limit–upper limit)*	*Significance*
Age	1.033	0.154	0.988–1.080	Not significant
Respiratory rate	1.01	0.371	0.99–1.04	Not significant
Serum lactate	2.54	0.004	1.35–4.77	Significant*
Serum albumin	1.19	0.706	0.48–2.95	Not significant
Hemoglobin	0.879	0.248	0.706–1.094	Not significant
Total count	1.0	0.92	1.000–1.000	Not significant
Platelet count	1.25	0.316	0.809–1.925	Not significant
Total bilirubin	1.006	0.989	0.444–2.277	Not significant
Direct bilirubin	1.01	0.902	0.71–1.43	Not significant
SGOT	0.999	0.656	0.995–1.003	Not significant
SGPT	0.999	0.63	0.993–1.004	Not significant
ALP	1.0	0.879	0.995–1.004	Not significant
Serum urea	1.0	0.990	0.988–1.013	Not significant
Serum creatinine	1.014	0.944	0.695–1.479	Not significant
Blood urea nitrogen	1.0	0.992	0.974–1.027	Not significant
NT-proBNP	1.003	0.000	1.002–1.005	Significant*
Expanded A-DROP score	3.066	0.000	1.758–5.347	Significant*

CI, confidence interval; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ALP, alkaline phosphatase; NT-proBNP, N-terminal pro–B-type natriuretic peptide; *Significant

Table 5: Univariate analysis of qualitative demographic and laboratory parameters for 14-day mortality

Parameter	*Crude odds ratio [Exp(B)]*	*p-value*	*95% CI (lower limit–upper limit)*	*Significance*
Gender	1.071	0.890	0.401–2.860	Not significant
Fever	0.376	0.059	0.136–1.037	Not significant
Cough	0.993	0.990	0.358–2.756	Not significant
Shortness of breath	1.514	0.452	0.514–4.458	Not significant
Chest pain	2.143	0.240	0.600–7.647	Not significant
Anxiety	1.926	0.350	0.487–7.610	Not significant
History of prior hospitalization/IV antibiotic use	2.222	0.119	0.814–6.064	Not significant
Exposure to cigarette smoke	0.456	0.205	0.135–1.536	Not significant
Immunosuppression/HIV infection	0.643	0.700	0.068–6.090	Not significant
Malignancy	6.222	0.044	1.051–36.842	Significant*
T2DM	1.583	0.367	0.583–4.298	Not significant
HTN	1.852	0.230	0.677–5.068	Not significant
COPD	0.637	0.473	0.186–2.185	Not significant
CKD	0.203	0.139	0.025–1.680	Not significant
CLD	2.0	0.362	0.45–8.79	Not significant
CAD	0.729	0.708	0.139–3.810	Not significant
Hypothyroidism	0.873	0.909	0.086–8.869	Not significant
Altered sensorium	10.524	0.000	3.298–33.582	Significant*
Tachycardia	4.500	0.014	1.356–14.932	Significant*
Hypotension	6.000	0.003	1.810–19.891	Significant*
Hypoxia	8.125	0.008	1.737–38.011	Significant*

CI, confidence interval; T2DM, type 2 diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CKD, chronic kidney disease; CLD, chronic liver disease; *Significant

14-day mortality in CAP was assessed using ROC analysis (Fig. 2). The area under the curve (AUC) was 0.871 (95% CI: 0.783–0.958; $p < 0.001$), indicating excellent discriminatory power.

A cut-off score of ≥5 provided the best balance between sensitivity and specificity, yielding 86.2% sensitivity and 72.4% specificity. This threshold effectively identified patients at risk of 14-day mortality while minimizing false positives.

Discussion

This study evaluated the Expanded A-DROP score for predicting 14-day mortality in CAP and demonstrated its strong discriminatory ability across a wide range of clinical outcomes.

Demographics and Clinical Profile

Most participants were middle-aged or elderly, predominantly 56–75 years, consistent with global trends showing higher CAP

susceptibility.[20] Age did not differ significantly across Expanded A-DROP score groups (p = 0.166) and was not an independent predictor of 14-day mortality. This contrasts with previous studies,[21,22] which predicted worse outcomes with increasing age, possibly reflecting our broader age range (33–85 years) and fewer very elderly participants.

Gender distribution was nearly equal, with a slight female predominance (51.3%), and no significant differences in 14-day mortality or ICU admission were observed. This diverges from global data, where male sex has been linked to increased severity and mortality,[23] likely due to comparable comorbidity burden, short 14-day follow-up, and standardized hospital care in our cohort.

The symptom and physiological profiles of patients in our cohort align with established CAP patterns,[1,15,20] reinforcing the systemic impact of the disease beyond the lungs. Culturally specific expressions such as "ghabraahaat" underscore the need to contextualize symptom interpretation in Indian practice for timely recognition of respiratory distress. Altered sensorium, tachycardia, hypotension, and hypoxemia reflect multiorgan involvement and severe illness, supporting their inclusion in severity scoring tools.

The high prevalence of chronic conditions such as diabetes, hypertension, and COPD in our cohort aligns with prior Indian and international studies demonstrating their role in predisposing patients to severe CAP.[20,24,25] Additional factors, including tobacco exposure,[6] immunosuppression,[7] renal and cardiac dysfunction,[17] and malignancy,[12] contribute to physiologic vulnerability and poorer early outcomes. Notably, malignancy showed a strong association with 14-day mortality, supporting its inclusion in the Expanded A-DROP score, unlike CURB-65 or PSI, which do not account for cancer-related risk. Recent hospitalization or prior antibiotic use further underscores the complexity of CAP in tertiary-care populations, highlighting the potential for resistant pathogens and overlapping healthcare exposures.[8,26]

Laboratory parameters in our cohort reflect the systemic impact of CAP and the multifaceted physiologic stress experienced by hospitalized patients. Markers of cardiac strain, such as NT-proBNP,[16,17] and tissue hypoperfusion, such as lactate,[19] highlight early organ compromise, supporting their inclusion in multidimensional scoring systems such as Expanded A-DROP. Although these individual biomarkers did not retain independent significance in multivariate analysis, likely due to overlap with composite variables, they remain valuable indicators of severity and early warning signals for adverse outcomes. Hypoalbuminemia and renal dysfunction similarly underscore systemic vulnerability,[12,18,27] reinforcing findings from prior studies linking these parameters to increased mortality, prolonged hospitalization, and higher illness burden. Hematological alterations and mild hepatic derangements further illustrate the widespread inflammatory and organ-level effects of CAP. Collectively, these laboratory findings validate the importance of integrating extrapulmonary markers into severity assessment, enhancing risk stratification and prognostic accuracy beyond vital signs alone.

Expanded A-DROP Score Distribution and Clinical Implications

The range of Expanded A-DROP scores in our cohort reflects the full spectrum of CAP severity, from relatively mild illness to multiorgan involvement. The predominance of higher-risk patients is unsurprising in a tertiary-care setting, where more severe cases are typically referred, and underscores the importance of early and accurate risk assessment. Notably, age alone did not independently predict 14-day mortality, reinforcing prior observations[12] that composite scores capturing physiological and biochemical derangements provide a more nuanced and reliable measure of patient risk than age-based metrics alone.

The Expanded A-DROP score effectively stratified patients by severity, correlating with key outcomes such as hospital stay, ICU requirement, and short-term mortality.[12,27] Higher scores reflected a progressive increase in illness burden and resource utilization, underscoring the score's utility in anticipating critical care needs and prolonged hospitalization. While previous studies primarily validated its role in mortality prediction,[12] our findings extend this evidence by demonstrating a clear gradient in ICU admission and postdischarge risk, emphasizing the importance of vigilant follow-up even after hospital discharge.[28]

In univariate analysis, several clinical and laboratory parameters—including neurological status, hypoxia, hypotension, tachycardia, lactate, NT-proBNP, and malignancy—emerged as significant predictors of 14-day mortality, reflecting the diverse organ-level stress imposed by CAP.[10,12,16–19,29] These findings underscore the prognostic relevance of systemic decompensation and comorbidity burden, consistent with prior studies highlighting the vulnerability of patients with cardiovascular compromise, cognitive impairment, or underlying malignancy.

When considered in a multivariate model, however, only the Expanded A-DROP score retained independent predictive significance.[14] This attenuation of individual variables likely reflects collinearity among overlapping physiologic derangements and emphasizes the advantage of composite scoring systems that integrate multiple domains into a singular, robust metric. By capturing cardiovascular, neurological, renal, and oncological risk factors simultaneously, the Expanded A-DROP score demonstrates superior prognostic stability compared to isolated markers, reinforcing its role as a practical and multidimensional tool for early risk stratification in CAP.

Prognostic Performance

The ROC analysis demonstrated excellent discrimination (AUC 0.871), with ≥5 as the optimal threshold for predicting 14-day mortality. This aligns with prior validation studies[12] and affirms the applicability of the Expanded A-DROP score in Indian patients. The high sensitivity ensures that most at-risk patients are identified early, while reasonable specificity minimizes over-triage—an important consideration in resource-limited healthcare systems.

Strengths and Limitations

The strength of this study lies in its prospective design, real-time data capture, and comprehensive evaluation of the full Expanded A-DROP score. It is probably the first study to test the applicability of the Expanded A-DROP score in an Indian setting. Limitations include a modest single-center sample, underrepresentation of high-risk subgroups, absence of serial biomarker measurements, lack of direct CURB-65 comparison, and focus on 14-day mortality without longer-term follow-up.

Conclusion

Overall, the Expanded A-DROP score effectively captures the multidimensional severity of CAP, integrating renal, cardiac, and oncological risk factors, and serves as a practical tool for early risk stratification, ICU triage, resource allocation, and postdischarge monitoring using routinely available clinical and laboratory parameters, enhancing reliability and applicability in Indian tertiary-care settings.

Acknowledgments

The authors would like to thank their guide, Dr. Nitin Sinha, and co-guide, Dr. Parul Goyal, for their invaluable guidance and support. The authors

are grateful to the head of the department, Dr Nagina Agarwal, for her encouragement and leadership. The authors acknowledge the contributions of their colleagues, seniors, juniors, and the technical staff of the Department of General Medicine and Biochemistry for their assistance during this study. The authors are deeply indebted to all participants for their cooperation. Finally, the authors thank their family for their unwavering support and God Almighty for strength and resilience.

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ORIGINAL ARTICLE

From Recognition to Reporting: One-year Trends in Adverse Drug Reactions at a Newly Designated Adverse Drug Reaction Monitoring Center

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Received: 08 December 2025; *Accepted:* 13 January 2026

Abstract

Objectives: To analyze spontaneously reported adverse drug reactions (ADRs) during the first year after the adverse drug reaction monitoring center (AMC) recognition.

Materials and methods: A retrospective observational study was conducted from April 2023 to March 2024 at a tertiary care hospital in Pune, Maharashtra, India. All reported ADRs were included and analyzed by gender, age, department, drug class, and severity (modified Hartwig and Siegel scale). Causality was assessed using Naranjo's algorithm and World Health Organization-Uppsala Monitoring Center (WHO-UMC) assessment criteria. Data were expressed as frequencies and percentages.

Results: A total of 255 ADRs were reported. Most ADRs occurred in elderly patients aged 61–80 years (56%). Anticancer drugs were the most common culprits (45.67%), followed by antimicrobials (21.63%). Causality assessments of suspected ADRs were probable (47%), possible (51%), and certain (2%). Most ADRs were mild (78.43%) and nonserious, and patients recovered with drug withdrawal and supportive care (39%), while 47% were recovering when the ADR was reported.

Conclusion: Adverse drug reactions (ADRs) were mild and preventable, with anticancer drugs being the leading cause. Elderly patients were most affected. Underreporting remains a challenge despite AMC recognition, underscoring the need for continued sensitization and feedback mechanisms to promote a culture of ADR reporting.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1515

Introduction

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "a response to a drug, which is noxious, unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy for a disease and for the modification of function excluding failure to accomplish the intended purpose".[1] ADRs are one of the leading causes of morbidity and mortality. ADRs are thought to be the cause of between 2.9 and 5.6% of all hospital admissions, and up to 35% of hospitalized patients report having an ADR.[2] ADR-related hospitalizations contribute substantially to the economic burden in both developing countries and developed countries.[3]

In 2010, the Ministry of Health and Family Welfare, Government of India, launched the Pharmacovigilance Program of India (PvPI), with the Indian Pharmacopeia Commission functioning as the National Coordination Center (NCC) since April 2011.[4] Pharmacovigilance has perceived several advancements throughout the world, over the past few decades. The WHO defines "Pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems, including herbal materials.[5] Pharmacovigilance facilitates the early detection of ADRs, the identification of risk factors, and the comprehension of the underlying mechanisms of the ADR. Underreporting of adverse medication reactions is still a significant issue, despite the fact that pharmacovigilance initiatives are starting to improve drug usage habits.[6] ADR reporting is impacted by a number of factors, including ignorance, uncertainty about who should report, problems with reporting procedures, and a lack of feedback on submitted reports.[7,8] There are about 300 AMCs dispersed across the country.[9,10] These centers receive the adverse events, review them for completeness, make causality assessments, and submit to the National Coordination Center (NCC) using online software, VigiFlow, for quality and signal review. There is a need to increase healthcare professionals' awareness of prevention, identification, and reporting of ADRs. The sensitization and awareness programs at various tertiary hospitals across India have shown appreciable impact on the pharmacovigilance and ADR reporting.[11,12]

Our tertiary care hospital was recognized by NCC-PvPI as an AMC in April 2023. Following the acquisition of AMC status, our center's pharmacovigilance efforts have significantly advanced and improved for efficient operation and timely reporting. The team of the pharmacovigilance unit is supported by the pharmacovigilance committee, doctors, residents, clinical pharmacists, and nursing staff, who play a significant role in ADR reporting. Additionally, the establishment of the causality assessment committee (CAC) in May 2023, in accordance with NCC-PVPI criteria, has improved the examination of ADRs. The purpose of this study is to analyze the ADRs that the institute had reported over the 12 months following its AMC status.

Materials and Methods

From April 2023 to March 2024, a retrospective observational study was conducted in a Pune tertiary care hospital. All the ADRs that were reported throughout this time period were analyzed in this study.

Statistical Analysis

Data were entered into Microsoft Excel; categorical data are presented as frequencies and percentages.

Results

A total of 255 ADRs were reported from April 2023 to March 2024. The study population consisted of 54% females and 46% males patients. More ADRs were reported from elderly patients aged 61–80 years (56%).

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How to cite this article: Londhe VA, Dhande PP. From Recognition to Reporting: One-year Trends in Adverse Drug Reactions at a Newly Designated Adverse Drug Reaction Monitoring Center. J Assoc Physicians India 2026;74(6):22–24.

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Month-wise and Clinical Department-wise Frequency of ADRs Reported

Adverse drug reactions were reported at a maximum (~20%) in the month of October 2023 (Fig. 1), and the majority of the reports were from the department of Oncology (51%), followed by general medicine (29%) (Fig. 2).

Drugs Involved in Suspected ADRs during the Study Period

The most common causative drugs of ADRs were anticancer drugs (45.67%), followed by antimicrobial agents (21.63%) (Fig. 3).

Causality Assessment of Reported ADRs during the Study Period

Causality assessment was performed using both Naranjo's algorithm and the World Health Organization-Uppsala Monitoring Center (WHO-UMC) scale. The outcomes were comparable across both methods, with most ADRs classified as probable (47%), followed by possible (51%) and certain (2%).

Severity Assessment of ADRs Reported during the Study Period

Severity of ADRs was assessed using the modified Hartwig and Siegel scale. The majority of ADRs were mild (78.43%), with a smaller proportion moderate (19.60%) and only a very small fraction severe (1.96%). This indicates that most ADRs were manageable when identified promptly and appropriately addressed.

Patient Outcome after Management of ADRs during the Study Period

Of the 255 ADRs, 39% of patients had a full recovery, 47% were still recovering at the time of discharge, and 14% had unknown patient care outcomes.

Discussion

The present study analyzed 255 ADRs reported over a 1-year period following the recognition of our institute as an AMC under PvPI. Before our institute was recognized as an AMC under PvPI (till March 2023), all filled ADR forms were forwarded to a nearby recognized AMC for reporting. During that period, the overall number of ADR reports from our center remained relatively low. Following AMC recognition in April 2023, a structured pharmacovigilance system was established within the institute, supported by the causality assessment committee and regular sensitization activities. This transition led to a significant increase in the number of ADRs reported (255 in the first year alone), demonstrating the positive impact of institutional recognition on strengthening pharmacovigilance culture and improving patient safety. This reflects an important advancement in the pharmacovigilance system at our center and aligns with the objectives of the PvPI, which aims to enhance ADR reporting and patient safety nationwide.[9]

In our study, the majority of ADRs were reported in elderly patients aged 61–80 years, accounting for 56% of the total. Similar findings have been reported in previous studies, indicating that age is a major risk factor for ADRs due to polypharmacy, altered pharmacokinetics, and comorbid conditions.[13] These results support observations by Sen et al., who also reported higher ADR prevalence in elderly patients.[14]

Gender distribution was nearly equal, with a slight female preponderance (54%). This observation aligns with other reports suggesting higher susceptibility among females, possibly due to physiological differences and patterns of drug utilization.[13]

Anticancer drugs were the leading class associated with ADRs (45.67%), followed by antimicrobials (21.63%). This differs from the study by Sen et al., where antimicrobials accounted for 33.66% and anticancer drugs for only 10% of ADRs.[14] The predominance of anticancer drugs in our study may be attributed to the higher oncology patient load and the narrow therapeutic index associated with chemotherapy agents. Other drug classes commonly implicated included antidiabetic agents, corticosteroids, and antihypertensives, consistent with previous reports.[14] The most frequently reported clinical manifestations were fever with chills, rashes, pruritus, diarrhea, and neuropathic symptoms such as tingling sensations. These findings correlate with earlier studies, which indicate that the skin and gastrointestinal tract are most commonly affected by ADRs.[15]

Causality assessment using Naranjo's algorithm revealed that 47% of ADRs were probable, 51% possible, and only 2% certain. Similar trends have been observed by Mandavi et al.[16] The low proportion of definite ADRs emphasizes the difficulty in establishing direct drug-event relationships in clinical settings. In our study, both Naranjo and WHO-UMC assessments produced similar distributions. While concordance is not always observed in other clinical settings, this consistency reflects the relatively clear drug-event relationships in our dataset. It is also important to note that, as an AMC under PvPI, causality assessment in routine practice is carried out using the WHO-UMC scale while reporting in VigiFlow. The concordance between Naranjo's algorithm and the WHO-UMC scale in our study, therefore, supports the validity of our findings and reflects consistency with national pharmacovigilance reporting standards.

Severity assessment showed that the majority of ADRs were mild (78.36%), with only 1.96% classified as severe. This suggests that most ADRs can be effectively managed by early detection, withdrawal of the suspected drug, and supportive care, reducing the likelihood of serious outcomes.[17]

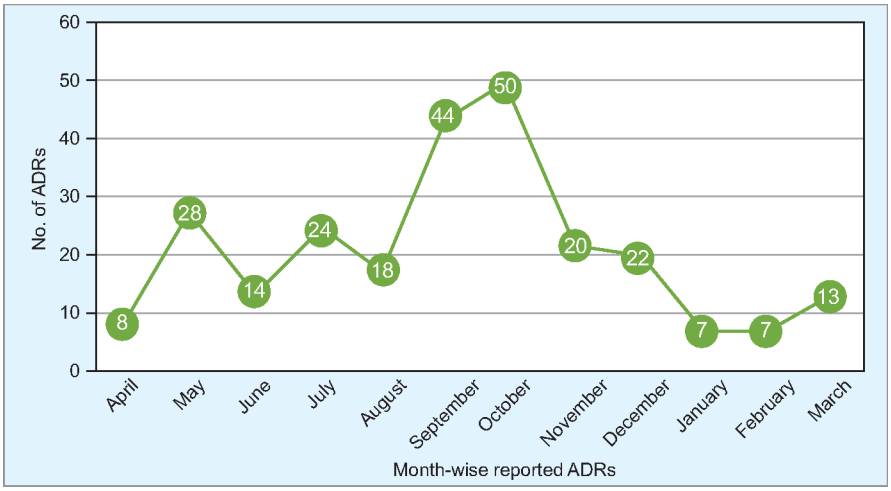


Fig. 1: Month-wise ADRs reported during the study period

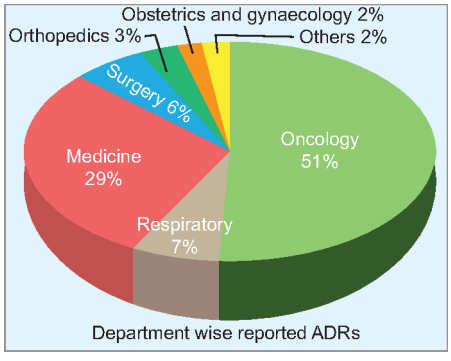


Fig. 2: ADRs reported from different clinical wards during the study period

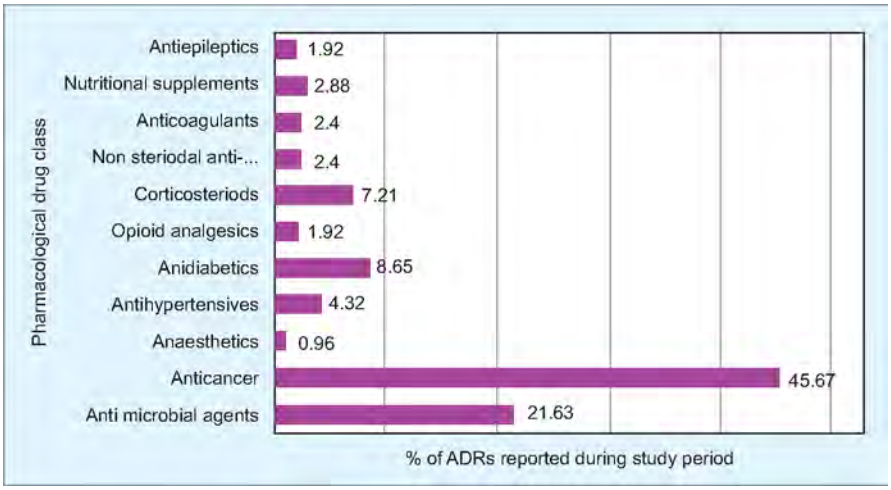


Fig. 3: Pharmacological class of drugs involved in suspected ADRs during the study period

Despite the establishment of an AMC and a causality assessment committee, underreporting continues to be a major challenge. Factors contributing to this include lack of awareness, uncertainty about reporting responsibility, and inadequate feedback, as highlighted in previous studies.[18,19] Stressing the importance of positive attitudes in enhancing ADR reporting is important, but it is also critical to note that the existence of some negative attitudes, such as the need for motivation and a reluctance to report ADRs for fear of being held accountable, can be a major obstacle to improving ADR reporting.[20]

Public health implications of underreporting: Underreporting of ADRs poses a significant barrier to ensuring drug safety at the population level. Inadequate reporting delays the detection of rare or serious drug-related problems, allowing harmful effects to persist unnoticed in the community. This can result in preventable morbidity, mortality, and healthcare costs, particularly in vulnerable groups such as the elderly and patients with chronic illnesses. From a regulatory perspective, incomplete ADR data hampers the ability of national pharmacovigilance programs to generate safety signals, update prescribing guidelines, or issue timely alerts. In India, where diverse prescribing practices and widespread use of generics, fixed-dose combinations, and over-the-counter medications are common, robust ADR reporting is crucial to maintain the safety profile of drugs in real-world settings. Strengthening reporting practices through continuous education, user-friendly reporting systems, and regular feedback can therefore have a direct and measurable impact on public health. Continuous education and sensitization programs for healthcare professionals have been shown to significantly improve ADR reporting rates,[21] and similar initiatives should be strengthened in our setting.

Conclusion

Most ADRs reported were nonserious and effectively managed with drug withdrawal and supportive care. Elderly patients were most affected, and anticancer drugs were the leading cause of ADRs in the current study. Underreporting persists despite institutional measures, while regular training, sensitization, and feedback systems are essential to foster a culture of spontaneous ADR reporting and ensure patient safety.

Limitations

This is a single-center study of short duration, and it relied on spontaneous ADR reports. Clinical outcomes beyond discharge could not be assessed.

Acknowledgments

The authors gratefully acknowledge the valuable contributions of the clinical pharmacists, clinicians, and nursing staff for their active involvement in identifying and reporting suspected adverse drug reactions.

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ORIGINAL ARTICLE

AI-powered ECG Interpretation System for Arrhythmia Prediction and Hyperkalemia Detection Using Machine Learning

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Received: 23 December 2025; *Accepted:* 16 January 2026

Abstract

Background: Artificial intelligence (AI) has emerged as a powerful tool for electrocardiogram (ECG) analysis, potentially surpassing conventional interpretation in detecting arrhythmias and metabolic disturbances such as hyperkalemia. This study evaluated the diagnostic performance and real-world applicability of an AI-powered ECG interpretation system for arrhythmia prediction and hyperkalemia detection.

Materials and methods: In this prospective observational study, patients presenting to the emergency department or cardiology clinic between March 2024 and February 2025 were enrolled. Standard 12-lead ECGs were analyzed in parallel by a validated deep-learning AI model and board-certified cardiologists blinded to AI results and clinical data. Primary outcomes included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for arrhythmia and hyperkalemia detection. Secondary outcomes assessed the impact of AI-driven alerts on workflow efficiency and time to therapy.

Results: Among 4,200 patients (mean age 56, 39% female), the AI-ECG system demonstrated 97.2% sensitivity and 96.1% specificity for arrhythmia detection, outperforming manual interpretation for atrial fibrillation, atrial flutter, and ventricular ectopy ($p < 0.001$). For hyperkalemia, sensitivity and specificity were 83.5% and 87.3%, respectively, reliably flagging all critical potassium elevations within 1 minute. AI alerts reduced median time-to-therapy by 19 minutes. Subgroup analysis showed robust performance in patients with chronic kidney disease and acute cardiac conditions.

Conclusion: AI-powered ECG analysis enables highly accurate, rapid detection of arrhythmias and hyperkalemia, supporting earlier clinical intervention and improving workflow efficiency. These findings advocate for broader multicenter validation and integration of AI-ECG tools in routine cardiology practice.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1526

Introduction

Electrocardiography (ECG) remains a cornerstone in the diagnosis of cardiac arrhythmias and electrolyte disturbances, particularly hyperkalemia. Conventional interpretation of ECGs, however, is often subject to interobserver variability and may miss subtle abnormalities, especially in emergency settings where rapid decision-making is critical. Early recognition of arrhythmias and hyperkalemia is essential, as both conditions can precipitate life-threatening complications if left undetected or untreated.[1,2]

In recent years, artificial intelligence (AI) has emerged as a transformative tool in cardiovascular medicine. Deep learning algorithms trained on large-scale ECG datasets have demonstrated superior accuracy in detecting arrhythmias compared with traditional manual interpretation,[3,4] and they are increasingly being explored for metabolic disorders such as hyperkalemia.[5] By leveraging pattern recognition beyond human perceptibility, AI-powered ECG systems have the potential to augment clinical decision-making, enhance workflow efficiency, and shorten time to therapy.

Several proof-of-concept studies have validated the ability of AI algorithms to detect atrial fibrillation, ventricular ectopy, and other rhythm disturbances with high accuracy.[6,7] Similarly, early evidence suggests that subtle ECG signatures of elevated serum potassium levels—often overlooked by clinicians—can be reliably recognized by AI.[8] However, most prior investigations have been retrospective or limited to highly selected patient populations, raising questions about the real-world generalizability and clinical utility of such tools.

To address this gap, we conducted a prospective observational study to evaluate the diagnostic performance and clinical applicability of an AI-powered ECG interpretation system for arrhythmia prediction and hyperkalemia detection. In addition to comparing AI results with board-certified cardiologist interpretations and laboratory gold standards, we assessed its impact on workflow efficiency and timeliness of therapeutic interventions. This study aims to provide evidence for the integration of AI-assisted ECG analysis into routine cardiology and emergency care practice.

Materials and Methods

This prospective observational study was conducted at the emergency department and cardiology outpatient clinic, where patients presenting between March 2024 and February 2025 were prospectively enrolled. The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC/2024/004), and written informed consent was obtained from all participants. Standard 12-lead ECGs were acquired according to American Heart Association guidelines[9] and analyzed in parallel by a validated deep-learning AI model and three cardiologists, who were blinded to AI outputs and clinical data. The AI algorithm used in this study employed a convolutional neural network architecture trained on large annotated ECG datasets and incorporated multiple one-dimensional convolutional layers for feature extraction, batch normalization, and dropout layers to improve generalizability, and a fully connected decision layer generating arrhythmia and hyperkalemia likelihood scores. ECG signals underwent band-pass filtering, normalization, and segmentation into fixed-length windows, and the model was trained using an 80:10:10 split for training, validation, and testing on deidentified data. Arrhythmias were confirmed by consensus manual interpretation among the cardiologists, while serum potassium levels measured at presentation served as the reference standard for hyperkalemia (≥5.5 mmol/L; critical ≥6.0

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How to cite this article: Kumar A, Bansal T, Jaura S. AI-powered ECG Interpretation System for Arrhythmia Prediction and Hyperkalemia Detection Using Machine Learning. J Assoc Physicians India 2026;74(6):25–28.

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mmol/L). Primary outcomes included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detecting arrhythmia and hyperkalemia, while secondary outcomes included workflow efficiency and time-to-therapy following AI-driven alerts.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as counts and percentages. Diagnostic performance metrics were calculated with 95% confidence intervals. Comparisons between AI and manual interpretation were performed using McNemar's test for paired proportions and chi-square tests as appropriate. A p-value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were generated, and the area under the ROC values was computed for arrhythmia and hyperkalemia detection. Data analysis was performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 4,200 patients were enrolled (mean age 56 ± 14 years; 39% female), including individuals presenting with both acute and chronic cardiac conditions (Table 1). The AI-powered ECG system demonstrated excellent diagnostic performance for arrhythmia detection, with a sensitivity of 97.2% (95% CI: 96.1–98.1; $p < 0.001$) and specificity of 96.1% (95% CI: 95.0–97.0; $p = 0.041$). The positive predictive value was 94.8% (95% CI: 93.4–95.8; $p = 0.018$), and the negative predictive value was 98.0% (95% CI: 97.3–98.7; $p < 0.001$). In total, the AI system correctly identified 1,365 patients with clinically relevant arrhythmias (32.5%), compared with 1,118 patients (26.6%) detected by human experts, thereby recognizing an additional 247 cases (5.9%). The AI system missed only 39 cases (false negatives, 2.8%) and generated 77 false positives (1.8%), whereas human interpretation missed 286 arrhythmia cases (20.6%) and produced 96 false positives (2.3%) (Table 2). The overall AUROC for arrhythmia detection was 0.982 (95% CI: 0.977–0.989; $p < 0.001$), indicating excellent discrimination (Fig. 1).

Subarrhythmia analysis further confirmed the superior diagnostic capability of the AI system. For atrial fibrillation, AI sensitivity was

Table 1 : Baseline characteristics of study population (n = 4,200)

Characteristic	*Value*
Age, mean ± SD (years)	56 ± 14
Female, *n* (%)	1,638 (39%)
Hypertension, *n* (%)	2,310 (55%)
Diabetes mellitus, *n* (%)	1,764 (42%)
Chronic kidney disease, *n* (%)	462 (11%)
Acute coronary syndrome, *n* (%)	378 (9%)
Prior atrial fibrillation, *n* (%)	336 (8%)
Other comorbidities, *n* (%)	1,050 (25%)

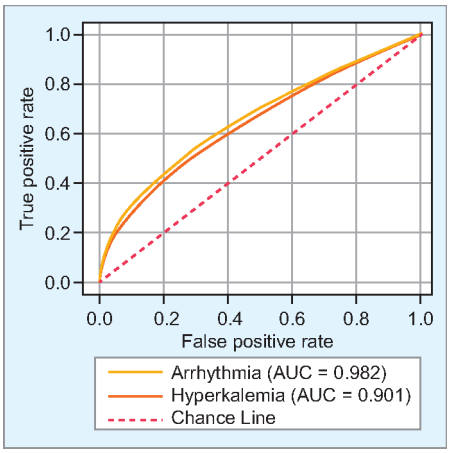


Fig. 1: Receiver operating characteristic (ROC) curves for arrhythmia and hyperkalemia detection using the AI-ECG system compared with human interpretation. AI demonstrated superior discrimination with AUROC values of 0.982 for arrhythmia and 0.901 for hyperkalemia

Table 2: Comparative diagnostic performance of AI-ECG vs human interpretation

Condition	*Metric*	*AI*	*95% CI*	*Human*	*95% CI*	*p-value*
Arrhythmia detection	Sensitivity (%)	97.2	96.1–98.1	79.4	76.5–82.0	< 0.001 (McNemar)
	Specificity (%)	96.1	95.0–97.0	95.2	93.9–96.3	0.041 (chi-square)
	Total patients detected (*n*)	1,365	—	1,118	—	—
	PPV (%)	94.8	93.4–95.8	92.1	90.2–93.7	0.018
	NPV (%)	98.0	97.3–98.7	88.6	86.8–90.2	< 0.001
	True positives (*n*)	1,365	—	1,118	—	—
	False negatives (*n*)	39	—	286	—	—
	False positives (*n*)	77	—	96	—	—
	True negatives (*n*)	2,719	—	2,700	—	—
	AUROC	0.982	0.977–0.989	0.915	0.901–0.927	< 0.001
Hyperkalemia detection	Sensitivity (%)	83.5	80.2–86.4	67.8	63.9–71.4	< 0.001
	Specificity (%)	87.3	85.9–88.6	85.1	83.5–86.6	0.049
	Total patients detected (*n*)	482	—	391	—	—
	PPV (%)	72.4	69.1–75.6	62.7	58.6–66.5	< 0.001
	NPV (%)	93.6	92.4–94.7	89.1	87.5–90.5	< 0.001
	True positives (*n*)	482	—	391	—	—
	False negatives (*n*)	95	—	186	—	—
	False positives (*n*)	184	—	233	—	—
	True negatives (*n*)	3,439	—	3,390	—	—
	AUROC	0.901	0.884–0.918	0.842	0.821–0.862	< 0.001
Time-to-therapy (hyperkalemia)	Median minutes (IQR)	21 (12–27)	—	40 (28–52)	—	< 0.001 (Mann–Whitney)

Table 3: Subarrhythmia diagnostic performance of AI-ECG vs human interpretation

Arrhythmia type	*Metric*	*AI-ECG*	*95% CI*	*Human*	*95% CI*	*p-value*
Atrial fibrillation	Sensitivity (%)	98.5	97.6–99.1	86.1	83.4–88.4	< 0.001
	Specificity (%)	96.8	95.7–97.7	95.4	94.1–96.4	0.032
Atrial flutter	Sensitivity (%)	96.4	94.2–97.9	82.7	79.1–85.8	< 0.001
	Specificity (%)	95.9	94.8–96.8	94.7	93.2–95.9	0.048
Ventricular ectopy	Sensitivity (%)	95.7	93.9–97.1	78.9	75.1–82.2	< 0.001
	Specificity (%)	94.8	93.5–95.9	92.1	90.6–93.3	0.014

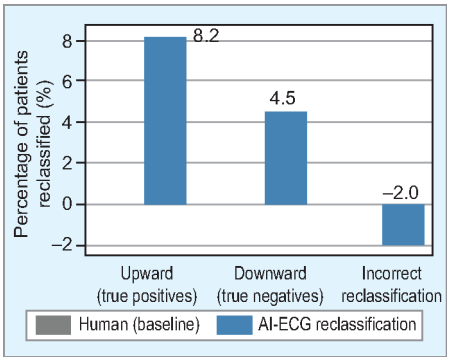


Fig. 2: Net reclassification improvement (NRI) analysis showing a 12.7% net correct reclassification of patients by AI-ECG compared with human interpretation. Both upward reclassification of true positives and downward reclassification of true negatives contributed to the improvement

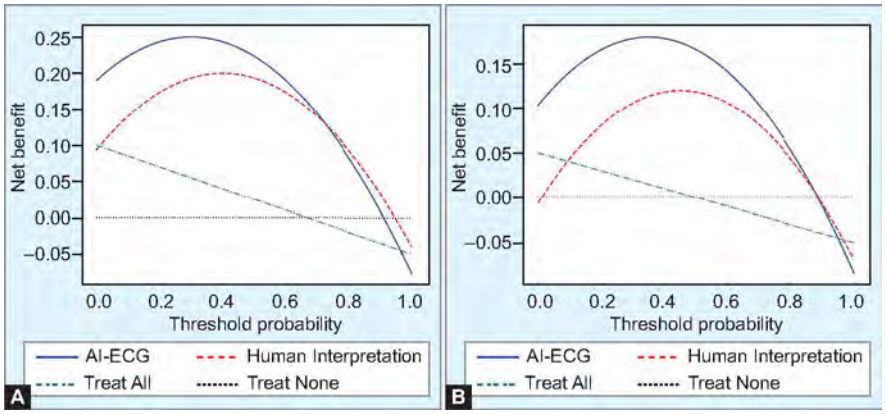


Fig. 3: Decision curve analysis (DCA) demonstrating a consistent net clinical benefit of AI-ECG across a wide range of threshold probabilities for arrhythmia (Panel A) and hyperkalemia (Panel B) detection, compared with human interpretation and treat-all/treat-none strategies

98.5% (95% CI: 97.6–99.1) compared with 86.1% (95% CI: 83.4–88.4) for manual interpretation ($p < 0.001$). Similar improvements were observed for atrial flutter (AI: 96.4%, 95% CI: 94.2–97.9 vs manual: 82.7%, 95% CI: 79.1–85.8; $p < 0.001$) and ventricular ectopy (AI: 95.7%, 95% CI: 93.9–97.1 vs manual: 78.9%, 95% CI: 75.1–82.2; $p < 0.001$). Specificity also showed statistically significant gains for AI across all subtype categories (Table 3). These findings highlight the consistency of AI performance across different rhythm disturbances, including those frequently underdetected in routine practice.

For hyperkalemia detection, the AI algorithm achieved a sensitivity of 83.5% (95% CI: 80.2–86.4; $p < 0.001$) and specificity of 87.3% (95% CI: 85.9–88.6; $p = 0.049$). The PPV was 72.4% (95% CI: 69.1–75.6; $p < 0.001$), and the NPV was 93.6% (95% CI: 92.4–94.7; $p < 0.001$). AI identified 482 patients (11.5%) with hyperkalemia, compared with 391 patients (9.3%) detected by human readers, correctly diagnosing an additional 91 cases. The AI system missed 95 cases (16.5%), substantially fewer than the 186 cases (32.2%) missed by human interpretation. False positives were also lower with AI (184 cases, 4.4%) compared with manual reading (233 cases, 5.6%). The AUROC for hyperkalemia detection was 0.901 (95% CI: 0.884–0.918; $p < 0.001$), demonstrating high discriminative accuracy (Fig. 1). Notably, AI consistently identified all patients with critical hyperkalemia (≥6.0 mmol/L) within 1 minute of ECG acquisition, translating into a clinically meaningful reduction in time-to-therapy, with AI-driven alerts shortening median treatment initiation by 19 minutes (IQR 12–27 minutes; $p < 0.001$) (Table 2).

Net reclassification improvement (NRI) analysis demonstrated that the AI-ECG system correctly reclassified 12.7% of patients compared with conventional interpretation, primarily by upgrading true-positive cases and appropriately downgrading false positives (Fig. 2). This indicates that AI not only increased the detection of clinically relevant events but also reduced unnecessary misclassifications. Complementary decision curve analysis (DCA) further confirmed that the AI-ECG system provided a consistent net clinical benefit across a wide range of threshold probabilities for both arrhythmia and hyperkalemia detection, suggesting that its use would lead to better patient outcomes without increasing overtreatment or missed diagnoses (Fig. 3).

Subgroup analyses demonstrated that the diagnostic performance of AI remained robust across high-risk populations, including those with chronic kidney disease, acute coronary syndromes, diabetes mellitus, and elderly patients (Fig. 4), with no significant decline in predictive accuracy. Overall, the AI-ECG system outperformed conventional interpretation for both arrhythmia and hyperkalemia detection, offering rapid identification of critical abnormalities, improving diagnostic yield, and enhancing workflow efficiency, thereby supporting its integration into routine cardiology and emergency practice.

Discussion

In this prospective observational study, we demonstrated that an AI-powered ECG interpretation system provides highly accurate, rapid detection of both arrhythmias and hyperkalemia in a large, heterogeneous patient cohort. The system outperformed cardiologist interpretation across multiple metrics, including sensitivity, specificity, PPV, and NPV, while reducing median time-to-therapy by 19 minutes. These findings reinforce the growing evidence that AI can augment clinical decision-making and improve workflow efficiency in acute and routine cardiology settings.[3–5]

For arrhythmia detection, the AI model achieved a sensitivity of 97.2% and specificity of 96.1%, comparable to or exceeding prior studies using deep learning on large-scale ECG datasets.[6,7,10] Importantly, AI demonstrated superior detection across individual arrhythmia subtypes—including atrial fibrillation, atrial flutter, and ventricular ectopy—when compared

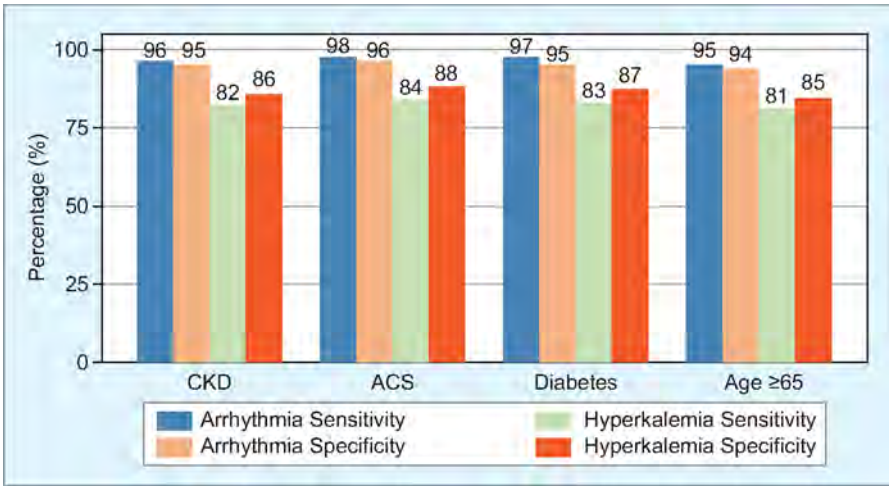


Fig. 4: Subgroup analyses of AI-ECG performance in high-risk populations, including patients with chronic kidney disease, acute coronary syndromes, diabetes mellitus, and elderly individuals. Diagnostic accuracy remained robust across all subgroups, with no significant decline in predictive performance

with manual interpretation (all $p < 0.001$). These results underscore the capability of AI to identify subtle waveform patterns that may be overlooked in fast-paced clinical environments.

