

Journal of The Association of Physicians of India



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India: Bridging the
Gaps and Shaping the
Future

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Understanding Obesity
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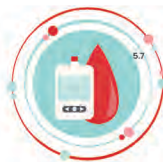
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Second and third trimesters of pregnancy. Biliary obstructive disorders. Severe hepatic impairment. The concomitant use of Telmisartan with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²). **Warnings And Precautions - Fetal Toxicity** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. **Hypotension** In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. **Hyperkalemia** may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered particularly in patients at risk. **Impaired Hepatic Function** As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan should be initiated at low doses and titrated slowly in these patients. **Impaired Renal Function** as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function should be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System:** Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, combined use of drugs from different classes of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes in patients on Telmisartan and other agents that affect the RAS should be closely monitored. Aliskiren must not be co-administered with Telmisartan in patients with diabetes. Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR < 60 mL/min/1.73 m²) must be avoided. **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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Telmisartan is an orally active and specific angiotensin II receptor (type AT1) blocker. **Contraindication:** The fixed dose combination of Bisoprolol fumarate and Telmisartan tablets is contraindicated in hypersensitivity to Bisoprolol and Telmisartan or to any of the excipients in the formulation. **Bisoprolol:** cardiogenic shock, AV block of second or third degree, symptomatic bradycardia and hypotension. **Telmisartan:** Second and third trimesters of pregnancy, Biliary obstructive disorders, severe hepatic impairment. The concomitant use of Telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²). **Warning & Precautions:** Bisoprolol-Especially in patients with ischaemic heart disease the cessation of therapy with Bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition. There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with coronary heart disease. Bisoprolol must be used with caution in bronchospasm, diabetes mellitus, AV block of first degree, Prinzmetal's angina, Peripheral arterial occlusive disease. **Telmisartan** is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since Telmisartan is mostly eliminated with the bile. Volume- and/or sodium-depleted patients: Volume and/or sodium depletion should be corrected prior to administration of Telmisartan. Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. **Drug Interactions:** Bisoprolol-Combination not recommended-Verapamil, Diltiazem, Methyldopa, Lidocaine. Combinations to be used with caution- Amlodipine, Amiodarone, Digoxin, NSAIDs. **Telmisartan-**When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. Concomitant use requiring caution- NSAIDs, Diuretics, ACEi, ARBs, Aliskiren. **Special Populations: Pregnancy:** Bisoprolol is not recommended during pregnancy unless clearly necessary and breast-feeding. **Telmisartan-**Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started. Telmisartan is not recommended in breast-feeding. **Hepatic or Renal impairment: Bisoprolol** - In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required. In patients with severe renal impairment (creatinine clearance < 20 mL/min) and in patients with severe liver function disorders it is recommended that a daily dose of 10 mg is not exceeded. **Telmisartan-**Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment. When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. **Adverse Reactions: Bisoprolol-** Most common adverse reactions include headache and dizziness. **Telmisartan-** sinus pain, stuffy nose, back pain. **Overdose: Bisoprolol:** With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, if overdose occurs, Bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Bradycardia: Administer intravenous atropine. Hypotension: Intravenous fluids and vasopressors should be administered. **Telmisartan:** The most prominent manifestations of Telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose.



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

Sanjay Tandon¹*, GM Prasad², Dilip Kadam³
Received: 24 July 2025; Accepted: 17 October 2025

ABSTRACT

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

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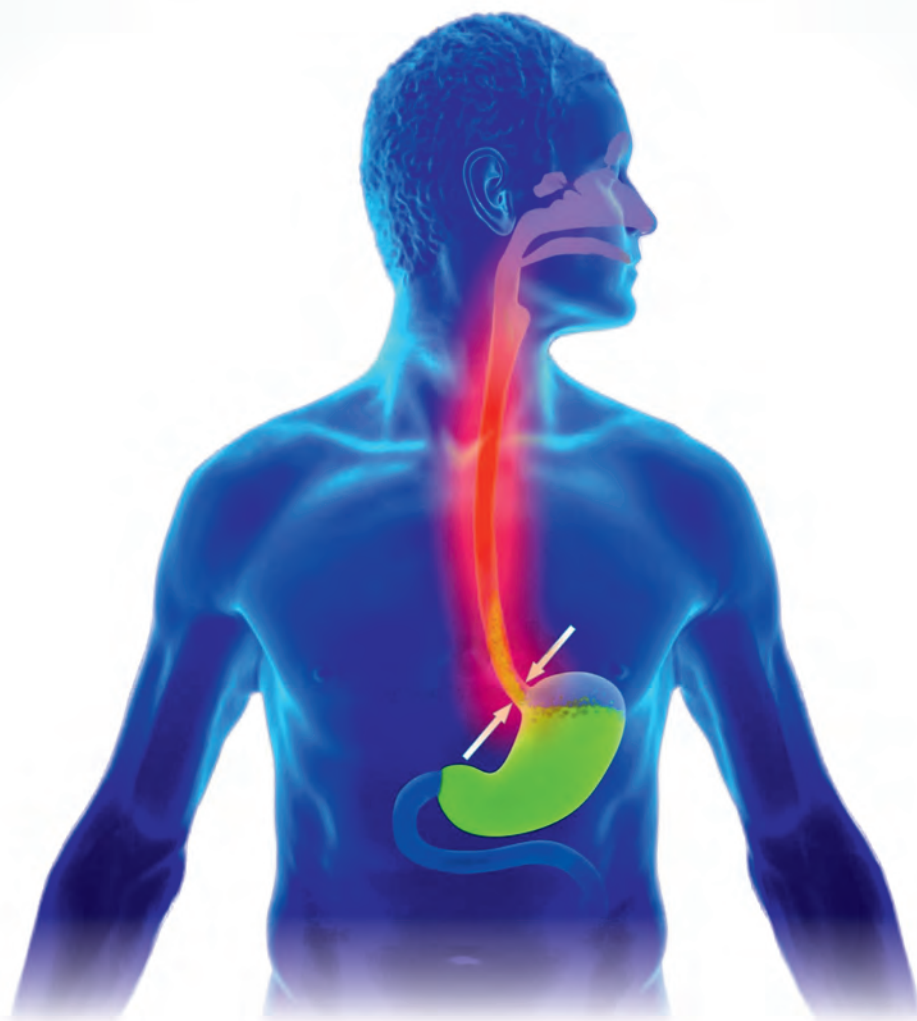
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Medical Research in India: Bridging the Gaps and Shaping the Future

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Keywords: Clinical trials, Medical research, Research funding, Research integrity, India.