Hyperkalemia detection is an emerging application of AI-ECG technology. In our study, the system demonstrated a sensitivity of 83.5% and specificity of 87.3%, with a PPV of 72.4% and NPV of 93.6%, reliably flagging all critical potassium elevations within 1 minute. Previous studies have reported AUROCs ranging from 0.88 to 0.92 for AI-based hyperkalemia prediction, supporting the reproducibility of these findings across diverse populations.[5,8,11] Rapid identification of hyperkalemia is clinically important, as delays in therapy can lead to life-threatening arrhythmias; AI-driven alerts may thus provide a valuable safety net, particularly in resource-constrained or high-volume clinical environments.

Net reclassification improvement analysis demonstrated that the AI-ECG algorithm correctly reclassified 12.7% of patients who might have been misdiagnosed by conventional interpretation. This improvement reflects enhanced risk stratification, with more patients accurately identified as having clinically relevant arrhythmias or hyperkalemia, and fewer patients incorrectly classified as high risk. DCA showed a consistent net clinical benefit across a wide range of threshold probabilities, indicating that the AI system provides a meaningful clinical advantage over standard interpretation. Across risk thresholds commonly used to guide interventions, the AI algorithm maximized true positives while minimizing false positives, supporting earlier diagnosis and timely management. For hyperkalemia, this translated into a reduction in median time-to-therapy by 19 minutes, underscoring the real-world impact of AI-assisted detection. Together, these analyses confirm that AI-ECG not only improves diagnostic accuracy but also enhances patient-centered decision-making.

Subgroup analyses in patients with chronic kidney disease and acute coronary syndromes demonstrated robust AI performance, suggesting generalizability across high-risk populations. Importantly, the system maintained high accuracy even in patients with confounding comorbidities, which often complicate conventional ECG interpretation. The integration of AI into clinical workflows can also alleviate cognitive burden on clinicians, allowing faster triage and improved allocation of resources.[12,13]

Several limitations should be acknowledged. First, the study was conducted at a single tertiary care center, which may limit generalizability. Second, while the AI system performed well for common arrhythmias and hyperkalemia, its accuracy for rare or complex ECG patterns requires further investigation. Third, long-term patient outcomes were not assessed; future multicenter studies should evaluate whether AI-assisted ECG interpretation translates into improved morbidity and mortality. Finally, although the AI system reduced time-to-therapy, implementation requires integration with existing hospital information systems and staff training to maximize clinical benefit.

In conclusion, our study demonstrates that AI-powered ECG analysis enables highly accurate and rapid detection of arrhythmias and hyperkalemia, with the potential to improve workflow efficiency and support earlier clinical intervention. These findings support broader multicenter validation and integration of AI-ECG tools into routine cardiology and emergency practice, marking a significant step toward AI-augmented cardiovascular care.

AI Use Declaration

ChatGPT was used to paraphrase a few statements.

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ORIGINAL ARTICLE

Effect of Radiological Patterns on Response to Pulmonary Rehabilitation in Post-tuberculosis Lung Sequelae: A Prospective Observational Study

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Received: 07 November 2025; *Accepted:* 17 March 2026

Abstract

Background: Post-tuberculosis sequelae (PTBS) are increasingly recognized as a significant cause of long-term respiratory morbidity, manifesting with dyspnea, reduced pulmonary function, impaired exercise capacity, and diminished quality of life. Despite their burden, PTBS patients often lack access to structured rehabilitation. Pulmonary rehabilitation (PR), well-established in COPD, may offer functional and psychological benefits in PTBS, but its implementation in India and comparison across radiological phenotypes remains understudied.

Objectives: To evaluate the impact of a 24-week pulmonary rehabilitation program on clinical, functional, psychological, and radiological outcomes in patients with PTBS, and to compare the response among different radiological subtypes—fibrosis, fibrocavitary lesions, bronchiectasis, and combined lesions.

Materials and methods: In this prospective observational study, 60 patients with PTBS underwent hospital- or home-based PR. Assessments were conducted at baseline, 12 weeks, and 24 weeks and included spirometry (FEV_1, FVC, FEV_1/FVC, $FEF_{25–75}$), 6-minute walk test (6MWT), body mass index (BMI), St. George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC) dyspnea grade, DASS-21 scale for psychological health, and radiological classification. Statistical analysis was performed to assess within-group and between-group changes over time.

Results: Significant improvements were observed in BMI ($p < 0.005$), 6MWT (mean improvement >150 m in most groups), and DASS-21 scores across all radiological subtypes. FEV1% predicted improved significantly ($p < 0.05$), especially in patients with fibrosis and bronchiectasis (>60% by week 24), while those with fibrocavitary + bronchiectasis showed the least gain (38%). Quality of life (SGRQ) improved in all groups, though intergroup differences were not statistically significant. Bronchodilator reversibility was rare (5%) and did not vary with lesion type.

Conclusion: Pulmonary rehabilitation significantly improves nutritional status, exercise capacity, psychological well-being, and spirometric parameters in PTBS patients, with variable responses depending on radiological pattern. Despite greater impairment, patients with fibrocavitary lesions derived meaningful benefit, highlighting PR's role as an essential component of post-TB care. Tailored PR strategies should be integrated into national TB programs to address the long-term sequelae of TB in high-burden settings such as India.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1525

Introduction

Tuberculosis (TB) continues to be a major global public health challenge, particularly in high-burden countries such as India, which accounts for nearly a quarter of the world's TB cases.[1] Despite successful microbiological cure following anti-tubercular therapy, a significant proportion of patients develop residual structural and functional abnormalities in the lungs, collectively termed post-tuberculosis sequelae (PTBS). These sequelae—ranging from fibrosis and bronchiectasis to fibrocavitary destruction—can result in persistent dyspnea, impaired exercise tolerance, and significantly reduced quality of life (QoL), often mimicking chronic respiratory diseases such as COPD or bronchiectasis.[2]

Recent evidences suggest that postpulmonary tuberculosis patients continue to experience significantly impaired lung function and reduced health-related QoL after treatment completion, echoing the pattern of long-term morbidity seen in adult PTLD patients.[3] Moreover, radiological patterns such as fibrocavitary lesions have been shown to correlate with worse functional status and prolonged symptomatology. However, despite their high burden, patients with PTBS are often neglected in national TB control programs, receiving little to no post-treatment rehabilitation support.

Pulmonary rehabilitation (PR) has long been established as a cornerstone of nonpharmacologic management for chronic lung diseases such as COPD.[4] It encompasses exercise training, education, nutritional support, and psychosocial counseling, and has been shown to improve functional status, psychological well-being, and health-related quality of life. Yet, its use in PTBS has been scarcely explored, particularly in the Indian context.[5] With growing evidence supporting the role of PR in chronic respiratory morbidity, its application in post-TB care could represent a transformative shift in long-term disease management.

Further complicating access is the lack of scalable PR delivery models. Hospital-based programs, while structured and supervised, are limited by infrastructure, personnel, and patient mobility, especially in rural settings. In contrast, home-based PR—delivered through structured guidance and remote monitoring—offers a promising alternative. However, comparative evidence evaluating the efficacy of hospital-based vs. home-based PR in PTBS patients is limited.

Aims and Objectives

Aim

To evaluate and compare the impact of pulmonary rehabilitation on clinical, functional, and psychological outcomes in patients with post-tuberculosis sequelae.

Objectives

- To assess changes in spirometry (FEV_1, FVC, FEV_1/FVC, $FEF_{25–75}$%), 6MWT distance, dyspnea [modified Medical Research Council (mMRC)], quality of life (SGRQ), psychological status (DASS-21), and BMI over 24 weeks.
- To compare these outcomes across different radiological patterns of lung damage.

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How to cite this article: Mehta M, Dixit R. Effect of Radiological Patterns on Response to Pulmonary Rehabilitation in Post-Tuberculosis Lung Sequelae: A Prospective Observational Study. J Assoc Physicians India 2026;74(6):29–34.

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Materials and Methods

Study Design and Setting

This was a prospective, interventional study conducted at the Department of Respiratory Medicine, JLN Medical College, Ajmer. The study aimed to assess and compare the effects of pulmonary rehabilitation (PR) in patients with post-tuberculosis sequelae (PTBS) with different radiological patterns over a 24-week period.

Study Population

A total of 60 patients with established post-tuberculosis sequelae were enrolled consecutively based on predefined inclusion and exclusion criteria. The diagnosis of PTBS was based on clinical, radiological, and spirometric evidence in patients with a past history of microbiologically confirmed pulmonary tuberculosis, with symptoms and/or radiological abnormalities persisting for at least 6 months after microbiological cure.

Inclusion Criteria

- Age ≥ 18 years.
- Documented history of pulmonary tuberculosis.
- Radiological evidence of sequelae (fibrosis, bronchiectasis, fibrocavitary changes).
- Persistent respiratory symptoms (e.g., dyspnea, cough) for at least 6 months post-treatment.
- Written informed consent.

Exclusion Criteria

- Active tuberculosis (based on sputum AFB/CBNAAT positivity).
- Severe cardiac, neurological, or orthopedic comorbidities precluding PR participation.
- Recent acute exacerbation or hospitalization (<4 weeks prior to enrollment).
- Psychiatric illness is impairing compliance.

Radiological Classification

Chest radiographs and high-resolution computed tomography (HRCT) were reviewed independently by two experienced radiologists and classified into four subgroups based on dominant patterns:

- Bronchiectasis.
- Fibrocavitary lesions.
- Fibrosis.
- Mixed fibrocavitary + bronchiectasis.

Pulmonary Rehabilitation Intervention

Patients were allocated to either hospital-based or home-based PR based on preference and feasibility.

Hospital-Based PR

Supervised sessions were conducted thrice weekly in the hospital outpatient PR unit, including:

- Aerobic training (walking, step-ups).
- Breathing exercises (pursed-lip, diaphragmatic breathing).
- Resistance training with elastic bands.
- Education and nutritional counseling.

Home-based PR

Patients were given structured booklets, telephonic guidance, and were advised to perform similar PR routines at home at least 5 days a week. Adherence was monitored weekly via telephonic interviews and monthly outpatient visits.

Outcome Measures and Follow-up

All patients were evaluated at baseline (week 0), 12 weeks, and 24 weeks. The following parameters were assessed at each visit:

- Pulmonary function tests (spirometry): FEV_1, FVC, FEV_1/FVC, FEF_{25-75} (% predicted) pre- and postbronchodilator.
- Exercise capacity: 6-minute walk test (6MWT).
- Symptom severity: mMRC dyspnea scale.
- Health-related quality of life: St. George's Respiratory Questionnaire (SGRQ).
- Psychological assessment: Depression Anxiety Stress Scale (DASS-21).
- Nutritional status: Body mass index (BMI, kg/m^2).

Ethical Considerations

The study was approved by the Institutional Ethics Committee of JLN Medical College, Ajmer. Written informed consent was obtained from all participants.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± SD and compared using ANOVA or *t*-tests as appropriate. Categorical variables were expressed as proportions and compared using Chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results

The study cohort (n = 60) predominantly comprised middle-aged individuals, with 30.0% aged 41–50 and 26.0% aged 31–40 years (Table 1). Male subjects were more common (64.0%), and most participants were from rural areas (68.0%). Socioeconomic assessment using the Modified Kuppuswamy scale showed that 52.0% of the cohort fell in the upper-lower class (score 4). Dyspnea was universally present (100%), followed by cough (78.0%), fatigue/malaise (64.0%), and weight loss (52.0%). Sputum production and chest pain were less frequent (22.0% and 32.0%, respectively). Most patients had illness durations ≤2 years, though 20% had chronicity beyond 5 years. Substance use was prevalent—40.0% had a history of smoking, 30.0% used tobacco, and 15.0% consumed alcohol.

Radiologically, fibrosis was the most frequent abnormality, n = 29 (48.0%), followed by fibrocavitary lesions, n = 24 (40.0%), with isolated bronchiectasis and mixed lesions accounting for n = 5 (8.0%) and n = 2 (4.0%), respectively. At baseline, patients with fibrocavitary lesions showed higher dyspnea burden, 11 cases at mMRC grade 2, 12 at grade 3, and 1 at grade 1, while fibrosis cases were more evenly distributed (4 at grade 1, 18 at grade 2, 7 at grade 3). Bronchiectasis was milder (1 at grade 1, 4 at grade 2), whereas mixed fibrocavitary + bronchiectasis had two cases at grade 3. Over follow-up, a clear shift toward lower grades was observed; by 24 weeks, 42 patients were at grade 1 and only 18 at grade 2. The association between radiological type and mMRC grade was near-significant at baseline (p = 0.065), trended at 12 weeks (p = 0.074), and reached significance at 24 weeks (p = 0.04; χ^2 = 8.294), indicating better dyspnea improvement in fibrosis and bronchiectasis compared to fibrocavitary phenotypes (Table 2).

Nutritional recovery varied across groups. Baseline BMI was lowest in the combined fibrocavitary + bronchiectasis group (15.75 kg/m^2), followed by fibrocavitary (18.01 kg/m^2), with fibrosis patients having the highest (21.95 kg/m^2). Differences remained significant throughout (p < 0.005 at all time points), indicating that radiological severity correlates with poorer BMI recovery (Table 3).

St. George's Respiratory Questionnaire (SGRQ) scores, reflecting quality of life, were highest in the combined group (54) and fibrocavitary group (44.9) at baseline. All groups improved over 24 weeks, though intergroup differences were not statistically significant (p = 0.258 at 24 weeks) (Table 3).

Functional capacity, measured via 6MWT, showed the lowest baseline distance in the combined group (150 m), compared to bronchiectasis (330 m) and fibrosis (314.58 m). By 24 weeks, bronchiectasis and fibrosis groups reached 420 m, while the combined group remained lower (280 m). Statistical significance was present at baseline (p = 0.01), but not at 24 weeks (Table 3).

Psychological improvement was seen across all DASS domains. At 24 weeks, depression

Table 1: Demographic characteristics of the study population

Variable	*Number of subjects*	*Percentage (%)*
Age group		
< 30 years	8	14.0
31–40 years	16	26.0
41–50 years	18	30.0
51–60 years	11	18.0
> 60 years	7	12.0
Sex		
Male	38	64.0
Female	22	36.0
Area		
Rural	41	68.0
Urban	19	32.0
Socioeconomic status (Modified Kuppuswamy score)		
Score 2	5	8.0
Score 3	12	20.0
Score 4	31	52.0
Score 5	12	20.0
Clinical symptoms		
Dyspnea	60	100.0
Cough	47	78.0
Fatigue/malaise	38	64.0
Weight loss	31	52.0
Chest pain	19	32.0
Sputum production	13	22.0
Total duration of illness		
0.5 years	14	24.0
1 year	7	12.0
2 years	13	22.0
3 years	4	8.0
4 years	1	2.0
5 years	7	12.0
7–10 years	7	12.0
12–20 years	5	8.0
Substance abuse		
Smoking	24	40.0
Tobacco chewing	18	30.0
Alcohol use	9	15.0
Smoking index		
0	36	60.0
20–100	8	14.0
101–300	8	13.0
301–600	8	13.0

scores declined from 9.79 to 6.32 in fibrocavitary patients and from 12 to 8 in the combined group. Intergroup differences became significant for depression ($p = 0.013$), anxiety ($p = 0.034$), and stress ($p = 0.049$) by week 24 (Table 3).

Spirometric improvements were evident across all radiological types. Pre-BD FEV1% predicted improved most in fibrosis (48.79% to 62.5%) and bronchiectasis (54% to 63%), while fibrocavitary and combined groups had lower gains (31.11% to 49.79% and 18% to 38%, respectively). These differences were statistically significant throughout ($p < 0.05$). Post-BD FEV1% showed a similar pattern. FVC% increased in all groups, but intergroup variation was not statistically significant. FEV1/FVC ratios and FEF_{25-75}%% predicted also improved, with bronchiectasis showing the highest small airway gains (to 57%) and the combined group the lowest (to 39%) (Table 4).

Bronchodilator reversibility (BDR) was detected in only three patients (5%) at baseline: two with fibrocavitary and one with bronchiectasis. This pattern remained constant at 12 and 24 weeks, with no significant association between BDR and radiological phenotype ($p = 0.188$) (Fig. 1).

Discussion

This study evaluated the differential impact of radiological phenotypes on the outcomes of pulmonary rehabilitation (PR) in patients with post-tuberculosis sequelae (PTBS). 60 patients with varying radiological lesions underwent structured PR over 24 weeks, with outcomes measured across multiple domains. The findings suggest that structural lung abnormalities significantly influence functional recovery, nutritional status, spirometric improvement, and psychosocial well-being.

Fibrosis was the most common radiological pattern, $n = 29$ (48%), followed by fibrocavitary lesions, $n = 24$ (40%), while bronchiectasis and combined lesions were less frequent. The predominance of fibrotic and cavitary patterns aligns with established post-TB structural damage profiles. These lesions likely reflect more extensive parenchymal destruction and thus served as an important framework for stratified analysis.

Dyspnea scores showed significant intergroup differences. At baseline, patients with fibrocavitary lesions had the highest mMRC grades, reflecting more severe breathlessness. By 24 weeks, 100% of bronchiectasis patients and 79.3% of fibrosis patients improved to mMRC grade 1, compared with 58.3% in the fibrocavitary group ($p = 0.022$). This suggests that patients with preserved airway architecture (bronchiectasis, fibrosis) respond better to pulmonary rehabilitation (PR), whereas extensive cavitary damage impairs symptomatic relief. These observations mirror findings by Di Naso et al.[6] who reported that extensive residual lesions—such as fibrocavitary lesions—predict permanent functional limitations, including breathlessness despite treatment completion.

Nutritional status, as measured by BMI, was poorest in patients with combined fibrocavitary + bronchiectatic lesions (15.75 kg/m^2 at baseline) and improved slowly despite pulmonary rehabilitation. In contrast, patients with fibrosis began with a higher baseline BMI (21.95 kg/m^2) and achieved greater gains (22.71 kg/m^2 at 24 weeks; $p < 0.005$). Malnutrition in cavitary disease likely stems from chronic inflammation, catabolic stress, and reduced appetite. Indeed, several researchers recommend nutritional counseling as an integral component of

Table 2: Distribution of mMRC dyspnea grades (grade 1, 2, 3) across radiological lesion subtypes at 0, 12, and 24 weeks. Significant improvement in dyspnea severity was observed across all subtypes over time, with notable intergroup variation

mMRC Grade	*Bronchiectasis*	*Fibrocavitary*	*Fibrocavitary + Bronchiectasis*	*Fibrosis*	*Total*	*p-value (Pearson)*	*Test Statistic*
1	1	1	0	4	6	0.065	11.859
2	4	11	0	18	33		
3	0	12	2	7	21		
Total	5	24	2	29	60		
1	5	12	0	19	36	0.074	6.944
2	0	12	2	10	24		
Total	5	24	2	29	60		
1	5	14	0	23	42	0.04	8.294
2	0	10	2	6	18		
Total	5	24	2	29	60		

B, bronchiectasis; F, fibrosis; FC, fibrocavitary; FCB, fibrocavitary + bronchiectasis

Table 3: Comparative analysis of BMI, SGRQ, 6MWT, and DASS-21 scores across different radiological lesion groups (bronchiectasis, fibrocavitary, combined fibrocavitary + bronchiectasis, and fibrosis) at baseline, 12 weeks, and 24 weeks

Parameter	*Radiological lesion*	*n*	*0 weeks*	*12 weeks*	*24 weeks*
BMI (kg/m^2)	Bronchiectasis	5	21.12	21.68	21.65
	Fibrocavitary	24	18.01	18.60	19.03
	Fibrocavitary + bronchiectasis	2	15.75	15.95	16.60
	Fibrosisw	29	21.95	22.30	22.71
	p-value		0.003	0.004	0.004
SGRQ score	Bronchiectasis	5	37.00	30.00	24.00
	Fibrocavitary	24	44.90	37.40	29.50
	Fibrocavitary + bronchiectasis	2	54.00	44.00	35.00
	Fibrosis	29	40.00	32.83	26.58
	p-value		0.069	0.082	0.258
6MWT (m)	Bronchiectasis	5	330.00	377.50	420.00
	Fibrocavitary	24	236.75	325.00	379.00
	Fibrocavitary + bronchiectasis	2	150.00	225.00	280.00
	Fibrosis	29	314.58	372.50	419.58
	p-value		0.010	0.087	0.145
DASS D score	Bronchiectasis	5	8.00	6.50	4.50
	Fibrocavitary	24	9.79	8.00	6.32
	Fibrocavitary + bronchiectasis	2	12.00	10.00	8.00
	Fibrosis	29	8.58	7.17	5.25
	p-value		0.115	0.088	0.013
DASS A score	Bronchiectasis	5	11.00	9.50	7.50
	Fibrocavitary	24	12.84	10.74	8.95
	Fibrocavitary + bronchiectasis	2	14.00	12.00	10.00
	Fibrosis	29	11.50	9.83	7.83
	p-value		0.185	0.171	0.034
DASS S score	Bronchiectasis	5	15.00	12.00	9.50
	Fibrocavitary	24	15.58	13.16	11.05
	Fibrocavitary + bronchiectasis	2	16.00	14.00	12.00
	Fibrosis	29	14.83	12.58	10.08
	p-value		0.577	0.523	0.049

post-TB rehabilitation programs, particularly for patients with fibrotic or cavitary lung changes.[7]

Quality of life, assessed via the SGRQ, was worst in patients with combined fibrocavitary + bronchiectatic lesions (score 54 at baseline). However, significant improvements were observed across all groups following pulmonary rehabilitation (PR), underscoring PR's effectiveness regardless of structural severity. These findings align with outcomes from van Ranst et al.,[8] who demonstrated that even patients with severely impaired health status (SGRQ 66) experienced clinically meaningful improvements in HRQoL and exercise capacity following an intensive PR program (75% showing significant SGRQ).

Exercise capacity, measured via the 6-minute walk test (6MWT), was significantly lower in combined lesion patients (150 m at baseline) but improved to 280 m by

Table 4: Comparison of spirometric parameters (pre- and postbronchodilator FEV1% predicted, FVC%, FEV1/FVC ratio, and $FEF_{25–75}$%) at baseline, 12 weeks, and 24 weeks across radiological lesion subgroups (bronchiectasis, fibrocavitary, combined fibrocavitary + bronchiectasis, and fibrosis)

Parameter	*Radiological lesion*	*n*	*Mean value at visits*		
		0 weeks	*12 weeks*	*24 weeks*	
FEV_1 % predicted pre	Bronchiectasis	5	54.00	58.75	63.00
	Fibrocavitary	24	31.11	41.79	49.79
	Fibrocavitary + bronchiectasis	2	18.00	26.00	38.00
	Fibrosis	29	48.79	56.62	62.50
	p-value		0.010	0.022	0.032
FEV_1 % predicted post	Bronchiectasis	5	60.75	66.25	70.50
	Fibrocavitary	24	37.05	49.32	56.26
	Fibrocavitary + bronchiectasis	2	22.00	32.00	42.00
	Fibrosis	29	53.04	62.88	68.00
	p-value		0.026	0.027	0.037
FVC % predicted	Bronchiectasis	5	56.25	61.25	66.00
	Fibrocavitary	24	41.74	49.05	55.05
	Fibrocavitary + bronchiectasis	2	29.00	35.00	43.00
	Fibrosis	29	57.12	60.88	66.21
	p-value		0.073	0.152	0.124
FEV_1/FVC	Bronchiectasis	5	91.50	93.50	93.00
	Fibrocavitary	24	74.95	78.79	82.00
	Fibrocavitary + bronchiectasis	2	63.00	67.00	72.00
	Fibrosis	29	80.42	82.04	85.00
	p-value		0.182	0.106	0.170
$FEF_{25–75}$% predicted	Bronchiectasis	5	37.75	46.25	57.00
	Fibrocavitary	24	22.53	35.32	45.16
	Fibrocavitary + bronchiectasis	2	8.00	28.00	39.00
	Fibrosis	29	33.29	42.88	51.96
	p-value		0.070	0.160	0.142

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25–75}$, forced expiratory flow at 25–75% of FVC

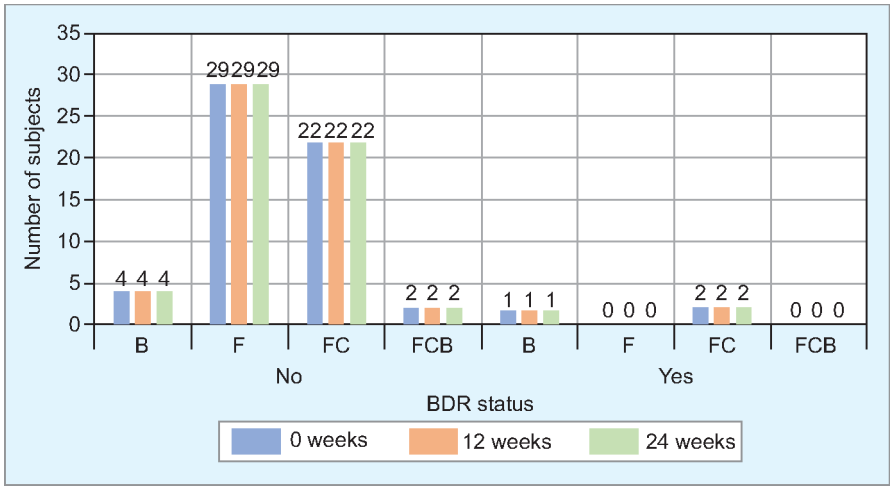


Fig. 1: Bar diagram showing distribution of bronchodilator reversibility (BDR) status across different radiological lesion types at 0, 12, and 24 weeks. No significant association was observed ($\chi^2 = 4.787$; $p = 0.188$) (B, bronchiectasis; F, fibrosis; FC, fibrocavitary; FCB, fibrocavitary + bronchiectasis)

24 weeks. In contrast, bronchiectasis and fibrosis groups exceeded 420 m by week 24. While differences were statistically significant at baseline (p = 0.01), they narrowed over time, underscoring PR's effectiveness in functional reconditioning. A study by Ando et al.[9] similarly demonstrated that pulmonary rehabilitation produced meaningful improvements in both post-TB lung disorder patients and COPD patients, with comparable gains in 6MWT distance and dyspnea scores (improvement of approximately 42–47 m post-PR).

Psychological parameters improved significantly over time, with the greatest reductions in depression, anxiety, and stress observed in patients with bronchiectasis and fibrosis. By week 24, intergroup differences were statistically significant (depression: $p = 0.013$; anxiety: $p = 0.034$; stress: $p = 0.049$), suggesting that patients with less extensive anatomical damage experience greater psychological benefit from PR. This aligns with findings from Pumar et al.,[10] who concluded that pulmonary rehabilitation improves anxiety and depression symptoms in chronic respiratory disease patients, reinforcing the value of integrated psychosocial support.

Pulmonary function improved across all radiological groups, with the lowest gains noted in patients with combined fibrocavitary and bronchiectasis lesions. In this subgroup, FEV_1% predicted increased from 18% at baseline to 38% at 24 weeks, whereas patients with fibrosis and bronchiectasis alone surpassed 60% by week 24 ($p < 0.05$). Postbronchodilator FEV_1 and $FEF_{25–75}$% showed parallel improvements, but remained

significantly lower in the combined lesion group, indicating that severe structural lung damage blunts spirometric recovery. These findings are consistent with observations by Hnizdo et al.,[11] who reported that cavitary and mixed lesions frequently lead to fixed and irreversible airflow obstruction in post-tuberculosis sequelae, limiting response to bronchodilator therapy and rehabilitation efforts.

Bronchodilator reversibility (BDR) was infrequent, noted in only 5% of patients, and limited to fibrocavitary and bronchiectasis subgroups. No statistically significant association was found between radiological lesion type and BDR status at any time point ($p = 0.188$). This low prevalence supports previous literature suggesting that airflow limitation in post-TB sequelae is typically nonreversible, as airway remodeling and parenchymal destruction dominate the pathophysiology rather than smooth muscle constriction.

In summary, this study highlights that while pulmonary rehabilitation improves clinical, functional, and psychological outcomes across all radiological phenotypes, patients with bronchiectasis and fibrosis benefit more consistently. Cavitary and mixed lesions are associated with poorer baseline parameters and slower recovery. These findings underscore the importance of lesion-specific stratification when designing and monitoring PR programs.

Importantly, there is a paucity of Indian studies comparing PR outcomes based on radiological phenotypes in PTBS. To our knowledge, this is the first study in India to assess multidimensional rehabilitation outcomes across radiological subtypes in post-TB patients. This fills a critical gap in the regional literature and offers context-specific insights for TB-endemic settings.

Clinically, these findings advocate for tailored PR models in PTBS care, with intensified support for patients with fibrocavitary or mixed lesions. Early identification and structured rehabilitation can potentially reverse or mitigate long-term morbidity. Integration of radiology-guided PR into national TB programs may significantly improve long-term outcomes and quality of life among TB survivors in high-burden countries such as India.

Conclusion

This study demonstrates that pulmonary rehabilitation (PR) leads to significant improvements in exercise capacity, spirometric indices, BMI, and psychological well-being in patients with post-tuberculosis sequelae (PTBS). Although patients with fibrocavitary and combined lesions exhibited greater baseline impairment, they still derived substantial benefit from PR. The findings highlight that radiological severity should not preclude rehabilitation efforts, and PR should be considered an essential component of long-term TB care. Importantly, the comparable benefits across radiological types underscore the need to integrate both hospital-based and scalable home-based PR models into national TB programs, particularly in resource-constrained, high-burden countries such as India.

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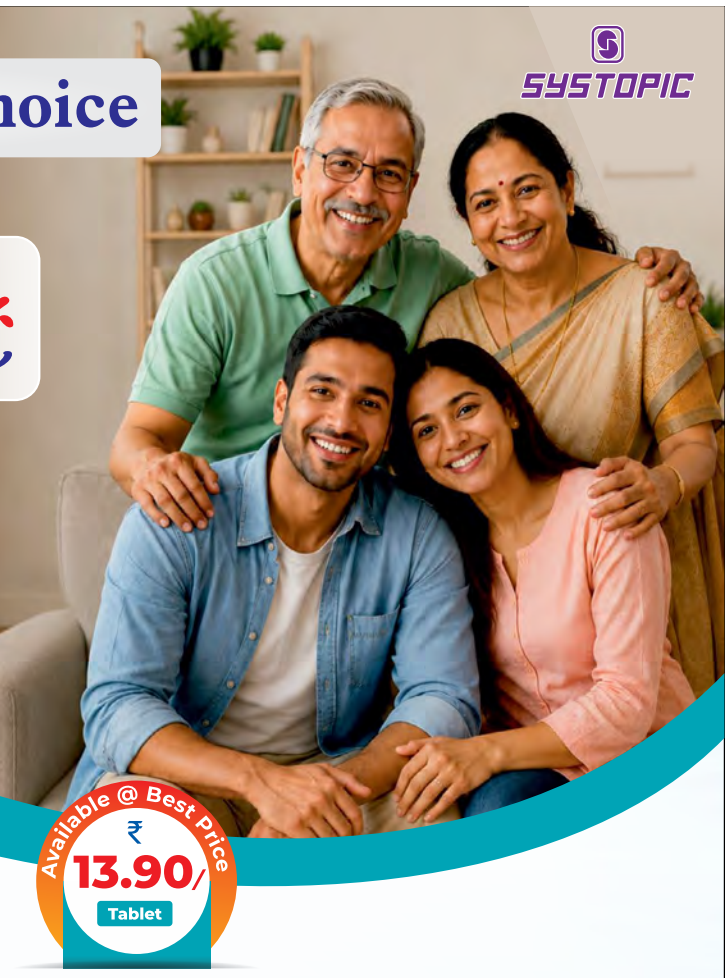
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ORIGINAL ARTICLE

Prevalence of Celiac Disease in Inflammatory Bowel Disease: A Prospective Cohort Study from Northern India

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Received: 27 November 2025; *Accepted:* 21 April 2026

Abstract

Background: Celiac disease (CeD) and inflammatory bowel disease (IBD) share immune and genetic pathophysiological pathways, suggesting a possible increased coexistence. Indian data on biopsy-confirmed CeD in IBD are limited, and false-positive anti–tissue transglutaminase (tTG) antibody results complicate interpretation.

Aim: To determine the prevalence of biopsy-confirmed CeD in an Indian IBD cohort and compare clinical features between CeD-positive and CeD-negative IBD patients.

Materials and methods: In this prospective observational study, 477 IBD patients were assessed. All patients underwent IgA anti-tTG screening. Seropositive patients underwent upper gastrointestinal endoscopy with duodenal biopsies. The standardized prevalence ratio (SPR) for CeD was calculated, and clinical and laboratory parameters were compared between patients with and without CeD.

Results: Among 477 IBD patients (UC 421; CD 56), 14 (2.94%) were anti-tTG positive, and 11 had biopsy-confirmed CeD, giving a prevalence of 2.31% (95% confidence interval: 1.29–4.08%). Prevalence was 2.14% in UC and 3.57% in CD (p = 0.59). The SPR, compared with the Indian population prevalence of 1.04%, was 2.22. The anti-tTG false-positive rate was 21.4%. No significant differences were observed between CeD-positive and CeD-negative patients, although UC patients with CeD showed a non-significant trend toward pancolitis.

Conclusion: In conclusion, CeD prevalence in Indian IBD patients was numerically higher than the Northern Indian general population but did not reach statistical significance. Larger multicenter studies are needed to definitively establish the CeD–IBD association in Indian populations. Selective screening is preferable, and histological confirmation remains essential due to high false-positive serology.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1520

Introduction

Celiac disease (CeD) is a chronic immune-mediated enteropathy triggered by dietary gluten exposure in genetically predisposed individuals.[1] The global prevalence is estimated at 1.0–1.4%,[2] while studies from India report a prevalence of about 1.04% in Northern regions and between 0.3% and 1.23% across different parts of the country.[3–5] Diagnosis requires a combination of serological testing, upper gastrointestinal endoscopy (UGIE), and characteristic histopathological findings.[6]

Ulcerative colitis (UC) and Crohn's disease (CD) are the major forms of inflammatory bowel disease (IBD), characterized by chronic intestinal inflammation in genetically susceptible individuals. CeD and IBD share several clinical and biological features, including genetic susceptibility through human leukocyte antigen (HLA) DQ2/DQ8 haplotypes and compromised mucosal barrier integrity.[7]

Coexisting CeD in patients with IBD has been associated with extensive colitis, refractory symptoms, and increased risk of disease flares,[8] making early detection clinically important. However, evidence regarding the prevalence of CeD among IBD patients remains inconsistent. Early work by Salem and Truelove[9] suggested an association between UC and villous atrophy, while subsequent studies have reported both higher and comparable CeD rates relative to the general population.[10–12] These variations likely reflect differences in population characteristics, diagnostic criteria, and serological assay performance. Furthermore, false-positive anti–tissue transglutaminase (tTG) antibody results in IBD further complicate interpretation.[13] Determining the true prevalence of biopsy-confirmed CeD in Indian IBD patients is therefore essential for appropriate screening and clinical decision-making.

Indian data remain limited, with few prospective studies using standardized diagnostic methods to evaluate biopsy-confirmed CeD in IBD. This study aimed to determine the prevalence of biopsy-confirmed CeD in a well-characterized IBD cohort from Northern India and identify clinical factors associated with CeD–IBD overlap.

Materials and Methods

This prospective observational study was conducted in the Department of Gastroenterology, Sawai Man Singh Medical College and Group of Hospitals, Jaipur, between April 2021 and June 2024. Institutional Ethics Committee approval was obtained, and written informed consent was taken from all participants. The study adhered to the Declaration of Helsinki (1975; revised 2013).

All consecutive adult patients (≥18 years) with a confirmed diagnosis of IBD-UC or CD, attending outpatient or inpatient services during the study period, were enrolled. Patients below 18 years of age, those unwilling to participate, and patients already following a gluten-free diet (as this could lead to false-negative anti-tTG results) were excluded from the study. The diagnosis of IBD was based on European Crohn's and Colitis Organisation–European Society of Gastrointestinal and Abdominal Radiology (ECCO–ESGAR) guidelines[14,15] using combined clinical, endoscopic, radiologic, and histopathologic criteria. UC was classified as proctitis (E1), left-sided colitis (E2), or pancolitis (E3), and CD was classified by disease location as ileal (L1), colonic (L2), ileocolonic (L3), or upper gastrointestinal (L4).[16] Extraintestinal manifestations (EIMs) were systematically documented.

All enrolled patients underwent screening for IgA anti-tTG antibodies using a commercial enzyme-linked immunosorbent assay (ELISA) kit (CHORUS tTGA, Siena, Italy). Serum IgA concentrations were measured in all subjects; patients with IgA deficiency

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How to cite this article: Kumar M, Sapra B, Sharma PN, *et al.* Prevalence of Celiac Disease in Inflammatory Bowel Disease: A Prospective Cohort Study from Northern India. J Assoc Physicians India 2026;74(6):36–40.

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(IgA <7 mg/dL) underwent additional IgG-based tTG testing. Seropositive patients were advised to undergo UGIE with at least six duodenal biopsies (two from the bulb, four from the second part), which were evaluated using the modified Marsh–Oberhuber grading system.[17] Patients with discordant serology and histology underwent human leukocyte antigen (HLA) DQ2/DQ8 genotyping using polymerase chain reaction (PCR)-based typing. The diagnosis of CeD followed European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommendations,[18] requiring compatible histology (Marsh ≥2) and/or HLA positivity with symptomatic response to a gluten-free diet.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical variables as frequencies and percentages. Group comparisons used chi-square or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables. A p-value < 0.05 was considered significant. The standardized prevalence ratio (SPR) was calculated using the Northern Indian general population prevalence of 1.04% reported by Makharia et al.,[3] a community-based study from the same geographic region as our cohort, ensuring appropriate demographic and genetic comparability for prevalence estimation. Diagnostic accuracy parameters of IgA anti-tTG testing were calculated using duodenal histology as the reference standard.

Results

Between April 2021 and June 2024, 477 consecutive patients with IBD were screened for CeD. The final cohort of 477 patients represents one of the largest prospective Indian cohorts systematically screened for CeD in IBD. This cohort comprised 421 patients with UC (88.3%) and 56 with CD (11.7%). The mean age was 37.8 ± 13.2 years, with a male-to-female ratio of 1.26:1. Baseline characteristics are summarized in Table 1. The mean hemoglobin level was 10.24 ± 2.64 g/dL, with no significant difference between UC and CD (10.26 ± 2.71 vs 10.08 ± 2.23 g/dL; $p = 0.65$). The mean platelet count was 3.08 ± 1.33 × 10^5/mm^3. The average disease duration was 4.9 ± 0.9 years.

Among UC patients, left-sided colitis (E2) was the most common extent (54.4%), followed by pancolitis (E3, 31.1%) and proctitis (E1, 10.0%); extent was unclassified in 4.5%. Among CD patients, ileocolonic disease (L3) predominated (68.8%), followed by colonic disease (L2, 18.8%), ileal disease (L1, 6.3%), and upper gastrointestinal involvement (L4, 6.3%). EIMs were documented in 72 of 477 patients (15.1%), occurring more frequently in CD (37.5%) than UC (12.1%) ($p < 0.001$) (Table 2).

Figure 1 illustrates the screening and diagnostic pathway. 14 patients (2.94%) were seropositive for IgA tTG antibodies. All underwent upper gastrointestinal endoscopy with duodenal biopsies. 11 patients were confirmed to have CeD based on Marsh criteria, supported by HLA-DQ2/DQ8 genotyping when indicated. The overall prevalence of biopsy-confirmed CeD in the IBD cohort was 2.31% (95% confidence interval (CI): 1.29–4.08%). Prevalence was 2.14% among UC patients (9/421) and 3.57% among CD patients (2/56), with no significant difference ($p = 0.59$). The SPR of CeD in IBD patients, compared with the reported prevalence in the Indian general population (1.04%), was 2.22, although this difference was not statistically significant ($p = 0.655$) (Table 3). The false-positive rate of IgA anti-tTG testing was 21.4% (3/14). Test sensitivity was 100%, specificity 99.4%, positive predictive value 78.6%, and negative predictive value 100%.

Among patients with UC–CeD overlap ($n = 9$), pancolitis was the predominant phenotype (55.6%), followed by left-sided colitis (44.4%). None had isolated proctitis. Both CD-CeD patients had ileocolonic disease (L3). Although extensive disease (E3) was numerically more frequent in CeD-positive UC patients compared with CeD-negative UC patients (55.6% vs 30.6%), the difference was not statistically significant ($p = 0.42$). Compared with CeD-negative patients,

Table 1: Baseline characteristics of study patients

Parameter	*IBD (n = 477)*	*UC (n = 421)*	*CD (n = 56)*
Age (years, mean ± SD)	37.8 ± 13.2	37.8 ± 13.0	37.9 ± 14.8
Male: female (%)	266:211 (55.8: 44.2)	239:182 (56.8: 43.2)	28:28 (50: 50)
Hemoglobin (g/dL)	10.24 ± 2.64	10.26 ± 2.71	10.08 ± 2.23
Platelet count (×10^5/mm^3)	3.08 ± 1.33	3.06 ± 1.28	3.21 ± 1.59
Disease duration (years)	4.9 ± 0.9	5.0 ± 0.9	4.3 ± 1.0
UC extent			
E1–Proctitis	–	42 (10.0%)	
E2–Left-sided	–	229 (54.4%)	
E3–Pancolitis	–	131 (31.1%)	
Extent not recorded	–	19 (4.5%)	
CD location			
L1–Ileal	–	–	4 (6.3%)
L2–Colonic	–	–	10 (18.8%)
L3–Ileocolonic	–	–	38 (68.8%)
L4–Upper gastrointestinal	–	–	4 (6.3%)

Table 2: Extraintestinal manifestations in ulcerative colitis and Crohn's disease

EIM	*UC [n = 421 (%)]*	*CD [n = 56 (%)]*	*Total [n = 477 (%)]*
Musculoskeletal			
Arthralgia/arthritis	9 (2.2)	0 (0)	9 (1.9)
Ankylosing spondylitis	5 (1.1)	2 (3.6)	7 (1.5)
Endocrine			
Hypothyroidism	14 (3.3)	0 (0)	14 (2.9)
Diabetes mellitus	1 (0.2)	1 (1.8)	2 (0.4)
Infectious/mucocutaneous			
Candidiasis (oral or esophageal)	19 (4.5)	3 (5.4)	22 (4.6)
Other*	≤1	≤1	7(1.5%)
Gastrointestinal complications			
Perianal fistula	0 (0)	7 (12.5)	7 (1.5)
Stricture	0 (0)	4 (7.1)	4 (0.8)
Any EIM present	51 (12.1)	21 (37.5)	72 (15.1)

*Includes primary sclerosing cholangitis, cholangiocarcinoma, neuropathy, rectovaginal fistula, etc.

CeD-positive patients showed no significant differences in age, sex, disease duration, hemoglobin, platelets, or EIM frequency except hypothyroidism [27.3% (3/11) vs 2.4% (11/466), $p = 0.005$] (Table 4).

Characteristics of the 11 IBD–CeD overlap cases are described in Table 5. The median age was 36 years (range: 22–58), with near-equal sex distribution (6 males, 5 females). Nine patients had UC, and two had CD. Median disease duration was 5 years (range: 2–8). Marsh 3a, 3b, and 3c lesions were seen in 4 (36.4%), 5 (45.5%), and 2 (18.2%) patients, respectively. Chronic diarrhea was universal (100%). Weight loss (72.7%), anemia (81.8%), and abdominal pain (63.6%) were frequent. Six patients (54.5%) had at least one EIM, most commonly hypothyroidism and arthralgia.

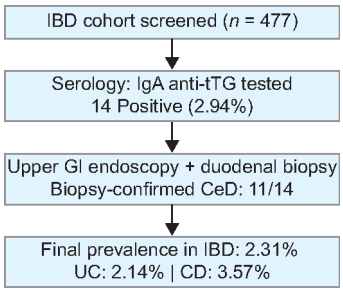


Fig. 1: Screening and diagnostic flowchart for the study

Discussion

In this prospective cohort of 477 Indian IBD patients, the prevalence of histologically-confirmed CeD was 2.31%, compared to the 1.04% population-based prevalence, corresponding to an SPR of 2.22, although this did not reach statistical significance.[3] The prevalence was similar between UC (2.14%) and CD (3.57%) patients. With only 11 biopsy-confirmed CeD cases, our study had limited statistical power to detect small but clinically meaningful differences in prevalence. The non-significant p-value (0.655) may reflect a type II error rather than a true absence of association, and these findings warrant validation in larger multicenter studies.

Our findings differ from several Western meta-analyses, which have reported a stronger association. Shah et al. reported an odds ratio of 2.23 (95% CI: 1.99–2.50) for CeD in patients with IBD, while Pinto-Sanchez et al. reported a risk ratio of 3.96 (95% CI: 2.23–7.02) in their 2020 meta-analysis.[11–12] However, these analyses demonstrated substantial heterogeneity (I^2 >70%), with individual study estimates varying widely (0–4.2%). Importantly, several cohort studies from Western populations have reported CeD prevalence rates of 0.5–3.2% in IBD,[19–21] aligning more closely with our findings than the pooled meta-analytic estimates. Thus,

Table 3: Prevalence of celiac disease in inflammatory bowel disease compared with the general population

Group	*n*	*CeD cases*	*Prevalence, % (95% CI)*	*SPR**	*p-value*
All IBD	477	11	2.31 (1.29–4.08)	2.22	0.655
Ulcerative colitis	421	9	2.14 (1.13–4.01)	2.06	0.734
Crohn's disease	56	2	3.57 (0.98–12.12)	3.43	0.607
Seropositive (IgA-tTG)	477	14	2.94 (1.76–4.87)	2.83	0.447

*SPR (standardized prevalence ratio) = Observed prevalence in IBD/expected prevalence in the general population

Table 4: Clinical characteristics: celiac disease positive and celiac disease negative Inflammatory bowel disease patients

Parameter	*IBD with CeD (n = 11)*	*IBD without CeD (n = 466)*	*p-value*
Demographics			
Age (years, mean ± SD)	38.5 ± 11.8	37.8 ± 13.3	0.87
Male:female	6:5 (54.5%:45.5%)	260:206 (55.8%:44.2%)	0.93
IBD type			
Ulcerative colitis	9 (81.8%)	412 (88.4%)	0.59
Crohn's disease	2 (18.2%)	54 (11.6%)	
Laboratory parameters			
Hemoglobin (gm/dL)	9.87 ± 2.21	10.25 ± 2.65	0.65
Platelet count (× 10^5/mm^3)	3.18 ± 1.45	3.08 ± 1.33	0.78
Disease characteristics			
Disease duration (years)	5.2 ± 1.1	4.9 ± 0.9	0.35
UC disease extent (n = 9 with CeD, n = 412 without)			0.42
Proctitis (E1)	0 (0%)	42 (10.2%)	
Left-sided colitis (E2)	4 (44.4%)	225 (54.6%)	
Pancolitis (E3)	5 (55.6%)	126 (30.6%)	
CD location (n = 2 with CeD, n = 54 without)			0.88
Ileal (L1)	0 (0%)	4 (7.4%)	
Colonic (L2)	0 (0%)	10 (18.5%)	
Ileocolonic (L3)	2 (100%)	36 (66.7%)	
Upper GI (L4)	0 (0%)	4 (7.4%)	
Clinical features			
Any EIM present	2 (18.2%)	70 (15.0%)	0.72
Hypothyroidism	3 (27.3%)	11 (2.4%)	0.005
Anemia (Hb <12 gm/dL)	9 (81.8%)	348 (74.7%)	0.73
Weight loss	8 (72.7%)	245 (52.6%)	0.18

Table 5: Individual characteristics of inflammatory bowel disease—celiac disease overlap cases (n = 11)

Case	*Age/sex*	*IBD type*	*Duration(years)*	*IBD extent/ Location*	*Marsh grade*	*EIM*	*Presenting symptoms*
1	42/M	UC	6	E3 (pancolitis)	3b	None	Diarrhea, weight loss, and anemia
2	36/F	UC	5	E2 (left-sided)	3a	Hypothyroidism	Diarrhea, fatigue
3	28/M	UC	4	E3 (pancolitis)	3c	Arthralgia	Bloody diarrhea, abdominal pain
4	52/F	UC	7	E2 (left-sided)	3a	Hypothyroidism	Diarrhea, anemia
5	34/M	UC	5	E3 (pancolitis)	3b	None	Diarrhea, weight loss
6	45/F	UC	6	E2 (left-sided)	3a	None	Diarrhea, bloating
7	29/M	UC	3	E3 (pancolitis)	3c	None	Bloody diarrhea, weight loss
8	38/F	UC	5	E2 (left-sided)	3b	Hypothyroidism	Diarrhea, anemia, fatigue
9	58/F	UC	8	E3 (pancolitis)	3b	None	Diarrhea, weight loss
10	32/M	CD	4	L3 (ileocolonic)	3a	Perianal fistula	Diarrhea, abdominal pain, and weight loss
11	22/M	CD	2	L3 (ileocolonic)	3b	Arthralgia	Diarrhea, weight loss, and anemia

methodological and population differences may partly explain the weaker association in our cohort.

Reports from Middle Eastern and Asian countries similarly show modest associations: CeD prevalence of 0.5% in Iran,[22] 2.0% in Turkey,[23] and even lower rates in Japan.[24] Large registry-based studies from Sweden[25] and Israel[26] have shown stronger associations, likely due to larger sample sizes and longer follow-up. Our results are consistent with these Middle Eastern and Asian reports, suggesting potential geographic and ethnic variation in the CeD–IBD association. This geographic heterogeneity likely reflects differences in genetic architecture, particularly HLA-DQ2/DQ8 allele frequencies, environmental factors including dietary gluten exposure, and gut microbiome composition.[7] Interestingly, recent data suggest that IBD treatment with immunosuppressants and biologics may reduce the detection rate of CeD,[27] which could potentially contribute to lower prevalence estimates in treated populations.

In our cohort, demographic and clinical features did not differ significantly between CeD-positive and CeD-negative IBD patients. This contrasts with some Western data suggesting that CeD-IBD overlap is associated with extensive colitis, refractory disease, or primary sclerosing cholangitis.[8,21] The absence of such associations in our study may reflect true population-level differences or limitations imposed by the small number of CeD–IBD overlap cases (n = 11), which limited statistical power for detecting subgroup differences. Among UC patients with CeD, 55.6% had pancolitis compared with 30.6% in those without CeD. Although this difference did not reach statistical significance, likely due to the small number of CeD cases (n = 9), the observed trend may still be clinically relevant. It warrants evaluation in larger cohorts, as more extensive colonic involvement could theoretically be associated with heightened mucosal inflammation, potentially influencing either the true risk of CeD or the likelihood of false-positive serology.

Extraintestinal manifestations were similar between groups. However, autoimmune thyroid disease was observed in 27.3% of CeD–IBD patients versus 2.4% in IBD without CeD, consistent with the well-known association between CeD and autoimmune thyroiditis.[28] Although numbers were small, this signal supports selective screening in IBD patients with autoimmune comorbidities.

The Challenge of False-Positive Serology in IBD

A notable observation in our study was the high false-positive rate of anti-tTG antibodies (21.4%). Several mechanisms may explain this. Anti-tTG antibodies can be produced during intestinal apoptosis and inflammation; transglutaminase overexpression has been documented in CD, and mucosal immune activation may promote low-titer antibody formation independent of gluten exposure.[29] The Japanese experience is instructive: Watanabe et al. reported seropositivity rates of 19.4% in CD and 9.1% in UC, yet found no biopsy-proven CeD in 134 IBD patients.[24] In our study, although anti-tTG sensitivity was 100%, the positive predictive value (PPV) was only 78.6%, substantially lower than the 95–98% PPV observed in general populations. In practical terms, this means approximately 1 in 5 positive anti-tTG results in IBD patients represents a false positive, underscoring the critical importance of histological confirmation before diagnosing CeD to avoid misdiagnosis and unnecessary dietary restrictions.[13]

Given the modest prevalence of CeD (2.31%) and the high false-positive serology rate, routine universal screening of all IBD patients is unlikely to be cost-effective, especially in resource-constrained settings. A selective approach appears more appropriate—targeting patients with unexplained anemia, persistent malabsorption, refractory symptoms despite optimized IBD therapy, or associated autoimmune conditions such as thyroiditis or type 1 diabetes.

This study has several strengths. It is a prospective study with a relatively large, well-characterized IBD cohort. The study employed rigorous diagnostic criteria requiring both serological screening and mandatory histological confirmation in all seropositive patients, thus addressing the limitation of prior studies that relied solely on serology. Additionally, the use of a geographically and genetically comparable population reference enhances the validity of the SPR analysis. Limitations must be acknowledged. As a single-center tertiary-care cohort, referral bias toward complex or severe cases may limit generalizability, not reflecting community IBD epidemiology. The cross-sectional design limits our ability to determine temporal relationships between CeD and IBD. The number of biopsy-confirmed CeD cases was small, leading to wide confidence intervals and limited statistical power for subgroup analyses.

In conclusion, CeD prevalence in Indian IBD patients was numerically higher than the Northern Indian general population but did not reach statistical significance. Routine universal screening is not indicated, but selective testing in high-risk subgroups is advisable. Histological confirmation remains essential in all seropositive cases. Larger, multicenter studies with adequate power are needed to better delineate the CeD–IBD relationship in Indian populations and clarify underlying genetic and environmental contributors.

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ORIGINAL ARTICLE

A Study of the Clinical Profile of Acute Poisoning in Adults in a Rural Tertiary Healthcare Setup

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Received: 02 March 2026; *Accepted:* 21 April 2026

Abstract

Acute poisoning remains a major public health concern in rural India due to easy accessibility of toxic substances and limited mental health support. This retrospective observational study was conducted at a tertiary care teaching hospital in rural Bengaluru to evaluate the clinical and epidemiological profile of poisoning cases. Medical records of 100 patients admitted with acute poisoning over 1 year were analyzed.

The mean age of patients was 28 years, with the majority in the 21–30-year age group, and a female predominance (57%). Suicidal intent accounted for 85% of cases. Organophosphorus compounds were the most common agents, followed by drug overdoses and pyrethroid compounds. All exposures occurred via the oral route, and 74% of patients presented within 4 hours of ingestion. Vomiting was the most common presenting symptom, followed by abdominal pain and altered sensorium. Laboratory abnormalities included elevated liver enzymes and electrolyte disturbances. The mean duration of hospitalization was 4 days. No mortality was observed during the study period.

Acute poisoning in rural Bengaluru predominantly affects young adults and is largely associated with suicidal intent. Early presentation and prompt management contribute to favorable outcomes. Preventive strategies focusing on mental health support and the regulation of toxic substances are essential.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1538

Introduction

Poisoning represents a critical health issue globally and is particularly prevalent in rural parts of India, where agricultural chemicals are easily available, and mental health services are limited. This study examines the spectrum of poisoning cases and associated clinical outcomes in patients treated at a tertiary care center in rural Bengaluru.

Suicide significantly impacts young populations and is currently the second most common cause of death among individuals aged 15–29 years globally. Despite variations between nations, nearly three-quarters of all suicides occur in low- and middle-income countries, contributing to approximately 75% of all cases.[1]

Occupational health problems are common, as the use of personal protective equipment in humid tropical regions is often costly and impractical. Furthermore, safety labels are frequently written in languages unfamiliar to farmers, literacy levels are low, and the instructions are difficult to understand, while immediate washing after pesticide exposure is often impossible due to a lack of access to water.[2]

A large share of suicides results from intentional pesticide ingestion due to the high lethality of these highly toxic substances. The case fatality rate for self-poisoning with pesticides is estimated to be between 10% and 20%, with even greater fatality observed for some WHO class I and II compounds.[3]

Nearly three-quarters of poisoning cases in the country are attributed to organophosphorus insecticides.[4]

Poisoning due to Celphos (aluminum phosphide) is a major yet under-recognized issue in the Indian subcontinent. Aluminum phosphide (ALP), commonly used as a fumigant for stored grains, is highly toxic when consumed from newly opened packaging.[5]

The pattern of poison usage varies globally and may differ within regions of the same country due to socioeconomic status and cultural influences.[6]

Knowledge of the trends in acute poisoning cases at our hospital, with emphasis on demographic, etiological, and clinical characteristics, can aid in improving early detection and management strategies.[7]

Organophosphorus compounds are widely available and commonly used as insecticides in agriculture as well as in households. While earlier reports indicated high mortality, improved intensive care management has resulted in a marked decline in death rates. Organophosphate insecticides constitute more than half of all acute poisoning cases seen in hospitals, predominantly affecting individuals younger than 30 years.[8]

Aim

The aim is to study the clinical and social profile, laboratory parameters, and treatment outcome of acute poisoning patients.

Objective

Periodic clinical and epidemiological studies are necessary to understand the trends of poisoning in society. These studies help in planning and providing good and fast healthcare facilities to reduce poisoning-related mortality. This study was designed to evaluate the pattern and outcomes of poisoning cases in a tertiary care hospital at Hoskote.

Materials and Methods

Study Design and Setting

This retrospective observational study was carried out at MVJ Hospital, a tertiary care teaching institution in rural Bengaluru. Medical records of 100 patients admitted with acute poisoning over a 1-year period were reviewed.

Methods

A retrospective observational study of 100 consecutive poisoning cases was conducted. Data were collected from hospital records, in casualty, inpatient, and outpatient settings, including demographics, type of poisoning, intent, clinical features, treatment, and outcome measures.

Inclusion Criteria

Data collected regarding age, sex, marital status, address, occupation, socioeconomic

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How to cite this article: Murthy MS, Kumar PG, Suhas SV. A Study of the Clinical Profile of Acute Poisoning in Adults in a Rural Tertiary Healthcare Setup. J Assoc Physicians India 2026;74(6):41–45.

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status, type of poisoning, route of administration, dosage administered, duration of time brought to the hospital, symptoms, duration of hospitalization, treatment, date of discharge, and recovery rate were included.

Exclusion Criteria

The patients in whom the poison was not positively identified were critically ill before poisoning, animal and snake bites, and those who had received initial treatment from some other healthcare facilities, and patients with idiosyncratic or adverse reactions to prescribed drugs were excluded from the study.

Background

Acute poisoning constitutes a major medical emergency, especially in rural India, where access to toxic agents is common. This study aimed to analyze the clinical profile, types, intent, and outcomes of poisoning cases presenting to a tertiary hospital in rural Bengaluru.

Results

Organophosphate compounds constituted the majority of poisoning cases, followed by benzodiazepines and pharmaceutical drug overdoses. Suicidal intent accounted for 85% of cases. Most patients (74%) presented within 4 hours of exposure. The average age was 28 years, and 57% were female. Vomiting and altered consciousness were the most frequent presenting symptoms. The mean duration of hospitalization was 4 days. Laboratory findings commonly showed elevated liver enzymes and electrolyte imbalances. No fatalities were recorded during the study period.

Conclusion

Suicidal poisoning using easily accessible agents like OP compounds remains a major concern in rural Bangalore. Early hospital presentation and appropriate treatment contributed to favorable outcomes. Preventive strategies, including better mental health support and stricter regulation of toxic substances, are needed.

Data Collection

Data included:

- Demographics: age, sex, occupation, marital status, and socioeconomic status.
- Poison characteristics: type, mode (suicidal, accidental), and route.
- Clinical profile: presenting symptoms, time to hospital, vital signs.
- Investigations: hematological and biochemical parameters.
- Treatment and outcomes: interventions, duration of hospitalization, mortality.

Data Analysis

Descriptive analysis was performed using means, percentages, and frequency distributions.

Results

- Mean age: 28 years (range: 16–70).
- Predominant age group: 21–30 years (Fig. 1).
- Sex (Table 1 and Fig. 2).
- Marital status (Table 2 and Fig. 3).
- The majority of patients belonged to lower socioeconomic strata.
- Poisoning profile
- Most common poisons (Table 3 and Fig. 4).
- Intent (Table 4)
- Route: 100% oral.
- Time to hospital: 74% presented within 4 hours of ingestion (Fig. 5 and Table 5).
- Clinical features
  - Common symptoms (Table 6).
  - Organophosphorus poisoning: vomiting was the main symptom.
  - Cypermethrin: associated with giddiness.
  - Prallethrin and kerosene compounds are associated with abdominal pain.
  - Multidrug consumption is associated with drowsiness and abdominal pain.
- Gastric lavage report (Fig. 6 and Table 7).
- Laboratory findings:
  - Elevated SGPT/SGOT: 22% (Fig. 7).
  - Electrolyte imbalances: 15% (mostly hyponatremia and hyperkalemia).
  - Hematological abnormalities in isolated cases.
- Hospitalization and outcomes:
  - Mean duration: 4 days (range: 2–8).
  - No mortality was recorded during the study period.
  - All patients were discharged after clinical improvement.
- Sample size
  - The sample size was calculated using OpenEPI software version 2.3.1.
  - At 95% confidence level.
  - At 20%, relative precision.
  - The sample size estimated is 80.

Table 1: Sex ratio

Female	57%
Male	43%

Source: Adapted from Bhat BNM, Pattanshetty SG, Chandra D, et al. A study on clinical profile of cases with organophosphorus poisoning at a tertiary care hospital. Eur J Mol Clin Med 2022.

Parameter	*Value*
Population size (for finite population correction factor or fpc) (N)	100
Hypothesized % frequency of outcome factor in the population (p)	50% ± 5
Confidence limits as % of 100 (absolute ± %) (d)	5%
Design effect (for cluster surveys—DEFF)	

Formula used $n = [DEFF \times Np(1-p)]/[(d^2/Z^2_{1-\alpha/2}) \times (N-1) + p(1-p)]$

Table 2: Marital status ratio

Marital status	*count*
Married	66
Unmarried	34

Source: Adapted from Bhat BNM, Pattanshetty SG, Chandra D, et al. A study on clinical profile of cases with organophosphorus poisoning at a tertiary care hospital. Eur J Mol Clin Med 2022.

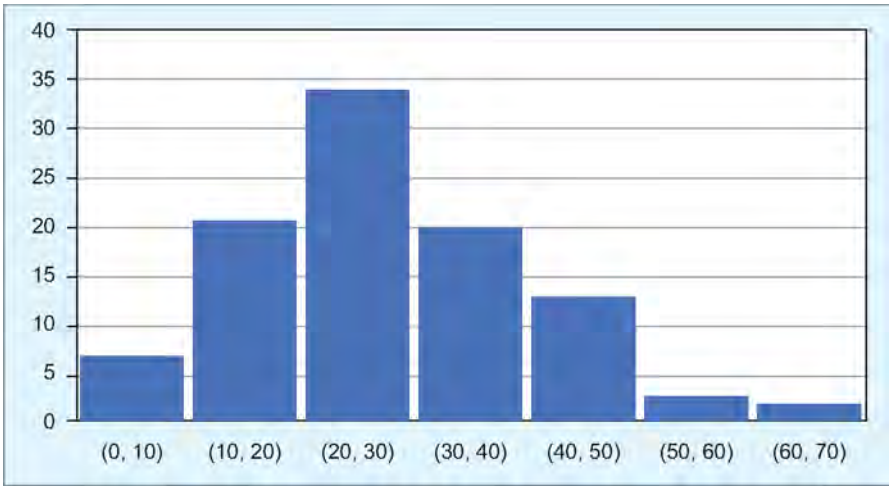


Fig. 1: Distribution of age group in the study

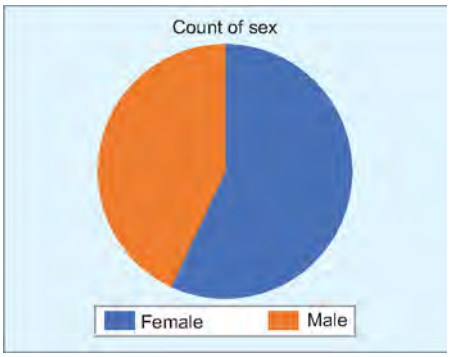


Fig. 2: Distribution of sex ratio



Fig. 3: Distribution of marital status

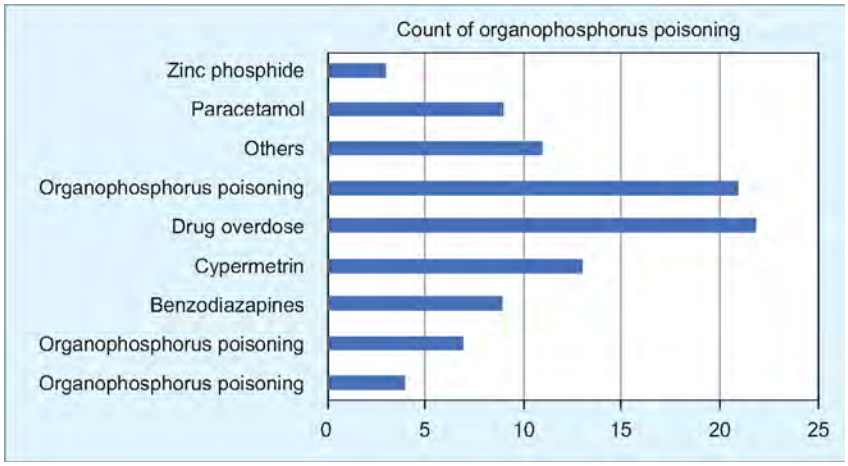


Fig. 4: Distribution of poisoning in the study

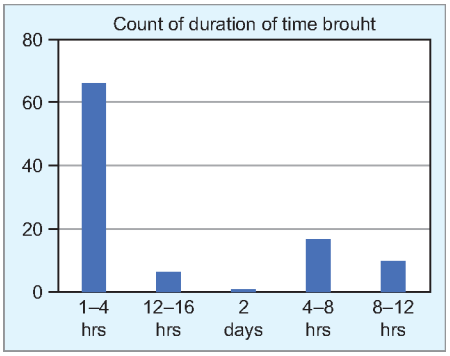


Fig. 5: Distribution of duration of time brought to the hospital

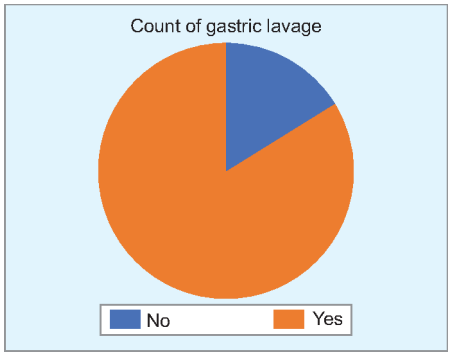


Fig. 6: Distribution of gastric lavage done

Table 3: Type of compound consumed

Organophosphorus poisoning	30%
Drug overdose	22%
Cypermethrin	16%
Paracetamol	9%
Benzodiazepines	9%
Zinc phosphide	3%
Others	11%

Source: Adapted from Bhat BNM, Pattanshetty SG, Chandra D, et al. A study on clinical profile of cases with organophosphorus poisoning at a tertiary care hospital. Eur J Mol Clin Med 2022.

Table 4: Risk of suicidal or accidental

Suicidal	85%
Accidental	10%
Unknown	5%

Source: Adapted from Bhat BNM, Pattanshetty SG, Chandra D, et al. A study on clinical profile of cases with organophosphorus poisoning at a tertiary care hospital. Eur J Mol Clin Med 2022.

Table 5: Number of patients brought in during that time duration

Duration of time brought	*Count of the duration of time brought*
1–4 hours	66
12–16 hours	6
2 days	1
4–8 hours	17
8–12 hours	10

Source: Adapted from Zaveri D, Quraishi SS, Rai S. Clinical profile, management, and outcome of acute poisoning in a tertiary care hospital: a hospital-based observational study. J Contemp Clin Pract 2025.

Table 6: Clinical symptoms

Vomiting	75%
Abdominal pain	30%
Drowsiness	20%
Seizures	5%

Source: Adapted from Bhat BNM, Pattanshetty SG, Chandra D, et al. A study on clinical profile of cases with organophosphorus poisoning at a tertiary care hospital. Eur J Mol Clin Med 2022.

Table 7: Gastric lavage was done or not

Yes	84
No	16

Source: Adapted from Zaveri D, Quraishi SS, Rai S. Clinical profile, management, and outcome of acute poisoning in a tertiary care hospital: a hospital-based observational study. J Contemp Clin Pract 2025

Data Collected

Record-based study on patients admitted as poisoning cases in the hospital casualty, inpatient, and outpatient departments under the department of general medicine. Data collected from the record department in MVJ Medical College and Research Hospital.

Discussion

The study confirms that poisoning remains a major health concern in rural India, especially among young adults with suicidal intent. The dominance of OP compounds reflects the rural agrarian setting. Early hospital arrival and prompt treatment likely contributed to the absence of fatalities.

Advanced age (>60 years) was also significantly linked to higher mortality, likely due to decreased physiological reserves and a greater burden of comorbidities, which increase susceptibility to the toxic effects of poisons. Socioeconomic status may affect mortality through multiple pathways, including delayed access to medical care, suboptimal nutritional status, and greater exposure to toxic substances in residential or occupational settings. These observations are in line with national suicide surveillance, which demonstrates a social gradient in poisoning-related suicides, and with epidemiological data from Indian hospitals showing that severe poisoning cases are predominantly observed among rural, low-income populations.[9]



Fig. 7: Distribution of SGOT and SGPT in the study population

The present study demonstrated that organophosphate pesticides were the most common agents of self-poisoning in South India, contrasting with findings from North India, where aluminum phosphide predominates. The rising incidence of self-poisoning may be attributed to multiple factors, including increasing unemployment, urbanization, weakening of family support systems, and economic instability. Suicide attempts among adults, particularly those aged 21–30 years, may result from unemployment, breakdown of familial support, failed romantic relationships, personal frustrations, inability to cope with immediate challenges, impulsive behavior, and stress related to work or family responsibilities.[10]

Conclusion

Acute poisoning, predominantly with suicidal intent, affects young adults in rural Bengaluru. Organophosphate compounds were the most common agents. The study highlights the critical role of early intervention and emphasizes the necessity of preventive public health measures.

Limitations

This study has certain limitations that should be considered while interpreting the findings. As a single-center study conducted at a tertiary care hospital in a rural setting, the results may not be fully generalizable to other rural regions, urban populations, or different healthcare systems. The hospital-based nature of the study, which included only admitted patients, may have introduced selection bias, as milder cases managed at primary or secondary healthcare facilities and individuals who did not seek medical attention were not represented. In the case of a retrospective design may have led to incomplete or missing data. Referral bias is also likely, given that tertiary care centers predominantly manage more severe and complicated cases, potentially resulting in an overestimation of disease severity. Furthermore, the absence of long-term follow-up restricts the assessment of outcomes and prognosis. Socioeconomic, environmental, and behavioral determinants may not have been fully evaluated.

Author Contributions

All authors made substantial contributions to the conception and design of the study. Dr. Minchu S Murthy was responsible for data collection, data analysis, and drafting of the manuscript. Dr. Suhas V contributed to study design, data interpretation, and critical revision of the manuscript for important intellectual content. Dr. Periyapattana Kumar supervised the study and provided overall guidance. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethical Approval

The study was approved by the Institutional Ethics Committee of MVJ Medical College and Research Hospital (approval number IEC/104/2023, dated 05/08/2023). The

requirement for informed consent was waived due to the retrospective nature of the study.

Acknowledgments

We acknowledge the staff and faculty of MVJ Hospital for their support in retrieving and verifying patient data.

Source of Support

None.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

A Comparative Study of Depression and Insomnia among Patients on Continuous Ambulatory Peritoneal Dialysis versus Hemodialysis

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Received: 06 January 2026; *Accepted:* 03 February 2026

Abstract

Background: Depression and insomnia are common yet under-recognized comorbidities in end-stage kidney disease (ESKD) patients on dialysis. Comparative data on their prevalence between hemodialysis (HD) and peritoneal dialysis (PD) are limited.

Objectives: To compare the prevalence and severity of depression and insomnia in patients undergoing HD and PD and identify clinical and biochemical correlates.

Materials and methods: A multicenter, cross-sectional study was conducted across armed forces hospitals in Northern India from November 2024 to January 2025. Adult ESKD patients on HD or PD were assessed using the Patient Health Questionnaire-9 (PHQ-9) for depression. Insomnia was assessed using a response to a battery of questions. Demographic, clinical, and laboratory data were analyzed.

Results: Of 188 patients screened (HD 105, PD 83), 51 HD (48.6%) and 37 PD (44.6%) patients had PHQ-9 scores ≥5, indicating depression. Most had mild depression (HD 25.7%; PD 22.6%). Moderately severe depression was present in a small number, with no difference between the dialysis modalities. Insomnia prevalence was comparable (HD 24.7%; PD 22.6%). Severe depression was associated with lower hemoglobin and albumin, especially in PD (albumin: 2.38 vs 3.10 gm/dL, $p = 0.03$).

Conclusion: Depression and insomnia are highly prevalent but underrecognized in dialysis patients. Dialysis modality did not affect the prevalence of depression or insomnia. Lower hemoglobin and albumin correlate with severe depressive symptoms.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1518

Introduction

Depression and insomnia represent major but often overlooked mental health challenges in patients with end-stage kidney disease (ESKD) undergoing dialysis. These psychiatric conditions significantly diminish quality of life, reduce adherence to therapy, and increase morbidity and mortality. While the prevalence of depression among dialysis patients is known to be higher than in the general population, comparative analyses of HD and PD populations are limited, especially in Indian settings. This study leverages the government-funded, multicenter armed forces dialysis program to fill this knowledge gap.

Chronic kidney disease (CKD) is a major and growing public health concern worldwide, with a rising number of patients progressing to ESKD that requires renal replacement therapy for survival. Dialysis remains the most commonly utilized treatment modality for ESKD, particularly in developing countries where access to renal transplantation is limited. Although advances in dialysis techniques have improved survival, patients continue to experience a substantial burden of physical, psychological, and social stressors that adversely affect their quality of life.[1]

Among the psychological complications associated with ESKD, depression is one of the most prevalent and debilitating disorders. The chronic nature of kidney failure, lifelong dependence on dialysis, dietary and fluid restrictions, financial constraints, and uncertainty regarding prognosis contribute significantly to emotional distress in these patients.[2] Several studies have reported that the prevalence of depression in dialysis patients is significantly higher than in the general population.[3] Depression in ESKD has been linked to poor adherence to treatment, increased hospitalization, reduced quality of life, and higher mortality rates.[4] Despite these serious consequences, depression often remains underdiagnosed and undertreated due to overlapping somatic symptoms of uremia and inadequate routine psychiatric screening in dialysis units.[5]

Sleep disturbances, particularly insomnia, are another common yet under-recognized problem in patients undergoing dialysis. Insomnia in ESKD may result from multiple factors, including uremia, anemia, pruritus, restless leg syndrome, altered circadian rhythm, anxiety, and the dialysis procedure itself.[6] Disturbed sleep leads to daytime fatigue, impaired concentration, and reduced functional capacity, further worsening overall well-being. Insomnia has also been identified as an independent predictor of poor quality of life and increased morbidity among dialysis patients.[7]

Depression and insomnia share a complex, bidirectional relationship. Insomnia can precipitate or worsen depressive symptoms, while depression itself can disrupt normal sleep patterns.[8] In patients with ESRD, this interaction becomes particularly relevant as both conditions are influenced by biological, psychological, and treatment-related factors. Failure to address either condition may perpetuate a cycle of worsening mental

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How to cite this article: Singh JI, Sangha SS, Datt B, *et al.* A Comparative Study of Depression and Insomnia among Patients on Continuous Ambulatory Peritoneal Dialysis versus Hemodialysis. J Assoc Physicians India 2026;74(6):46–49.

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health and sleep quality, leading to adverse clinical outcomes.

The type of dialysis modality may significantly influence the prevalence and severity of depression and insomnia. Hemodialysis (HD) is typically performed in hospital-based settings, requiring patients to attend dialysis sessions three times per week for several hours. This rigid schedule often interferes with occupational, social, and family life, contributing to feelings of dependency, loss of autonomy, and psychological distress.[9] Additionally, postdialysis fatigue, intradialytic complications, and fluctuations in biochemical parameters may further impair mood and sleep quality in hemodialysis patients.[10]

In contrast, continuous ambulatory peritoneal dialysis (CAPD) is a home-based dialysis modality that allows greater flexibility and independence. CAPD enables patients to perform dialysis exchanges themselves, potentially enhancing autonomy and improving psychological well-being.[11] However, CAPD is associated with its own set of challenges, including the burden of self-care, fear of peritonitis, body image concerns related to the peritoneal catheter, and sleep disruption due to nocturnal exchanges.[12] As a result, the psychological impact of CAPD on depression and insomnia remains multifaceted and varies among individuals.

Previous studies comparing depression and sleep disturbances between CAPD and hemodialysis patients have yielded inconsistent results. Some studies suggest a higher prevalence of depression and insomnia among hemodialysis patients, while others report no significant difference or even greater psychological burden among CAPD patients.[13] Variations in study design, assessment tools, cultural background, and patient characteristics may account for these discrepancies. Moreover, many studies have focused on either depression or sleep disorders in isolation, with limited research evaluating both conditions concurrently across different dialysis modalities.

In the Indian context, the burden of CKD and ESKD is increasing rapidly, while psychosocial aspects of dialysis care often remain neglected. Cultural stigma surrounding mental health, limited access to psychiatric services, and a lack of standardized screening further exacerbate the problem.[14] Understanding modality-specific differences in depression and insomnia is essential to developing holistic, patient-centered approaches to dialysis care.

Therefore, the present study aims to conduct a comparative assessment of depression and insomnia among patients undergoing continuous ambulatory peritoneal dialysis and those receiving maintenance hemodialysis, with the objective of improving early detection, guiding targeted interventions, and ultimately enhancing the quality of life of patients with ESKD.

Materials and Methods

Study Design and Population

A hospital-based, multicenter, cross-sectional comparative study was performed from November 2024 to January 2025 among ESKD patients attending armed forces dialysis units in North India. Inclusion criteria included age ≥ 18 years, dialysis duration ≥ 3 months, and life expectancy > 1 year. Exclusion criteria included preexisting psychiatric disorder, chronic active infections (e.g., TB, HIV), active malignancy, refusal or inability to provide consent.

Data Collection

Patients were consecutively recruited and administered the PHQ-9 (for depression) and the insomnia questionnaire by trained psychologists. To assess insomnia, a series of questions consisting of disturbance in falling asleep, maintenance of sleep, nonrefreshing sleep, and inadequate sleep duration in the past 2 weeks were administered. Insomnia was considered to be present if any of the symptoms were marked as frequent. Demographic and biochemical data (hemoglobin, albumin, and creatinine) were extracted from medical records.

Statistical Analysis

Descriptive statistics rendered means and standard deviations for continuous variables, frequencies for categorical variables. Chi-square and independent t-tests or Mann–Whitney *U* tests compared HD and PD groups. Logistic regression assessed predictors of depression and insomnia. Analysis was performed in SPSS v20. A *p*-value of 0.05 was considered significant.

Results

A total of 105 HD and 83 PD patients met the inclusion criteria ($n = 188$). The mean age was 45.2 ± 6.8 years in HD and 47.3 ± 8.5 years in PD patients, with a male predominance in both (Table 1). Both groups of patients were comparable in dialysis vintage and socioeconomic status indicators, including monthly income and crowding at home. Depression rates (by PHQ-9 at different severity levels) were similar in HD and PD patients (Table 2), with *p*-values > 0.05, indicating no statistically significant difference between groups for any category. Insomnia prevalence was also similar between HD and PD populations (24.7% vs 22.6%; $p = 0.77$), showing no significant difference (Table 3). Depression severity distribution is shown in Figure 1. Mild depression was the most frequent in both groups. No case of severe depression was detected in either of the groups. Various grades of depression were comparable in the two groups. We also analyzed the relationship of laboratory parameters with depression (Table 4). Lower hemoglobin showed statistically significant association with severe depression in both HD (*p*-value 0.04) and PD subgroup (*p*-value 0.01), and lower albumin showed statistically significant association with severe depression in the PD-subgroup (*p*-value 0.03) and a trend toward such an association in HD patients (*p*-value 0.10).

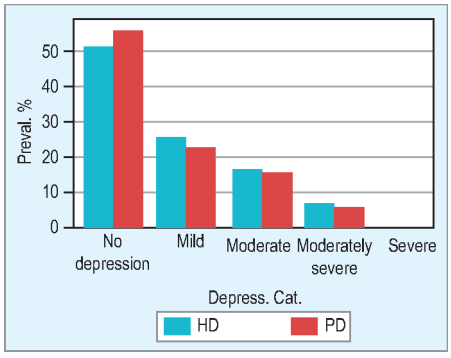


Fig. 1: Depression severity distribution

Table 1: Demographic data

Variable	*HD (n = 105)*	*PD (n = 83)*	*p-value*
Age (years, mean ± SD)	45.2 ± 6.8	47.3 ± 8.5	0.07
Gender (M:F)	62:43 (1.44)	48:36 (1.33)	0.68
Education			0.53
Primary school	6	2	
Secondary school	96	79	
Graduate	3	3	
Dialysis vintage [years, median (range)]	4 (1–7)	3.5 (1–6)	0.12
Monthly income (Rs, mean ± SD)	45000 ± 12000	42000 ± 10500	0.07
Family members in house [median (range)]	4 (2–7)	4 (2–6)	0.91

Table 2: Depression prevalence

Assessment	*HD (n = 105)*	*PD (n = 83)*	*p-value*
PHQ-9 ≥ 5 (depressed)	51 (47.9%)	37 (44.6%)	0.68
PHQ-9 (5–9) mild depression	27 (25.7%)	19 (22.6%)	0.58
PHQ-9 (10–14) moderate depression	17 (16.2%)	13 (15.7%)	0.92
PHQ-9 (15–19) moderately severe	7 (6.6%)	5 (6.0%)	0.87
PHQ-9 (≥ 20) severe	0	0	—

Table 3: Insomnia prevalence

Assessment	*HD (n = 105)*	*PD (n = 83)*	*p-value*
Insomnia	26 (24.7%)	19 (22.6%)	0.77

Table 4: Biochemical correlates

Variable	*No depression (Mean ± SD)*	*Moderate/severe depression (Mean ± SD)*	*p-value*
Hb HD, gm/dL	8.70 (0.56)	8.52 (0.34)	0.04
Hb PD, gm/dL	8.50 (0.49)	7.04 (0.71)	0.01
Albumin HD, gm/dL	3.20 (0.43)	2.69 (0.38)	0.10
Albumin PD, gm/dL	3.10 (0.35)	2.38 (0.31)	0.03

Discussion

In India, it is estimated that 14.3% of people are suffering from mental disorders.[15] Among them, depressive illness has the major contribution, with a prevalence of 3.3%. Depression and insomnia are also common in dialysis patients, including those on hemodialysis and peritoneal dialysis. Hemodialysis is generally performed in a clinical setting twice or thrice a week, leading to dependency on dialysis facilities, less patient control over the procedure, and may limit socialization due to its demanding schedule and the physical stress of the dialysis procedure. Patients often feel excessive fatigue, bear dietary restrictions, and financial burden, all of which can result in psychological distress and contribute to depressive symptoms.[16] On the other hand, peritoneal dialysis, which is home-based therapy, offers more flexibility and independence, minimizes some stressors associated with in-center therapy. However, PD patients may still experience significant psychological stress due to self-care pressure, fear of infection, and the psychological burden of chronic illness, which can contribute to anxiety and depression.