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Medical research serves as the cornerstone of healthcare advancements, directly influencing patient outcomes and public health policies. India, home to over a billion people and facing a unique disease burden, holds enormous potential for pioneering transformative medical research. Yet, substantial gaps remain in fully harnessing this potential.¹ Here, we discuss the key areas where focused efforts can significantly enhance India's contribution to global medical research.

FUNDING GAPS: A PERSISTENT CHALLENGE

One critical impediment to India's medical research landscape is inadequate funding. India's expenditure on research and development (R and D) remains disappointingly low, around 0.7% of its GDP, far behind developed economies spending 2–3% or more.^{2,3} Alarmingly, public investment specifically directed toward health research is even lower, constituting merely 0.02% of GDP.¹

Additionally, a limited pool of dedicated researchers remains a persistent problem. India's researcher-to-population ratio remains disproportionately low—approximately 262 researchers per million people, in contrast to 4,300+ per million in the U.S. or 8,7000+ in South Korea—underscoring the need for a significant expansion of human resource capacity.⁴

Furthermore, much of India's medical research is industry-driven, biased toward commercially viable endeavors at the expense of fundamental and public health research. Recent initiatives, such as the establishment of the National Research Foundation (NRF), with a substantial budget allocation, promise to alleviate these constraints. Nevertheless, sustained advocacy and a strategic increase in public funding are urgently needed.

RESEARCH OUTPUT: QUANTITY VS QUALITY

India has made notable strides in research output, ranking third globally in scientific

publication volume and ninth in the field of medicine, with over 0.70 million medical publications to date.^{5,6} However, this expansion is tempered by a consistent gap in citation impact and presence in high-impact clinical studies. Indian publications average 15.5 citations per paper, significantly lower than the 36–37 citations per paper observed in the US and the UK.⁷ Furthermore, India accounts for only 2% of the world's top-cited medical research, despite having 20% of the global disease burden.⁷

This discrepancy underscores systemic issues, including smaller-scale studies, limited multicenter collaborations, and a tendency toward quantity-driven academic incentives.² Nevertheless, encouraging developments are underway. India is now the third-largest global hub for clinical trials, following the US and China, and has hosted over 5,800 trials as of 2024.⁸

Although signs of progress are evident, more Indian researchers should engage in collaborative, multicenter trials addressing pertinent national health concerns.^{9,10} Collaborative, hypothesis-driven research—particularly in domains such as noncommunicable diseases—can significantly improve the impact and visibility of Indian medical research.

EVOLVING POLICY FRAMEWORK AND INSTITUTIONAL SUPPORT

Institutions such as the Indian Council of Medical Research (ICMR), the Department of Biotechnology (DBT), and other key bodies, including the All India Institute of Medical Sciences (AIIMS), have played pivotal roles in transforming India's research ecosystem. ICMR's network of 27 national research centers and its leadership in COVID-19 vaccine development and disease surveillance illustrate India's growing scientific capacity. Recent policy reforms, such as the mandatory Basic Course in Biomedical Research (BCBR) for

postgraduate medical trainees and the expansion of ICMR's shared infrastructure, aim to nurture research capabilities across the country.¹¹ Furthermore, the Ayushman Bharat Digital Mission promises unprecedented opportunities for data-driven research.¹² Nevertheless, cohesive coordination between central bodies (ICMR, DBT, and AIIMS) and academic institutions must improve. Establishing regional centers of excellence, fostering robust interinstitutional collaborations, and streamlining regulatory pathways are imperative to scale and strengthen India's medical research footprint.

ENSURING ACADEMIC INTEGRITY

Academic integrity is foundational to credible and impactful medical research. India has historically struggled with plagiarism, predatory publishing, and ethical breaches in clinical research.¹³ Recent regulatory interventions—such as the University Grants Commission's stringent anti-plagiarism policies and the establishment of the CARE list to combat predatory journals—demonstrate a strong commitment to restoring integrity.^{14,15} Clinical trials are now governed by tighter protocols ensuring informed consent, participant safety, and ethical accountability, thereby aligning India more closely with international standards. Strengthening research governance at the institutional level and promoting responsible research conduct must remain a national priority.

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GLOBAL STANDING AND COMPARATIVE INSIGHTS

India's rise in medical research is evident across multiple global benchmarks, ranking ninth worldwide in publication volume and third in clinical activity. India's top medical bodies—ICMR, AIIMS Delhi, and the Postgraduate Institute of Medical Education and Research, Chandigarh—are playing pivotal roles. AIIMS is ranked among the top 150 global medical schools, and ICMR had the highest percentage of Q1 journal publications among Indian research bodies.

India's strengths include its position as the world's largest vaccine producer, a cost-effective trial environment, and growing public health research capacity. Yet, it remains underrepresented in landmark international trials, patents, and high-impact journal authorship.

FUTURE DIRECTIONS AND RECOMMENDATIONS

India stands on the cusp of significantly advancing its global medical research impact. To sustain and accelerate the trajectory, we recommend the following:

- *Increase and diversify funding:* Expand government allocations, enable philanthropic endowments, and incentivize public-private partnerships.
- *Enhance research quality:* Promote multicenter, collaborative, and hypothesis-driven studies with international partnerships.
- *Strengthen institutional frameworks:* Expand infrastructure, develop regional

centers of excellence, and harness digital health data for large-scale epidemiological research.

- *Foster global partnerships:* Encourage Indian investigators to lead international consortia, ensuring equitable representation in global guidelines and trials.
- *Promote a culture of integrity:* Embed ethics training in curricula, implement rigorous peer review, and support mentorship to build a future-ready research workforce.

CONCLUSION

India's medical research landscape is in a state of dynamic transformation. While impressive gains in output and infrastructure are evident, bridging the persistent gaps in quality, innovation, and global influence remains critical. With coordinated efforts by government agencies, academic institutions, clinicians, and the private sector, India can evolve from being a volume leader to a value- and innovation-driven powerhouse in global medical science.

This transformation will not only reshape healthcare delivery for over a billion Indians but also enable India to meaningfully contribute to solving global health challenges, reinforcing its position as a leader in equitable, affordable, and impactful research.

REFERENCES

1. Dandona L, Dandona R, Kumar GA, et al. Mapping of health research funding in India. *Natl Med J India* 2017;30(6):309–316.
2. Burt T, Sharma P, Dhillon S, et al. Clinical research environment in India: challenges and proposed solutions. *J Clin Res Bioeth* 2014;5(6):1–8.