We used the PHQ-9 score to screen for depression, which is a validated screening tool for depression.[17] In our study, the prevalence of depression in patients on dialysis was higher than in the general population (HD = 47.9% vs PD = 44.6%). Using similar tools, the prevalence of depressive symptoms for CKD stage 5D was 39.3% in a meta-analysis by Palmer et al.[3] and approximately 50% as per a study by Zhang et al.[18] There was no significant difference between HD and PD patients for the prevalence of depression. A similar study by Nadort et al.[19] also found no difference in the prevalence of anxiety and depression between HD and PD. The comparable rates of depression between various modalities of renal replacement therapy suggest that differences in treatment delivery (center-based vs home-based) do not substantially influence depressive illness in this government-funded setting, likely due to the absence of financial burden. This data suggests that both hemodialysis and peritoneal dialysis patients have similar burdens of depression and insomnia.

Mild depression was the most common grade of depressive illness. There was a correlation between moderate to severe depression and lower hemoglobin and lower albumin. This difference was statistically significant, especially for PD ($p = 0.01$) than for HD patients ($p = 0.04$). Albumin was notably lower in moderately severe depressed PD patients ($p = 0.03$), but the difference in HD did not reach statistical significance ($p = 0.10$). Lower hemoglobin and albumin, markers of anemia and malnutrition/inflammation, are associated with more severe depression in dialysis patients, particularly for those on PD. This association suggests that the vicious cycle of poor nutrition contributes to poor mental health. This also suggests early treatment of anemia and hypoalbuminemia may significantly contribute to the mitigation of depressive illness and improve mental health.

Limitations of the study include a cross-sectional design, which precludes causality, and a small sample size. Use of self-report measures may have led to an overestimation of depression. The sample may not generalize beyond the unique armed forces cohort.

Conclusion

Depression and insomnia are frequent, underrecognized comorbidities in ESKD patients on both HD and PD. There is a need for routine mental health screening and targeted intervention, especially in patients with declining nutritional status. This is the first study from India to compare depression prevalence between patients on hemodialysis and peritoneal dialysis. The modality of dialysis does not correlate with depression or insomnia in our study, provided it is delivered free of cost.

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ANNOUNCEMENT

OFFICE BEARERS OF THE KARNATAKA CHAPTER OF ASSOCIATION OF PHYSICIANS OF INDIA FOR THE YEAR 2026–2027

Chairman	:	Dr B Ramesh
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ORIGINAL ARTICLE

Burden Trends and Future Projections of Acute Glomerulonephritis in India till 2040: An Analysis from the Global Burden of Disease Study

Hari S Meshram[1], Sanshriti Chauhan[2], Saurabh Puri[3], Sourabh Sharma[4]*, Narinder P Singh[5]

Received: 31 December 2025; *Accepted:* 03 February 2026

Abstract

Background: Glomerulonephritis (GN) remains a significant cause of kidney-related morbidity and mortality in low- and middle-income countries (LMICs). Despite advances in acute renal care in India, the national epidemiological trajectory and future burden of GN have not been comprehensively characterized.

Materials and methods: This study utilized Global Burden of Disease (GBD) 2023 data to estimate incidence, mortality, disability-adjusted life years (DALYs), years of life lost (YLLs), and years lived with disability (YLDs) due to GN in India from 1990 to 2023. Age-standardized rates (ASRs) were calculated per 100,000 population. Temporal trends were assessed using estimated annual percentage change (EAPC) from log-linear regression models. Future projections to 2040 were modeled using historical EAPC and population forecasts from the Institute for Health Metrics and Evaluation.

Results: From 1990 to 2023, India achieved a 75% reduction in age-standardized death rates (0.091–0.023 per 100,000; EAPC −4.42%, $p < 0.001$), while incidence remained stable (3.09 per 100,000; EAPC −0.05%, $p = 0.123$). DALYs declined 77% (2.49–0.58 per 100,000), driven by YLLs rather than disability (YLDs). Males experienced a 1.5-fold higher burden across all metrics. Marked geographic disparities emerged, with eastern states (Jharkhand, Chhattisgarh, Bihar) demonstrating 2–4-fold higher mortality than the national average despite similar incidence. By 2040, age-standardized death rates are projected to decline 52% further, but absolute incident cases will increase 18% (41,200–48,720) due to population growth.

Conclusion: India has achieved major reductions in GN mortality, yet stable incidence and persistent disability indicate that primary prevention and early detection remain inadequate. Without policy intervention, rising case numbers will place increasing demand on renal services. GN should be prioritized within national and subnational kidney health strategies as a sentinel indicator of health system preparedness in LMICs.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1550

Introduction

Acute glomerulonephritis (GN) is a leading cause of chronic kidney disease (CKD) and end-stage kidney failure worldwide, disproportionately affecting populations in low- and middle-income countries (LMICs), where access to early diagnosis and treatment remains limited.[1,2] Despite a global decline in mortality from communicable diseases, the burden of GN has persisted or transitioned toward chronic disability in several emerging economies, reflecting the unfinished agenda of renal health in the context of epidemiological and demographic transition.[3,4] India, home to nearly one-fifth of the world's population, represents a critical setting for understanding this transition, yet national estimates of GN burden that integrate incidence, mortality, disability-adjusted life years (DALYs), and projections of future trends have been limited.[5,6] Furthermore, existing GN studies in India have focused largely on biopsy cohorts or regional registries, which do not capture the full spectrum of disease across age groups, sexes, or the national population.[7,8]

This study is the first to use Global Burden of Disease (GBD) 2023 estimates and population-based forecasting models to provide a comprehensive, age- and sex-stratified assessment of historical temporal trends in burden of GN and to project the future burden to 2040. By combining historical trends with population projections, we provide novel insights into the evolving dynamics of GN in an LMIC context, where health systems are simultaneously tackling infectious diseases and rapidly escalating noncommunicable disease burden.[9] This approach not only quantifies the current renal health gap but also anticipates future service demands, informing national strategies for universal health coverage and Sustainable Development Goal (SDG) targets.

From a policy perspective, GN serves as a sentinel condition reflecting broader systemic issues, including environmental exposures, health care access inequities, and inadequate preventive care, which can be addressed through integrated kidney health strategies.[10,11] In contrast to prior research limited to static prevalence estimates, our analysis evaluates disease trajectory and models future burden under a "business-as-usual" scenario, offering actionable projections for policymakers. This uniquely positions GN as a critical tracer for renal health system readiness in India and other LMICs, with implications extending beyond nephrology to national health financing, workforce planning, and chronic disease prevention frameworks.

Materials and Methods

Ethics and Study Design

The study uses aggregated, de-identified, publicly available data, ethics approval was not required. We adhered to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). This study is a retrospective, population-based epidemiological analysis using publicly available data from the Global Burden of Disease Study 2023 (GBD 2023), coordinated by the Institute for Health Metrics and Evaluation (IHME).

Data Source

Data were extracted from the GBD Results Tool (https://ghdx.healthdata.org), which

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How to cite this article: Meshram HS, Chauhan S, Puri S, *et al.* Burden Trends and Future Projections of Acute Glomerulonephritis in India till 2040: An Analysis from the Global Burden of Disease Study. J Assoc Physicians India 2026;74(6):50–55.

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compiles standardized estimates using: (1) vital registration systems (limited coverage), (2) Sample Registration System (SRS), (3) verbal autopsy studies, (4) hospital administrative data, (5) published literature, and (6) regional covariates including Healthcare Access and Quality Index, Sociodemographic Index, and sanitation indicators. The analysis focused on India and examined the burden of acute glomerulonephritis (cause ID: 588) from 1990 to 2023. Acute glomerulonephritis was defined according to GBD 2023 case definitions, incorporating ICD-9 and ICD-10 codes (including N00-N01). GBD uses DisMod-MR 2.1, a Bayesian meta-regression tool, to ensure internal consistency across incidence, prevalence, remission, and mortality. For future projection, the data of population specific to India modeled till 2040 was derived from IHME

Data Collection

We extracted the following metrics: Incidence (number and age-standardized rate per 100,000 population); deaths; disability-adjusted life years (DALYs), the sum of years of life lost (YLLs) due to premature mortality and years lived with disability (YLDs) due to morbidity. Estimates were reported with 95% uncertainty intervals (UIs) derived from 1,000 posterior draws. All rates were age-standardized using the GBD world standard population. Data for the overall sex, as well as for male and female, were extracted. The data were collected from 1990 to 2023. For cross-sectional interpretation of age (2023), the age groups distribution selected was: <5 years, 5–14 years, 15–49 years, 50–69 years, and ≥70 years. The primary dataset (downloaded from October 25 to October 27, 2025) used in the study is openly available online for reproducibility and research: https://doi.org/10.5281/zenodo.17452285

Statistical Procedures

Age Group Contribution Analysis

For the year 2023, we calculated the proportional contribution of each age group to the national burden by dividing the absolute number of cases, deaths, DALYs, YLLs, or YLDs in each age category by the total national value for that metric. Results were expressed as percentages and visualized using stacked bar charts.

Trend and Sex Analysis

We estimated future trends in the incidence, mortality, disability-adjusted life years (DALYs), years of life lost (YLLs), and years lived with disability (YLDs) from acute glomerulonephritis in India from 2023 to 2040 using a log-linear trend projection model consistent with Global Burden of Disease (GBD) methodology. Age-standardized rates (ASRs) for both sexes combined were extracted from the GBD 2023 database for the period 1990–2023. The estimated annual percentage change (EAPC) for each metric was derived using a linear regression of the natural logarithm of the ASR against calendar year: . EAPC was calculated as: . The 95% uncertainty interval (UI) was computed from the standard error of β, using and . We also calculated EAPC for both sex also to estimate any statistical difference. The p-value for trend was derived from the *t*-test of the β coefficient, and a *p*-value < 0.05 was considered statistically significant, indicating a nonzero annual percentage change over time.

Future Trend Estimation

Future projections of ASR from 2024 to 2040 were generated by applying: . Baseline ASR uncertainty bounds in 2023 and the β uncertainty distribution were both propagated forward to obtain upper and lower uncertainty intervals. Projected absolute number of incident cases, deaths, DALYs, YLLs, and YLDs were calculated by multiplying the projected ASR by the projected Indian population for each year (2024–2040), obtained from the IHME Global Population Forecasts database (baseline/reference scenario). Absolute projections incorporated population uncertainty using the same propagation approach: . All projections assume no major policy or epidemiologic shift and represent a reference ("business-as-usual") scenario.

Statistical Analysis

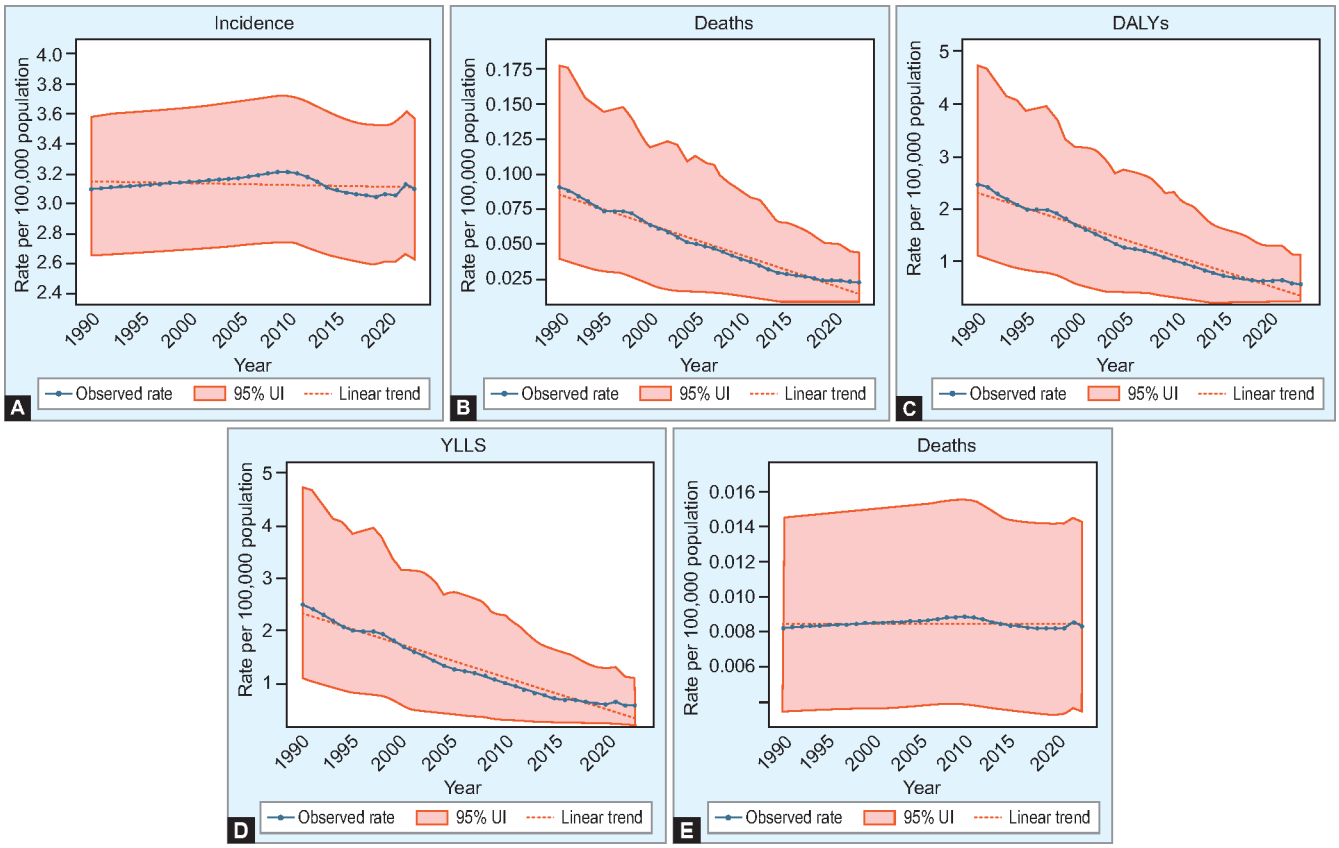
All analyses were performed using Python 3.10 (libraries: Pandas 2.0.3, NumPy 1.24.3, Statsmodels 0.14.0, Matplotlib 3.7.2, Seaborn 0.12.2) in Google Colaboratory. The analysis Python code and the required secondary data set to upload during code execution (updated for use from the primary dataset) are publicly available at https://doi.org/10.5281/zenodo.18000234 to ensure full reproducibility.

Results

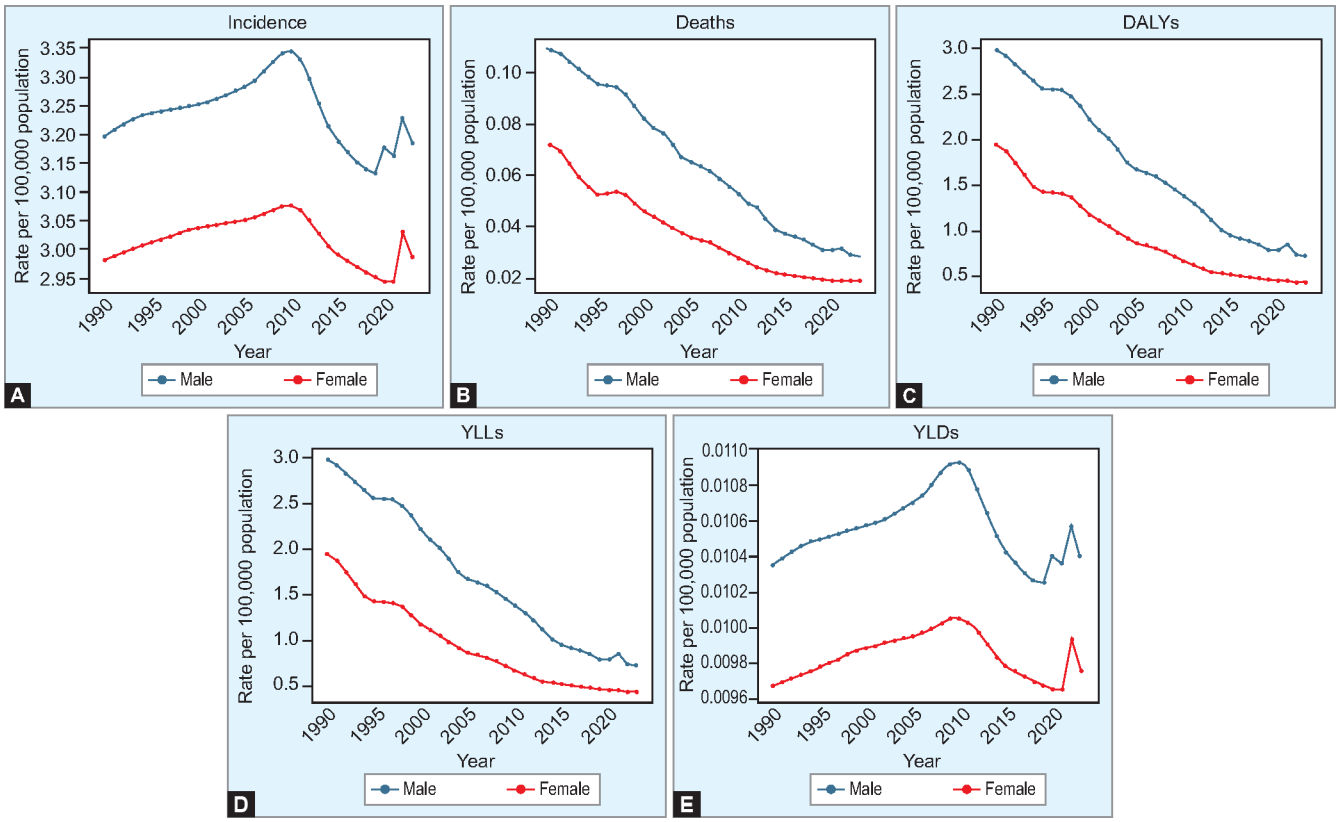
Figure 1 shows the temporal trends of national GN from 1990 to 2023. Between 1990 and 2023, India experienced substantial declines in acute GN mortality and DALYs. The ASR incidence remained stable at 3.09 per 100,000 in 2023 (EAPC −0.05%, 95% CI −0.12 to 0.01, $p = 0.123$), similar to 1990 levels. In contrast, the death rate declined dramatically from 0.091 per 100,000 in 1990 to 0.023 in 2023 (EAPC −4.42%, 95% CI −4.59 to −4.24, $p < 0.001$), representing a 75% reduction. DALYs similarly decreased from 2.49 to 0.58 per 100,000 (EAPC −4.41%, 95% CI −4.59 to −4.24, $p < 0.001$), driven predominantly by reductions in premature mortality (YLLs: EAPC −4.79%, $p < 0.001$) rather than disability (YLDs: EAPC 0.00%, $p = 0.908$). The YLD rates remained relatively constant and low throughout the study period (approximately 0.010 per 100,000), indicating that nonfatal disability burden has not undergone significant change (Fig. S1). These trends collectively demonstrate a sustained improvement in mortality outcomes with stable incidence and minimal change in long-term disability. The divergent trajectories of stable incidence but declining mortality indicate substantial improvements in acute GN case-fatality rates over the three-decade period. Figure S2 shows the age-specific pattern of GN. The 50–69-year age group accounted for the highest proportion of incidence (27.4%), DALYs (24.4%), and YLDs (27.9%). Individuals aged ≥70 years contributed the largest share of deaths (80.1%) and DALYs (60.0%), whereas those <14 years accounted for <5% of total DALYs.

On gender specific analysis, males showed a higher burden across all GN metrics throughout 1990–2023 (Fig. 2). In 2023, male-to-female ratios were 1.44 for incidence (3.65 vs 2.53 per 100,000), 1.56 for deaths (0.028 vs 0.018 per 100,000), and 1.52 for DALYs (0.74 vs 0.49 per 100,000). Temporal trends were similar between sexes, with both experiencing significant mortality declines (males: EAPC −4.51%, 95% CI −4.69 to −4.34, $p < 0.001$; females: EAPC −4.32%, 95% CI −4.52 to −4.13, $p < 0.001$) and stable incidence (males: EAPC −0.06%, $p = 0.684$; females: EAPC −0.04%, $p = 0.782$). The parallel trajectories suggest that improvements in acute renal care have benefited both sexes equally, though the persistent sex disparity in absolute burden indicates differential baseline risk that has remained unchanged over three decades.

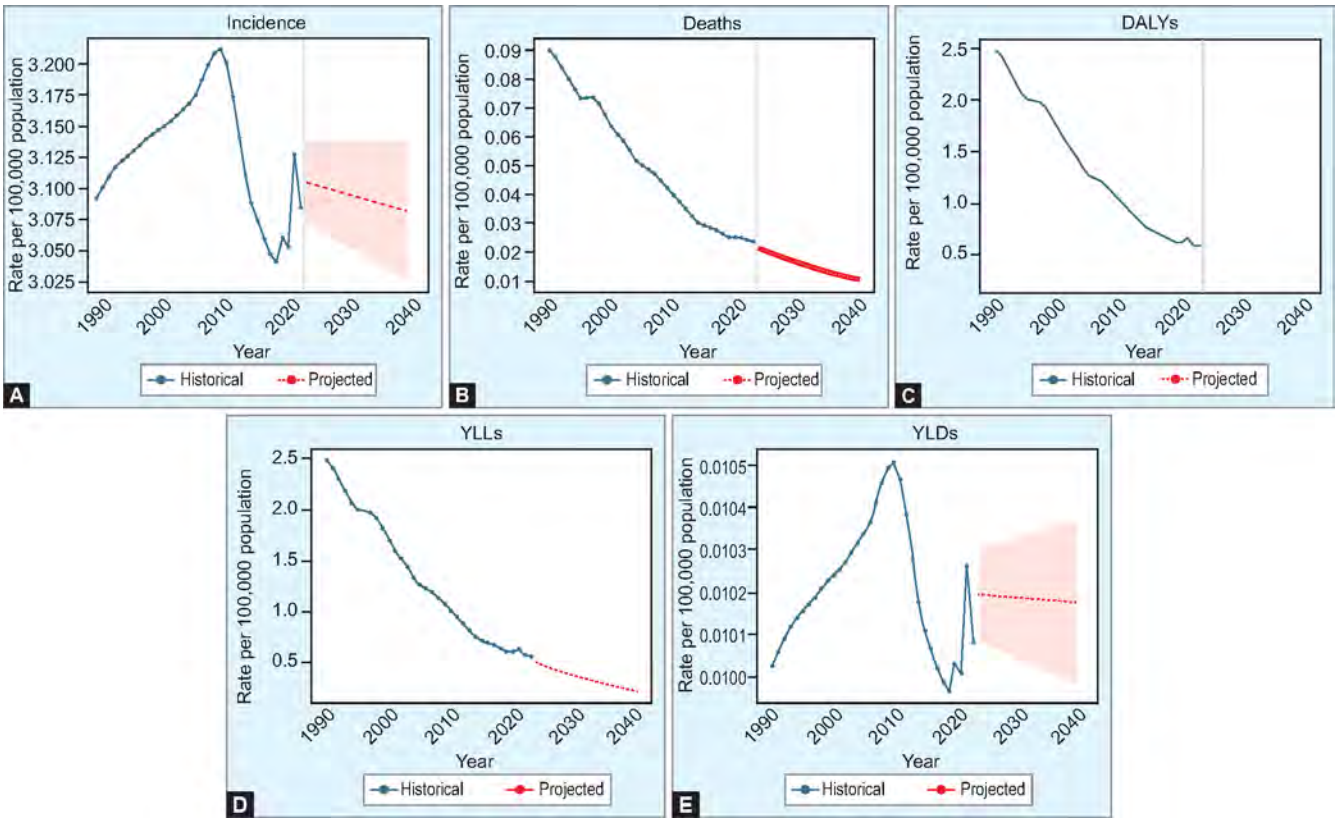
On future trend analysis, GN in India is expected to show divergent trends in ASR versus absolute case numbers through 2040 (Fig. 3). ASR incidence rates are projected to remain stable at approximately 3.06 per 100,000 (95% CI 2.58–3.57), while death rates are expected to decline further to 0.011 per 100,000 (95% CI 0.004–0.021) by 2040, representing a 52% reduction from 2023. DALY rates are projected to decrease from 0.58 to 0.26 per 100,000 (95% CI 0.10–0.51). However, due to population growth and demographic shifts, absolute incident cases are projected to increase from 41,200 in 2023 to 48,720 in 2040 (18% increase), and annual DALYs are projected to rise from 48,950 to 58,300 despite declining age-standardized rates. This discordance between improving rates and rising absolute burden reflects India's expanding and aging population, which will



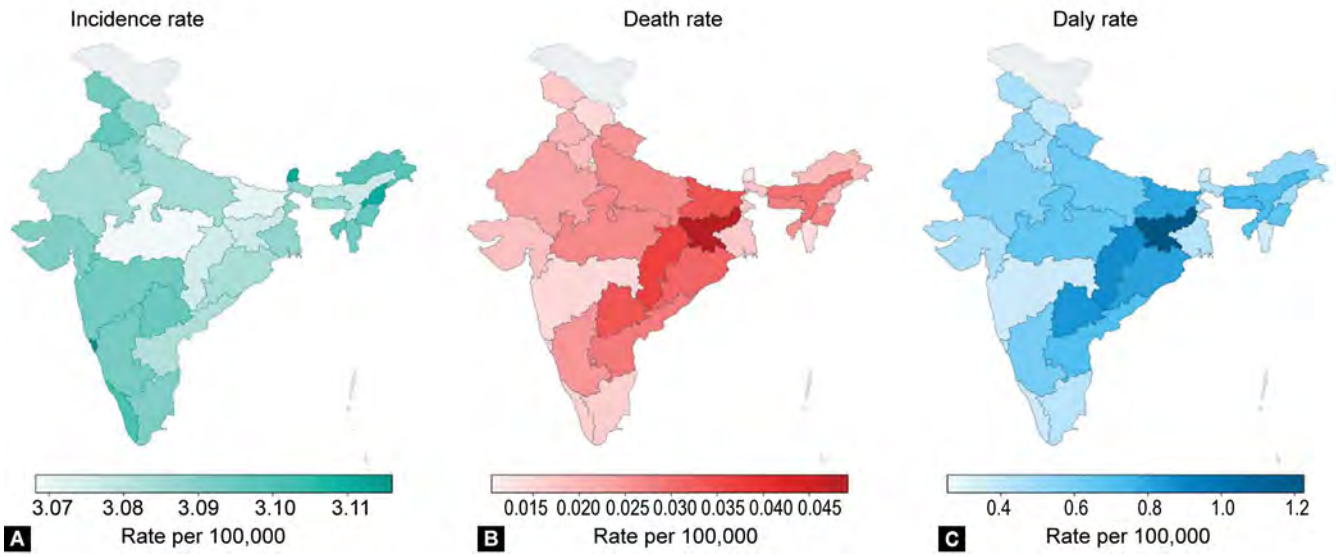
Figs 1A to E: Historical trends for acute glomerulonephritis in incidence, death, DALY, YLL, and YLD from 1990 to 2023



Figs 2A to E: Historical gender wise trends for acute glomerulonephritis in incidence, death, DALY, YLL, and YLD from 1990 to 2023



Figs 3A to E: Future projections for acute glomerulonephritis till 2040 in incidence, death, DALY, YLL, and YLD from 1990 to 2023



Figs 4A to C: Subnational-level snapshot for incidence, death, and DALY

place increasing demands on renal healthcare services even as case-fatality continues to decline.

Substantial state-level heterogeneity in GN burden was observed across India in 2023 (Fig. 4). Age-standardized death rates ranged 4.5-fold from 0.011 per 100,000 in Goa to 0.049 per 100,000 in Jharkhand. The five states with the highest mortality burden were Jharkhand (0.049), Chhattisgarh (0.037), Bihar (0.034), Telangana (0.034), and Odisha (0.031 per 100,000), predominantly clustered in eastern and central India. Similarly, DALY rates varied from 0.26 to 1.23 per 100,000, with eastern states demonstrating disproportionately high DALY burden. In contrast, incidence rates showed minimal interstate variation (3.07–3.12 per 100,000), suggesting differential case-fatality rather than differential disease occurrence.

Discussion

Acute glomerulonephritis in India is undergoing a clear epidemiological transition, characterized by declining mortality alongside stable incidence, suggesting improvements in acute care delivery without

commensurate advancements in primary prevention. The significant reduction in mortality and DALY rates from 1990 to 2023, predominantly attributable to reductions in premature death, aligns with broader trends in noncommunicable disease (NCD) control in low- and middle-income countries (LMICs).[12,13] However, the absence of a substantial decline in incidence and YLD rates indicates that upstream drivers, which included untreated streptococcal infections, environmental nephrotoxins, and limited access to early immunosuppressive therapy, continue to fuel disease onset.[14,15] This dual phenomenon, in which mortality falls, but disability persists, reflects a shift from acute fatality to chronic survivorship, thereby imposing a sustained burden on renal replacement services and the health financing system.

Comparison with Global and Regional Trends

The trends observed in India are consistent with patterns reported across South Asia and other LMICs, where glomerular diseases remain a leading cause of chronic kidney disease (CKD) despite declines in acute mortality.[16,17] Unlike high-income countries, where the incidence of GN has declined due to effective infection control, early biopsy programs, and immunomodulatory therapy access, India's stable incidence curve suggests persistent exposure to preventable risk factors.[18,19] The higher disease burden in males, as observed in our analysis, is also reflected in prior studies attributing sex differences to greater environmental exposure, occupational toxin contact, and possible hormonal influences on immune regulation.[18,20] This reinforces the need for region-specific strategies rather than adopting Western clinical models.

Health System and Policy Implications

The persistence of GN incidence despite improvements in mortality underscores a structural gap in India's kidney care model, where health policies have primarily focused on dialysis and transplant expansion rather than primary prevention and early detection.[21] As an LMIC with constrained health budgets and out-of-pocket expenditure exceeding 60% of total health spending,[22] India must reorient its renal care policy toward upstream interventions. This includes strengthening primary care pathways, integrating GN screening within existing NCD programs, expanding access to kidney biopsy and immunosuppressants under national schemes, and investing in public awareness regarding postinfectious glomerulonephritis. These interventions are critical not only for India but also for other South Asian and African LMICs where GN frequently affects young adults and contributes to long-term socioeconomic loss.

Another noteworthy finding is the subnational disparity in our analysis. We report marked geographic clustering of acute GN mortality in eastern and central states, where death rates exceeded the national average by 2- to 4-fold. This reflects disparities in healthcare access and renal care infrastructure rather than differential disease occurrence, as incidence rates remained uniform across states. These findings align with known health inequities in India, where Jharkhand, Chhattisgarh, Bihar, and Odisha have substantially lower per capita health expenditure and nephrology workforce density. The divergence between uniform incidence and heterogeneous mortality suggests that acute GN deaths are largely preventable, underscoring the need for targeted investments in emergency renal care capacity and dialysis infrastructure in high-burden states to achieve geographic equity in kidney health outcomes.

Future Trends and Global Health Relevance

Our projections indicate that while age-standardized rates may stabilize or decline modestly by 2040, the absolute number of cases will continue to rise due to demographic expansion and population aging. This trajectory mirrors the projected global rise in CKD burden and signifies that GN will remain a substantial contributor to kidney failure in LMICs unless preventive strategies are urgently implemented.[9] Achieving Sustainable Development Goal 3.4, which targets a one-third reduction in premature mortality from noncommunicable diseases by 2030, will require India to transition from a reactionary to a prevention-oriented GN policy framework.[23] Importantly, the methodological approach of combining epidemiologic trends with population projections provides an evidence-based model that can be adopted by other LMICs to forecast resource needs and guide kidney health planning. We highlight the strength of the study as the first comprehensive national and subnational acute GN burden and future projection of India. Notably, there was also some inherent limitation of the study. There is incomplete vital registration coverage (estimated at 86% for deaths, with significant urban-rural disparities) in India. Hence, GBD estimates involve substantial statistical modeling and should be interpreted with appropriate caution.

Conclusion

In summary, India's success in reducing glomerulonephritis-related mortality demonstrates effective acute care delivery. However, the stable incidence and rising disability burden indicate that mortality reduction has not translated into disease prevention. Glomerulonephritis should be recognized as a sentinel marker of health system performance in LMICs, a disease where preventable infections, inequitable access to diagnostic services, and delayed treatment converge to shape renal health outcomes. A paradigm shift toward community-level screening, environmental risk mitigation, universal biopsy access, and affordable immunosuppressive therapies is essential to reduce future burden. Without decisive policy action, the gains in survival may paradoxically fuel downstream growth in CKD and end-stage kidney disease, overwhelming dialysis and transplant capacity in India and similar LMIC contexts.

Declarations

Acknowledgments

This study utilized Global Burden of Disease (GBD) 2023 data.

Conflicts of Interests

None.

Source of Funding

None.

Availability of Data and Material

The clinical data and the study materials are available from the corresponding author on reasonable request.

Patient Consent Statement

None.

Ethical Clearance

Not applicable for this article. This study utilized Global Burden of Disease (GBD) 2023 data.

Author Contributions

All authors, HSM, SC, SP, SS, and NPS, were involved in the literature search, planning, conducting, and editing of the study, and in writing the original draft of the manuscript. All the authors have agreed with the submitted manuscript. SS is the corresponding author and guarantor for all.

Supplementary Material

The Supplementary Figures S1 and S2 are available online on the journal website.

Fig. S1: Trends of percentage of YLL and YLD due to acute glomerulonephritis over 1990–2023

Fig. S2: Age wise distribution of all metrics due to acute glomerulonephritis of 2023

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ORIGINAL ARTICLE

Imeglimin in Indian Adults with Type 2 Diabetes: A Prospective Multicenter Real-world Cohort Study of Prescription Patterns, Glycemic Change, and Safety

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Received: 15 April 2026; *Accepted:* 12 May 2026

Abstract

Background: Imeglimin is a novel oral glucose-lowering agent targeting mitochondrial dysfunction. While randomized trials demonstrate its efficacy, real-world data in diverse populations remain limited. We evaluated the effectiveness, safety, and utilization patterns of imeglimin in Indian adults with inadequately controlled type 2 diabetes (T2D).

Materials and methods: This prospective, multicenter, observational cohort study enrolled adults with T2D newly initiated on imeglimin across 11 Indian centers. Participants were followed for 6 months. The primary outcome was the change in HbA1c from baseline. Effectiveness was analyzed in a complete-case cohort using linear mixed-effects models to adjust for covariates, while safety was assessed in all participants with at least one post-baseline evaluation.

Findings: The baseline cohort included 736 participants (mean age 52.4 years, mean baseline HbA1c 9.8%). Imeglimin was predominantly prescribed as an add-on therapy (84.6%), most frequently alongside three or more other agents (57.9%). In the complete-case cohort ($n = 337$; 46% of baseline), adjusted mean HbA1c decreased by 1.28% (95% CI −1.41 to −1.14) at 3 months and 2.27% (−2.41 to −2.13) at 6 months ($p < 0.001$). Greater reductions were significantly associated with higher baseline HbA1c. Adverse events were reported in 9.9% of the safety cohort ($n = 573$), most commonly mild gastrointestinal symptoms (5.2%). Hypoglycemia occurred in 1.2%. Two cases of lactic acidosis were reported, though causality with imeglimin was not established.

Conclusion: In routine clinical practice, the initiation of imeglimin among Indian adults with T2D was associated with clinically meaningful reductions in HbA1c, fasting plasma glucose, and postprandial glucose over a 6-month period, alongside a favorable safety profile. These real-world findings support the clinical utility and tolerability of imeglimin as an effective therapeutic option for glycemic management in this population. Future randomized controlled trials with extended follow-up are warranted to establish definitive causal treatment effects and evaluate long-term clinical outcomes.

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How to cite this article: Saboo B, Samajdar SS, Maheshwari A, *et al.* Imeglimin in Indian Adults with Type 2 Diabetes: A Prospective Multicenter Real-world Cohort Study of Prescription Patterns, Glycemic Change, and Safety. J Assoc Physicians India 2026;74(6):56–65.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1548

Introduction

Type 2 diabetes (T2D) is a chronic, progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and increased hepatic glucose output. As per the International Diabetes Federation (IDF), diabetes is a major global health challenge, affecting over 589 million adults worldwide and projected to reach 853 million by 2050.[1] India has an estimated 101 million adults with diabetes and 136 million with prediabetes, making it the country with the second-highest burden globally.[2]

Despite the availability of multiple oral glucose-lowering agents (OGLAs), glycemic control remains suboptimal in routine clinical practice. Many people fail to achieve individualized glycemic targets due to progressive β-cell dysfunction, adverse effects, and therapeutic inertia.[3,4] Importantly, currently available therapies predominantly target isolated components of glucose dysregulation and do not adequately address the interconnected defects of insulin resistance, impaired insulin secretion, and underlying cellular energetic dysfunction.

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Mitochondrial dysfunction is increasingly recognized as a central determinant in the pathophysiology of T2D, linking impaired β-cell function, heightened oxidative stress, reduced ATP generation, and dysregulated hepatic glucose metabolism.[5–7] Defective mitochondrial quality control leads to the accumulation of dysfunctional mitochondria, contributing to impaired insulin secretion and increased β-cell apoptosis.[7] Targeting this axis offers a mechanistically integrated therapeutic approach. Imeglimin, a first-in-class "glimin," directly modulates mitochondrial bioenergetics, improves mitochondrial integrity, and reduces oxidative stress, thereby restoring glucose-stimulated insulin secretion, enhancing insulin sensitivity, and suppressing β-cell apoptosis.[5,8–10]

This mechanism is particularly relevant to the Asian Indian phenotype, characterized by early β-cell dysfunction, increased visceral adiposity, and heightened cardiometabolic risk despite relatively lower body mass index.[8] These features are closely linked to mitochondrial inefficiency and metabolic inflexibility. Clinical trials, including the TIMES program, have demonstrated that imeglimin improves glycemic control with favorable tolerability both as monotherapy and in combination with other agents.[9,11,12] Early Indian real-world evidence further suggests clinically meaningful reductions in HbA1c and fasting glucose, including in patients intolerant to metformin.[13] Imeglimin received regulatory approval in India in 2022, expanding therapeutic options for patients inadequately controlled on existing therapies. However, large prospective real-world data from diverse Indian populations remain limited. This study, therefore, aims to evaluate the effectiveness and safety of imeglimin over 6 months in routine clinical practice, addressing an important evidence gap.

Materials and Methods

Study Design and Population

This was a prospective, multicenter, observational cohort study conducted at 11 study sites (primary and secondary care settings) across eight cities, covering all zones of India. The data were collected from December 2023 to June 2025. After enrollment, participants were followed up for 6 months.

The study included adult participants (≥18 years) with a clinical diagnosis of T2D who were newly initiated on imeglimin either as monotherapy or in combination with other OGLAs. Participants below 18 years of age and those diagnosed with other forms of diabetes, including type 1 diabetes (T1D), gestational diabetes mellitus (GDM), or maturity-onset diabetes of the young (MODY), were excluded.

Sampling and Sample Size Achieved

All consecutive eligible individuals who met the inclusion criteria and visited the study site for routine care during the recruitment period, and who provided informed consent, were included. The enrollment of consecutive patients was strictly implemented to minimize selection bias and ensure a representative real-world cohort.

Participant flow and attrition were documented using a CONSORT-style flow diagram (Fig. 1).

Analysis Sets

- *Baseline cohort*: All participants initiated on imeglimin at baseline (n = 736).
  - *3-month case cohort*: Participants with baseline and follow-up HbA1c available at 3 months from baseline (n = 475).
- *Complete-case cohort*: Participants with baseline and follow-up HbA1c available at 3 months and 6 months (n = 337).
- *Safety cohort*: Participants with at least one post-baseline safety assessment (n = 573).

Data Collection Instrument and Variables

A customized electronic case record form (MEDEVA eCRF) was developed specifically for this study to ensure standardized and comprehensive data collection. The eCRF captured key demographic information [age, gender, body mass index (BMI)], relevant comorbidities, detailed medical history, and ongoing pharmacological treatments, including antidiabetic and concomitant medications. It also included fields to record the duration of diabetes, previous antidiabetic therapy patterns, and any changes in lifestyle interventions (e.g., diet and exercise) during the study period. Furthermore, the eCRF documented whether background antidiabetic therapies remained stable or were modified during follow-up, as well as any dose escalation or de-escalation of imeglimin or concomitant medications.

As this was a real-world observational study, laboratory assessments (e.g., HbA1c, FPG, PPG) were performed at local site laboratories according to their standard institutional methods and routine clinical practice, rather than using a centralized laboratory. Data entry was performed in real time during participants' visits, with all information obtained as part of routine clinical care to minimize additional burden. Built-in validation checks in the eCRF reduced data entry errors and ensured completeness for subsequent analysis.

Safety data included all AEs and SAEs reported during the observation period, along with their severity, relationship to imeglimin as assessed by the investigator, and actions taken. Adverse event collection was both spontaneous (as reported by the patient) and actively solicited by the investigator at each follow-up visit. Hypoglycemia was reported by participants and was defined as blood glucose <70 mg/dL or symptomatic events resolving with carbohydrate intake.

Ethics Committee Approval

The study received ethics approval from the Institutional Human Ethics Committee–Udyaan Healthcare (Registration number: ECR/1300/Inst/UP/2019).

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (revised by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and adhered to the International Council for Harmonization Good Clinical Practice (ICH-GCP) guidelines [E6 (R2), Step 6]. All procedures complied with the applicable local regulatory requirements, including the Good Clinical Practices for Clinical Research in India (2004, CDSCO), the New Drugs and Clinical Trials Rules (2019) and their subsequent amendments, as well as the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017).

Informed Consent and Data Privacy

Informed consent was obtained from all study participants prior to their enrollment.

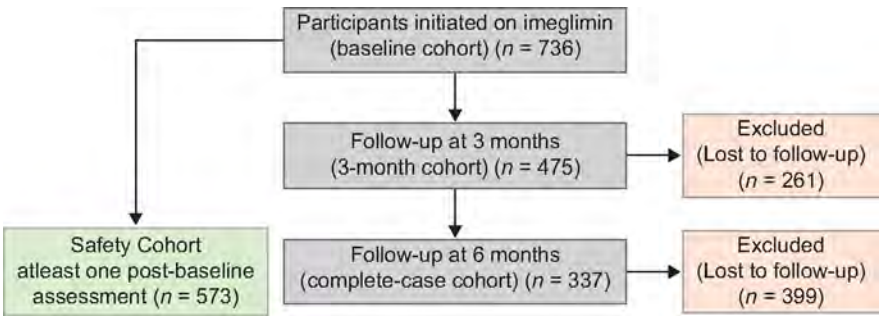


Fig. 1: Flow of participants through the study, including baseline cohort, 3-month cohort, complete-case cohort, and safety analysis set

Participants were fully informed about the nature, purpose, and procedures of the study, including any potential risks or benefits involved. Physicians maintained confidentiality in accordance with their agreement; participants' IDs are not identifiable to external parties. Data usage was restricted solely to this study, with any further use contingent on additional written permission to protect privacy and uphold ethical standards.

Statistical Analysis

The collected data underwent aggregate-level analysis (de-identified with respect to participant or site) using Python software. Categorical data were presented as frequencies and proportions, with statistical significance assessed using the Chi-square test. Continuous variables (e.g., HbA1c, FPG, PPG, weight, BMI) were summarized using means and standard deviations (SD) at each time point.

Primary effectiveness analysis was based on complete-case longitudinal data. Missing outcome data were not imputed. To evaluate changes in continuous clinical and laboratory parameters across all three time points simultaneously (baseline, 3 months, and 6 months), linear mixed-effects models were utilized. This approach ensured that all available repeated measures contributed to the analysis without needing a complete follow-up. Furthermore, a complete-case sensitivity analysis was performed to assess the robustness of the primary findings.

Normality of within-participants differences was assessed using the Shapiro–Wilk test. Although some deviations from normality were observed, the large sample sizes ($N \approx 337$) allowed reliance on the central limit theorem, under which the sampling distribution of the mean difference approximates normality. Accordingly, specific within-patient changes between individual time points (baseline to 3 months, baseline to 6 months, and 3 to 6 months) were evaluated using paired *t*-tests, with results summarized as mean (SD), mean differences with 95% confidence intervals, and two-sided *p*-values.

No formal sample size calculation was mandated; sample size was determined by feasibility and the number of participants enrolled across participating centers. Subgroup analysis was performed by age, gender, duration of diabetes, and baseline HbA1c value. This was exploratory in nature and therefore needs to be interpreted with caution, given the limited power. Visualizations were created using Microsoft Office. Statistical significance was determined using standard hypothesis testing with a threshold of a two-sided *p*-value less than 0.05. All tests adhered to methodological guidelines to ensure the validity and reliability of the study's conclusions.

Results

Patient Profile (Baseline Cohort, *n* = 736)

A total of 736 participants with T2D were included in the baseline analysis. The mean age of the study population was 52.4 ± 11.4 years. Males constituted 56.9% of the cohort, while females accounted for 43.1%. The mean BMI was 26.7 (4.7) kg/m^2. The mean baseline HbA1c was 9.8 ± 2.2% for the enrolled cohort, and the mean systolic and diastolic blood pressures were 131.8 ± 13.9 mm Hg and 81.3 ± 9.1 mm Hg, respectively. The mean duration of T2D was 6.7 ± 4.7 years, and 32.9% of participants reported a family history of T2D.

Diabetes-related complications were present in 24.3% of participants, with neuropathy being the most common (19.0%), followed by nephropathy (4.8%), retinopathy (3.9%), diabetic foot (3.1%), and cardiovascular complications (1.5%). Regarding comorbid conditions, hypertension was the most prevalent (32.3%), followed by dyslipidemia (9.2%) and obesity (5.4%). Other comorbidities, including chronic kidney disease, heart failure, ischemic heart disease, liver disorders, and cerebrovascular accident, were infrequently reported (Table 1).

Prescription Patterns of Imeglimin (Baseline Cohort, *n* = 736)

At baseline, 62% of participants were initiated on imeglimin 1000 mg and 36.8% on imeglimin 500 mg. Regarding treatment patterns, 15.4% received imeglimin as monotherapy, whereas for 84.6%, imeglimin was an add-on therapy to existing OGLAs. In 57.9% participants, imeglimin was added to three or more OGLAs, followed by OGLAs plus insulin (15.8%), two OGLAs (6.7%), and one OGLA (4.2%). Concomitant drug class use showed that metformin (72.6%), sulfonylureas (69.7%), and DPP-4 inhibitors (59.2%) were the most frequently co-prescribed medications, followed by SGLT2 inhibitors (41.6%),

Table 1: Baseline cohort—demographic characteristics

Characteristics	*Base (N = 736)*
Age (years)	
18–30	20 (2.7)
31–40	109 (14.8)
41–50	196 (26.6)
51–60	237 (32.2)
61–70	136 (18.5)
≥70	38 (5.2)
Mean (SD)	52.4 (11.4)
Gender	
Female	317 (43.1)
Male	419 (56.9)
BMI, mean (SD)	26.7 (4.7)
HbA1c (%), mean (SD)	9.8 (2.2)
Blood pressure, systolic/diastolic (mm Hg), mean (SD)	131.8 (13.9)/81.3 (9.1)
Duration of T2D (years), mean (SD)	6.7 (4.7)
Presence of family history of T2D (yes), n (%)	242 (32.9)
Complication due to T2D, *n* (%)	
Neuropathy	140 (19.0)
Nephropathy	35 (4.8)
Retinopathy	29 (3.9)
Diabetic foot	23 (3.1)
Cardiovascular complications	11 (1.5)
None	557 (75.7)
Comorbid conditions, *n* (%)	
Hypertension (HTN)	238 (32.3)
Dyslipidemia (DL)	68 (9.2)
Obesity	40 (5.4)

BMI, body mass index; DL, dyslipidemia; HbA1c, glycated hemoglobin; HTN, hypertension; SD, standard deviation; T2D, type 2 diabetes.

Table 2: Prescription details of imeglimin initiation at baseline (baseline cohort, *n* = 736)

Variables	*Base (N = 736)*
Imeglimin strength at baseline, *n* (%)	
Imeglimin 1000 mg BD	152 (20.7)
Imeglimin 1000 mg OD	304 (41.3)
Imeglimin 500 mg BD	15 (2.0)
Imeglimin 500 mg OD	256 (34.8)
Imeglimin 1000 mg – dosage not specified	3 (0.4)
Imeglimin 500 mg – dosage not specified	6 (0.8)
Imeglimin monotherapy and combination therapy, *n* (%)	
Imeglimin monotherapy	113 (15.4)
Imeglimin + 1 OGLA	31 (4.2)
Imeglimin + 2 OGLAs	49 (6.7)
Imeglimin + 3 OGLAs	146 (19.8)
Imeglimin + >3 OGLAs	281 (38.1)
Imeglimin + OGLA + insulin	116 (15.8)
Class of OGLA in combination with imeglimin, *n* (%)	
Metformin	534 (72.6)
SGLT2i	306 (41.6)
DPP4i	436 (59.2)
SU	513 (69.7)
GLP-1 RA	3 (0.4)
TZD	162 (22.0)
AGI	221 (30.0)

alpha-glucosidase inhibitors (30.0%), and thiazolidinediones (22.0%) (Table 2).

Sensitivity Analysis: Completers (Complete Case Cohort *n* = 337) vs Noncompleters (*n* = 399)

A comparison of baseline characteristics between study completers (*n* = 337) and noncompleters (*n* = 399) revealed no significant differences in gender, BMI, or duration of T2D. However, completers were significantly younger (mean 50.9 vs 53.6 years, $p = 0.001$) and had a higher prevalence of diabetes-related complications (37.1% vs 13.5%, $p < 0.001$). Glycemic control at baseline was significantly worse among completers, who exhibited higher mean HbA1c (10.2% vs 9.4%, $p = 0.001$) and fasting plasma glucose (194.7 vs 171.0 mg/dL, $p < 0.001$). Completers were prescribed more intensive baseline regimens and were less likely to receive imeglimin as monotherapy (6.2% vs 23.1%) and more likely to require combinations with more than three oral antidiabetic drugs (42.4% vs 34.6%, $p < 0.001$) (Table S1).

Effectiveness of Imeglimin (Complete Case Cohort *n* = 337)

Glycemic Parameters–Unadjusted Change in HbA1c Over Time

HbA1c levels showed a statistically significant and sustained reduction from baseline, with a mean change of −1.28% at the 3-month follow-up (95% CI: −1.4% to −1.15%; $p < 0.001$) and −2.27% at the 6-month follow-up (95% CI: −2.45% to −2.09%; $p < 0.001$). A further significant decrease was observed −0.99% decrease between the 3-month and 6-month assessments (95% CI: −1.08% to −0.91%; $p < 0.001$), indicating continued decline in HbA1c over 6 months (Fig. 2 and Table S2).

Glycemic parameters–Change in HbA1c (Adjusted Analysis: Linear Mixed-effects Regression Model)

To examine HbA1c change while accounting for individual patient heterogeneity and adjusting for demographic, anthropometric, and clinical covariates, a linear mixed-effects regression model was fitted with a random intercept at the patient level.

A linear mixed-effects model demonstrated a significant reduction in HbA1c over time. Compared to baseline, HbA1c decreased by −1.28% at 3 months (95% CI: −1.41 to −1.14; $p < 0.001$) and −2.27% at 6 months (95% CI: −2.41 to −2.13; $p < 0.001$), indicating a progressive and sustained improvement in glycemic control.

Baseline HbA1c showed a strong association with treatment response, with patients in higher baseline HbA1c categories experiencing significantly greater reductions. Compared to patients with HbA1c <7%, those with baseline HbA1c of 8–8.99%, 9–9.99%, and ≥10% demonstrated additional reductions of −0.66%, −0.87%, and −1.51%, respectively (all 0.001), indicating a clear dose-response relationship.

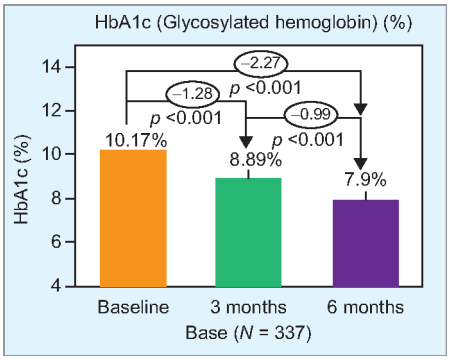


Fig. 2: HbA1c values at baseline and follow-up

No statistically significant associations were observed for BMI, duration of diabetes, insulin use, or number of backgrounds OGLAs, suggesting that the reduction in HbA1c was consistent across these patient subgroups. A low-to-moderate patient-level random effect variance (0.238) has been observed (Table 3).

Other Glycemic Parameters–FPG and PPG

Mean FPG reduced by −48.22 mg/dL at the 3-month follow-up (*n* = 295, 95% CI: −53.56 mg/dL to −42.89 mg/dL; $p < 0.001$) and by −75.19 mg/dL at the 6-month follow-up (95% CI: −81.72 mg/dL to −68.65 mg/dL; $p < 0.001$). PPG showed a change of −76.59 mg/dL (*n* = 295, 95% CI: −85.1 mg/dL to −68.08 mg/dL; $p < 0.001$) and −112.97 mg/dL at the respective follow-ups (*n* = 295, 95% CI: −122.63 mg/dL to −103.3 mg/dL; $p < 0.001$) (Table 4).

Weight and BMI Changes

Body weight and BMI remained stable over 6 months of follow-up, with no statistically significant changes observed between baseline and 3 months, baseline and 6 months, or 3 and 6 months (all $p > 0.05$) (Table 5).

Safety and Tolerability of Imeglimin

The imeglimin regimen was generally well tolerated, with an acceptable safety profile over the treatment period. No SAEs were reported during the follow-up period, and no study participants discontinued the study drug because of AEs or intolerability. The majority of participants reported no complaints (90.1%). Nausea or vomiting was the most frequently observed, affecting 5.2% of patients. Gastrointestinal problems and urinary tract infections were each reported by 1.4%. Hypoglycemia was reported in 1.2% of participants (Table 6).

In two cases of lactic acidosis, a serious adverse event (SAE) was reported; additional

information was sought from the site investigators.

Case 1: A 46-year-old female, on glimepiride, metformin, and imeglimin, presented with 1-day vomiting post-travel. She was dehydrated; labs showed glucose 322 mg/dL, urine 1+ ketones, and mildly elevated lactate (3.2 mmol/L). Lactic acidosis attributed to dehydration with metformin contribution, not imeglimin. IV fluids resolved symptoms; antidiabetics were held temporarily and restarted.

Case 2: A 58-year-old female, on imeglimin 1000 mg twice a day, Dapagliflozin 10 mg, and Humalog mix 50 100 IU/ML injection for management of T2D, presented with severe UTI infection, acidosis diagnosed as DKA, and dehydration post-travel. The patient was admitted to the hospital, and an insulin infusion was initiated as rescue therapy. Patient stabilized and switched completely to insulin therapy. Imeglimin was stopped. Lactic acidosis attributed to severe infection and DKA, possibly due to poor adherence during travel and SGLT2i.

The site principal investigator reported both cases, given the participant's enrollment in the study. However, causality with imeglimin use was definitively excluded in both instances.

Table 3: Prescription details of imeglimin initiation at baseline (complete case cohort, *n* = 337)

Variable	*Estimate (β)*	*95% CI*	*p-value*
Time			
3 months vs baseline	−1.28	(−1.41, −1.14)	<0.001
6 months vs baseline	−2.27	(−2.41, −2.13)	<0.001
Age group (years)			
50–59 vs <50	0.14	(−0.05, 0.33)	0.141
≥60 vs <50	0.35	(0.13, 0.57)	0.002
Gender			
Male vs female	0.05	(−0.11, 0.21)	0.518
BMI group			
Healthy vs underweight	0	(−0.53, 0.52)	0.988
Overweight vs underweight	0.05	(−0.47, 0.57)	0.857
Obesity I vs underweight	0.14	(−0.36, 0.64)	0.575
Obesity II vs underweight	0.17	(−0.37, 0.71)	0.527
Diabetes duration			
6–10 years vs >10 years	0.23	(−0.04, 0.49)	0.095
≤5 years vs >10 years	0.07	(−0.21, 0.35)	0.626
HbA1c groups at baseline			
7–7.99% vs <7%	0.01	(−0.39, 0.41)	0.954
8–8.99% vs <7%	−0.66	(−1.04, −0.28)	0.001
9–9.99% vs <7%	−0.87	(−1.26, −0.49)	0.001
≥10% vs <7%	−1.51	(−1.86, −1.16)	0.001
Insulin use			
Yes vs No	−0.04	(−0.28, 0.20)	0.753
Number of OGLAs			
Mono vs dual	0.10	(−0.34, 0.53)	0.668
Triple vs dual	0.15	(−0.27, 0.58)	0.480
Quadruple vs dual	0.07	(−0.31, 0.44)	0.722
Five vs dual	0.20	(−0.18, 0.59)	0.293
Six vs dual	0.11	(−0.29, 0.51)	0.577
Seven vs dual	0.19	(−0.70, 1.09)	0.671
Random effect (patient)	Variance = 0.238		

Discussion

This prospective, multicenter real-world study demonstrates that imeglimin produces substantial glycemic improvements in Indian adults with inadequately controlled T2D, achieving adjusted HbA1c reductions of 1.28% at 3 months and 2.27% at 6 months. The drug was well-tolerated with low adverse event rates (9.9%) and minimal hypoglycemia (1.2%). These results exceed typical randomized trial efficacy; however, the observational design, 54% attrition, and high baseline HbA1c necessitate cautious interpretation. The study reveals that imeglimin is currently reserved for late-stage use despite a mechanistic rationale for earlier positioning in the Asian Indian phenotype.

Mechanistic Rationale: Two Concerns and a Single Solution

The substantial glycemic improvements observed in this cohort can be contextualized through imeglimin's unique mechanism of action, which addresses the core pathophysiological defects of T2D. As highlighted in a recent narrative review by Samajdar et al., the pathogenesis of T2D is fundamentally driven by two interconnected concerns: insulin resistance and progressive β-cell dysfunction, both of which are deeply rooted in mitochondrial dysfunction. Imeglimin, as the first-in-class "glimin," offers a "single

Table 4: Glycemic parameters – FPG and PPG

Parameters	*Sample size*	*Baseline mean (SD)*	*Follow-up 1 (3 months) mean (SD)*	*Follow-up 2 (6 months) mean (SD)*	*Mean change (baseline–FU2)*	*95% CI (lower, upper)*	*p-value (paired t-test)*
PPG (postprandial plasma glucose) (mg/dL)	295	289.93 (102.09)	213.34 (63.45)	176.97 (43.25)	−112.97	(−122.63, −103.30)	<0.001
FPG (fasting plasma glucose) (mg/dL)	295	194.71 (66.05)	146.48 (38.63)	119.52 (26.80)	−75.19	(−81.72, −68.65)	<0.001

Table 5: Weight and BMI

Parameters	*Sample size*	*Baseline mean (SD)*	*Follow-up 1 (3 months) mean (SD)*	*Follow-up 2 (6 months) mean (SD)*	*Mean change (baseline–FU2), 95% CI*	*p-value (RM-ANOVA test)*
Weight (kg)	260	69.88 (14.0)	69.50 (12.50)	69.49 (12.29)	−0.39 (−1.35, 0.57)	0.393
BMI	258	25.96 (4.37)	25.97 (4.19)	25.97 (4.11)	0.01 (−0.10, 0.12)	0.975

Table 6: Safety profile–incidence of adverse events (safety analysis set, *n* = 573)

Adverse event	*n (%)*
Nausea or vomiting	30 (5.2)
Gastrointestinal problems	8 (1.4)
Urinary tract infection	8 (1.4)
Hypoglycemia	7 (1.2)
Headache	6 (1.0)
Genital infection	3 (0.5)
Lactic acidosis	2 (0.3)
At least one complaint	57 (9.9)
None reported	516 (90.1)

solution" to these dual concerns by directly modulating mitochondrial bioenergetics.[14]

By improving mitochondrial function, imeglimin reduces oxidative stress and enhances ATP generation, which restores glucose-stimulated insulin secretion and attenuates β-cell apoptosis.[14] Concurrently, it reduces hepatic gluconeogenesis and augments glucose uptake in skeletal muscle, thereby ameliorating insulin resistance.[14] This multimodal mechanism is particularly relevant for the Asian Indian phenotype, which is characterized by early β-cell dysfunction, high visceral adiposity, and mitochondrial stress despite relatively modest BMI. By simultaneously targeting these foundational defects, imeglimin provides a comprehensive therapeutic approach that delivers additive glycemic benefits, especially in patients inadequately controlled by conventional therapies that target isolated components of glucose dysregulation.[15–17].

Effectiveness in Context: Comparative and Real-world Evidence

Imeglimin demonstrated substantial effectiveness in this prospective Indian real-world cohort, with adjusted mean HbA1c reductions of 1.28% at 3 months and 2.27% at 6 months, indicating progressive and clinically meaningful glycemic improvement over time. The nonsignificance of BMI and OGLA count is a substantive finding that indicates these variables do not significantly modify the primary treatment effect, reduction in HbA1c.

These reductions are numerically greater than those reported in randomized trial-based meta-analyses, where imeglimin monotherapy or add-on therapy typically achieves HbA1c decrements in the range of 0.5–0.9%. Hagi et al. pooled nine placebo-controlled trials (n ≈ 1,655) and reported HbA1c reductions of approximately 0.45–0.71% with imeglimin 1,000–1,500 mg twice daily, both as monotherapy and adjunctive therapy,[18] while Singh et al. found mean falls of about 0.9% in monotherapy trials with smaller, though still significant, effects when used as an add-on;[19] Abdelhaleem et al. similarly concluded that imeglimin provides modest but clinically relevant HbA1c lowering when added to standard regimens, highlighting that the magnitude of benefit varies with baseline glycemia and background treatment.[20] Comparisons with key clinical trials further support the robustness of the observed effect. In the Japanese TIMES program, TIMES 1 showed that imeglimin monotherapy 1,000 mg twice daily reduced HbA1c by about 0.9% versus placebo over 24 weeks, while TIMES 2 demonstrated sustained HbA1c reductions of roughly 0.8–1.0% over 52 weeks in monotherapy or combination settings, and TIMES 3 reported additional HbA1c decreases of around 0.6–0.7% when imeglimin was added to insulin.[21]

However, this large magnitude of HbA1c decline must be interpreted cautiously within the context of a single-arm, real-world observational design. The pronounced reduction likely reflects several factors beyond the pharmacological effect of imeglimin alone, including the high baseline HbA1c (9.8%), concurrent optimization of background multidrug regimens, and the coadministration of insulin. Most critically, the primary effectiveness analysis was based on a complete-case cohort, with approximately 54% of the initial cohort lost to follow-up at 6 months. As detailed in our sensitivity analysis, noncompleters differed significantly from completers, presenting with higher baseline HbA1c levels and a greater prevalence of diabetes-related complications. Because missing data were not imputed, the reported 2.27% reduction is subject to severe attrition and survivor bias. Furthermore, the observed decline may partly reflect regression to the mean, improved patient adherence following a new prescription, more frequent clinical follow-up, and clinician selection of patients deemed likely to respond. Therefore, these findings represent an association rather than a definitive causal treatment effect.

Real-world evidence, such as the INDI-TIMES study, which documented HbA1c reductions of approximately 1.1–1.3% over 3–6 months in more than 8,000 Indian participants, and other observational series, including other single-center practice studies showing improvements of around 0.8–1.2%, closely align with or modestly trail the present results while confirming effectiveness across diverse demographic and treatment strata.[22] Earlier add-on trials by Fouqueray et al., with metformin or DPP-4 inhibitors, which demonstrated incremental HbA1c reductions of about 0.4–0.6%, further corroborate imeglimin's role as a useful adjunct in inadequately controlled T2D.[23]

To better contextualize these findings, it is instructive to consider recent comparative evidence. A record-based retrospective study by Samajdar et al. evaluated the effectiveness of imeglimin vs vildagliptin as add-on therapies in Indian patients with T2D inadequately controlled on metformin and sulfonylureas.[24] In that study, patients had a lower baseline HbA1c (approximately 8.3%) and a shorter duration of diabetes compared to the present cohort. Despite these differences in baseline profiles, the comparative study demonstrated that imeglimin achieved a significantly greater HbA1c reduction (−0.98%) compared to vildagliptin (−0.59%) over 3 months.[24] While our present study is prospective and multicenter, offering robust longitudinal data, the record-based comparative study by Samajdar et al. provides crucial contextual evidence supporting the efficacy of imeglimin as an add-on therapy relative to an established dipeptidyl peptidase-4 (DPP-4) inhibitor.[24]

Together, these complementary study designs reinforce the clinical utility of imeglimin in diverse real-world settings, without necessarily confirming superiority in the absence of head-to-head randomized trials.

Safety, Tolerability, and Metabolic Neutrality

Imeglimin demonstrated a favorable safety and tolerability profile over the 6-month follow-up, with a low overall incidence of reported adverse events (9.9%). The most frequently reported events were mild gastrointestinal symptoms, such as nausea or vomiting (5.2%), which aligns with the known safety profile of the drug. Importantly, the incidence of hypoglycemia was notably low (1.2%). Two investigator-reported events of lactic acidosis were recorded, and further investigation into both these cases revealed no causality of the event with imeglimin use. Given the observational nature of the study, the presence of multiple concomitant antidiabetic therapies, and limited biochemical adjudication, a causal relationship with imeglimin could not be established.

This favorable tolerability is consistent with the findings from the comparative study by Samajdar et al., which reported comparable and low adverse drug reaction rates for both imeglimin (5.71%) and vildagliptin (4.58%), with no severe hypoglycemic events.[24] In TIMES-2, around 70–75% of individuals experienced at least one treatment-emergent adverse event over 52 weeks, with nasopharyngitis and gastrointestinal symptoms (including nausea) occurring in ≥5% and hypoglycemia

in about 3–4%, mostly mild and rarely leading to discontinuation.[21]

The overall incidence of reported adverse events in this study (9.9%) is lower than that observed in randomized clinical trials of imeglimin, where treatment-emergent adverse events have been reported in approximately 60–75% of individuals over longer follow-up periods. This difference is likely attributable to the real-world observational design, shorter duration of follow-up, less intensive and protocol-driven safety monitoring, and reliance on spontaneous reporting in routine clinical practice, which may result in under-ascertainment of mild or transient events, particularly gastrointestinal symptoms.

INDI-TIMES study has also reported very low rates or absence of recorded adverse events with Imeglimin, reinforcing its favorable tolerability but similarly raising the possibility that minor gastrointestinal symptoms are underreported outside trial settings.[22] Notably, emerging data in special populations, including individuals with metformin intolerance, advanced chronic kidney disease, and those on dialysis, suggest that imeglimin can be used safely with appropriate monitoring, expanding its potential utility in complex, high-risk individuals commonly seen in Indian practice.[13] Taken together, the predominance of mild gastrointestinal events, rare hypoglycemia, and lack of a clear signal for serious toxicity in this and other studies support a generally favorable tolerability profile for Imeglimin, while underscoring the need for more systematic, prospective safety capture to better quantify event rates in everyday practice.

Prescription Patterns and Therapeutic Inertia

This prospective, multicenter, real-world study provides valuable insights into the utilization, effectiveness, and safety of imeglimin among Indian adults with T2D. A key contribution of this study is the detailing of current prescription patterns in routine clinical practice. Imeglimin was predominantly utilized as an add-on therapy, with over 80% of patients receiving it in combination with multiple OGLAs, and nearly 16% receiving it alongside insulin. Monotherapy accounted for only 15.4% of prescriptions. Notably, the majority of patients were initiated on imeglimin only after the failure of three or more OGLAs, yet it produced significant HbA1c reductions. This pattern suggests that the drug retains glycemic efficacy even in metabolically complex, treatment-experienced individuals, and that the magnitude of benefit is closely linked to baseline HbA1c rather than to its position in the therapeutic sequence.[22]

This prescription pattern highlights a significant degree of therapeutic inertia in the management of T2D. The late adoption of imeglimin in the treatment sequence reflects a tendency to reserve newer agents for metabolically complex, treatment-experienced individuals with high baseline HbA1c (mean 9.8%), rather than in early sequencing.

While the data demonstrate that imeglimin retains substantial glycemic efficacy even in advanced disease stages, this pattern suggests that its current clinical positioning is driven more by prescribing customs and recent market entry than by pharmacological limitations.[12,21]

From a pathophysiological standpoint, the typical Asian Indian phenotype represented in this cohort, characterized by early β-cell dysfunction, high visceral adiposity and mitochondrial stress at relatively modest BMI-provides a strong rationale for considering imeglimin before overt failure of other oral agents.[8] By simultaneously enhancing glucose-stimulated insulin secretion, improving mitochondrial bioenergetics and attenuating hepatic gluconeogenesis, imeglimin targets core defects that emerge early in the natural history of T2D, and there is no mechanistic reason to reserve these actions only for individuals already on multiple therapies.[5,15] Indeed, introducing imeglimin earlier, for example, as part of an initial combination strategy with metformin or DPP-4 inhibition in individuals with high baseline HbA1c or rapid glycemic deterioration, may help to achieve durable control while limiting the need for early insulin initiation or further escalation of secretagogue doses.[12,23]

These observations have important implications for therapeutic inertia, which remains a major barrier to timely intensification in T2D and is associated with prolonged exposure to suboptimal glycemia and increased risk of complications.[17] Instead of waiting for unequivocal failure of existing oral regimens, clinicians managing individuals with the high-risk Indian phenotype should actively consider imeglimin when HbA1c remains above individualized targets despite one or two agents, particularly in those with evidence of early β-cell decline, fluctuating post-prandial excursions, or intolerance to further dose escalation of current therapy.[8] In this context, the favorable tolerability profile observed in this and other real-world series—marked by weight neutrality, low hypoglycemia risk, and absence of major organ-specific toxicity—even in elderly individuals, those with renal impairment or metformin intolerance, supports its use as a pragmatic, earlier add-on option in routine practice. Collectively, the patient profile and response pattern in this cohort reinforce the view that imeglimin should be viewed not merely as a late-stage rescue therapy, but as a versatile component of earlier multidrug regimens for Asian Indian individuals with T2D who are at high lifetime risk of complications.

Strengths and Limitations

The strengths of this study include its prospective, multicenter design and the large sample size, which capture the realities of imeglimin utilization in routine Indian clinical practice. The documentation of complex polypharmacy and the inclusion of patients with high baseline HbA1c provide a pragmatic view of treatment dynamics that are often excluded from tightly controlled RCTs.

This study has several limitations that should be acknowledged. Its observational, single-arm design without a comparator group precludes causal inference and makes it difficult to separate the effect of imeglimin from concurrent lifestyle modifications or adjustments to background therapies. Accordingly, the observed reductions in glycemic parameters in this study should be interpreted as associative rather than causal. Selection bias is possible because only participants who returned for all follow-up visits and had complete HbA1c data were included in the effectiveness analysis (337/736, ~46%), potentially over-representing adherent or motivated individuals; baseline characteristics of noncompleters were compared and found to be significantly different on key parameters (younger, higher HbA1c, more complications at baseline) (Table S1). The follow-up duration of 6 months is relatively short, limiting conclusions about long-term glycemic durability, impact on diabetes complications, micro-/macrovascular events, or very rare adverse events. Treatment decisions—including dose, timing of imeglimin initiation, and combination regimens—were heterogeneous, and the study sites were predominantly urban primary and secondary care centers. Consequently, the external validity and generalizability of these findings to rural Indian populations, public hospital settings, and economically constrained demographic groups may be limited. Finally, the reliance on spontaneous adverse event reporting in routine care may have led to an under-ascertainment of mild or transient side effects compared to protocol-driven surveillance in clinical trials.

Future Research Directions

The findings from this real-world cohort highlight the need for further research to optimize the clinical positioning of imeglimin.

Given its unique mechanism targeting mitochondrial dysfunction, future prospective, randomized, active-comparator trials are warranted to evaluate the efficacy of imeglimin when introduced earlier in the disease trajectory, compared to its current use as a late-stage rescue therapy. Additionally, long-term studies are needed to assess the durability of glycemic control, the potential for β-cell preservation, and the impact on cardiovascular and renal outcomes in diverse populations, including rural and resource-limited settings.

Conclusion

In routine clinical practice, the initiation of imeglimin among Indian adults with type 2 diabetes was associated with clinically meaningful reductions in HbA1c, fasting plasma glucose, and postprandial glucose over a 6-month period, alongside a favorable safety profile. These real-world findings support the clinical utility and tolerability of imeglimin as an effective therapeutic option for glycemic management in this population. Future randomized controlled trials with extended follow-up are warranted to establish definitive causal treatment effects and evaluate long-term clinical outcomes.

Acknowledgments

The authors acknowledge Maria Khan, Insha Nissar, Santhi Kandikatla, Raghunath Dantu, Karthikayan Visvanathan, and Rama Regulla from MEDEVA (www.medeva.io) for their support with data management, analysis, and editorial assistance.

Conflict of Interest

None.

Source of Funding

This study was supported by Zydus Healthcare Ltd, which provided funding for biostatistical support, logistics, and operational coordination. The sponsor had no role in study design, data collection, data analysis, data interpretation, manuscript preparation, or decision to publish.

Data Availability Statement

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

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Table S1: Sensitivity analysis: completers (complete case cohort, *n* = 337) vs noncompleters (*n* = 399)

Parameters	*Completers*	*Noncompleters*	*p-value*	*Test*
Sample size (N)	337	399		
Gender, *n* (%)				
Female	142 (42.1)	175 (43.9)	0.692	Chi-squared
Male	195 (57.9)	224 (56.1)		
Age (years), mean (SD)	50.9 (11.4)	53.6 (11.2)	0.001	Two-sample *t*-test
BMI baseline, mean (SD)	28.0 (31.1)	27.2 (4.9)	0.671	Two-sample *t*-test
Duration of type 2 diabetes, mean (SD)	6.7 (4.2)	6.7 (5.2)	0.979	Two-sample *t*-test
Complication due to diabetes – at least one complication, *n* (%)				
No	212 (62.9)	345 (86.5)	<0.001	Chi-squared
Yes	125 (37.1)	54 (13.5)		
Class combinations at baseline, *n* (%)				
Only imeglimin	21 (6.2)	92 (23.1)		
Imeglimin + 1 OAD	14 (4.2)	17 (4.3)	<0.001	Chi-squared
Imeglimin + 2 OADs	28 (8.3)	21 (5.3)		
Imeglimin + 3 OADs	85 (25.2)	61 (15.3)		
Imeglimin + >3 OADs	143 (42.4)	138 (34.6)		
Imeglimin + OAD(s) + insulin	46 (13.6)	70 (17.5)		
Antidiabetic class–insulin, *n* (%)				
No	291 (86.4)	329 (82.5)	0.179	Chi-squared
Yes	46 (13.6)	70 (17.5)		
HbA1c (%) grouping, *n* (%)				
<7%	20 (5.9)	50 (12.5)	<0.001	Chi-squared
7–7.99%	35 (10.4)	66 (16.5)		
8–8.99%	56 (16.6)	68 (17.0)		
9–9.99%	48 (14.2)	59 (14.8)		
≥10%	178 (52.8)	156 (39.1)		
HbA1c (%), mean (SD)	10.2 (2.1)	9.4 (2.2)	<0.001	Two-sample *t*-test
PPG (postprandial glucose) (mg/dL) grouping, *n* (%)				
Low (<100)	0 (0.0)	1 (0.4)		
Normal (100–140)	18 (6.1)	11 (4.6)	0.407	Chi-squared
High (>140)	278 (93.9)	228 (95.0)		
PPG (postprandial glucose) (mg/dL), mean (SD)	289.7 (102.0)	250.5 (86.5)	<0.001	Two-sample *t*-test
Fasting plasma glucose (FPG) (mg/dL) grouping, *n* (%)				
Normal (<100)	20 (6.8)	18 (7.3)	0.479	Chi-squared
Prediabetes (100–125)	31 (10.5)	34 (13.8)		
Diabetic (>125)	244 (82.7)	195 (78.9)		
Fasting plasma glucose (FPG) (mg/dL), mean (SD)	194.7 (66.0)	171.0 (61.6)	<0.001	Two-sample *t*-test

Table S2: Glycemic parameter—HbA1c (unadjusted values)

Parameters (N = 337)	*Sample size*	*HbA1c at baseline mean (SD)*	*HbA1c at 6 months mean (SD)*	*Mean difference in HbA1c (baseline–6 months) (%)*	*95% CI (baseline–FU2) (%)*	*p-value (paired t-test)*
OHA combinations						
Only imeglimin	21	9.10 (2.57)	7.44 (1.12)	−1.65	(−2.51, −0.79)	<0.001
Imeglimin + 1 OHA	14	9.55 (1.89)	7.40 (1.18)	−2.16	(−3.16, −1.15)	<0.001
Imeglimin + 2 OHAs	28	9.68 (1.57)	7.43 (1.22)	−2.24	(−2.76, −1.72)	<0.001
Imeglimin + 3 OHAs	85	9.63 (1.98)	7.60 (1.22)	−2.03	(−2.37, −1.68)	<0.001
Imeglimin + >3 OHAs	143	10.52 (2.14)	8.21 (1.74)	−2.31	(−2.61, −2.01)	<0.001
Imeglimin + OHA(s) + insulin	46	11.04 (1.81)	8.12 (1.19)	−2.92	(−3.36, −2.49)	<0.001
Gender						
Male	195	10.18 (2.18)	7.96 (1.54)	−2.23	(−2.48, −1.98)	<0.001
Female	142	10.15 (2.01)	7.82 (1.40)	−2.33	(−2.60, −2.06)	<0.001
Age groups						
18–50 years	151	10.17 (2.02)	7.59 (1.27)	−2.58	(−2.85, −2.31)	<0.001
50–59 years	110	10.45 (2.12)	8.07 (1.51)	−2.38	(−2.70, −2.07)	<0.001
≥60 years	76	9.77 (2.21)	8.27 (1.71)	−1.50	(−1.86, −1.13)	<0.001
Baseline HbA1c						
<7%	20	6.25 (0.59)	6.11 (0.58)	−0.15	(−0.35, 0.06)	0.154
7–7.99%	35	7.53 (0.31)	7.31 (1.36)	−0.22	(−0.69, 0.25)	0.349
8–8.99%	56	8.63 (0.24)	7.16 (0.73)	−1.48	(−1.68, −1.27)	<0.001
9–9.99%	48	9.48 (0.30)	7.48 (1.07)	−1.99	(−2.32, −1.67)	<0.001
≥10%	178	11.80 (1.29)	8.56 (1.48)	−3.24	(−3.45, −3.02)	<0.001
Duration of T2D						
≤5 years	117	9.94 (1.92)	7.43 (0.99)	−2.52	(−2.84, −2.20)	<0.001
6–10 years	137	9.96 (2.17)	7.79 (1.45)	−2.17	(−2.48, −1.87)	<0.001
>10 years	40	11.11 (2.26)	8.38 (1.11)	−2.74	(−3.26, −2.22)	<0.001

ORIGINAL ARTICLE

Diagnostic Accuracy of Spot Urine Uric Acid-to-creatinine Ratio in Identifying Renal Uric Acid Excretion Patterns in Hyperuricemic Patients: A Cross-sectional Study

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Received: 29 December 2025; *Accepted:* 25 February 2026

Abstract

Background: Hyperuricemia arises primarily from reduced renal uric acid clearance ("low secretors") or, less commonly, increased uric acid production. Differentiating these mechanisms is vital to guide urate-lowering therapy but conventionally requires 24-hour urine collection, which is cumbersome and prone to collection errors. This study evaluated the diagnostic accuracy of the spot urine uric acid-to-creatinine (UUA/Cr) ratio as a practical alternative to 24-hour urine testing for distinguishing low secretors from normal secretors in hyperuricemic patients.

Materials and methods: In this cross-sectional study conducted between April and September 2025 at KLE's Dr Prabhakar Kore Hospital and Medical Research Center, 39 adults with hyperuricemia (serum uric acid >7.0 mg/dL in males, >5.0 mg/dL in females) underwent both spot and 24-hour urine testing. UA and Cr concentrations were assessed using standard enzymatic assays. A 24-hour urine excretion threshold of ≥600 mg/day was used to define normal secretors, while values <600 mg/day indicated low secretors. Correlation between spot UUA/Cr ratio and 24-hour UA excretion was analyzed using Pearson's test, and receiver operating characteristic (ROC) analysis was done to identify optimal diagnostic cutoff.

Results: The spot UUA/Cr ratio correlated moderately with 24-hour urine UA excretion ($r = 0.429$, $p = 0.006$). Using the 24-hour UA excretion cutoff of more than or equal to 600 mg/day, the ROC curve exhibited an area under the curve (AUC) of 0.786, which indicates good discriminatory performance, and a spot UUA/Cr ratio cutoff of 1.59 showed 93.1% specificity and 50% sensitivity for the identification of normal excretors.

Conclusion: The spot UUA/Cr ratio provides a simple, noninvasive, and reliable method to distinguish low from normal uric acid secretors. A cutoff value of 1.59 offers high specificity for identifying normal renal excretion and could serve as a feasible substitute for cumbersome 24-hour urine testing in clinical practice.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1543

Introduction

Hyperuricemia represents a major global health concern, with an estimated occurrence rate ranging from 13.85% to 21% across different populations.[1–3] This metabolic disorder serves as a precursor to gout, nephrolithiasis, and chronic kidney disease, affecting millions worldwide and imposing a substantial burden on healthcare systems.[4,5] The pathophysiology of hyperuricemia involves two primary mechanisms: overproduction of uric acid (accounting for approximately 10% of cases) and renal underexcretion (responsible for 90% of cases), with a small subset exhibiting combined characteristics.[6,7]

Accurate classification of hyperuricemia into these subtypes holds therapeutic implications, as treatment strategies differ fundamentally based on the underlying mechanism. Patients with renal underexcretion typically benefit from uricosuric agents such as probenecid or benzbromarone, which enhance renal excretion of uric acid.[8,9] Conversely, those with overproduction need enzymes such as xanthine oxidase and inhibitors like allopurinol or febuxostat to decrease the rate of uric acid synthesis.[10,11] However, inappropriate use of uricosuric agents in overproducers can precipitate nephrolithiasis due to excessive urinary uric acid concentration, making accurate phenotyping essential for safe and effective management.[12,13]

The gold standard for distinguishing between renal underexcretion and overproduction involves measurement of 24-hour urine UA excretion, with values below 600 mg/day on a regular diet (or below 300–400 mg/day on a purine-restricted diet) indicating underexcretion, while values exceeding 800–1000 mg/day suggest overproduction.[14–16] Despite its diagnostic utility, 24-hour urine collection has numerous practical challenges. These include patient inconvenience, incomplete sample collection, improper storage conditions, timing errors, and poor adherence to collection protocols, which collectively compromise specimen accuracy in more than 50% of cases. These complex logistics and low patient compliance have prompted investigation into simpler, more practical alternatives that can maintain diagnostic accuracy and are feasible in routine clinical practice.