3. Ahuja M, Pradeep Y. Medical research in India: let us plug the holes! *J Midlife Health* 2023;14(2):63–65.
4. UNESCO Institute for Statistics. (2024). Launch of the 2024 Survey of Research and Development (R&D) Statistics for SDG 9.5. [online] Available from: <https://uis.unesco.org/en/news/launch-2024-survey-research-development-statistics-sdj9-5> [Last accessed July, 2026].
5. Plackett B. (2024). Nature Index 2024 Research Leaders: India follows in China's footsteps as top ten changes again. *Nature Index*. [online] Available from: <https://www.nature.com/nature-index/news/nature-index-research-leaders-india-follows-china-footsteps> [Last accessed July, 2026].
6. National Science Board. (2023). Publications Output: U.S. Trends and International Comparisons. *Science and Engineering Indicators 2022*. Alexandria, Virginia: National Science Foundation.
7. SCImago. (2024). SJR—International Science Ranking. [online] Available from: <https://www.scimagojr.com/countryrank.php> [Last accessed July, 2026].
8. ClinIRx. (2024). India's emergence as an attractive destination for clinical trials. [online] Available from: <https://clinirx.com/conducting-clinical-trials-in-india/> [Last accessed July, 2026].
9. Sapkal G, Yadav PD, Ella R, et al. Neutralization of VUI B.1.1.28 P2 variant with sera of COVID-19 recovered cases and recipients of Covaxin, an inactivated COVID-19 vaccine. *J Travel Med* 2021;28(7):taab077.
10. Pathan SR, Bhende VV, Sharma KB, et al. Across time: a chronological progression of clinical trials in India. *Cureus* 2024;16(3):e56786.
11. Joshi KJ, Singhal S, Gupta S. Impact of Basic Course in Biomedical Research (BCBR) on medical teachers and postgraduate students across India: a cross-sectional survey-based study. *Cureus* 2024;16(6):e62908.
12. Athavle P. Co-WIN and Ayushman Bharat Digital Mission: the way forward. *Natl Med J India* 2024;37(3):149–152.
13. Laine C, Babski D, Bachelet VC, et al. Predatory journals: what can we do to protect their prey? *PLoS Med* 2025;22(4):e1004542.
14. Kampa RK, Padhan DK, Karna N, et al. Identifying the factors influencing plagiarism in higher education: an evidence-based review of the literature. *Account Res* 2025;32(2):83–98.
15. Balakumar P, Jagadeesh G. India: neutralizing temptation by predatory journals. *Nature* 2023;621(7979):474.



Real-world Outcomes of Neoadjuvant Dual HER2 Blockade with TCHP in Early and Locally Advanced HER2-Enriched Breast Cancer: Experience from a South Indian Tertiary Oncology Center

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ABSTRACT

Background: HER2-enriched breast carcinomas are biologically aggressive but highly responsive to targeted therapy. Data on the real-world effectiveness of neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) from Indian oncology practices remain sparse.

Objectives: To assess pathological complete response (pCR), treatment-related toxicities (CTCAE v5.0), and survival outcomes among patients with nonmetastatic HER2-positive breast cancer receiving neoadjuvant TCHP.

Materials and methods: A bidirectional observational analysis was conducted on 55 patients with HER2-positive nonmetastatic breast carcinoma who were treated at a tertiary oncology center. Patients received neoadjuvant TCHP followed by definitive surgery. Clinical response, radiological response, pCR, treatment compliance, toxicity, disease-free survival (DFS), and overall survival (OS) were evaluated. Statistical associations with pCR were analyzed using Fisher's exact test.

Results: The median age of the patients was 47 years. Stage III disease was the most common (70.9%). Hormone receptor negativity was observed in 56% of the patients. Clinical complete response was achieved in 85% of the patients, whereas radiological complete remission occurred in 58%. A pCR was documented in 60% of the cohort. A significant correlation with pCR was observed for clinical response ($p < 0.001$), radiological response ($p = 0.002$), and uninterrupted treatment completion within 18 weeks ($p = 0.013$). Hormone receptor expression and baseline stage did not significantly influence pCR rates. Diarrhea and neutropenia were the predominant toxicities, whereas clinically relevant cardiotoxicity was not encountered. At a median follow-up of 29 months, the estimated 3-year DFS and OS were 95% and 97.2%, respectively.

Conclusion: Neoadjuvant TCHP demonstrated substantial pathological response rates, acceptable tolerability, and encouraging survival outcomes in HER2-positive breast cancer. Adherence to the planned treatment timeline significantly influenced therapeutic efficacy.

Keywords: Dual HER2 blockade, HER2-amplified breast cancer, Neoadjuvant systemic therapy, Pathological complete response, Pertuzumab, Trastuzumab.

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INTRODUCTION

Breast carcinoma remains the leading malignancy affecting women globally and continues to be a major contributor to cancer-related mortality. Approximately one-fifth of breast cancers demonstrate amplification or overexpression of the human epidermal growth factor receptor-2 (HER2), which is associated with increased tumor aggressiveness, rapid disease progression, and poorer clinical outcomes when untreated. The introduction of HER2-targeted agents has markedly improved survival and transformed the therapeutic management of this molecular subtype.

Neoadjuvant systemic therapy has become an integral component in the treatment of early-stage and locally advanced HER2-positive breast cancer. In addition to facilitating surgical

downstaging, neoadjuvant therapy offers an opportunity to evaluate *in vivo* tumor sensitivity to treatment. The achievement of pathological complete response (pCR) following neoadjuvant treatment has emerged as an important surrogate marker associated with improved long-term survival outcomes.

The combination of trastuzumab and pertuzumab with taxane- and platinum-based chemotherapy has become a widely accepted neoadjuvant approach for HER2-positive disease. Major clinical trials including NeoSphere, TRYPHAENA, and BERENICE have demonstrated substantial improvements in pCR rates and encouraging survival outcomes with dual HER2 blockade strategies.

Although evidence from international clinical trials is well established, published

data describing outcomes in routine Indian oncology practice remain relatively limited. Real-world studies are particularly relevant in resource-constrained settings where treatment delays, financial limitations, and variations in supportive care may influence therapeutic outcomes. The present study was therefore conducted to evaluate pathological response, treatment tolerability, and short-term survival outcomes among patients with nonmetastatic HER2-positive breast cancer treated with neoadjuvant TCHP at a tertiary oncology center in South India.