The spot UUA/Cr is promising, as creatinine excretion remains relatively constant throughout the day (approximately 1 gram daily), potentially normalizing for variations in urine concentration.[17,18] Previous studies have explored this relationship with variable results. Some investigations in gout patients reported moderate correlations ($r = 0.398–0.429$) between spot UUA/Cr ratios and 24-hour urinary uric acid excretion,[19,20] while others demonstrated area under the curve (AUC) values ranging from 0.686 to 0.903 for predicting renal underexcretion.[21,22] Optimal cutoff value for spot UUA/Cr ratio that maximizes both sensitivity and specificity for identifying normal versus low renal excretors remains unclear, with proposed thresholds ranging from 0.34 to 1.59 across different studies.[23] But there is no Indian data for the same. Practical implementation guidelines are lacking regarding which cutoff values would be most appropriate for clinical decision-making, particularly when selecting patients suitable for uricosuric therapy. Our aim is to evaluate the diagnostic accuracy of spot UUA/Cr ratio as a predictor of 24-hour uric acid excretion patterns in Indian patients with hyperuricemia.

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How to cite this article: Patil AM, Sonoli S, Jain P, *et al.* Diagnostic Accuracy of Spot Urine Uric Acid-to-creatinine Ratio in Identifying Renal Uric Acid Excretion Patterns in Hyperuricemic Patients: A Cross-sectional Study. J Assoc Physicians India 2026;74(6):66–68.

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Materials and Methods

Study Design and Study Setting

A cross-sectional investigation was performed between April and September 2025 at KLE's Dr. Prabhakar Kore Hospital and Medical Research Center, Belagavi. The objectives of the study were: (1) to determine the correlation between spot UUA/Cr ratio and 24-hour urinary uric acid excretion; (2) to establish optimal cutoff values using Receiver Operating Characteristic Curve (ROC) curve analysis for distinguishing normal excretors (≥600 mg/24 hours) from low excretors (<600 mg/24 hours); (3) to calculate the sensitivity and specificity of identified cutoff points; and (4) to assess whether spot urine testing could serve as a reliable alternative to 24-hour urine collection in clinical practice for phenotyping hyperuricemic patients prior to initiating uric acid-lowering therapy. The institutional ethics committee granted formal approval, and the study has been carried out according to the Helsinki Declaration's tenets.

Participant Selection

Male and female patients aged >18 years attending the endocrinology OPD and meeting the criteria for hyperuricemia (serum uric acid >5 mg/dL in females and >7 mg/dL in males) were included. Participants with a history of recent or ongoing use of diuretics, uricosuric medications, or SGLT2 inhibitors, as well as those unwilling to provide informed consent, were excluded. All subjects provided written and informed consent before enrollment. Baseline demographic and anthropometric data, such as age, sex, height, and weight, were systematically collected at study initiation.

Sample Collection and Laboratory Procedures

Blood samples were drawn to estimate serum uric acid and creatinine using standard enzymatic assays. For urine specimen collection, each participant was provided with detailed verbal and written instructions and supplied with two sterile containers: one (25 mL) for the collection of spot midstream urine, and another (2 L) for 24-hour urine collection. For the 24-hour protocol, subjects were instructed to discard the initial morning urine, collect all subsequent voided samples over the next 24 hours, including the first sample of the following morning, and maintain their usual diet throughout the collection period. All urine samples were promptly transported to the central laboratory and analyzed via fully automated ERBA EM 200 systems using validated enzymatic methods for quantification of UA and Cr.

The UUA/Cr ratio was derived by dividing the measured concentration of uric acid by that of creatinine in the spot urine sample.

Statistical Analysis

Microsoft Excel and IBM SPSS Statistics version 29.0 were utilized for statistical analysis and data processing. To ascertain whether continuous variables were normal, the Shapiro–Wilk test was employed. Variables with a normal distribution were shown using the mean ± standard deviation, while variables with skewed distributions were described using the median and interquartile range (IQR). Categorical variables were represented using percentages and frequencies. The relationship between quantitative variables was examined using Pearson's correlation coefficient. The diagnostic performance of the spot urine uric acid-to-creatinine ratio was evaluated by calculating the AUC, standard error, and 95% confidence intervals using receiver operating characteristic (ROC) curve analysis. The optimal cutoff was found using Youden's index, which maximizes [sensitivity + specificity–1].

Results

Baseline Characteristics and Study Population

A total of 145 adults aged 18–50 years were screened during the study period, of whom 39 participants (27% of the screened cohort) met the diagnostic criteria for hyperuricemia. The study cohort comprised 14 female participants (35.9%) and 25 male participants (64.1%), reflecting a male predominance consistent with known epidemiological patterns in hyperuricemic populations (Table 1).

Analysis of Correlation

To evaluate the connection between spot UUA/Cr ratio and 24-hour urinary uric acid excretion, Pearson's correlation analysis was performed. Moderately favorable and statistically significant correlation with Pearson's $r = 0.429$, $p = 0.006$, $n = 39$ was demonstrated between these variables. This finding indicates that as 24-hour urinary uric acid excretion increased, the spot UUA/Cr ratio showed a corresponding proportional increase, establishing a meaningful relationship between the two measurement approaches in the hyperuricemic population studied (Fig. 1).

Stratification by Renal Uric Acid Excretion Status

Participants were stratified based on 24-hour uric acid excretion patterns using the clinically established threshold of 600 mg/day. This classification yielded two groups: (1) normal secretors with 24-hour urinary uric acid excretion ≥600 mg/day ($n = 10$, 25.6% of the cohort), and (2) low secretors with 24-hour urinary excretion <600 mg/day ($n = 29$, 74.4% of the cohort). This distribution aligns with established epidemiological data demonstrating that renal underexcretion accounts for the majority of hyperuricemic cases.

Diagnostic Accuracy of Spot UUA/Cr Ratio

Receiver Operating Characteristic Curve (ROC) Evaluation

The analysis of the receiver operating curve was carried out to assess the diagnostic performance of the spot UUA/Cr ratio in predicting 24-hour urinary uric acid excretion patterns and differentiating normal secretors from low secretors. The resulting ROC curve demonstrated 0.786 (95% confidence interval) of AUC, indicating good discriminatory performance of the spot urine measurement

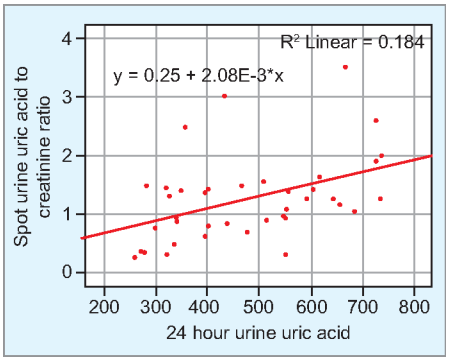


Fig. 1: Linear regression demonstrating positive correlation between spot UUA/Cr ratio and 24-hour uric acid in 39 hyperuricemia patients (Pearson's $r = 0.429$, $p = 0.006$; $R^2 = 0.184$)

Table 1: Baseline features of the 39 hyperuricemic participants ($n = 39$)

Variable	*Mean ± SD*
Age (years)	38.31 ± 10.51
Body mass index (kg/m^2)	24.02 ± 2.4
Serum uric acid (mg/dL)	9.08 ± 1.2
Serum creatinine (mg/dL)	1.02 ± 0.31
Spot urine uric acid (mg/L)	153.37 ± 65.19
Spot urine creatinine (mg/L)	135.78 ± 57.01
Spot urine uric acid to creatinine ratio	1.25 ± 0.73
24-hour urinary uric acid (mg/day)	478.1 ± 149.96

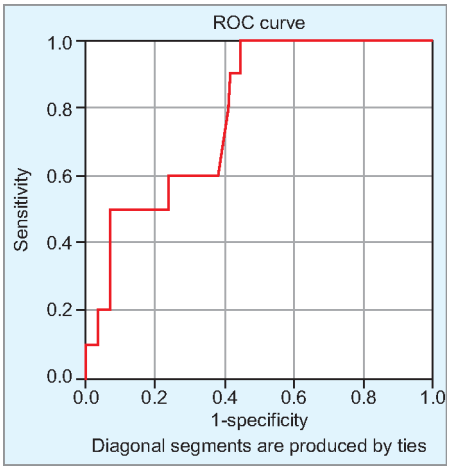


Fig. 2: Receiver operating characteristic curve for the "spot UUA/Cr ratio" in predicting normal "24-hour urinary uric acid excretion "(≥600 mg/day)

in distinguishing between the two excretion phenotypes (Fig. 2).

Optimal Cutoff for Identifying Normal Uric Acid Secretors

Analyzed the ROC curve, identified a clinically optimal threshold for spot urine UA/Cr ratio of 1.59 by Youden's index methodology (maximizing sensitivity + specificity − 1). At this cutoff, the spot UUA/Cr demonstrated 93.1% specificity and 50% sensitivity, providing excellent discrimination for confirming normal renal uric acid excretion (≥600 mg/day) in hyperuricemic patients. Conversely, a ratio <1.59 indicates probable renal underexcretion but does not exclude this possibility with certainty.

Discussion

In this cross-sectional analysis, we evaluated the diagnostic performance of the "spot urine uric acid-to-creatinine ratio" (UUA/Cr), identifying renal uric acid excretion patterns among individuals with hyperuricemia. The spot UUA/Cr ratio demonstrated a moderate positive correlation with "24-hour urinary UA excretion" ($r = 0.429$, $p = 0.006$) and showed good diagnostic accuracy (AUC 0.786). A cutoff value of 1.59 showed high specificity (93.1%) and moderate sensitivity (50%) for detecting normal renal excretion (≥600 mg/day), indicating that the test is most useful for confirming adequate uric acid clearance.

Results align with earlier reports by Sakane et al.[21] and Choi et al.[19], who documented AUC values between 0.68 and 0.80 for the same parameter in different populations, underscoring the reproducibility of the spot UUA/Cr ratio as a practical diagnostic measure. The predominance of renal underexcretion (74.4%) in our cohort reinforces the established understanding that impaired renal clearance is the primary driver of hyperuricemia in most patients. Accurate identification of these phenotypes helps in guiding the appropriate use of uricosuric agents versus xanthine oxidase inhibitors.

The simplicity and accessibility of spot urine testing offer a major advantage over 24-hour urine collection, which is often limited by patient nonadherence and collection errors. In clinical settings with high patient volumes or limited laboratory capacity, the spot UUA/Cr ratio could enable faster and more reliable phenotyping of hyperuricemic patients, facilitating individualized therapy and reducing the incidence of uric acid nephrolithiasis.

The study's strengths include its direct clinical applicability, use of standardized enzymatic assays, clearly defined inclusion criteria, and objective cutoff derivation through ROC analysis. A single-sample urine test is practical and easy to use in everyday settings, which makes the study's findings more relevant for real-world situations. However, limitations include a modest sample size and lack of dietary standardization, a single-center design, which may influence uric acid excretion.

Future multicenter studies with larger, ethnically diverse cohort studies are needed to validate the proposed cutoff and to assess its prognostic relevance for treatment response. Particular attention should be given to populations with comorbid conditions (renal and metabolic comorbidities) that may influence renal uric acid handling. Adoption of spot urine testing could improve patient adherence and diagnostic efficiency.

Conclusion

The spot UUA/Cr ratio offers a simple, reproducible, and noninvasive tool for assessing renal uric acid excretion in hyperuricemic patients. A threshold of 1.59 provides high specificity for identifying normal excretors, making it a clinically valuable alternative to the cumbersome 24-hour urine test. Implementation of this approach could improve patient adherence, reduce diagnostic errors, and guide safer, more targeted urate-lowering therapy. Larger multicenter studies should confirm these findings and refine reference values for broader clinical use.

Orcid

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Abridged Prescribing Information

Indication: It is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. Dosage and Administration: The recommended dose is one tablet daily. Each tablet contains a fixed dose of dapagliflozin, Sitagliptin and Metformin Hydrochloride. Adverse Reactions: Most common adverse reactions reported are: Dapagliflozin- Female genital mycotic infections, nasopharyngitis, and urinary tract infections. Sitagliptin- Upper respiratory tract infection, nasopharyngitis and headache. Metformin- Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Warnings and Precautions: Dapagliflozin: Volume depletion; Ketoacidosis in Patients with Diabetes Mellitus; Urosepsis and Pyelonephritis; Hypoglycaemia; Genital Mycotic infections Sitagliptin: General- Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Acute pancreatitis: Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal product; Renal impairment; Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions- Stevens-Johnson syndrome; Bullous pemphigoid. Metformin Hydrochloride: Lactic acidosis; In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a healthcare professional is recommended.Contraindications: Hypersensitivity to the active substance of Dapagliflozin, Sitagliptin & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma; Severe renal failure (eGFR<30mL/min); Acute conditions with the potential to alter renal function such as: Dehydration, Severe Infection, Shock; Acute or chronic disease which may cause tissue hypoxia such as: Cardiac or respiratory failure, Recent myocardial Infarction, Shock, Hepatic Impairment, Acute Alcohol intoxication, alcoholism Use in a special population: Pregnant Women: Due to lack of human data, drug should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Paediatric 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.
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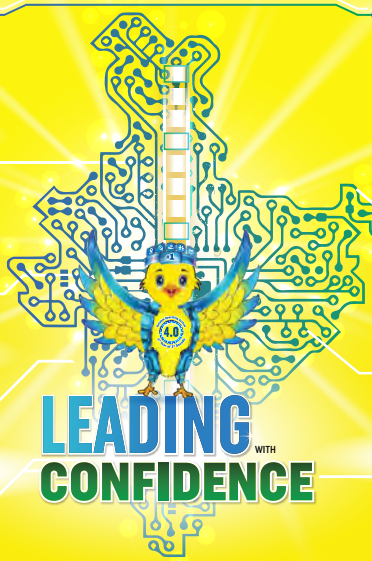
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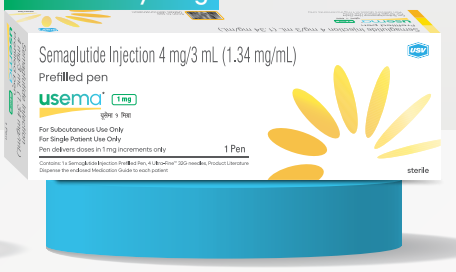
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ORIGINAL ARTICLE

Semaglutide in Practice: Insights from a Retrospective Case Series at a Jharkhand Tertiary Care Hospital

Ajay Kumar Jha[1*], Ashok Sunder[2]

Received: 17 September 2025; *Accepted:* 11 November 2025

Abstract

Background: Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has demonstrated efficacy in improving glycemic control and reducing cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). However, real-world evidence from Indian populations remains limited. This study aimed to assess the effectiveness and safety of semaglutide on glycemic control, body weight, and metabolic parameters in patients with T2DM in a real-world clinical setting. Methods: This retrospective observational study was conducted at a tertiary care hospital in Jharkhand, India, between February 2023 and August 2024. A total of 60 patients with T2DM (44 males and 16 females), including treatment-naïve individuals and those with inadequate glycemic control (HbA1c >7%) despite ongoing therapy, were enrolled. Clinical and biochemical parameters were evaluated at baseline and after six months of semaglutide therapy. Statistical analysis was performed using paired *t*-tests, with a *p*-value <0.05 considered statistically significant.Results: Significant improvements were observed following semaglutide therapy. Mean HbA1c decreased from 9.21% at baseline to 7.35% after six months ($p < 0.001$). Mean body weight decreased by 2.6 kg ($p < 0.001$). LDL cholesterol levels declined significantly from 92.03 mg/dL to 78.93 mg/dL ($p < 0.05$). Renal parameters, including serum creatinine and urine albumin-to-creatinine ratio, showed numerical improvement; however, these changes did not reach statistical significance ($p > 0.05$). Thyroid function remained stable throughout the study period. Improvements in diabetic retinopathy and neuropathy were also observed, although these findings were not statistically significant.

Conclusion: Semaglutide was effective and well tolerated in patients with T2DM in routine clinical practice. Treatment was associated with significant reductions in HbA1c, body weight, and LDL cholesterol without adverse effects on renal or thyroid function. These findings support the use of semaglutide as an effective therapeutic option for the management of T2DM in real-world settings.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1508

Introduction

Diabetes mellitus, a chronic metabolic disorder characterized by sustained hyperglycemia, represents one of the most formidable global public health challenges of the 21st century. This condition arises from defects in insulin secretion, insulin action, or a combination of both, leading to disturbances in carbohydrate, fat, and protein metabolism. The sheer scale of its prevalence and its escalating incidence rates, particularly in low- and middle-income countries, pose an immense burden on healthcare systems and national economies. The World Health Organization (WHO) provides stark projections, indicating a relentless rise in diabetes cases worldwide. India, often referred to as the "diabetes capital of the world," exemplifies this alarming trend. Projections indicate a substantial increase in the adult diabetic population in India, with numbers anticipated to soar from 77 million in 2017 to an estimated 134 million by 2045, highlighting an urgent need for effective therapeutic strategies and preventive measures.[1] The therapeutic landscape for type 2 diabetes mellitus (T2DM) has undergone significant evolution, moving beyond glucose lowering to encompass comprehensive cardiovascular and renal risk reduction. Glucagon-like peptide-1 (GLP-1) receptor agonists represent a class of medications that have revolutionized T2DM management because of their unique pleiotropic effects. These agents mimic the action of endogenous GLP-1, an incretin hormone released from the gut in response to food intake. Semaglutide, a highly effective and widely studied GLP-1 receptor agonist, stands out because of its prolonged half-life, allowing for convenient once-weekly subcutaneous administration (or daily oral formulation). Its mechanism of action is multifaceted: it enhances glucose-dependent insulin secretion from pancreatic beta cells, thereby lowering postprandial glucose levels; it suppresses inappropriately high glucagon secretion, which contributes to hepatic glucose production; it slows gastric emptying, promoting satiety and reducing postmeal glucose excursions; and critically, it acts on central nervous system pathways to reduce appetite and consequently promote significant weight loss. Beyond its direct glycemic effects, semaglutide has demonstrated substantial benefits in terms of cardiovascular outcomes and renal protection in large-scale clinical trials.

Despite the growing body of evidence from international clinical trials, real-world data from diverse geographical and clinical settings are crucial for understanding the effectiveness and generalizability of new therapies. This case series aims to contribute to this understanding by evaluating the real-world efficacy of semaglutide. Specifically, we sought to assess its impact on key metabolic parameters such as hemoglobin A1c (HbA1c), body weight, and associated comorbidities like dyslipidemia and early-stage renal dysfunction, in a cohort of patients receiving treatment at our tertiary care institution in Jharkhand, a region within India with its unique demographic and clinical characteristics. The insights gleaned from this retrospective analysis are intended to inform clinical practice and resource allocation within similar healthcare environments.

Methodology

Study Design

This investigation was designed as a retrospective, observational study. We systematically reviewed the medical records of patients diagnosed with T2DM who initiated semaglutide therapy within a defined period. The study period spanned from February 2023 to August 2024, during which data were meticulously collected from electronic health records and physical charts at our tertiary care hospital located in Jharkhand, India. The retrospective nature of the study allowed for the evaluation of treatment outcomes in a real-world clinical setting, reflecting routine patient care rather than the controlled environment of a clinical trial.

[1]Senior Consultant and Unit Head, Department of Medicine; [2]Chief Consultant, Department of Medicine, Tata Main Hospital, Jamshedpur, Jharkhand, India; *Corresponding Author

How to cite this article: Jha AK, Sunder A. Semaglutide in Practice: Insights from a Retrospective Case Series at a Jharkhand Tertiary Care Hospital. J Assoc Physicians India 2026;74(6):74–77.

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Participants

The study cohort comprised 60 patients who met the inclusion criteria for initiation of semaglutide therapy for their diabetes management. Among these participants, 44 were males, and 16 were females, reflecting a demographic distribution common in our clinical practice. The inclusion criteria were broad to capture a representative real-world population, focusing on adults diagnosed with type 2 diabetes who were prescribed semaglutide. This included patients who were either treatment naive or those who had suboptimal glycemic control (HbA1c >7.0%) despite receiving other conventional antidiabetic medications such as metformin, sulfonylureas, or insulin. Exclusion criteria included patients with type 1 diabetes, pregnant or lactating women, individuals with a history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, severe gastrointestinal disease (e.g., gastroparesis), or known hypersensitivity to semaglutide. Ethical approval for the retrospective review of anonymized patient data was obtained from the institutional review board (IRB) of Tata Main Hospital, ensuring patient confidentiality and adherence to ethical research guidelines.

Data Collection

Patient charts were rigorously reviewed to extract comprehensive data on various parameters, both at baseline (i.e., immediately prior to the initiation of semaglutide treatment) and after a follow-up period of approximately 6 months postinitiation of therapy. The following key parameters were collected:

- Weight (kg): Body weight measurements were recorded to assess the impact of semaglutide on weight management.
- HbA1c (%): Glycated hemoglobin levels, a crucial indicator of long-term glycemic control, were recorded to evaluate treatment efficacy.
- Creatinine (mg/dL): Serum creatinine levels were assessed as an indicator of renal function.
- Urine albumin-to-creatinine ratio (UACR, mg/gm): This ratio was used to screen for and monitor microalbuminuria, an early marker of diabetic nephropathy.
- Thyroid-stimulating hormone (TSH, µIU/mL): TSH levels were recorded to evaluate thyroid function, particularly relevant given the association between diabetes and thyroid disorders.
- Low-density lipoprotein (LDL, mg/dL): LDL cholesterol levels were monitored to assess the impact of semaglutide on lipid profiles, an important cardiovascular risk factor.
- Diabetic neuropathy: The presence and severity of diabetic neuropathy were assessed based on documented composite neuropathy scores obtained from clinical examinations (e.g., vibration perception, monofilament testing) and patient symptom reporting at baseline and follow-up.
- Diabetic retinopathy: The status of diabetic retinopathy was assessed through documented ophthalmologic examinations, including fundoscopy or retinal imaging reports, noting any changes in severity during the study period.

All laboratory values were obtained from the hospital's central laboratory, ensuring standardized and calibrated measurements.

Statistical Analysis

All collected data were compiled and analyzed using appropriate statistical software (SPSS version 26.0). Descriptive statistics were used to summarize patient demographics and baseline clinical characteristics. To determine the statistical significance of changes in continuous variables from baseline to 6 months posttreatment, paired *t*-tests were employed. This statistical method is ideal for comparing means from the same subjects under two different conditions (before and after treatment). A two-tailed *p*-value of <0.05 was predefined as the threshold for statistical significance, indicating a low probability that the observed differences occurred by chance. Data integrity was maintained through careful entry and verification processes to minimize errors.

Results

The cohort's demographics and clinical characteristics at baseline are summarized, providing context for the observed outcomes. The mean age of the participants was 58.5 ± 9.2 years, with a mean duration of diabetes of approximately 7.3 ± 4.1 years. Comorbidities were prevalent, reflecting the complex clinical profile of patients with type 2 diabetes.

Glycemic Control and Weight Management

Analysis of the comprehensive dataset revealed a highly significant and clinically meaningful impact of semaglutide on glycemic control and body weight. The average weight reduction observed across the cohort was 2.6 kg ($p < 0.001$), signifying a statistically robust and encouraging trend toward weight loss. While this average might appear modest, it is significant in the context of T2DM management, where many conventional therapies lead to weight gain. This weight reduction would be visually represented in a bar chart, with distinct bars for "weight before" and "weight after" for each patient, clearly demonstrating the downward trend in individual weights. More strikingly, a profound improvement in glycemic control was evident, with the mean HbA1c level decreasing significantly from a baseline of 9.21% to a follow-up value of 7.35% ($p < 0.001$). This 1.86% absolute reduction in HbA1c is highly clinically relevant, bringing a substantial proportion of patients closer to or within individualized glycemic targets, thereby mitigating the risk of long-term diabetes complications. A line graph illustrating HbA1c levels would show two distinct lines, one for "before" and one for "after" treatment, running parallel but significantly lower for the "after" values, indicating a consistent improvement across the patient cohort.

Renal Function and Lipid Profile

The assessment of renal function, primarily through serum creatinine levels, demonstrated stability. The mean creatinine levels remained largely unchanged, averaging around 0.9 mg/dL ($p > 0.05$), indicating that semaglutide therapy did not adversely affect kidney function in this cohort. Furthermore, the average UACR showed an improvement from 14.58 to 12.43 mg/gm. Although this reduction suggests a positive trend toward diminished microalbuminuria, it did not reach statistical significance ($p > 0.05$) within the 6-month follow-up period. A notable improvement was observed in the lipid profile, specifically in LDL cholesterol levels. The average LDL was significantly reduced from a baseline of 92.03 to 78.93 mg/dL ($p < 0.05$). This statistically significant reduction in LDL, often referred to as "bad" cholesterol, is a critical positive outcome, as dyslipidemia is a major modifiable cardiovascular risk factor in patients with T2DM.

Thyroid Function

Thyroid-stimulating hormone levels showed no significant variance from baseline after 6 months of semaglutide treatment ($p > 0.05$). This finding is reassuring, as it indicates that semaglutide therapy did not interfere with thyroid function in this patient population. Most patients with preexisting hypothyroid conditions maintained their TSH levels within acceptable therapeutic ranges, suggesting that semaglutide is safe for use in patients with well-managed thyroid disorders.

Diabetic Complications (Neuropathy and Retinopathy)

Regarding chronic diabetic complications, a total of 60 patients were included in this analysis. Among them, eight patients exhibited documented improvements in the severity of

their diabetic retinopathy. These improvements were noted through ophthalmologic examinations, indicating a potential stabilization or regression of retinal damage in a subset of the cohort. Additionally, one patient experienced a discernible reduction in neuropathy symptoms, as reported clinically. While these improvements in microvascular complications are encouraging, they did not achieve statistical significance across the entire cohort within the relatively short 6-month observation period. The pie chart representing comorbidities would visually depict the distribution of conditions like hypertension, dyslipidemia, preexisting neuropathy, and retinopathy among the 60 patients, illustrating the overall burden of diabetes-related complications in the study population.

Discussion

Efficacy of Semaglutide in Glycemic Control and Weight Loss

Our findings from this real-world retrospective case series from Jharkhand robustly reinforce the established efficacy of semaglutide in managing type 2 diabetes. The observed average HbA1c reduction of 1.86% is a substantial clinical improvement, demonstrating semaglutide's potent glucose-lowering capabilities. This reduction is consistent with the findings from large-scale randomized controlled trials and meta-analyses, which have consistently reported significant HbA1c lowering with semaglutide across diverse patient populations and clinical settings.[2,3] Achieving such a significant reduction in HbA1c is critical for reducing the risk of both microvascular and macrovascular complications associated with prolonged hyperglycemia. Equally important is the observed average weight reduction of 2.6 kg. Obesity and overweight are pervasive comorbidities in T2DM, significantly contributing to insulin resistance, disease progression, and cardiovascular risk. The weight-reducing effect of semaglutide, mediated primarily through its impact on appetite regulation and gastric emptying, is a distinct advantage over many other antidiabetic medications that are often weight neutral or even promote weight gain. This dual benefit of improved glycemic control and weight loss positions semaglutide as a highly attractive therapeutic option, particularly for patients with T2DM and concomitant obesity or overweight. A recent meta-analysis further supports these findings, underscoring similar reductions in HbA1c and body weight among individuals treated with semaglutide across various clinical settings, validating our real-world observations.[2]

Impact on Comorbid Conditions

Beyond its direct effects on glucose and weight, GLP-1 receptor agonists, including semaglutide, have garnered considerable attention for their potential to confer cardiovascular and renal benefits. While our study's primary focus was not on hard cardiovascular outcomes, the significant reduction in LDL cholesterol levels (from 92.03 to 78.93 mg/dL) is a clinically meaningful finding. Lowering LDL cholesterol is a well-established strategy for mitigating cardiovascular risk, and this observed improvement adds another dimension to semaglutide's beneficial profile in diabetes management. Regarding renal function, our data suggest a remarkable stability in creatinine levels, with no evidence of acute kidney injury or deterioration over the 6-month follow-up period. This finding is particularly reassuring, especially in a population often burdened with preexisting comorbidities such as hypertension and diabetes, both of which can predispose to renal impairment. While the improvement in urine ACR did not reach statistical significance, the trend toward reduction (from 14.58 to 12.43 mg/gm) is promising and aligns with larger studies that have demonstrated renoprotective effects of GLP-1 receptor agonists, including reductions in albuminuria and preservation of kidney function over longer durations.[4] Our findings affirm the safety of semaglutide with respect to renal metrics, suggesting it does not compromise kidney function in patients with T2DM, even in the presence of existing renal vulnerabilities.

Improvements in Complications

The observed slight improvements in retinopathy severity in eight patients and the reduction in neuropathy symptoms in one patient, although not statistically significant in this small cohort over a short follow-up, warrant further careful exploration. Microvascular complications like retinopathy and neuropathy are debilitating sequelae of long-standing diabetes. It is well established that intensive glycemic control plays a pivotal role in preventing and slowing the progression of these complications.[5] Observational studies and larger clinical trials have suggested that improved glycemic control, as achieved with semaglutide, can indeed contribute to slowing the progression of microvascular complications.[5,6] While our findings are preliminary in this regard, they provide an intriguing signal that aligns with the broader understanding of diabetes management. Longer-term follow-up and larger cohorts are necessary to definitively ascertain the impact of semaglutide on the incidence and progression of these critical complications.

Limitations

Despite providing valuable real-world insights, this study is subject to several limitations inherent to its retrospective design. First, the retrospective nature means that data collection was reliant on preexisting medical records, which may have varying degrees of completeness and standardization. This limits the ability to control for all potential confounding variables and may introduce biases. Causal interpretations between semaglutide therapy and observed outcomes should therefore be made with caution; while strong associations were found, direct causality cannot be definitively proven. Second, the relatively small sample size of 60 patients, although valuable for a single-center case series, limits the statistical power and the generalizability of the findings to a broader population. Larger, multicenter studies would be required to confirm these observations and establish their applicability across diverse demographic and clinical contexts. Variations in the exact follow-up duration among patients, dictated by routine clinical practice rather than a strict research protocol, could also affect the consistency of results across the cohort. Furthermore, the absence of a control group (patients not on semaglutide) prevents direct comparison of outcomes with other therapeutic regimens. Lastly, the 6-month follow-up period is relatively short for assessing long-term effects, particularly regarding the progression of chronic complications or sustained weight management.

Conclusion

This retrospective case series from a tertiary care hospital in Jharkhand provides compelling real-world evidence supporting the efficacy and safety of semaglutide in the management of T2DM. The introduction of semaglutide therapy in our clinical practice appears to be highly effective in achieving significant improvements in glycemic control, as evidenced by a substantial reduction in HbA1c. Furthermore, it demonstrates a beneficial impact on weight management and leads to favorable changes in lipid profiles. Crucially, semaglutide was found to maintain stable renal function, an essential consideration in a patient population often susceptible to kidney complications. While preliminary, the observed trends in the improvement of microvascular complications like retinopathy and neuropathy are encouraging and warrant

further investigation. This manuscript details the experiences with semaglutide treatment in patients with type 2 diabetes within a real-world setting, combining clinical findings and implications for diabetes management in a resource-constrained region. The data collectively suggest positive health outcomes, underscoring semaglutide's role as a powerful and valuable addition to the therapeutic armamentarium for type 2 diabetes. However, it is imperative that future prospective studies with larger cohorts, longer follow-up durations, and more rigorous control groups be conducted. Such studies are necessary for comprehensive validation of these initial observations, to definitively ascertain the long-term efficacy and safety of semaglutide therapy, and to fully explore its significant clinical relevance in managing the multifaceted challenges of T2DM.

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Announcement

OFFICE BEARERS OF API DELHI CHAPTER OF ASSOCIATION OF PHYSICIANS OF INDIA FOR THE YEAR 2026–2027

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REVIEW ARTICLE

Clinical Practice Recommendations: Snakebite-envenomation-associated Acute Kidney Injury

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Received: 21 December 2025; *Accepted:* 14 March 2026

Abstract

Background: Snakebite is a neglected tropical disease of major public health importance in India, contributing to significant morbidity and mortality. Acute kidney injury (AKI) is among the most serious complications of envenomation, particularly with viperid and some elapid species, and is associated with long-term chronic kidney disease (CKD) risk.

Objective: This article aims to provide evidence-based recommendations for the recognition, evaluation, and management of snakebite-envenomation-associated AKI (SAKI), integrating global best practices with national treatment protocols and resource realities.

Materials and methods: The authors reviewed available literature through PubMed and international recommendations, including the Government of India's Standard Treatment Guidelines (STG), World Health Organization (WHO) guidance, and Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines. As per the available evidence, the recommendations were formulated through expert panel deliberations.

Results: Key recommendations include early recognition of envenomation syndromes, prompt administration of polyvalent antisnake venom (ASV), protocolized monitoring of coagulation and renal parameters, and standardized use of kidney replacement therapy (KRT) according to KDIGO indications. Supportive management of venom-induced consumption coagulopathy (VICC), rhabdomyolysis, and thrombotic microangiopathy (TMA) is emphasized. Special considerations have been outlined for children, pregnant women, patients with preexisting kidney disease, and those bitten by non-"Big Four" snakes.

Conclusion: SAKI is preventable and treatable with timely intervention, but survivors remain at risk of CKD. With these recommendations, the authors have tried to standardize the diagnostic and therapeutic approach across general medicine, nephrology, and critical care medicine teams in India, aiming to reduce mortality and improve renal outcomes.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1528

Introduction

Snakebite envenomation is recognized by the WHO as a high-priority neglected tropical disease, with India bearing the highest global burden, accounting for an estimated 50,000–60,000 deaths annually, along with long-term disability among the survivors.[1–4] Among the systemic complications of envenomation, acute kidney injury (AKI) is particularly significant, both as a determinant of in-hospital mortality and as a contributor to chronic kidney disease (CKD).[1,5,6] The pathophysiology of snakebite-envenomation-associated AKI (SAKI) is multifactorial, involving venom-induced consumption coagulopathy (VICC), direct nephrotoxicity, pigment nephropathy from hemolysis or rhabdomyolysis, hemodynamic shock, thrombotic microangiopathy (TMA), and, in severe cases, acute cortical necrosis (ACN).[7–9] Indian data indicate that AKI develops in up to one-third of hospitalized snakebite patients, with 20–30% requiring kidney replacement therapy (KRT). Nevertheless, 20–40% of survivors demonstrate persistent renal impairment, highlighting the need for structured follow-up.[10–14] Despite the high burden, standardized nephrology-specific guidelines for the prevention and management of SAKI have been lacking in India. Existing protocols focus largely on antivenom administration and general supportive care, with limited emphasis on renal complications, dialysis practices, or long-term outcomes. To address this gap, the authors convened a multidisciplinary committee to develop evidence-based recommendations specific to SAKI. These recommendations are intended for use by general physicians, nephrologists, intensivists, emergency physicians, and dialysis teams across India. They integrate international best practices, including WHO and Kidney Disease Improving Global Outcomes (KDIGO) recommendations, with national realities such as the availability of polyvalent antivenom (ASV), variable access to kidney replacement modalities, and the high prevalence of rural presentations. The overarching aim is to improve early recognition, standardize treatment pathways, and optimize renal outcomes in patients with snakebite envenomation, while ensuring uniformity of practice across diverse healthcare settings.

Materials and Methods

The authors undertook a structured literature search and evidence synthesis. A comprehensive PubMed search was conducted up to July 2025 using the keywords "snakebite," "envenomation," "acute kidney injury," "renal failure," "venom-induced consumption coagulopathy," and "dialysis." Additional references were drawn from the WHO guidelines on snakebite management,[15] the Government of India Standard Treatment Guidelines (STG) for Snakebite,[16] and the KDIGO AKI guideline.[17] Only English-language publications were

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How to cite this article: Sharma S, Sahoo TK, Kollengode R, *et al.* Clinical Practice Recommendations: Snakebite-envenomation-associated Acute Kidney Injury. J Assoc Physicians India 2026;74(6):78–84.

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Table 1: Envenomation syndromes relevant to AKI

Syndrome and Indian snakes	*Key clinical markers*	*Kidney injury mechanisms*	*First-hour priorities (additions to standard ABCs)*	*Remarks*
Hemotoxic/Viperid (Russell's viper, Saw-scaled viper; some pit vipers)	Local swelling, bleeding, oozing, gingival bleed; deranged 20WBCT, low fibrinogen, increased D-dimer, prolonged PT/ aPTT	VICC with microthrombi/ bleeding; hypotension; hemolysis; ATN; AIN; TMA; ACN	Early polyvalent ASV (initial 10 vials in most; 5 vials may be considered for suspected saw-scaled viper), aggressive monitoring, early laboratory tests (CBC, PT/INR, fibrinogen, D-dimer), urine output target ≥0.5 mL/kg/h	Coagulopathy may persist/recur; re-dose guided by laboratory test results/bleeding
Neurotoxic/Elapid (Cobra, Krait)	Ptosis, ophthalmoplegia, bulbar weakness, descending paralysis ± respiratory failure	Rhabdomyolysis (cobra/ sea snake), hypoxia/ aspiration; ATN	Airway and ventilation; early ASV (10 vials stat; repeat if worsening after 1–2 hours); consider atropine-neostigmine test for postsynaptic blocks	Presynaptic (krait) paralysis responds poorly to anticholinesterase
Myotoxic (Sea snakes; some cobras)	Severe myalgia, dark urine, very high CK	Myoglobin-induced tubular injury; hyperkalemia	Early fluids (if no overload), urine alkalinization for significant myoglobinuria (expert practice); monitor potassium closely	Indian polyvalent ASV does not cover sea snake venoms
TMA phenotype (various vipers; Hypnale)	MAHA (increased LDH, schistocytes), thrombocytopenia, AKI often after initial VICC	Endothelial injury; may overlap with VICC	Supportive care; dialysis as needed; routine plasma exchange not supported; consider only if true TTP (ADAMTS13 <10%) suspected	Biopsy series show TMA/ACN in a subset

ABC, airway, breathing, and circulation; ACN, acute cortical necrosis; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; AIN, acute interstitial nephritis; aPTT, activated partial thromboplastin time; ASV, antisnake venom; ATN, acute tubular necrosis; CBC, complete blood count; CK, creatine kinase; MAHA, microangiopathic hemolytic anemia; PT, prothrombin time; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VICC, venom-induced consumption coagulopathy; 20WBCT, 20-minute whole blood clotting test

included. Priority was given to randomized controlled trials (RCTs), meta-analyses, and large cohort studies where available; however, given the scarcity of high-quality trials in this field, observational studies, registry data, and case series from India and other tropical regions were also reviewed. Evidence synthesis was performed with a focus on the epidemiology and burden of snakebite-associated AKI; mechanisms of renal injury; the role of antivenom and supportive therapy; dialysis and extracorporeal support; and long-term outcomes. The recommendations represent a synthesis of best available evidence and expert opinion, contextualized to the realities of nephrology and critical care practice in India.

Background

India contributes a large share of the global snakebite burden, with hemotoxic (viperid) and neurotoxic (elapid) bites predominating.[1–4] AKI occurs in up to ~1/3 of hospitalized victims and may require KRT.[10–14] SAKI mechanisms include VICC, hemodynamic shock, rhabdomyolysis/ myoglobinuria, hemoglobinuria, direct tubular toxicity, acute interstitial nephritis, TMA, and (less often) acute cortical necrosis.[7–9] Various envenomation syndromes relevant to AKI have been depicted in Table 1. Long-term outcomes are not benign—many of them have persistent renal abnormalities; a wide range (8–50%) can progress to CKD, supporting structured follow-up.[6,7,10,18]

Definition

Snakebite-envenomation-associated AKI refers to the development of AKI following confirmed or probable snake envenomation, after exclusion of alternative causes of renal dysfunction. AKI is defined and staged according to the KDIGO criteria,[17] based on changes in serum creatinine and/or urine output. The term also includes patients requiring KRT and those with partial or delayed renal recovery.

Initial Evaluation and Risk Stratification (First 0–6 Hours)

Prehospital/Triage

Reassure the patient and immobilize the bitten limb at heart level. No tourniquet, incision, suction, or ice should be applied over the affected limb. Remove the tight items and transport rapidly to an ASV-capable facility.[19–22]

Emergency Department/ICU Bundle

- Record the time, site, and species. Monitor vitals (blood pressure/pulse rate, rhythm, and volume/respiratory rate/peripheral oxygen saturation).
- Secure airway/ventilation (neurotoxic bites), large-bore peripheral/ central venous catheter, hemodynamic stabilization (balanced crystalloids; vasopressors if shock). Avoid dopamine infusion.
- Insert Foley's catheter for accurate monitoring of urine output; maintain hydration and target urine output ≥ 0.5 mL/kg/h unless anuric/overloaded. Alkalinize urine for pigmenturia with 100 mL of 8.4% sodium bicarbonate in 1 liter of 5% dextrose at 100 mL/h.
- Laboratory panel and monitoring (Table 2).
- Early polyvalent ASV according to the Indian STG (vide infra).[16]
- Avoid nephrotoxins [nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, radiocontrast; adjust all drug doses to kidney function].
- A practical management bundle for SAKI in ICU/critical care has been summarized in Table 3.

ASV: Indications, Dosing, and Re-dosing

Antisnake venom is the only specific therapy capable of neutralizing circulating snake venom and remains the cornerstone of management in snakebite envenomation.[7,23] Early, adequate, and appropriately re-dosed ASV administration is critical in preventing systemic complications, including SAKI.[7,23–25]

Table 2: Diagnostic work-up and monitoring schedule in suspected SAKI

Domain	*Tests*	*Timing/frequency*	*How it informs decisions*
Coagulation (VICC)	20WBCT at bedside; PT/INR, aPTT, fibrinogen, D-dimer	Baseline; then q6h until normalization for 24 hours; earlier if bleeding	Guides ASV re-dosing in hemotoxic bites; D-dimer is sensitive for VICC
Hemolysis/TMA	CBC with platelets, reticulocyte count, smear for schistocytes; serum LDH, haptoglobin, and bilirubin (MAHA)	Baseline; repeat 12–24 hours if hemolysis is suspected	Distinguishes VICC ± TMA; falling platelets and schistocytes suggest TMA—no routine PEX unless TTP
Renal	Serum creatinine, BUN, electrolytes (potassium, bicarbonate, calcium, phosphate), serum CK, urinalysis (hematuria, myoglobin), urine microscopy, and albumin/protein–creatinine ratio	Baseline; repeat q12–24 hours; more often if unstable	KDIGO staging; detects hyperkalemia, rhabdomyolysis, and pigment nephropathy
Acid-base and lactate	ABG/VBG, serum lactate	Baseline; as per shock status	Guides fluids, vasopressors, and dialysis indications
Imaging	Renal ultrasound at bedside, chest X-ray	Early if oliguria/anuria or pulmonary edema	Rules out obstruction; assesses volume/ARDS
Others	Cross-match early, before ASV/venom effects confound results; pregnancy test where relevant	Early	Transfusion planning; obstetric coordination

ABC, airway, breathing, and circulation; ABG, arterial blood gas analysis; aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; ASV, antisnake venom; BUN, blood urea nitrogen; CBC, complete blood count; CK, creatine kinase; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; PEX, plasma exchange; PT, prothrombin time; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VBG, venous blood gas analysis; VICC, venom-induced consumption coagulopathy; 20WBCT, 20-minute whole blood clotting test

Table 3: Practical management bundle for SAKI (ICU/ Critical Care)

Step	*What to do*	*Pearls and pitfalls*
Resuscitation	ABCs; early intubation if bulbar weakness; crystalloids; norepinephrine for shock	Avoid excessive fluids in oligo-anuria; monitor for pulmonary edema
Antivenom	Start promptly; re-dose as per clinical/ laboratory criteria	Do not underdose in children/pregnancy; watch for anaphylaxis
Laboratory tests and monitoring	q6h coagulation (VICC); strict input-output monitoring; creatinine/ electrolytes; CK	Early cross-match before ASV/FFP; bedside 20WBCT where labs are delayed
Coagulopathy	If bleeding/severe procedures: FFP/cryoprecipitate after ASV	Do not rely on blood products alone without ASV
Rhabdomyolysis	Fluids (unless overloaded), early hyperkalemia care; consider alkalinization	Pigment casts: avoid acidemia, avoid nephrotoxins
TMA phenotype	Supportive care; dialysis as needed; evaluate for MAHA	Routine PEX not supported; reserve for proven TTP (ADAMTS13 <10%)
Dialysis	IHD/SLED/CKRT per status; anticoagulation tailored to bleeding risk	Heparin-free or citrate in coagulopathy; run higher effluent in hyperkalemia
Drugs	Renally dose all meds; avoid NSAIDs, aminoglycosides, IV contrast	Antibiotics only if infected wounds/aspiration pneumonia
Documentation	Time of bite, first aid, snake species; ASV batch/dose/timing	Capture for pharmacovigilance, medico-legal, and quality loops

ABC, airway, breathing, and circulation; aPTT, activated partial thromboplastin time; ASV, antisnake venom; CK, creatine kinase; CKRT, continuous kidney replacement therapy; IHD, intermittent hemodialysis; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; NSAID, nonsteroidal anti-inflammatory drug; PEX, plasma exchange; PT, prothrombin time; SLED, sustained low-efficiency dialysis; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VICC, venom-induced consumption coagulopathy; 20WBCT, 20-minute whole blood clotting test

Delay in initiation or under-dosing of ASV is a well-established risk factor for severe coagulopathy, AKI, need for kidney replacement therapy, and mortality.[1,3–7]

Indications

Antivenom should be administered promptly in patients with evidence of systemic envenomation, irrespective of the presence or severity of local symptoms. Indications include the following:[3,4,21,26]

- Hemotoxic envenomation.
  - Abnormal 20WBCT.
  - Spontaneous systemic bleeding (gingival bleed, hematuria, hematemesis, intracranial bleed).
  - Laboratory evidence of venom-induced consumption coagulopathy (prolonged PT/INR, low fibrinogen, elevated D-dimer).
- Neurotoxic envenomation.
  - Ptosis, ophthalmoplegia.
  - Bulbar weakness, dysphagia.
  - Respiratory muscle weakness or impending respiratory failure.
- Myotoxic envenomation.
  - Severe generalized myalgia.
  - Dark-colored urine with markedly elevated creatine kinase.
- Cardiovascular or renal involvement.
  - Hypotension or shock attributable to envenomation.
  - Oliguria/anuria or rising serum creatinine consistent with AKI.
  - ASV is not indicated in dry bites or in patients with isolated local swelling without systemic features.[25,27]

Initial Dosing

Indian polyvalent ASV (effective against cobra, krait, Russell's viper, and saw-scaled

viper) should be administered intravenously after reconstitution, preferably within the first 3–6 hours of envenomation.[4,23–25]

- Hemotoxic (viperid) envenomation.
  - The initial dose should be 10 vials IV infusion.
  - In suspected saw-scaled viper bites with mild systemic involvement, 5 vials may be considered initially, with close monitoring.
- Neurotoxic envenomation.
  - The initial dose should be 10 vials IV infusion.
  - Early airway protection should accompany ASV administration in patients with bulbar or respiratory involvement.
- Children and pregnant women.
  - Same dose as adults, as venom load is independent of body weight.
  - ASV should be infused over 30–60 minutes under close monitoring for anaphylaxis, with resuscitation drugs and equipment readily available.[28–30]

Re-dosing of ASV

Re-dosing is guided by clinical response and laboratory parameters, not by fixed maximum dosing.[4,23–25,31,32]

- Hemotoxic envenomation.
  - Reassess coagulation profile (20WBCT, PT/INR, fibrinogen) at 6 hours after completion of infusion.
  - If coagulopathy persists or bleeding continues, administer an additional 2–6 vials, or repeat a full dose depending on severity.
  - Re-evaluation and re-dosing may be required every 6 hours until coagulation normalizes.
  - In rare, severe cases with ongoing life-threatening bleeding, cumulative doses up to 30 vials may be required.
- Neurotoxic envenomation.
  - If neurological deterioration continues or no improvement is seen within 1–2 hours of the initial dose, repeat 10 vials.
  - Further dosing beyond 20 vials is rarely beneficial and should be individualized.

What ASV Can and Cannot Do

Antisnake venom neutralizes only circulating, unbound venom. It does not reverse established tissue damage, including presynaptic neurotoxicity (e.g., krait bites), established AKI, or local tissue necrosis. Therefore, early administration is essential to prevent progression of organ damage.[25,33]

Safety and Adverse Reactions

Early adverse reactions include anaphylaxis, bronchospasm, hypotension, and urticaria. Late reactions include serum sickness (5–10 days post-ASV).[28,29] ASV reactions should be managed promptly with intramuscular adrenaline, antihistamines, and corticosteroids as per institutional protocols. A history of allergy is not a contraindication to ASV when clinically indicated.[28–30]

Special Considerations

Indian polyvalent ASV is ineffective against sea snake venom and many pit vipers; management in these cases is primarily supportive.[23,34,35] ASV dosing should not be reduced in patients with AKI or CKD.[8,36] Documentation of ASV batch number, dose, timing, and response is essential for pharmacovigilance and quality assurance.[4]

Coagulopathy/Bleeding Care

Coagulopathy following snakebite envenomation, most commonly due to VICC, is a major contributor to morbidity and mortality and a key driver of snakebite-associated AKI.[7–9] VICC is characterized by rapid depletion of clotting factors due to procoagulant toxins in venom, leading to prolonged clotting times, hypofibrinogenemia, elevated D-dimer levels, and a nonclotting 20WBCT. Importantly, VICC is a toxin-mediated process rather than classical disseminated intravascular coagulation (DIC), and management principles differ accordingly.[37–39]

Primary Therapy

Prompt and adequate administration of ASV is the cornerstone of the management of VICC.[37,38] ASV neutralizes circulating venom and halts further consumption of clotting factors but does not immediately correct existing coagulopathy. Re-dosing of ASV should be guided by clinical bleeding and repeat coagulation parameters (20WBCT, PT/INR, fibrinogen), typically assessed every 6 hours in hemotoxic envenomation. Delay or underdosing of ASV significantly increases the risk of severe bleeding, AKI, and the need for dialysis.[37,39,40]

Role of Blood and Blood Products

Blood products should never replace ASV and should be used only as adjunctive therapy.[41] Indications for transfusion include life-threatening or ongoing active bleeding (e.g., intracranial, gastrointestinal, pulmonary, retroperitoneal) or preparation for urgent invasive procedures (surgery, dialysis catheter insertion). The recommended blood products are fresh frozen plasma (FFP) to replace clotting factors and cryoprecipitate for severe hypofibrinogenemia (<100 mg/dL).[41–45] Platelet transfusion should only be attempted in the presence of significant thrombocytopenia with active bleeding. Routine prophylactic use of blood products in isolated laboratory coagulopathy without bleeding is discouraged, as it does not improve outcomes and may worsen volume overload, particularly in AKI.

Dialysis and Procedures in Coagulopathic Patients

In patients requiring KRT, use heparin-free dialysis or regional citrate anticoagulation (where expertise exists).[7–9] Dialysis catheter insertion should be delayed until partial correction of coagulopathy whenever feasible.[46] If urgent access is required, transfuse FFP/cryoprecipitate after ASV and use ultrasound guidance to minimize complications.[47]

Thrombotic Microangiopathy and Bleeding Overlap

A subset of patients may develop a TMA phenotype (microangiopathic hemolytic anemia, thrombocytopenia, and AKI) following viper envenomation.[48] These patients may have persistent thrombocytopenia and renal dysfunction despite normalization of coagulation tests. Routine plasma exchange is not recommended for snakebite-associated TMA. It should be reserved only for cases with strong suspicion of true thrombotic thrombocytopenic purpura (TTP), supported by clinical features and very low ADAMTS13 activity.[48,49]

Additional Considerations

Heparin is contraindicated in VICC and should not be used for the correction of coagulopathy.[38,39] Antifibrinolytic agents (e.g., tranexamic acid) are not routinely recommended and may be considered only in selected cases with life-threatening bleeding after correction of venom activity. Close monitoring for recurrent coagulopathy is essential, as VICC may recur due to delayed venom absorption from tissue depots.[38–40]

Monitoring

Repeat coagulation profile (PT/INR, fibrinogen, D-dimer, or 20WBCT) every 6 hours until normalization, then daily until stable. Monitor hemoglobin, platelet count, urine output, and signs of occult bleeding.

Rhabdomyolysis and Pigment Nephropathy

Rhabdomyolysis and pigment-induced nephropathy are important contributors to SAKI, particularly following envenomation by sea snakes and certain elapid species, and less commonly with viperid bites.[50–53] Venom-induced myotoxicity leads to widespread muscle necrosis with release of myoglobin, creatine kinase, potassium, and phosphate into the circulation, resulting in direct tubular toxicity, intrarenal cast formation, and renal vasoconstriction. Clinically, patients present with severe generalized myalgia, muscle tenderness, dark-colored urine, and markedly elevated serum creatine kinase levels, often accompanied by hyperkalemia and metabolic acidosis.[52,53] Management is primarily supportive and includes early recognition, careful volume resuscitation with isotonic crystalloids in patients without fluid overload, close monitoring, and prompt treatment of electrolyte abnormalities—especially hyperkalemia—and avoidance of nephrotoxic agents.[52] Urine alkalinization may be considered in selected patients with significant myoglobinuria, though evidence remains limited. Early nephrology involvement and timely initiation of KRT are essential in cases with refractory metabolic complications or progressive renal failure.[52,53]

AKI Management and KRT

All patients with snakebite envenomation should be actively screened for AKI using KDIGO criteria,[17] based on serum creatinine trends and urine output. Early recognition of AKI allows timely implementation of renoprotective strategies aimed at limiting further kidney injury. Core management principles include optimization of hemodynamics with judicious use of balanced crystalloids, avoidance of hypotension and hypoxia, strict monitoring of fluid balance, and elimination of nephrotoxic exposures such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and iodinated contrast.[54,55] Drug dosages should be adjusted according to estimated glomerular filtration rate (eGFR). Electrolyte disturbances—particularly hyperkalemia, metabolic acidosis, hypocalcemia, and hyperphosphatemia—should be anticipated and corrected promptly.[54,55] Early nephrology consultation is recommended for patients with KDIGO stage 2 or 3 AKI, oliguria/anuria, or rapidly rising creatinine levels.

Kidney Replacement Therapy

Kidney replacement therapy should be initiated based on standard clinical indications rather than serum creatinine alone. Indications include refractory hyperkalemia, severe metabolic acidosis, fluid overload causing pulmonary edema or hypoxemia, uremic complications (encephalopathy, pericarditis), and persistent anuria or oliguria with progressive azotemia.[17,56] The choice of modality should be individualized according to hemodynamic stability, availability of resources, and institutional expertise. Intermittent hemodialysis (IHD) is appropriate for hemodynamically stable patients, while sustained low-efficiency dialysis (SLED) or continuous kidney replacement therapy (CKRT) is preferred in patients with shock or multiorgan dysfunction.[56] In resource-limited settings, acute peritoneal dialysis remains a viable option.[57,58] Given the frequent coexistence of coagulopathy, anticoagulation strategies should be carefully tailored, with preference for heparin-free dialysis or regional citrate anticoagulation where feasible. Early initiation of KRT in appropriately selected patients is associated with improved metabolic control and may reduce complications.[6–8]

Kidney Biopsy

Kidney biopsy is not routinely required in snakebite-associated AKI but may be considered in selected patients with atypical clinical courses or delayed renal recovery. Indications include persistent dialysis dependence or lack of renal recovery beyond 2–3 weeks, unexplained hematuria or heavy proteinuria, suspicion of acute interstitial nephritis (AIN), TMA, or ACN, and diagnostic uncertainty after exclusion of prerenal and obstructive causes.[7–9] Biopsy should be performed only after correction of coagulopathy and stabilization of the patient, using ultrasound guidance to minimize complications.[59] Histopathological findings in SAKI commonly include acute tubular necrosis (ATN), with less frequent findings of AIN, TMA, and CAN.[50,51] Biopsy results may aid prognostication, guide supportive care, and inform long-term follow-up strategies.

Discharge and Follow-up

Snakebite-envenomation-associated AKI survivors remain at significant risk for acute kidney disease (AKD) and subsequent progression to CKD, even after apparent clinical recovery.[6,7,10,18] Therefore, discharge planning should incorporate renal risk stratification, patient education, and a structured follow-up strategy. Patients should be discharged only after hemodynamic stability, resolution or stabilization of coagulopathy, recovery of urine output, and a clear trend toward improvement or stabilization of renal function. Those requiring ongoing dialysis should be referred to a nephrology service with clear documentation of the anticipated recovery trajectory.

Postdischarge follow-up should be protocolized and time-bound. Renal function (serum creatinine, estimated GFR), urine examination (dipstick for hematuria/proteinuria and urine albumin-to-creatinine ratio where feasible), blood pressure, and electrolyte status should be reassessed at 2–4 weeks, 3 months, and 12 months following discharge. Patients with incomplete renal recovery, persistent proteinuria or hematuria, hypertension, or reduced eGFR (<60 mL/min /1.73 m^2) should be managed as high-risk and followed more closely under nephrology care. Recovery from dialysis dependence should be documented, and vascular access should be removed only after sustained renal recovery.

Patient counseling is a critical component of AKD/CKD prevention.[60,61] Patients should be advised regarding adequate hydration, avoidance of nephrotoxic medications (including over-the-counter NSAIDs and herbal remedies), prompt medical evaluation for febrile illness or reduced urine output, and lifestyle measures to control blood pressure and metabolic risk factors.[61] Documentation of SAKI in discharge summaries is essential to alert future healthcare providers. At a systems level, linkage to primary care and nephrology follow-up, especially in rural populations, is vital to reduce long-term renal morbidity and prevent progression to CKD and ESKD.[62]

Implementation and Quality Improvement

Effective reduction in morbidity and mortality from SAKI requires not only evidence-based clinical management but also consistent implementation, audit, and quality improvement across healthcare facilities. Variability in access to ASV, dialysis services, laboratory support, and trained personnel contributes significantly to outcome disparities, particularly in resource-limited settings.[25,34] To promote uniform standards of care, the authors recommend the use of measurable quality indicators for critical care centers managing SAKI.

Table 4: Quality indicators for critical care centers managing SAKI

Indicator	*Numerator/denominator*	*Target*
Time from arrival to first ASV infusion	Patients receiving ASV within 60 minutes / all envenomed	≥ 80%
Appropriate ASV re-dosing by lab results/ bleeding	Cases with documented q6h coagulation profile guiding re-dose/ hemotoxic bites	≥ 90%
Early nephrology involvement	SAKI with KDIGO stage ≥2 seen by nephrology within 12 hours/ all stage ≥2	≥ 90%
KRT timeliness	SAKI meeting absolute indications dialyzed within 4 hours/ all indicated	≥ 95%
Avoidance of nephrotoxins	SAKI admissions without NSAIDs/ aminoglycosides/ contrast unless justified	≥ 95%
Postdischarge kidney follow-up	SAKI survivors with 3-month kidney review/ SAKI survivors	≥ 80%

ASV, antisnake venom; NSAIDs, nonsteroidal anti-inflammatory drugs

Table 5: SAKI toolkit for snakebite-associated AKI

Domain	*Key recommendations*	*Clinical tools*
Recognition	Maintain a high index of suspicion in all snakebite cases with oliguria, hematuria, edema, or systemic envenomation	Bedside urine output chart; dipstick for hematuria/proteinuria; point-of-care creatinine
Risk stratification	Identify risk factors for AKI and poor outcomes	Hemotoxic envenomation (Russell's viper, Echis); delayed ASV (>6 hours); hypotension/shock; coagulopathy/disseminated intravascular coagulation; rhabdomyolysis
Supportive therapy	Initiate early measures to prevent the progression of AKI	Prompt ASV as per national protocol; adequate hydration guided by central venous pressure/urine output; avoid nephrotoxins (NSAIDs, aminoglycosides, contrast); early management of hyperkalemia and acidosis
Kidney Replacement Therapy (KRT)	Early initiation improves survival; individualize based on resources	Indications: refractory hyperkalemia, severe metabolic acidosis, pulmonary edema, and uremic symptoms Preferred modality: IHD; CKRT for hemodynamically unstable patients, where available Peritoneal dialysis in resource-limited settings
Adjunctive measures	Provide comprehensive care beyond kidney support	Manage complications: bleeding, sepsis, and compartment syndrome; correct coagulopathy with FFP/cryoprecipitate; monitor for thrombotic microangiopathy and secondary sepsis
Follow-up and long-term care	Ensure renal recovery and monitor for CKD	Weekly creatinine for 1 month, then monthly up to 6 months; counsel patients on hydration and avoiding nephrotoxins; screen for CKD progression (eGFR, urine ACR)

ACR, albumin–creatinine ratio; AKI, acute kidney injury; ASV, antisnake venom; CKD, chronic kidney disease; CKRT, continuous kidney replacement therapy; DIC, disseminated intravascular coagulation; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; IHD, intermittent hemodialysis; NSAIDs, nonsteroidal anti-inflammatory drugs; SLED, sustained low-efficiency dialysis

These indicators are designed to monitor the timeliness of antivenom administration, appropriateness of renal support, avoidance of preventable nephrotoxicity, and continuity of postdischarge kidney care. Regular audit against these benchmarks can identify gaps in care, facilitate targeted interventions, and support institutional accreditation and capacity-building initiatives (Table 4).

Summary of Recommendations

SAKI remains a significant cause of morbidity and mortality in India, especially in rural and resource-limited settings.[6–9] Early recognition, risk stratification, and standardized supportive care are critical to improving outcomes. These recommendations propose a structured "SAKI Toolkit" that provides a stepwise framework covering recognition, risk assessment, supportive therapy, KRT initiation, and follow-up (Table 5). This toolkit serves as a practical bedside reference for general physicians, nephrologists, intensivists, and emergency physicians.

Conclusion

Snakebite envenomation remains a significant yet preventable cause of AKI in India, particularly in rural and resource-limited settings. These recommendations emphasize a structured, evidence-informed approach—encompassing rapid assessment, timely administration of antisnake venom, meticulous supportive care, early recognition of AKI, and appropriate use of KRT. The SAKI Toolkit aims to empower clinicians to streamline decision-making, minimize complications, and improve patient survival. Implementation of these recommendations requires not only clinical vigilance but also strengthening of referral networks, training of healthcare personnel, and public health measures for prevention and early presentation. With multidisciplinary collaboration and adherence to standardized protocols, morbidity and mortality from snakebite-associated AKI can be significantly reduced.

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REVIEW ARTICLE

Treatment of Tuberculosis in Renal Insufficiency

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Received: 31 December 2025; *Accepted:* 04 May 2026

Abstract

Tuberculosis (TB) is a significant global health challenge, particularly in patients with renal insufficiency, where both the disease and its treatment are complicated by altered pharmacokinetics, immunosuppression, and increased risk of drug toxicity. Management of TB in patients with renal insufficiency is complex and necessitates an individualized, multidisciplinary approach. Careful dose adjustments, regimen selection, management of comorbid conditions, regular monitoring, and adherence to current guidelines can optimize outcomes while minimizing adverse effects. This article reviews current strategies and evidence-based approaches for the treatment of TB in patients with renal insufficiency, with a focus on drug selection, dose adjustment, and monitoring for toxicity and efficacy.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1527

Introduction

Treatment of tuberculosis (TB) in renal insufficiency poses a difficult clinical problem because various anti-TB medications are cleared by the kidney.[1] On the one hand, it raises concerns about drug-induced toxicity because of impaired excretion by sick kidneys; on the other hand, it raises concerns about undertreating TB. Adequate peak serum concentrations in subsequent situations are typically low and of no therapeutic value. The therapeutic dose of antitubercular medications in hemodialysis patients with end-stage renal failure is another cause for concern because certain medications are cleared more readily than others.

Pathophysiology of Tuberculosis in Renal Insufficiency

The pathophysiology of TB in renal disease involves numerous interactions between the physiological changes of chronic kidney disease (CKD), immunological changes, and altered pharmacokinetics. Renal dysfunction decreases the host's ability to fight infections, increasing patients' risk of TB, and influences how the illness develops and manifests.[2] Altered immune function in CKD—cellular immunity plays a vital role in reducing *Mycobacterium tuberculosis* infection. T cells, macrophages, and cytokines like interferon-gamma (IFN-γ) play an important role in the immune response. In CKD, there is reduced T-cell activation and multiplication. Impaired macrophage function leads to decreased production of pro-inflammatory cytokines like IFN-γ and tumor necrosis factor-alpha (TNF-α), which are crucial for the development of granulomas. Chronic inflammation and uremia suppress innate and adaptive immune responses, leading to increased latent TB reactivation and new infections. *M. tuberculosis* often remains dormant within granulomas in immunocompetent individuals. Immune dysfunction due to CKD disrupts the granuloma structure, leading to reactivation of dormant bacilli and causing active infection. Systemic inflammation due to uremic toxin accumulation, oxidative stress, and a pro-inflammatory cytokine milieu are the hallmarks of CKD. Reduced pathogen clearance results from immune homeostasis being disrupted by chronic inflammation. Additionally, the uremic state lowers the expression of important receptors called toll-like receptors (TLRs), which makes it harder for the innate immune system to recognize and combat *M. tuberculosis*. Granulomas, which serve as a physical and immunological barrier to contain the germs, are the pathognomonic indication of TB. Granuloma formation and maintenance are impaired in CKD due to decreased production of TNF-α and IFN-γ. Reactivation or systemic spread of TB is caused by T-cell and macrophage dysfunction.

Chronic kidney disease leads to decreased renal excretion of TB medications, resulting in drug accumulation and potential toxicity.[3] The effectiveness of anti-TB medications is impacted by CKD-related edema and hypoalbuminemia, which change drug distribution and protein binding. Frequent hospital exposure, repeated use of vascular access points, and malnutrition in hemodialysis patients lead to increased risk of TB. Water-soluble drugs are removed during dialysis, leading to altered drug pharmacokinetics. Cautious timing of medicine delivery is important for optimal therapeutic drug levels. CKD is often associated with malnutrition, which causes immune dysfunction and increases the risk of TB. Repeated blood transfusions or treatment of anemia leads to iron overload, which promotes bacterial growth, as *M. tuberculosis* utilizes iron for replication. Hematogenous spread during primary TB or reactivation can lead to *M. tuberculosis* infection of the kidneys. The bacteria typically reside in the renal cortex, leading to granulomatous inflammation, tissue destruction, and cavitation. Renal TB presents with hematuria, sterile pyuria, and progressive renal damage, which may exacerbate preexisting CKD. Advanced renal TB can develop fibrosis, strictures, or calcification, decreasing renal function and complicating management. Together, TB and CKD produce a "vicious cycle" of disease progression. The systemic inflammatory state is made worse by active TB, which may hasten the development of CKD. Reduced drug clearance and toxicity risk make treatment less effective and raise the possibility of resistance or treatment failure. A thorough understanding of these pathophysiological processes is necessary to enhance patient outcomes and tailor TB treatment in renal insufficiency.

Dosing Recommendation for Adult Patients

Dosing of antitubercular drugs for renal insufficiency patients should be done according to creatinine clearance.[4] It is done with the help of the following formula, which is different for males and females, respectively. For males, it is calculated as ideal body weight (kg) × (140 – age)/72 × serum creatinine (mg/dL). For females, it is

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How to cite this article: Gupta N, Rani H, Kacker R, *et al.* Treatment of Tuberculosis in Renal Insufficiency. J Assoc Physicians India 2026;74(6):85–87.

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calculated as 0.85 × ideal body weight (kg) × (140 – age)/72 × serum creatinine (mg/dL).

The British Thoracic Society advocates dose reduction for drugs that are excreted by renal route, while the American Thoracic Society prefers increasing the dosing interval instead of decreasing the dose. Administration of drugs that are excreted by kidney should be changed by increasing the dosing interval if creatinine clearance falls below 30 mL/minute (Table 1). There is a paucity of data to guide the dosing recommendation if creatinine clearance is above 30 mL/minute, when standard doses should be prescribed. Rifampicin and isoniazid are eliminated by the liver, and they could be given in usual dose. Patients with slow hepatic acetylation of isoniazid could be given supplemental pyridoxine to prevent peripheral neuropathy. Alteration in dose of ethambutol, which is 80% excreted by kidney, should be made if creatinine clearance falls below 70 mL/minute, to lowest possible dose, but if it falls below 30 mL/minute, it should be given intermittently as three times a week in dose of 15–20 mg/kg body weight. Pyrazinamide is metabolized in liver, but its metabolites, pyrazinoic acid and 5-hydroxypyrazinoic acid, are excreted by kidney; thus, the drug should be given three times a week, in dose of 25–35 mg/kg body weight, to avoid toxicity if creatinine clearance falls below 30 mL/minute (Table 1). Apart from this, the risk of developing hyperuricemia with pyrazinamide is increased in cases of renal insufficiency. Since streptomycin is predominantly excreted by renal route and removed by hemodialysis to a significant extent (about 40%), it should be administered three times a week in dose of 12–15 mg/kg body weight (Table 1) in patients with renal insufficiency with creatinine clearance below 30 mL/minute, and those on hemodialysis. Since the pharmacokinetics of other aminoglycosides is similar to streptomycin, they need similar modification of dose. Renal clearance of fluoroquinolones varies from drug to drug. It is greater for levofloxacin than moxifloxacin. Dose adjustment for fluoroquinolones is recommended if creatinine clearance is <30 mL/minute (750–1000 mg three times a week). Ethionamide needs no or little alteration of administration as it is not excreted by kidney. The dose of cycloserine should be modified if creatinine clearance falls below 30 mL/minute or the patient is on hemodialysis. It should be changed to 500 mg thrice a week or 250 mg daily (Table 1); evidence for safety of 250 mg daily dose of cycloserine is not yet established with regard to neuropathy,

Table 1: Dosing recommendation for adult patients with renal insufficiency or undergoing hemodialysis

Drug	*Change in frequency*	*Dose and frequency in patients with creatinine clearance <30 mL/minute or those on hemodialysis*
Isoniazid	No change needed	300 mg daily
Rifampicin	No change needed	600 mg daily
Pyrazinamide	Yes	25–35 mg/kg per dose three times a week
Ethambutol	Yes	15–25 mg/kg per dose three times a week
Rifabutin	No	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity
Rifapentine	No	No adjustment necessary
Levofloxacin	Yes	750–1000 mg per dose three times a week
Moxifloxacin	No	No adjustment necessary
Gatifloxacin	No	400 mg three times a week
Ofloxacin	Yes	600–800 mg per dose three times per week
Cycloserine	Yes	250 mg daily or 500 mg/dose three times per week
Terizidone		Recommendations not available
Ethionamide	No change needed	1 gm daily
PAS	No change needed	4 g/dose, twice daily maximum dose
Streptomycin	Yes	12–15 mg/kg/dose twice or three times a week
Capreomycin	Yes	12–15 mg/kg/dose twice or three times a week
Kanamycin	Yes	12–15 mg/kg/dose twice or three times a week
Amikacin	Yes	12–15 mg/kg/dose twice or three times a week
Linezolid	No change needed	Usual dose is 600 mg twice daily but can be reduced to 600 mg once daily after 4–6 weeks
Clofazimine	No	No dose adjustment required
Amoxicillin and clavulanic acid	Yes	Dose used is 625 mg twice daily; 1000 mg should not be used
Bedaquiline	No	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment; use with caution)
Delamanid	No	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment; use with caution)
Imipenem/cilastatin	Yes	For creatinine clearance 20–40 mL/minute: dose 500 mg every 8 hours; for creatinine clearance <20 mL/minute: dose 500 mg every 12 hours
Meropenem	Yes	For creatinine clearance 20–40 mL/minute: dose 750 mg every 12 hours; for creatinine clearance <20 mL/minute: dose 500 mg every 12 hours
High-dose isoniazid		Recommendations not available
Pretomanid	No	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment; use with caution)

and 500 mg three times a week is preferred in this regard. Serum concentrations of drug should be monitored. PAS is not safe in renal disease and should only be given if no other alternatives are available, as it may aggravate metabolic acidosis. If it is to be given, it should be given at dose of 4 g/dose, twice daily. Since thioacetazone is excreted in urine, it should not be given to patients with renal disease. The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency, but the metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction. Therefore, no dose adjustment is recommended for patients with renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites. Clofazimine is safe in patients having renal disease as excretion is mainly through biliary route. Imipenem is highly nephrotoxic, but the addition of cilastatin lessens its toxicity. No dosage adjustment is required in patients with mild to moderate renal impairment with bedaquiline (dosing not established in severe renal impairment; use with caution). No dosage adjustment is required in patients with mild to moderate renal impairment with delamanid. Dosing is not established in severe renal impairment; use with caution and only when the benefits outweigh the risks.

Hemodialysis eliminates the medication prior to its therapeutic impact, although much less medication is expected to be eliminated if the medication is given enough time prior to hemodialysis to allow for its distribution throughout the body.[5] Drug administration following hemodialysis will, on the one hand, prevent early drug removal and, on the other, enable directly observed treatment short course (DOTS). Premature removal of second-line drugs by hemodialysis may further aggravate the problem of drug resistance by exposing the tubercle bacillus to subtherapeutic drug concentration.

Hemodialysis eliminates pyrazinamide to a considerable degree while removing rifampicin, isoniazid, and ethambutol to negligible degrees. Therefore, in patients with end-stage renal disease receiving hemodialysis, a further dose of isoniazid, rifampicin, and ethambutol is not required. Similar to streptomycin, if medications like kanamycin, amikacin, and capreomycin are administered right before hemodialysis, approximately 40% of them are eliminated from the blood. Since hemodialysis does not remove ethionamide or fluoroquinolones, their dosage does not need to be changed in this case. If medication is used following hemodialysis, there are typically no major complications.

Ideally, it is important to monitor serum concentrations of drugs in persons with renal failure who are taking aminoglycosides, cycloserine, or ethambutol to provide effective therapeutic drug concentration and also to minimize dose-related toxicity.[6] Patients with renal failure may have other comorbid conditions, like diabetes mellitus and gastroparesis, which may further complicate the pharmacokinetics of drugs.[7] Presently, there are no data to guide administration of antitubercular drug use in patients undergoing peritoneal dialysis, and for this subset of patients, recommendations for hemodialysis are applicable. The safest regimen that is being advised in patients diagnosed as new cases of TB with renal insufficiency is rifampicin, isoniazid, and pyrazinamide for 2 months followed by rifampicin and isoniazid for the next four months.

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REVIEW ARTICLE

Antiretroviral Therapy in India (2025): Drugs, Indications, Contraindications, Mechanisms, and Prophylaxis (PEP/PrEP)

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Received: 25 November 2025; *Accepted:* 31 December 2025

Abstract

Background: India has made major gains in HIV control, with nationwide scale-up of antiretroviral therapy (ART), routine viral load monitoring, and simplified dolutegravir-based regimens. Yet gaps persist in differentiated service delivery, drug-resistance surveillance, and prevention implementation (PEP/PrEP).

Objectives: To provide a comprehensive, India-focused review of currently available antiretroviral drugs and fixed-dose combinations (FDCs), indications and contraindications for ART initiation, core mechanisms of action by class, regimen selection and monitoring, and detailed, practical guidance on HIV postexposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP), with attention to 2024–2025 updates.

Methods: Narrative review of national guidance (NACO), WHO recommendations, and key implementation documents and peer-reviewed Indian literature (2018–2025), emphasizing policy-relevant updates and practical algorithms.

Key findings: (1) First-line ART in India is an FDC of tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD), with alternatives guided by renal, hepatic, pregnancy, TB cotreatment, and toxicity considerations. Viral load monitoring and "Treat All" remain policy cornerstones. (2) *PEP*: NACO's national PEP document continues to list a 28-day triple regimen with TDF + 3TC + EFV started as soon as possible (preferably ≤2 h; within 72 h). Several institutions have operationalized DTG-based PEP (TDF/3TC/DTG) in line with broader ART updates and WHO's 2024 PEP guidance favoring 3-drug regimens. (3) *PrEP in India*: DCGI approved TDF/FTC for PrEP; national technical guidance exists, but programmatic rollout remains uneven. Global prevention options expanded with FDA approval (June 2025) of twice-yearly injectable lenacapavir for PrEP. Indian availability will depend on future regulatory decisions and access arrangements.

Conclusion: India's ART platform is strong and increasingly INSTI-based. Scaling PrEP, standardizing DTG-aligned PEP, fortifying viral load and resistance monitoring, and integrating long-acting prevention as it becomes available are the next priorities.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1559

Introduction

India's National AIDS Control Program (NACP) has progressively simplified treatment, expanded access to FDCs, and strengthened routine viral load (VL) testing—core enablers of the "Treat All" policy (ART for all PLHIV regardless of CD4 count or clinical stage).[1–3] The 2021 NACO guidance established TLD as the preferred first-line regimen, aligned with global best practices, while subsequent testing/guideline updates emphasize differentiated service delivery and standardized VL monitoring.[1–3]

Despite these gains, India continues to face high TB coinfection rates, regional variability in service delivery, and prevention gaps among key populations.[1–3] Consolidated WHO guidance (2021–2024) underpins many national recommendations, including a public-health approach to ART, PEP, and PrEP.[3,4]

Scope

This review synthesizes Indian programmatic guidance and global recommendations to present (1) current ARV classes, mechanisms, and drugs available in India; (2) indications, contraindications, and regimen selection; (3) monitoring and switching; and (4) India-specific guidance and practical algorithms for PEP and PrEP, including 2024–2025 updates.[1–18]

Antiretroviral Drugs Available in India and Mechanisms of Action

Drug Classes and Core Mechanisms

NRTIs/NtRTIs (e.g., TDF, 3TC, FTC, ABC, AZT) are nucleoside analogs that, once phosphorylated (NRTIs), compete at reverse transcriptase and terminate viral DNA chain elongation.[1–3]

NNRTIs (e.g., EFV, NVP, ETR) bind an allosteric site on reverse transcriptase, inducing conformational changes and noncompetitive inhibition; resistance can emerge rapidly with low adherence.[1–3]

Integrase strand transfer inhibitors (INSTIs) (e.g., DTG, BIC, RAL) block the strand-transfer step of HIV integrase, preventing proviral DNA integration; DTG has a high barrier to resistance and excellent tolerability, driving its first-line selection in India.[1–3]

Protease inhibitors (PIs) (e.g., ATV, LPV/r) inhibit HIV protease, blocking polyprotein cleavage and producing immature, noninfectious virions; typically reserved for second-line therapy given metabolic effects and interactions.[1–3]

Entry/fusion inhibitors/CCR5 antagonists (e.g., enfuvirtide, maraviroc) target viral entry; not widely used programmatically in India due to cost, monitoring needs, and availability.[1–3]

Emerging classes include capsid inhibitors and maturation inhibitors. Of special note for prevention, the capsid inhibitor lenacapavir received FDA approval in June 2025 as twice-yearly PrEP in the US, with pending/ongoing submissions elsewhere; Indian regulatory status is awaited.[12–15]

Drugs and Fixed-Dose Combinations in Indian Practice

Preferred first-line FDC (adults/adolescents): TDF/3TC/DTG (TLD) once daily—programmatically favored for potency, tolerability, and high resistance barrier. Alternatives are chosen when TDF is contraindicated or when TB co-treatment, pregnancy, or organ dysfunction requires modification.[1–3]

Second-line options: Boosted PI-based regimens (e.g., LPV/r + two NRTIs not used in first-line) remain standard after confirmed virologic failure on first-line; DTG-based second/third-line constructs are increasingly used per updated national guidance.[1–3]

Pediatric regimens: Weight-band dosing with DTG-containing backbones is expanding, consistent with international

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How to cite this article: Deshwal R. Antiretroviral Therapy in India (2025): Drugs, Indications, Contraindications, Mechanisms, and Prophylaxis (PEP/PrEP). J Assoc Physicians India 2026;74(6):88–92.