MATERIALS AND METHODS

This bidirectional observational study was conducted at the Department of Medical Oncology, ESIC Medical College and Hospital, Hyderabad, Telangana. The study included both retrospective and prospective evaluations of patients with nonmetastatic HER2-positive breast cancer treated with a neoadjuvant TCHP regimen followed by definitive surgery.

Patient Selection

Patients with histopathologically confirmed HER2-positive invasive breast carcinoma who received neoadjuvant systemic therapy with the TCHP regimen were enrolled in the study.

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Inclusion Criteria

- Age ≥ 18 years.
- Histologically confirmed HER2-positive breast carcinoma.
- Clinical stage I–III disease without distant metastasis.
- HER2 positivity confirmed by immunohistochemistry (IHC 3+) or *in situ* hybridization (ISH) as per the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.
- Eastern Cooperative Oncology Group (ECOG) performance status 0–2.

Exclusion Criteria

- Presence of metastatic disease at diagnosis.
- Significant uncontrolled cardiac disease or baseline left ventricular dysfunction.
- Patients unfit for systemic chemotherapy.

Treatment Protocol

Patients received neoadjuvant chemotherapy combined with dual HER2-directed therapy using the TCHP regimen at 3-week intervals. A total of six cycles was planned whenever clinically feasible.

The treatment protocol consisted of intravenous docetaxel at a dose of 75 mg/m² and carboplatin calculated at an area under the curve (AUC) of 6 on day 1 of each cycle. Trastuzumab was administered with an initial loading dose of 8 mg/kg followed by maintenance doses of 6 mg/kg every 3 weeks. Pertuzumab was delivered as an 840 mg loading dose during the first cycle followed by 420 mg every 3 weeks thereafter.

All patients received standard supportive care measures including corticosteroid premedication, antiemetic prophylaxis, hydration, and hematopoietic support according to institutional practice guidelines. Use of granulocyte colony-stimulating factor support was individualized based on hematological tolerance and clinician assessment. Definitive surgical management was performed after completion of neoadjuvant systemic therapy.

Evaluation of Response

Treatment response was assessed using clinical examination and imaging studies following completion of neoadjuvant therapy. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging was utilized for radiological evaluation wherever available. Clinical complete response (cCR) and radiological complete response (rCR) were documented based on posttreatment assessment findings.

Resected surgical specimens from both the breast and axillary tissue were examined histopathologically to determine treatment response. pCR was defined as the absence of residual invasive carcinoma in both breast tissue and regional lymph nodes (ypT0/is ypN0).

Statistical Analysis

Continuous variables were summarized using the median and range. Categorical variables were expressed as frequencies and percentages. Associations between clinicopathological parameters and pCR were analyzed using Fisher's exact test. Survival analysis was performed using the Kaplan–Meier estimates.

RESULTS

Clinicopathological Profile

A total of 55 patients with nonmetastatic HER2-positive breast cancer were included in this study. The median age at diagnosis was 47 years (range, 33–67 years). Postmenopausal women constituted the majority of the study population (36/55, 65.5%), and 19 patients (34.5%) were premenopausal. One male patient was included in the study of 55 patients. Hormone receptor-negative tumors were slightly more common and were identified in 31 patients (56.4%), whereas hormone receptor positivity was observed in 24 patients (43.6%).

With respect to primary tumor stage, T2 disease was the most frequent presentation and was noted in 23 patients (41.8%), followed by T4 tumors in 15 (27.3%) and T3 tumors in 13 (23.6%) patients. T1 lesions were identified in four patients (7.3%). Axillary nodal involvement was common, with N2 disease observed in 21 patients (38.2%) and N1 disease in 17 patients (30.9%). N0 and N3 diseases were present in nine (16.4%) and eight patients (14.5%), respectively. All patients had nonmetastatic disease at the time of presentation. According to the American Joint Committee on Cancer (AJCC) 8th edition staging system, stage III disease constituted the largest subgroup and was observed in 39 patients (70.9%), whereas stage II and stage I diseases were present in 14 patients (25.5%) and 2 patients (3.6%), respectively. A total of 52 patients (94.5%) received all six cycles of the TCHP regimen. Treatment interruption with completion of only four cycles occurred in three patients (5.5%) secondary to grade 3 diarrhea. Additionally, 48 patients (87.3%) completed treatment within the intended duration of 18 weeks, whereas treatment delays beyond 18 weeks were documented in seven patients (12.7%).

Therapeutic Response

Response Outcomes

Clinical complete response (cCR) was documented in 47 patients (85%), and radiological complete remission (rCR) was achieved in 32 patients (58%). A pCR was observed in 33 patients (60%), whereas residual invasive disease persisted in 22 patients. Minimal residual disease (<1 mm) was identified in one patient.

Clinical complete response was observed in all patients who achieved pCR (33/33, 100%), whereas only 14 of 22 patients (63.6%) with residual pathological disease showed cCR. This association between clinical response and pCR was statistically significant ($p < 0.001$). Similarly, rCR showed a strong correlation with the pathological eradication of the disease. rCR was documented in 28 of 33 patients (84.8%) who achieved pCR, compared with only 4 of 22 patients (18.2%) with residual pathological disease. This difference was statistically significant ($p = 0.002$).

Hormone receptor co-expression and baseline stage were not significantly associated with pCR achievement. The distribution of hormone receptor status between the pCR and residual disease groups was comparable and did not reach statistical significance ($p > 0.9$). The proportion of patients across clinical stages was similar between the pCR and residual disease groups, and no statistically significant association was observed ($p > 0.9$) (Table 1).

Impact of Treatment Timeliness

Completion of neoadjuvant therapy within the planned 18-week duration was significantly associated with improved pathological response outcomes. Among the 48 patients who completed treatment on schedule, 32 (66.7%) achieved pCR, whereas only one of seven patients (14.3%) with treatment delays beyond 18 weeks attained pCR. Delays in treatment were primarily attributed to drug nonavailability, hematological toxicities, and treatment-related diarrhea, and were associated with a significantly higher incidence of residual pathological disease (85.7% vs 33.3%; $p = 0.013$).

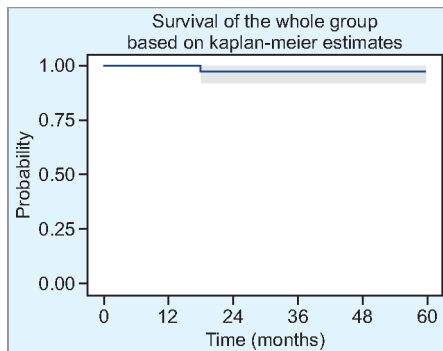
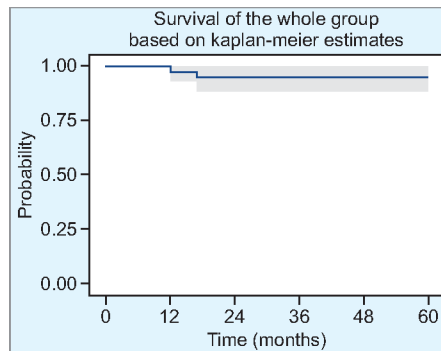
Adverse Events and Treatment Tolerability

Treatment-related toxicities were generally manageable and consistent with the established safety profiles of the TCHP regimen.

Diarrhea represented the most frequently encountered adverse event, affecting

Table 1: Association of clinical variables with pCR

Subgroup variable	Overall (N = 551)	pCR achieved (N = 33) ¹	Residual disease (N = 22) ¹	p-value ²
Clinical response (cCR)				<0.001
cCR achieved	47/55 (85%)	33/33 (100%)	14/22 (64%)	
Clinical residual	8/55 (15%)	0/33 (0%)	8/22 (36%)	
Radiological response (rCR)				0.002
rCR achieved	32/55 (58%)	28/33 (85%)	4/22 (19%)	
Radiological residual	23/55 (42%)	5/33 (15%)	18/22 (81%)	
Hormone receptor status				>0.9
HR positive	24/55 (44%)	15/33 (45%)	9/22 (41%)	
HR negative	31/55 (56%)	18/33 (55%)	13/22 (59%)	
Clinical stage				>0.9
Stage I	2/55 (3.6%)	1/33 (3.0%)	1/22 (4.5%)	
Stage II	14/55 (25%)	8/33 (24%)	6/22 (27%)	
Stage III	39/55 (71%)	24/33 (73%)	15/22 (68%)	
Treatment duration				0.013
18 weeks	48/55 (87%)	32/33 (97%)	16/22 (73%)	
>18 weeks	7/55 (13%)	1/33 (3.0%)	6/22 (27%)	

¹n/N (%); ²Fisher's exact test**Fig. 1:** Kaplan–Meier curve for OS Kaplan–Meier survival curve showing OS among patients treated with neoadjuvant TCHP regimen for nonmetastatic HER2-positive breast cancer. The estimated 3-year OS was 97.2%, with median OS not reached because of the very low number of death events observed during the study period**Fig. 2:** Kaplan–Meier curve for DFS Kaplan–Meier survival curve showing DFS among patients treated with neoadjuvant TCHP regimen for nonmetastatic HER2-positive breast cancer. The estimated 3-year DFS was 95.0%, with median DFS not reached due to the low number of recurrence events during follow-up

17 patients overall, including grade 3 diarrhea in seven patients. Neutropenia occurred in three patients, with grade 3 neutropenia documented in two cases. One patient experienced grade 2 thrombocytopenia.

Importantly, no patient developed symptomatic cardiac dysfunction or a clinically meaningful decline in the left ventricular ejection fraction during therapy.

Survival Analysis

The median follow-up duration for the study cohort was 29 months (range, 5–60 months). During follow-up, two patients who had initially achieved pCR subsequently developed isolated intracranial recurrence in the form of brain metastases without evidence of extracranial disease; one patient died following recurrence, while the other

remained on palliative systemic therapy with ongoing follow-up. The median disease-free survival (DFS) and overall survival (OS) were not reached during the study period because of the low number of recurrence and death events observed. The estimated 3-year DFS and OS rates for the study population were 95.0% and 97.2%, respectively, reflecting favorable short-term survival outcomes with neoadjuvant TCHP therapy (Figs 1 and 2).

DISCUSSION

The current study demonstrates favorable real-world outcomes with neoadjuvant TCHP therapy in patients with HER2-positive nonmetastatic breast cancer treated in a tertiary care oncology setting in India. A pCR rate of 60% was observed in our cohort, which

is broadly consistent with findings reported in major international studies evaluating dual HER2 blockade in the neoadjuvant setting. Previous landmark trials including NeoSphere, TRYPHAENA, and BERENICE have documented pCR rates ranging from approximately 45–66% depending on chemotherapy backbone and patient characteristics. Our findings support the reproducibility of these outcomes in routine clinical practice outside highly controlled trial environments.

An important finding from the present analysis was the strong relationship between clinical response, radiological response, and final pathological eradication of disease. Patients who demonstrated complete response on clinical examination and imaging were significantly more likely to achieve pCR after surgery. This observation highlights the practical value of posttreatment response assessment in predicting therapeutic effectiveness and guiding postoperative management decisions. Similar associations between imaging response and pathological outcomes have been reported previously in HER2-positive breast cancer cohorts.

Another clinically relevant observation in this study was the influence of treatment adherence and timely completion of therapy on pathological response. Patients who completed neoadjuvant treatment within the planned treatment duration showed significantly higher pCR rates than those who experienced delays. In our setting, interruptions were largely related to toxicities, supportive care limitations, and occasional issues with drug availability. Such challenges are commonly encountered in real-world oncology practice, particularly in resource-limited healthcare systems. These findings emphasize the importance of uninterrupted delivery of HER2-targeted therapy to maximize treatment efficacy.

Hormone receptor co-expression did not demonstrate a statistically significant effect on pCR rates in our cohort. Although several larger studies have reported comparatively higher pCR rates among hormone receptor-negative tumors, the relatively limited sample size in the present study may have influenced subgroup analysis. Nevertheless, meaningful pathological responses were observed across both hormone receptor-positive and hormone receptor-negative disease categories.

The toxicity profile observed in this study was generally manageable and aligned with previously published safety data for TCHP-based therapy. Gastrointestinal adverse events, particularly diarrhea, represented the most common toxicity, while neutropenia was the predominant hematological complication. Importantly, clinically significant cardiac

toxicity was not observed in our cohort. The absence of major cardiotoxicity further supports the safety profile of anthracycline-sparing HER2-directed regimens described in earlier studies.

During follow-up, two patients experienced isolated central nervous system (CNS) relapse despite initially achieving pCR. HER2-positive breast cancer has a known tendency for brain metastasis, partly related to limited penetration of monoclonal antibody therapies across the blood–brain barrier. This finding suggests that although pCR is associated with favorable outcomes, it does not completely eliminate the risk of disease recurrence, particularly within the CNS.