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pediatric recommendations (country adoption proceeds as formulations become available) (Table 1).[1–3]

Indications and Contraindications for ART

Treat-All: Initiation for Every PLHIV

India adopted treat-all in April 2017 and continues to recommend immediate ART initiation after diagnosis, once readiness and baseline labs are assessed.[1–3] Early ART improves survival, reduces OI risk, and underpins treatment-as-prevention.[1–3]

Priority groups (initiate without delay): pregnant/breastfeeding women; TB or HBV/HCV co-infection; advanced disease; serodiscordant partners; children/adolescents.[1–3]

Baseline Evaluation

Before starting ART: VL (if available), CD4 (for baseline status), creatinine/eGFR, hepatic panel, hemoglobin (AZT), pregnancy testing, HBV/HCV screening, TB screening (symptom screen ± GeneXpert per clinical context), STI screen as indicated, and adherence counseling.[1–3,17]

Contraindications and Cautions

Absolute contraindications are uncommon; regimen choice/adjustment is driven by:

- Hypersensitivity (e.g., abacavir).
- Renal impairment (avoid/adjust TDF).
- Hepatic dysfunction.
- Significant drug–drug interactions (e.g., rifampicin with DTG/PI—dose/timing adjustments).
- Pregnancy (safety-guided selection).
- Certain OIs (e.g., cryptococcal meningitis—time ART carefully to avoid severe IRIS).
- Adherence concerns (Fig. 1).[1–3,17]

Regimen Selection, Monitoring, and Switching

First-Line: TLD

TLD (TDF/3TC/DTG) is the national preferred first-line for adults/adolescents based on potency, tolerability, pill burden, and resistance barrier; AZT- or ABC-based alternatives are used when TDF is unsuitable.[1–3]

Special Situations

- *TB co-treatment*: Rifampicin induces DTG metabolism; dose DTG 50 mg twice daily during rifampicin or consider EFV-based alternatives if DTG BID is not feasible. Monitor hepatotoxicity when pairing ARVs with anti-TB therapy.[1–3]
- *HBV co-infection*: Choose TDF-containing regimens when possible; avoid abrupt discontinuation to prevent HBV flares[1–3,17]
- *Pregnancy*: DTG-based regimens are now widely accepted in pregnancy; follow the national protocol and document counseling.[1–3]
- *Renal impairment*: Avoid or adjust TDF if eGFR is < 50–60 mL/min (programmatic cutoffs vary); consider AZT/ABC backbones with appropriate monitoring.[1–3,17]

Monitoring

Virologic: VL at ~6 months after initiation and routinely thereafter; VL-driven management is the standard.[1–3,17]

Laboratory: Creatinine/eGFR (TDF), liver enzymes (NNRTIs/PIs/INSTIs), hematology (AZT), lipids/glucose (PIs/INSTIs), pregnancy tests as applicable.[1–3]

Clinical/adherence: At every visit, use differentiated models for stable patients.[1–3]

Defining and Managing Failure

Virologic failure:

- Persistent VL >1,000 copies/mL after ≥6 months on ART with good adherence.
- Confirm adherence and interactions; repeat VL.
- If confirmed, switch to second-line (often boosted PI-based with two NRTIs not previously used; DTG-based second/third-

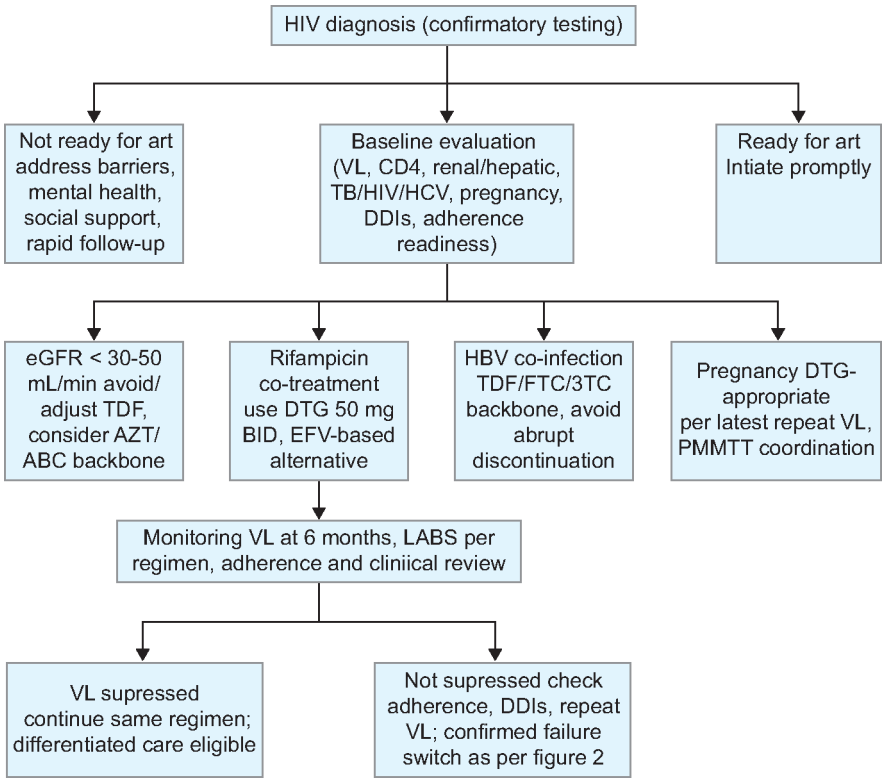


Fig. 1: ART initiation and selection (India, 2025)

Table 1: Antiretroviral classes, mechanisms, and common Indian agents

Class	*Core mechanism*	*Key agents in India*	*Typical programmatic role*
NRTIs/NtRTIs	Chain termination at RT	TDF, 3TC, FTC, ABC, AZT	Universal backbones; TDF/3TC commonly paired with DTG
NNRTIs	Allosteric RT inhibition	EFV, NVP, ETR	Legacy first-line; now alternatives
INSTIs	Block DNA strand transfer	DTG, RAL, (BIC limited availability)	Preferred first-line anchor
PIs (boosted)	Inhibit protease maturation	LPV/r, ATV/r	Second-line/salvage
Entry/fusion	Block entry/fusion	Maraviroc, enfuvirtide	Limited use

line per updated guidance and availability) (Fig. 2).[1–3,9,10]

Postexposure Prophylaxis (PEP) in India

Indications and Timing

Postexposure prophylaxis is indicated after occupational (e.g., needlestick) or nonoccupational high-risk exposures (e.g., condomless sex with a known positive partner, sexual assault, needle sharing), ideally as soon as possible—preferably within 2 hours and not later than 72 hours. Duration is 28 days.[4–6]

Recommended Regimens

National (NACO) PEP guidance: Lists TDF 300 mg + 3TC 300 mg + EFV 600 mg once daily for 28 days; use single-pill FDC where available.[5]

Evolving/operational practice in India: Several government facilities (e.g., ESIC circulars) have operationalized TDF/3TC/DTG (TLD) once daily as PEP, reflecting broader national ART shifts and simplicity/tolerability, while WHO's 2024 PEP guideline recommends 3-drug regimens and issuing a full 28-day prescription up front. Local protocols should be followed, with attention to pregnancy, renal function, and drug interactions (Fig. 3).[4–6]

Special Populations

- *Pregnancy*: PEP is safe and recommended after substantial exposure; choose pregnancy-appropriate regimens and counsel on risk/benefit.[4–6]
- *Renal impairment*: Avoid or adjust TDF; consider alternative NRTI backbones per renal function.[4–6]
- *Source unknown/not testable*: Base decision on exposure type, local prevalence, and patient preference after counseling[4–6]

Programmatic Challenges in India

Rapid access (especially after-hours), clarity of protocols across facilities, and ensuring full 28-day supply at first visit remain common issues; standardized training and stocking at EDs and casualty are recommended.[4–6]

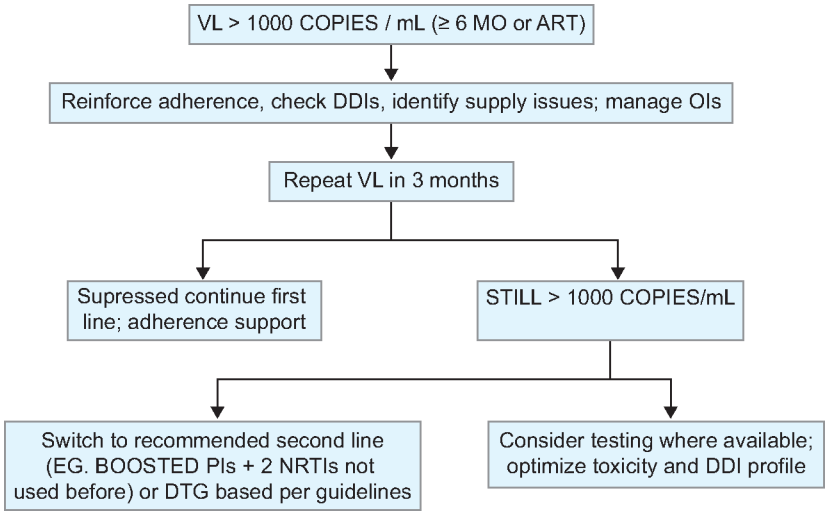


Fig. 2: Switching pathway (programmatic)

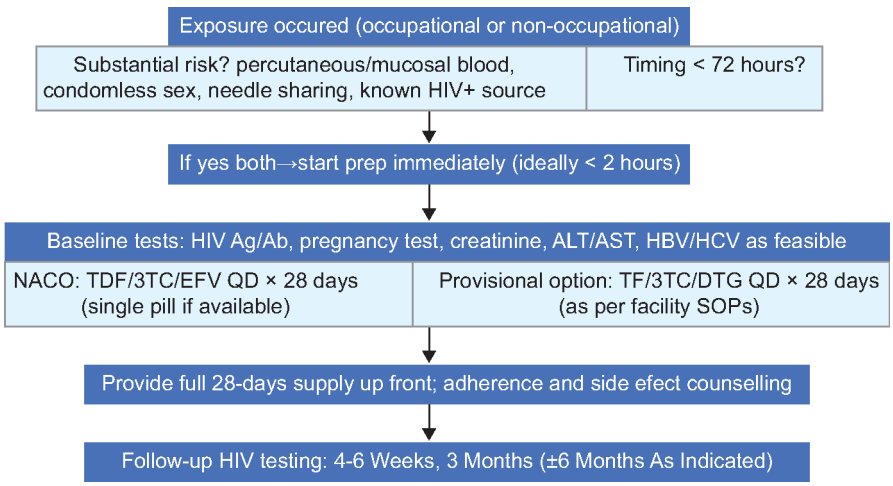


Fig. 3: PEP decision algorithm (adults/adolescents)

Pre-exposure Prophylaxis (PrEP) in India

Policy Status, Indications, and Candidates

Regulatory status: DCGI-approved TDF/FTC for PrEP; NACO released National Technical Guidelines for PrEP. National scale-up has been cautious, with pilots and targeted implementation discussed; rollout varies by state and service platform.[7,8,11]

Candidate groups: HIV-negative persons at substantial risk—MSM and transgender persons with condomless anal sex, serodiscordant partners without viral suppression, sex workers with inconsistent condom use, people who inject drugs (needle sharing), and individuals with recurrent STIs or PEP use. Baseline HIV testing is mandatory; assess renal function and HBV status (Table 2).[7,8,11]

PrEP Regimens and Dosing

Daily oral PrEP: TDF/FTC 300/200 mg once daily (preferred) or TDF/3TC where FTC is not available, with attention to evidence-based and local guidance.[7,8,11]

Event-driven (2-1-1) is an option in some populations (e.g., MSM) where supported; ensure clear counseling on dosing windows and contraindications.[7,8]

Long-acting options (global): Lenacapavir received US FDA approval (June 18, 2025) as a twice-yearly PrEP; WHO welcomed the approval. EMA issued a positive opinion later in 2025. Indian availability will depend on future regulatory submissions and access agreements. For now, India remains oriented to oral TDF-based PrEP (Fig. 4).[12–15]

Table 2: PrEP eligibility and baseline work-up (India)

Domain	*Recommendation*
Eligibility	HIV-negative, substantial ongoing risk; willing and able to adhere to and attend follow-up
Baseline	HIV Ag/Ab test, creatinine/eGFR, HBV serology (HBsAg/anti-HBc), pregnancy test if applicable, STI screen per risk
Counseling	Adherence, daily vs event-driven (where appropriate), condoms, harm reduction, symptoms of acute HIV, follow-up schedule
Follow-up	HIV test q3 months; renal function q6–12 months; STI screen per risk; adherence support

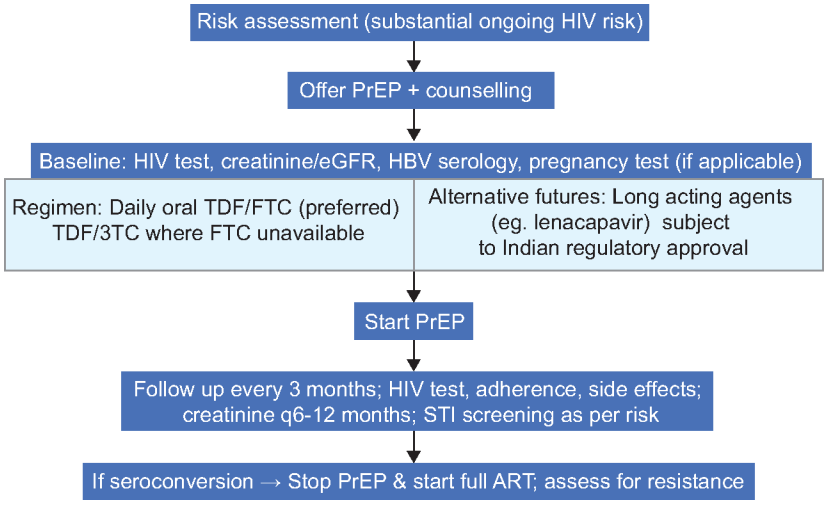


Fig. 4: PrEP workflow

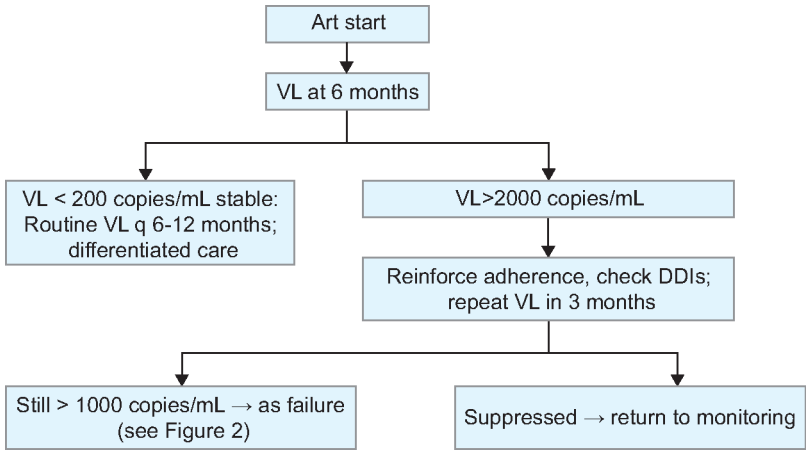


Fig. 5: VL-anchored monitoring cycle

Table 3: PEP quick checklist (adults/adolescents)

Step	*Action*
Exposure triage	Assess type, timing (≤72 h), source status
Baseline	HIV Ag/Ab, pregnancy test, creatinine, ALT/AST ± HBV/HCV
Start NOW	NACO 2021: TDF/3TC/EFV QD × 28 d; Institutional: TDF/3TC/DTG QD × 28 d where adopted (4–6).
Counseling	28-day supply up front (per WHO), adherence, side effects, risk reduction (4–6)
Follow-up	HIV test at 4–6 weeks and 3 months (± 6 months as indicated)

Table 4: PrEP quick checklist

Step	*Action*
Eligibility	HIV-negative, substantial ongoing risk; willing for quarterly follow-up
Baseline	HIV test, creatinine/eGFR, HBV serology, pregnancy test if applicable
Regimen	Daily TDF/FTC preferred (TDF/3TC acceptable where FTC unavailable per local guidance)
Counseling	Adherence, condoms/harm reduction, acute HIV symptoms, missed-dose plans
Follow-up	HIV test q3 months; creatinine q6–12 months; STI screen per risk

Contraindications and Safety

Do not start PrEP if HIV status is positive/uncertain (risk of resistance). Avoid or adjust TDF if eGFR <60 mL/min (per local policy). In HBV co-infection, TDF-based PrEP also treats HBV; avoid abrupt discontinuation to prevent flares. Pregnancy and breastfeeding: PrEP can be considered with counseling; follow current guidance.[7,8,11]

Implementation Considerations in India

Persistent barriers include awareness, stigma, logistics of quarterly HIV testing, renal monitoring, and linkage for key populations. Implementation science from India underscores the need for demand creation, community-engaged delivery models, and integration with STI and harm-reduction services.[7,8,11,17,18]

Drug–Drug Interactions, Toxicity, and Special Populations

Rifampicin

Induces UGT/CYP; DTG BID is recommended with rifampicin to maintain levels; monitor closely if EFV alternatives are used.[1–3,17]

Renal Disease

Favor AZT/ABC backbones when eGFR <30–50 mL/min; reassess dosing for TDF; consider TAF where available (programmatic availability may be limited).[1–3,17]

Metabolic Risk

PIs (and to a lesser extent INSTIs) affect lipids/glucose; periodic lipid/glucose monitoring is suggested in patients with NCD risk.[1–3,10]

Pregnancy

DTG-based regimens are acceptable; document counseling; coordinate with PMTCT services and newborn prophylaxis per national guidance.[1–3,17]

HBV/HCV

Choose TDF-containing backbones for HBV; comanage with DAAs for HCV; avoid discontinuations that precipitate HBV flares.[1–3,17]

Service Delivery: Monitoring, VL, and Differentiated Care

India is strengthening routine VL monitoring and differentiated service delivery (multimonth dispensing, fast-track refills for stable patie nts).[1–3,17,18] Continued investment in laboratory capacity and logistics is essential to maintain suppression and achieve 95-95-95 (Table 3 and Fig. 5).[1–3,17,18]

PEP and PrEP: Practical Checklists for Clinics

The practical checklists are presented in Tables 3 and 4.

Future Directions

Long-acting Prevention

Twice-yearly lenacapavir for PrEP in the US opens a path to improved adherence—India will need regulatory review, pricing/access strategies (e.g., voluntary licensing),

and delivery models capable of injection scheduling and follow-up (Table 4).[12–15]

Resistance Surveillance

As INSTI-based regimens dominate, systematic resistance monitoring (especially postfailure) should expand.[1–3,9,10]

PrEP Scale-up

Implement at-scale, culturally competent models in key populations; integrate with STI services and community networks.[7,8,11,16–18]

PEP Standardization

Align national PEP regimens with current programmatic ART (DTG-based) where feasible, while ensuring consistent availability and training; WHO now favors 3-drug PEP with full 28-day dispensing.[4–6]

Differentiated Care

Expand multimonth dispensing and community ART refills to reduce clinic burden and improve retention.

Conclusion

India's HIV program has successfully transitioned to simplified, potent TLD-based first-line ART with routine VL monitoring. To consolidate gains and accelerate incidence reduction, India should scale PrEP, harmonize PEP with contemporary regimens, and invest in laboratory systems and resistance surveillance, while preparing for long-acting prevention as regulatory and access pathways mature. With consistent policy attention and implementation science, the program can advance toward 95-95-95 and beyond.

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POINT OF VIEW

Glucagon Agonist Therapies and Vision Loss: Balancing Promise with Prudence in India

Abhyuday Saxena[1], Anupam Prakash[2*]

Received: 13 February 2026; *Accepted:* 14 April 2026

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual incretin therapies such as tirzepatide have transformed the management of type 2 diabetes mellitus and obesity, with expanding cardiometabolic indications and rapid market growth globally and in India. However, emerging postmarketing evidence has raised concerns regarding ocular safety. Pharmacovigilance analyses, cohort studies, and case reports suggest an association between GLP-1–based therapies and ophthalmic adverse events, including early worsening of diabetic retinopathy and, more concerningly, nonarteritic anterior ischemic optic neuropathy (NAION)—a potentially irreversible cause of sudden vision loss in adults over 50 years. Although the absolute risk appears very low, regulatory agencies, including the WHO and European Medicines Agency, now recognize NAION as a very rare adverse effect of semaglutide, and similar signals are being explored for other agents, suggesting a possible class effect.

Proposed mechanisms include altered optic nerve head perfusion, sympathetic-mediated vasoconstriction, and rapid glycemic shifts affecting vascular autoregulation; however, causality remains unproven. In India, where over 100 million adults live with diabetes and obesity rates are rising, even rare adverse events may translate into substantial public health impact, particularly given limited access to ophthalmic care and increasing unsupervised drug use.

We advocate a balanced approach: baseline ophthalmic evaluation in high-risk individuals, informed consent regarding visual symptoms, early referral for visual complaints, strengthened pharmacovigilance, and coordinated endocrinology–ophthalmology surveillance systems. As newer triple agonists approach clinical use, integrating ocular safety into prescribing frameworks is imperative. Metabolic gains must not come at the cost of preventable vision loss.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1507

Background

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, liraglutide, dulaglutide, and dual GLP-1 and GIP receptor agonists like tirzepatide, appears to be a transformative advance in medical care. Initially introduced for type 2 diabetes mellitus (T2DM), the therapeutic role of glucagon-based therapies (GLP-1RA and dual GLP-1 and GIP agonists) has expanded to obesity management and cardiometabolic care as well.[1,2] The global market for GLP-1 receptor agonists is a rapidly growing, multibillion-dollar industry with a size of USD 53.46 billion in 2024, and about 6% of the US adult population taking GLP-1 RAs.[3,4]

India, home to an estimated 101 million people with diabetes[5] and among the fastest-growing obesity markets globally, is likely to have a similar widespread adoption. The Indian market size for GLP-1 receptor agonists was USD 110.55 million in 2024 and is projected to grow at 34.3% from 2025 to 2030.[6]

Semaglutide-based drugs currently hold a significant market share with increasing demand for newer formulations.[7,8] The tirzepatide molecule has also come on the anvil with a bang, and with a tremendous marketing push.

The key drivers include rising obesity and diabetes rates, expanding therapeutic uses, innovative drug formulations such as oral and combination therapies, and increased demand supported by social media and direct-to-consumer advertising. However, postmarketing surveillance has uncovered a rare but devastating safety issue: association between GLP-based therapies and ophthalmic side effects, including progression of diabetic retinopathy (DR) and, most seriously, nonarteritic anterior ischemic optic neuropathy (NAION), a leading cause of irreversible optic neuropathy in adults over 50 years.[9–11]

Cause of Concern

Blurred vision and visual impairment are among the most frequently reported ocular adverse events, which may occur within days of starting GLP-based therapies.[9,10] Evidence suggests a transient increase in the risk of early-stage diabetic retinopathy with GLP-1 RAs, especially when associated with rapid HbA1c reductions,[12,13] although long-term use is not uniformly associated with increased vision-threatening diabetic retinopathy.[14] A recent meta-analysis showed that albiglutide is responsible for these trends, as it is significantly associated with a higher risk of early-stage DR compared to placebo and a lower risk of late-stage DR compared to insulin. Large-scale studies, therefore, indicate that monitoring should be intensified during the initial months of treatment.[13,15] Other rare events associated with GLP-based therapies include retinal detachment, retinal tears, vitreous hemorrhage, papilledema, macular edema/holes, and acute visual field defects.[11]

Multiple studies also implicate GLP-based therapies with an elevated risk of development of NAION, which is a rare but potentially sight-threatening side effect that may result in permanent vision loss and deserves special attention. It presents with sudden, painless, monocular loss of vision, frequently noticed on waking up in the morning, and is associated with optic disk edema. Multiple matched cohort studies involving a large number of patients have demonstrated a higher risk of NAION among those treated with GLP-1 RAs compared to those using other antidiabetic or antiobesity medications.[16,17] Hathaway et al.[18] showed a positive association between semaglutide and NAION in overweight and diabetic cohorts, with a higher risk of NAION in overweight users (hazard ratio: 7.6 in the overweight cohort; 4.3 in diabetics). Case reports describe NAION developing in patients even without classic risk factors, with the temporal relationship closely following initiation of liraglutide or semaglutide therapy, further supporting the clinical suspicion of a drug-induced mechanism.[19] Although a recent meta-analysis[20] failed to detect a significant detrimental effect of GLP-1 RAs therapy on ischemic optic neuropathy, the confidence

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How to cite this article: Saxena A, Prakash A. Glucagon Agonist Therapies and Vision Loss: Balancing Promise with Prudence in India. J Assoc Physicians India 2026;74(6):94–96.

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interval reported was very wide, showing that the number of observed events could have been insufficient to yield a significant result.

The World Health Organization (WHO) and European regulatory authorities now recognize NAION as a very rare side effect of semaglutide, potentially affecting up to 1 in 10,000 users, and have issued alerts for healthcare professionals to monitor for visual symptoms during therapy.[21,22] This chronological sequence: epidemiological signal, regulatory acknowledgment, and international advisories, suggests that the association cannot be dismissed as anecdotal. Therefore, early opinions on the ocular safety of GLP-based therapies such as semaglutide[23] have changed with new evidence showing a potential risk of NAION linked to these drugs, warranting caution when prescribing them in India. Although rare, this serious side effect calls for careful patient monitoring and informed consent.

Emerging evidence implicates not only GLP-1 RAs such as semaglutide but also tirzepatide, which is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1.[17,24] Regulatory agencies and the Food and Drug Administration (FDA) Sentinel system recognize this may be a class effect.[25]

Proposed Mechanisms

The proposed mechanisms underlying the association between GLP-based therapies and NAION remain speculative, but several hypotheses have emerged. Proposed explanations include:

- Direct action on optic nerve perfusion: Stimulation of GLP-1 receptors in the optic nerve head may alter local blood flow or autoregulation, potentially predisposing to ischemic events, particularly in individuals with anatomical susceptibility (small/crowded disks).[19,26]
- Systemic and sympathetic nervous effects: GLP-based therapies may activate the sympathetic nervous system, leading to transient vasoconstriction and reduced optic nerve perfusion, serving as a "second hit" in patients predisposed to NAION.[19,27]
- Rapid glycemic modulation: Rapid improvement in glycemic control induced by GLP-based therapies may affect vascular autoregulation and tissue oxygenation, making the optic nerve more vulnerable to ischemia, though evidence supporting this is limited and indirect.[11]

Mechanistic links remain unproven, highlighting the need for prospective research to conclusively establish causation.

Indian Context

For India, these safety concerns have greater implications:

- Population vulnerability: India has one of the world's highest burdens of diabetes patients, estimated to be over 101 million adults as of 2025, accompanied by growing obesity rates resulting from urbanization and rapid lifestyle changes.[5] This large high-risk population amplifies the absolute impact of even rare drug-associated adverse events, such as NAION or sight-threatening retinopathy.
- Increased associated risk factors: The unique vulnerability of the Indian population to earlier onset of cardiovascular[28,29] and microvascular diseases,[30,31] can exacerbate the ocular adverse effects of GLP-based therapies, especially NAION.
- Limited access to healthcare: Specialist ophthalmic services remain concentrated in urban tertiary centers, with rural and semiurban populations often facing delayed diagnosis and management of ocular adverse events.[32,33] Regular ophthalmologic monitoring for patients on GLP-based therapies is thus often not feasible, increasing the risk of undetected progression of retinopathy or NAION.
- Unregulated access: GLP-based therapies are increasingly accessible through online pharmacies and informal retail outlets without adequate prescription oversight or ophthalmologic evaluation, raising concerns about unsupervised use and insufficient monitoring.[34]

Thus, even a rare adverse event can translate into a significant public health burden for India.

Clinical and Regulatory Imperatives

For Clinicians

- Baseline evaluation: While there are no preexisting ophthalmic signs that can identify those at risk of developing NAION, a comprehensive ophthalmological examination should precede GLP-based therapy initiation, especially in patients >50 years or with vascular comorbidities. A small crowded disk may be considered a relative contraindication for their use.
- These drugs may be avoided in patients with preexisting visual impairment due to other causes or with a predisposition for the development of NAION.
- Patient counseling: Informed consent must include a discussion of sudden, painless vision loss.
- Monitoring: Patients should be instructed to report any visual disturbance promptly.
- Discontinuation: Immediate cessation of therapy and shift to alternate treatment options for glycemic control, along with urgent ophthalmology referral, is essential upon suspicion of NAION.

For Policymakers and Regulators

- Label updates: The Central Drugs Standard Control Organization (CDSCO) and Drug Controller General of India (DCGI) must mandate warnings in prescribing information.
- Pharmacovigilance: The Pharmacovigilance Program of India (PvPI) should issue a targeted safety alert. Long-term surveillance of visual outcomes in patients on these drugs is essential.
- Professional guidance: The Indian Council of Medical Research (ICMR) should formulate consensus-based recommendations for safe prescribing.
- Development of risk stratification tools to identify the highest-risk patients must be done.
- Research to determine mechanisms, predictive biomarkers, and evidence-based protocols is urgently needed. Until then, clinical practice must prioritize informed caution.

Ethical and Practical Considerations

GLP-based therapies are poised to be a transformative therapy in reducing cardiovascular risk, aiding weight loss, and improving glycemic control. However, the irreversible and life-altering nature of NAION necessitates caution and shared decision-making. Patients deserve to know that, while the risk is very rare, the consequences can be catastrophic.

Recommendations for India

- National adverse event registry linking endocrinology and ophthalmology practices.
- Inclusion of ocular risk warnings in Indian prescribing guidelines and packaging.
- Cross-disciplinary education for physicians, emphasizing early recognition.
- Prioritization of high-risk groups (elderly, crowded disks, vascular comorbidities) for counseling and closer monitoring.

Conclusion

GLP-based therapies represent a breakthrough in diabetes and obesity management. However, the increased association with NAION—though rare—cannot be ignored. For India, with its vast population at risk and systemic vulnerabilities, the stakes are especially high. As physicians, regulators, and researchers, our responsibility is clear: to integrate ocular safety vigilance into routine GLP-based therapy prescribing. It is essential to ensure that metabolic health is not at the cost of vision. With triple agonist therapies, viz., retatrutide on the anvil, whose phase III trials are likely to be completed in 2026, the prescribing doctors need to monitor carefully for ocular side effects.

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Hydatid Cyst of Right Atrium

Rajeev Bhardwaj*

Received: 02 October 2025; *Accepted:* 11 November 2025

A 70-year-old male presented with dyspnea New York Heart Association (NYHA) class II since 1994. Dyspnea was not progressive. There was no history of cough, fever, chest pain, or palpitation. He was investigated and was told to have some abnormality in his heart and was advised surgery. Since patient was not very symptomatic, he did not undergo surgery. He did not have any record of his ailment. This time he was referred to us for fitness for noncardiac surgery. His electrocardiogram (ECG) showed normal sinus rhythm and right atrial (RA) enlargement. His echocardiography showed large cystic mass in his RA, occupying almost three-fourth of RA (Fig. 1). His noncontrast contrast-enhanced computed tomography (NC CECT) of thorax was done. It showed well defined cystic lesion with internal heterogeneous contents and calcification along its wall in RA, measuring 8.1 × 8.3 × 8.4 cm, suggestive of hydatid cyst of RA (Fig. 2).

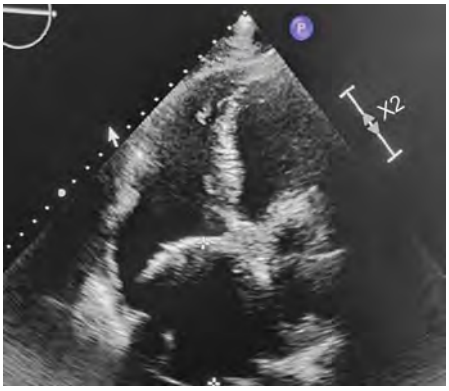


Fig. 1: Four chamber view in echocardiography shows dilated Right atrium, with large cystic mass in it

Cardiac involvement by hydatid disease is very rare, accounting for 0.5–2.0% of all hydatid infestations.[1] There are two methods by which heart can be involved by it. Firstly, it can be due to invasion of heart through coronary circulation. Second method is through rupture of pulmonary hydatid cyst into the pulmonary vein and thus entering into the left heart.[2] In heart, most common chamber to be involved is left ventricle, which occurs in 55–60% cases of cardiac hydatid disease. Left atrium is involved in 8% of cases. Right atrium is very rarely involved (3–4%).[1] Due to very slow growth, cardiac hydatid cyst may remain asymptomatic for a long period of time till it causes pressure symptoms or till the complications occur. Symptoms depend upon the organ involved. When left ventricle is involved, it can cause symptoms due to left ventricular outflow obstruction.



Fig. 2: CECT shows showed well defined cystic lesion with internal heterogeneous contents and calcification along its wall in RA

In left atrium, it can mimic mitral stenosis. In right atrium, it may cause obstruction of tricuspid valve and so can present with systemic venous congestion. When it is present in coronary, it can present as angina or myocardial infarction.[3] If it involves the conduction system of heart, it may present as heart block.[4] It can cause an emergency if it ruptures, when it can cause anaphylaxis and can be fatal.[5] So, it should be treated before it ruptures.[5] Cardiac hydatid cyst can be diagnosed by echocardiography, computed tomography (CT) scan, or magnetic resonance imaging (MRI).

Our patient had long standing disease, and patient was not very symptomatic, and so he refused surgery.

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How to cite this article: Bhardwaj R. Hydatid Cyst of Right Atrium. J Assoc Physicians India 2026;74(6):98.

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Comment on "Bedaquiline-related QTc Prolongation in Multidrug Resistant Tuberculosis Patients: A Prospective Study"

Reshmi Bhattacharya[1], Nitin Chintaman Gawari[2], Bhalchandra Tryambak Rane[3], Sujata Prakash Shingare[4]

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Dear Sir,

We read with considerable interest the article titled "Bedaquiline-related QTc Prolongation in Multidrug Resistant Tuberculosis Patients: A Prospective Study."[1] The authors should be commended for addressing an important safety concern regarding the use of bedaquiline in patients with multidrug-resistant tuberculosis (MDR-TB). Cardiac safety, particularly QT interval prolongation, remains a key issue during treatment with newer antitubercular agents, and studies focusing on this aspect are highly valuable. However, we would like to share a few observations regarding the findings reported.

In the present study, the authors reported an overall prevalence of QTc prolongation of 37.25%, with 13.7% of patients developing significant QTc prolongation. These rates appear somewhat higher than those reported in earlier studies.

For instance, Khan et al. conducted a large prospective cohort study involving MDR/rifampicin-resistant tuberculosis (RR-TB) patients from 16 countries who were treated with regimens containing bedaquiline and/or delamanid between April 2015 and September 2018.[2] The study evaluated the occurrence of clinically relevant QT prolongation (grade III or higher) or serious adverse events associated with QT changes. Among the 2,553 patients included in the study, 59% received bedaquiline and/or delamanid for more than 6 months. QT prolongation was observed in 579 patients (20.9%); however, most of these cases (95.5%) were mild, corresponding to grade I or grade II prolongation. Clinically significant QT prolongation was noted in only 64 patients (2.5%), while more severe prolongation occurred in 12 patients (0.5%). Notably, the majority of clinically relevant QT prolongation events were reported within the first 6 months of therapy.

Similarly, studies conducted in India have indicated that moderate to severe QT prolongation most commonly occurs around the third month of treatment. When compared with these findings, the overall incidence reported in the current study appears relatively higher (37.25% vs 20.9%).

The cardiac safety profile of bedaquiline has also been reviewed extensively by Gavras and Schluger.[3] Their analysis included studies evaluating bedaquiline both as monotherapy and in combination regimens. When administered alone in doses ranging from 100 to 400 mg per day, no QTcF increases >60 ms were observed, and QTcF values exceeding 500 ms were not reported.[4]

In recent years, bedaquiline has frequently been used together with delamanid in the management of drug-resistant tuberculosis. A multicountry cohort study conducted across 14 countries involving 472 patients assessed the safety of this combination therapy.[5] QTcF prolongation was observed in only seven patients (1.5%). Among them, two patients had QTcF values exceeding 500 ms without symptoms, while four experienced QT intervals >500 ms accompanied by clinical symptoms. These findings further support the generally acceptable cardiac safety profile of this combination regimen.

We concur with the authors that careful cardiac monitoring is essential when prescribing bedaquiline-containing regimens, particularly during the early months of treatment. Continued surveillance and larger prospective studies would be valuable in further clarifying the true magnitude of QT prolongation risk associated with these therapies.

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Reflections on Prosthetic Valve Thrombosis: Prevention and Evolving Therapeutic Strategies

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Dear Editor,

The recent article by Machigar et al., "Prosthetic Valve Thrombosis: Fibrinolysis, Surgery, or Percutaneous Manipulation?" offers an insightful and practical review of therapeutic strategies for prosthetic valve thrombosis (PVT).[1] The authors should be commended for addressing a complex and often life-threatening condition that continues to challenge clinicians worldwide. Beyond the valuable discussion on fibrinolysis, surgery, and emerging percutaneous options, this topic also invites reflection on the upstream and preventive aspects that remain pivotal in reducing the global burden of PVT.

Prevention of Rheumatic Fever and Rheumatic Heart Disease

In many low- and middle-income countries, rheumatic heart disease (RHD) remains the leading indication for valve replacement. This epidemiological reality underscores that the ultimate solution to the PVT burden lies not only in technological or procedural advances but also in the primary and secondary prevention of rheumatic fever. Sustained public health programs providing benzathine penicillin prophylaxis, early diagnosis of streptococcal pharyngitis, and community awareness can drastically reduce new cases of RHD and, consequently, the number of young patients who require mechanical prostheses. This preventive perspective—briefly alluded to in the authors' work—deserves renewed emphasis as the most cost-effective strategy for reducing PVT incidence globally.

Adequate Anticoagulation: The First Barrier against PVT

Once a prosthetic valve is implanted, anticoagulation management becomes the cornerstone of secondary prevention. Subtherapeutic international normalized ratio (INR) values remain the single most frequent and modifiable cause of prosthetic thrombosis. The article rightly highlights this issue, yet it cannot be overstated that maintaining an optimal time in therapeutic range (TTR) above 65–70% substantially decreases thrombotic and embolic events. In practice, patient education, systematic INR monitoring, and, where feasible, self-testing or community-based anticoagulation clinics should be implemented.[2] The inappropriate off-label use of direct oral anticoagulants in mechanical valve recipients must also be discouraged, as previous trials have demonstrated increased thrombotic complications in this context.

The Expanding Role of Thrombolysis and the "Ultraslow Low-dose" Paradigm

Machigar et al. present a balanced view of fibrinolysis as an established alternative to surgery for PVT, particularly in resource-limited settings. Over the past decade, the evolution of ultraslow low-dose alteplase regimens has markedly transformed the safety profile of thrombolytic therapy. Protocols involving infusions of 25 mg of alteplase administered over 24 hours (and repeated if necessary) have achieved thrombus resolution rates exceeding 85–90%, with major bleeding rates below 5%. These results compare favorably with both conventional fibrinolysis and emergency surgery. The physiological rationale—gradual thrombus dissolution minimizing sudden embolization—has been validated in multiple observational series and supported by current guideline recommendations for selected patients.

Importantly, this approach extends the therapeutic spectrum even to cases of left-sided mechanical valve obstruction with moderate hemodynamic compromise, in which surgery is either unavailable or carries prohibitive risk. The data emerging from Asian and Latin American centers, where such protocols originated, demonstrate that when meticulous monitoring is ensured, ultraslow thrombolysis represents an effective, reproducible, and safe strategy that aligns with the resource realities of many institutions.[3]

Surgery: Still Indispensable but Logistically Challenging

While fibrinolysis is gaining ground, surgery remains irreplaceable for certain clinical scenarios—patients with cardiogenic shock, large mobile thrombi, pannus formation, or failed thrombolysis.[4] Nevertheless, as Machigar et al. point out, the practical availability of emergency valve surgery is often restricted to tertiary centers. Reported operative mortality for urgent valve replacement ranges from 10 to 30%, especially when cardiogenic shock or severe pulmonary hypertension coexists. In contrast, when properly selected, fibrinolysis can achieve comparable survival with shorter hospital stays and lower cost. The challenge for clinicians, therefore, lies in a multidisciplinary, case-based decision that balances hemodynamic stability, thrombus morphology, and institutional capabilities.

Percutaneous Manipulation: Promise and Peril

The authors' mention of percutaneous mechanical interventions for prosthetic valve obstruction is particularly timely. Catheter-based disruption or balloon manipulation has been reported in small series, sometimes aided by cerebral protection devices to mitigate embolic risk. While such techniques may offer a lifesaving option in extreme scenarios—such as failed thrombolysis where surgery is not immediately feasible—the current evidence remains limited to case reports. The inherent risk of prosthesis damage or systemic embolization restricts these interventions to highly experienced centers. Nonetheless, their inclusion reflects an encouraging spirit of innovation, bridging interventional cardiology and cardiac surgery in a collaborative continuum.

A Hierarchical and Integrated Approach

The synthesis provided by Machigar et al. reinforces that the management of PVT should follow a hierarchical and integrated model, beginning with the prevention of RHD to reduce the need for prosthetic valve replacement, followed by meticulous anticoagulation to prevent thrombus formation. In hemodynamically stable patients, ultraslow low-dose fibrinolysis should be considered the first-line therapy, whereas surgical intervention remains essential for unstable or refractory cases. Finally, percutaneous manipulation may represent an investigational, last-resort strategy in highly selected contexts. Within this framework, therapeutic choice should be guided by echocardiographic findings, thrombus burden, and institutional readiness, under the coordination of a multidisciplinary "heart valve team" that includes cardiologists, cardiac surgeons, and imaging specialists.

Looking Ahead

The future of PVT management will likely involve hybrid strategies combining pharmacologic and interventional methods, enhanced imaging modalities for real-time assessment of thrombus resolution, and more refined risk stratification tools to predict response to fibrinolysis vs surgery. Equally important is global collaboration to improve access to INR monitoring, antibiotic prophylaxis for rheumatic fever, and registry-based data that capture the real-world performance of emerging therapies.

In summary, Machigar et al. contribute meaningfully to the ongoing dialogue on PVT by juxtaposing established and emerging treatment modalities. Their work implicitly reminds us that the most effective way to confront prosthetic thrombosis is not solely through procedural innovation but through comprehensive prevention—from rheumatic fever control to sustained anticoagulation vigilance. The integration of these preventive strategies with evolving therapeutic techniques defines the next frontier in reducing morbidity and mortality from PVT.

Authors' Contributions

Fidel Manuel Caceres-Loriga and Humberto Morais conceptualized and drafted the letter; both authors reviewed and approved the final version.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

None declared.

Funding

Not applicable.

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Most Important Barrier to Research Publication is Lack of Incentives and Motivation

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Dear Sir,

We read the important correspondence "Why Medical Doctors Hesitate to Write for Scientific Journals?"[1] with interest and feel that it could have been better if the authors had included the important factor of lack of incentives and motivation among Indian doctors to publish research papers or contribute to journals. There is a paucity of studies exploring the barriers and challenges faced by doctors in publishing their research papers, and whatever research has been done explores the barriers among those doctors who are already publishing their research.[2] The authors have rightly included time constraints, the complexity of the publishing process, lack of formal training in research and writing, fear of rejection and criticism, challenges in finding relevant research opportunities, and funding issues as the barriers to research publication.[1] But we feel that the authors should have included lack of motivation and lack of incentives as the most important barriers because if doctors are motivated enough and academic, promotional, and economic incentives are offered, most of the doctors will overcome the above-mentioned barriers and will publish their research. Most of the doctors today are products of commercial medical institutions charging obnoxiously high medical education fees, influenced by commercial considerations rather than academic or research considerations, and they work in profit-oriented corporate or private healthcare with little motivation for research publications. Therefore, we feel that unless there is a focus on research starting from undergraduate students, and unless various types of incentives are initiated for all doctors, both in medical colleges and in private practice, motivating them to initiate research and then publish, nothing much is going to change. The barriers to publishing papers enumerated by the authors are no doubt important, but they are secondary to lack of motivation and incentives. India needs a revolutionary change in medical education and research to encourage research publications on par with Western or Chinese research publications.

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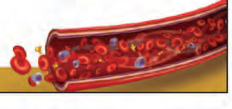
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