Short-term survival outcomes in the present study were encouraging, with estimated 3-year DFS and OS rates of 95% and 97.2%, respectively. Because only a small number of relapse and mortality events occurred during follow-up, median survival endpoints were not reached. These findings are consistent with previously published long-term analyses demonstrating improved survival with effective HER2-targeted neoadjuvant therapy.

Real-world evidence from Asian and European populations has similarly demonstrated substantial pathological response rates with dual HER2 blockade in routine oncology practice. Such studies are valuable because real-world patient populations frequently include individuals with advanced-stage disease, comorbidities, and treatment interruptions that are often underrepresented in clinical trials.

The present study contributes important Indian real-world data regarding neoadjuvant TCHP therapy in HER2-positive breast cancer. However, certain limitations should be acknowledged, including the

modest sample size, single-center design, and relatively short follow-up duration. Larger prospective multicentric studies with longer surveillance are required to better characterize long-term survival outcomes and recurrence patterns in the Indian population.

CONCLUSION

This study provides supportive real-world evidence regarding the efficacy and tolerability of neoadjuvant TCHP therapy in patients with HER2-positive nonmetastatic breast cancer treated in a tertiary oncology setting in India. High pCR rates and encouraging short-term survival outcomes were observed with acceptable treatment-related toxicity. Achievement of cCR and rCR showed a strong association with pathological eradication of disease, while delays in treatment delivery adversely affected therapeutic outcomes. These findings reinforce the value of dual HER2 blockade as an effective neoadjuvant strategy and underscore the importance of treatment adherence and supportive care optimization in routine oncology practice. Further large-scale prospective studies with extended follow-up are warranted to validate these observations.

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ETHICAL STATEMENT

Institutional Ethics Committee approval was obtained prior to the commencement of the study (approval no. IEC-S0401/06/2024).

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016;17(6):791–800.
2. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013;24(9):2278–2284.
3. Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol* 2018;29(3):646–653.
4. Marinovich ML, Houssami N, Macaskill P, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. *J Natl Cancer Inst* 2013;105(5):321–333.
5. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014;384(9938):164–172.
6. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol* 2004;22(17):3608–3617.
7. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019;380(7):617–628.
8. Ahn HK, Park YH, Lee SJ, et al. Real-world clinical outcomes of neoadjuvant pertuzumab-containing therapy in HER2-positive breast cancer patients. *Cancer Res Treat* 2021;53(3):719–728.
9. Schneeweiss A, Denkert C, Fasching PA, et al. Real-world effectiveness of neoadjuvant dual HER2 blockade in early HER2-positive breast cancer. *Breast Cancer Res Treat* 2020;181(3):647–656.

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Beyond Fever—The Changing Face of Acute Leptospirosis: A Retrospective Observational Study from Western India



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ABSTRACT

Background: Leptospirosis is a zoonotic infection caused by pathogenic *Leptospira* species and remains a significant cause of acute febrile illness in tropical regions. Its clinical spectrum ranges from mild, self-limiting illness to severe multi-organ dysfunction. The disease is broadly classified into anicteric and icteric (Weil's disease) forms, the latter associated with jaundice and increased morbidity. In India, diagnosis is often challenging due to overlapping features with other endemic infections such as dengue and scrub typhus. Coinfections and changing epidemiological patterns, including increasing urban cases, further complicate clinical assessment. This study evaluated the demographic profile, clinical characteristics, organ involvement, coinfections, severity, management, and outcomes of adults hospitalized with acute leptospirosis, with comparison between icteric and anicteric phenotypes.

Materials and methods: This retrospective observational study included 78 adults with laboratory-confirmed acute leptospirosis admitted over 30 months to a tertiary care hospital in Rajasthan, India. Diagnosis was established by positive *Leptospira*-specific immunoglobulin M (IgM) serology (>11 NTU) and/or polymerase chain reaction (PCR). Data regarding demographics, comorbidities, clinical features, organ involvement, coinfections, treatment, and outcomes were extracted from medical records.

Organ involvement was defined using predefined clinical and laboratory criteria across major systems. Severe disease was defined as dysfunction of two or more organ systems. Icteric leptospirosis was defined by clinical jaundice and/or serum bilirubin ≥ 3 mg/dL. Coinfections were confirmed through appropriate laboratory testing. Continuous variables were expressed as median (interquartile range) and categorical variables as frequency (%). Subgroup comparisons were performed using the Mann-Whitney *U* test and Fisher's exact test.

Results: The median age was 57 years (interquartile range 41–68), with slight male predominance (52.6%). Although 59% of patients were from rural areas, 41% were urban residents. Hypertension (25.6%) and diabetes mellitus (29.5%) were common comorbidities, while 42.3% had no prior illnesses. Anicteric disease predominated (84.6%), and 15.4% had icteric leptospirosis. Fever was present in 93.6% of patients. Hepatic (69.2%) and respiratory (66.7%) involvement were most frequent, and multi-organ dysfunction occurred in 61.5%. Coinfections were identified in 52.6% of cases, most commonly dengue (17.9%) and scrub typhus (14.1%). Coinfected patients were younger and had fewer comorbidities, with lower rates of renal, respiratory, and neurological involvement and reduced need for ventilatory support. Icteric patients were significantly younger (median 31.5 vs 58 years) and had longer hospital stays (10.5 vs 7 days). Hepatic involvement was universal in the icteric group, and secondary hemophagocytic lymphohistiocytosis (HLH) was markedly more frequent. Mortality was higher among icteric patients but did not reach statistical significance. Mechanical ventilation was required in 10.3% of patients. The median hospital stay was 7 days, and overall mortality was 2.6%, with both deaths occurring in patients with severe multi-organ dysfunction.

Conclusion: Acute leptospirosis exhibits diverse clinical presentations with frequent multi-organ involvement in hospitalized adults. Coinfections are common but did not consistently worsen outcomes. Icteric disease represents a more severe phenotype associated with greater complications and prolonged hospitalization. Early diagnosis and timely supportive management are critical to achieving favorable outcomes in endemic settings.

Keywords: Acute febrile illness, Coinfection, Icteric leptospirosis, Leptospirosis, Mortality, Multi-organ dysfunction, Tropical infections.

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INTRODUCTION

Leptospirosis is a widespread zoonotic infection caused by pathogenic *Leptospira* species, presenting with a broad spectrum ranging from mild, self-limiting febrile illness to severe multi-organ disease.^{1,2} Clinically,

it is classified as anicteric or icteric (Weil's disease), the latter associated with jaundice, higher morbidity, and increased risk of complications.^{1,3}

In India, leptospirosis remains underreported due to overlapping symptoms with other endemic febrile illnesses, low

clinical suspicion, and limited diagnostic resources.^{2,4} Traditionally linked to rural occupational exposures, recent studies report increasing urban cases, likely reflecting environmental changes and evolving epidemiology.^{3,5}

Comorbidities such as diabetes and hypertension are common, but healthy individuals are also frequently affected.²

Coinfections with pathogens such as dengue and scrub typhus further complicate diagnosis and management and may influence organ involvement and disease severity.^{5–8} Despite effective antibiotics and supportive care, severe leptospirosis with multi-organ involvement continues to carry significant morbidity and mortality, particularly in icteric cases.^{1,3,9}

This study aims to describe the demographic and clinical spectrum, organ involvement, coinfections, and outcomes of 78 acute leptospirosis patients admitted to a tertiary care center in Rajasthan, India, with emphasis on differences between icteric and anicteric phenotypes. The findings aim to inform clinical management and highlight evolving epidemiological patterns in endemic regions.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective observational study conducted at Fortis Escorts Hospital, Jaipur, India, a tertiary care hospital, over a period of 30 months (time period, e.g., July 2023 to December 2025). The study

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was approved by the Institutional Ethics Committee vide letter No. FEHJ/IEC/25/004, and the requirement for informed consent was waived due to the retrospective nature of the study. The aim of this study was to assess the varied clinical manifestations, including demographics, comorbidities, coinfections (if any), organ involvement, severity, complications, and outcomes of patients with icteric and anicteric leptospirosis.

Study Population

All patients with a confirmed diagnosis of leptospirosis admitted to the Department of Medicine in the authors' unit during the study period were included. As this was a retrospective observational study, all consecutive eligible patients admitted during the study period were included. A formal sample size estimation was not performed.

Leptospirosis was diagnosed based on positive serology [*Leptospira*-specific immunoglobulin M (IgM) antibody] or a positive molecular test [polymerase chain reaction (PCR)]. A *Leptospira*-specific IgM value >11 NTU was considered positive, 9–10.9 borderline, and <9 negative. Patients with incomplete medical records were excluded. A total of 78 patients met the inclusion criteria and were included in the final analysis.

Data Collection

Data were extracted from patient case files procured from the Medical Records Department using a standardized data collection form. The following variables were recorded.

Demographics

Age, gender, and background (rural/urban).

Comorbidities

Preexisting conditions documented in the medical history, including hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), hypothyroidism, chronic obstructive pulmonary disease (COPD)/asthma, chronic kidney disease (CKD), cerebrovascular accident (CVA), and chronic liver disease (CLD)/fatty liver.

Clinical Presentation

Symptoms at admission, including fever, cough, breathlessness, abdominal pain, body aches, nausea/vomiting, weakness, headache, jaundice, loose stools, chills, reduced appetite, altered sensorium, rash, chest pain, bleeding manifestations, oliguria, and other symptoms.

Leptospirosis Phenotype

Classified as icteric (Weil's disease) or anicteric based on the presence of clinical jaundice and/or explicit diagnosis in the medical records.

Organ System Involvement

Hepatic, respiratory, hematological, renal, neurological, cardiac, rhabdomyolysis, uveitis, and secondary hemophagocytic lymphohistiocytosis (HLH), as documented in the case files or diagnosis notes. The following features were used to identify organ involvement, and the presence of at least one feature indicated involvement of the respective organ:

Respiratory—Shortness of breath, cough, hemoptysis, abnormal respiratory auscultation, partial pressure of arterial oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) <300.

Hepatic—Icterus, hepatomegaly, serum bilirubin >2 mg/dL, transaminitis.

Renal—Oliguric or nonoliguric renal failure, need for supportive renal replacement therapy.

Cardiac—Findings of cardiogenic shock, myocarditis, elevated cardiac enzymes, two-dimensional echocardiography correlation, and heart failure.

Nervous system—Neck stiffness or rigidity, seizures, Glasgow Coma Scale score <15/15.

Hematological—Bleeding manifestations, thrombocytopenia, and findings consistent with disseminated intravascular coagulation (DIC).

Uveitis—Pain/tenderness with redness in the eye, visual changes such as floaters or decreased visual acuity.

Rhabdomyolysis—Muscle tenderness, elevated creatine phosphokinase.

Coinfections

Presence of other pathogens, including dengue, scrub typhus, hepatitis A, enteric fever (typhoid), brucellosis, tuberculosis (TB), influenza A, coronavirus disease 2019 (COVID-19), human immunodeficiency virus (HIV), and varicella (chickenpox), was diagnosed using standard laboratory methods, including serology, PCR, nucleic acid amplification tests (NAAT), or culture, where available. Efforts were made to correlate laboratory findings with the clinical presentation to improve diagnostic accuracy.

Severity Indicators

Multi-organ dysfunction (defined as involvement of ≥ 2 organ systems), acute respiratory distress syndrome (ARDS), shock, intensive care unit (ICU) admission, need for

noninvasive ventilation (NIV), and need for invasive mechanical ventilation.

Treatment

Antibiotics, corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis (PLEX), hemodialysis, and ventilatory support.

Outcomes

Outcome was measured as discharge to home, left against medical advice (LAMA), or death. Length of stay included days of stay in the medical intensive care unit (MICU) and/or hospital floor.

Definitions

Severe leptospirosis was defined as involvement of ≥ 2 organ systems based on the organ involvement documented in the medical records.

Multi-organ dysfunction was defined as involvement of two or more of the following organ systems: hepatic, respiratory, hematological, renal, neurological, cardiac, or others (rhabdomyolysis, uveitis, and HLH).

Icteric leptospirosis (Weil's disease) was defined by the presence of clinical jaundice (serum bilirubin ≥ 3 mg/dL or clinical diagnosis) along with other systemic features.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. Continuous variables were assessed for normality using appropriate methods, and as most variables showed nonnormal distribution, they are presented as median (interquartile range). Categorical variables are presented as frequency (%). Comparisons were performed using the Mann-Whitney *U* test and Fisher's exact test. A *p*-value <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Patient confidentiality was maintained by anonymizing all data prior to analysis. The Institutional Ethics Committee waived the need for informed consent due to the retrospective design.

RESULTS

Demographic and Baseline Characteristics

Table 1 provides the foundation of the study cohort. The median age of 57 years (interquartile range 41–68) indicates that leptospirosis affects a wide age range, with a slight male predominance (52.6%). The

rural predominance (59.0%) suggests the traditional understanding of leptospirosis as an occupationally acquired disease, although a significant urban proportion (41.0%) suggests changing epidemiology.

Hypertension (25.6%) and diabetes mellitus (29.5%) were the most common comorbidities, reflecting the background burden of noncommunicable diseases. Notably, 42.3% of patients had no comorbidities, highlighting that leptospirosis can affect previously healthy individuals.

Clinical Symptoms and Laboratory Features

Table 2 and Figure 1 capture the *Leptospira* phenotype, severity indicators, and clinical spectrum of leptospirosis. The majority (84.6%) presented with anicteric disease, while 15.4% had the icteric (Weil's) form. Although fever was present in 93.6% of patients, detailed characteristics such as duration, pattern, and peak temperature were inconsistently documented in the records and could not be reliably analyzed. It was followed by cough (48.7%) and breathlessness (44.9%).

Table 1: Demographic and baseline characteristics of patients with leptospirosis (N = 78)

Characteristic	N = 78
Age (years)	
Median (IQR) [range]	57 (41–68) [18–83]
Gender, n (%)	
Male	41 (52.6)
Female	37 (47.4)
Background, n (%)	
Rural	46 (59.0)
Urban	32 (41.0)
Comorbidities, n (%)	
Hypertension	20 (25.6)
Diabetes mellitus	23 (29.5)
Coronary artery disease/ ischemic heart disease	9 (11.5)
Hypothyroidism	11 (14.1)
Chronic obstructive pulmonary disease/asthma	18 (23.1)
Chronic kidney disease	6 (7.7)
Cerebrovascular accident	2 (2.6)
Chronic liver disease/fatty liver	3 (3.8)
Number of comorbidities, n (%)	
0	33 (42.3)
1	20 (25.6)
2	8 (10.3)
≥3	17 (21.8)

IQR, interquartile range

Jaundice was present in 15.4%, correlating exactly with the icteric cases. Hepatic (69.2%) and respiratory (66.7%) involvement were the most common, highlighting the hepatopulmonary predominance. Figure 2 depicts the organ systems involved in these patients. Multi-organ dysfunction (≥2 organs) occurred in 61.5%, indicating significant

Table 2: Distribution of patients with *Leptospira* phenotype (N = 78), severity indicators and IgM titers

Characteristic	N = 78
Leptospirosis phenotype, n (%)	
Icteric (Weil's disease)	12 (15.4)
Anicteric	66 (84.6)
Severity indicators, n (%)	
Multi-organ dysfunction (≥2 organs)	48 (61.5)
Acute respiratory distress syndrome	8 (10.3)
Shock	11 (14.1)
ICU admission	13 (16.7)
Noninvasive ventilation	10 (12.8)
Invasive mechanical ventilation	7 (9.0)
<i>Leptospira</i> IgM	
IgM positive, n (%)	78 (100)
IgM value, median (IQR)†	13.4 (11.9–14.7)

ARDS, acute respiratory distress syndrome; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation; SOB, shortness of breath; †All 78 patients had quantitative immunoglobulin M (IgM) results; the median and IQR were calculated from all values

disease severity. All included patients had laboratory-confirmed leptospirosis based on predefined diagnostic criteria. The median *Leptospira*-specific IgM value was 13.4 NTU.

Coinfections

Figure 3 highlights that over half (52.6%) of patients had at least one coinfection. Dengue (17.9%) and scrub typhus (14.1%) were the most frequent, reflecting the endemicity

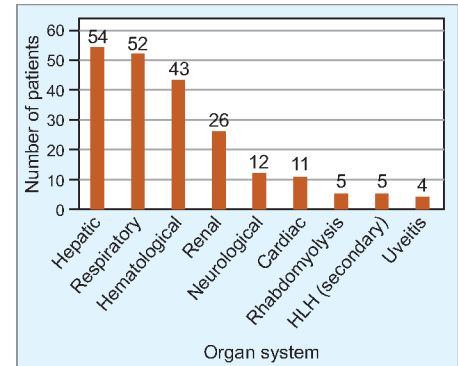


Fig. 2: Frequency of involvement of various organ systems (N = 78)

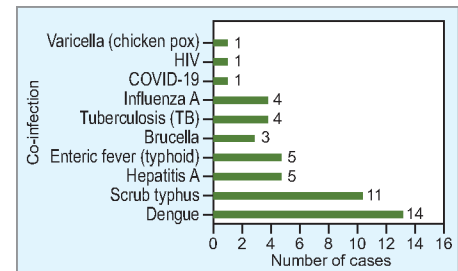


Fig. 3: Frequency of coinfection observed among all patients with leptospirosis

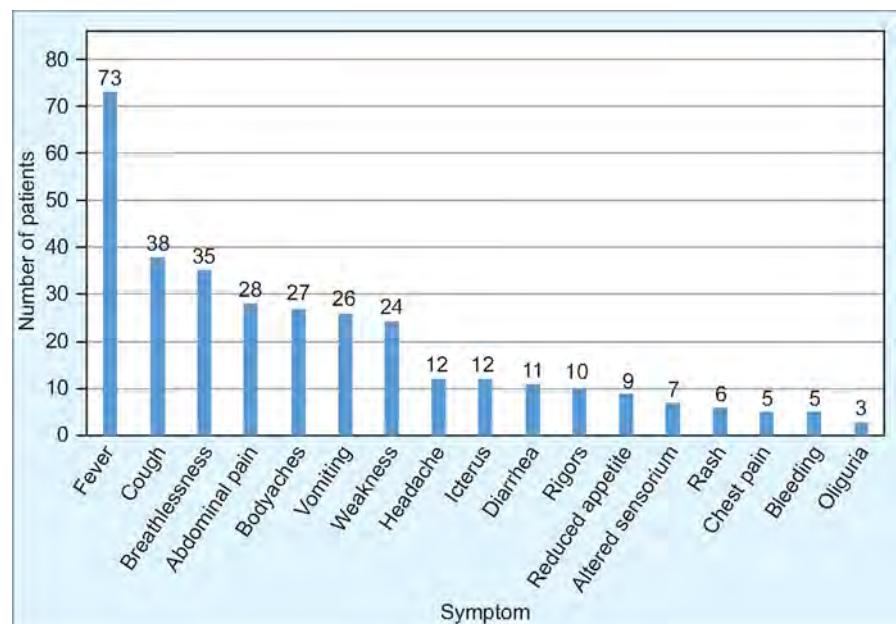


Fig. 1: Distribution of symptoms among all patients with leptospirosis (N = 78)

Table 3: Treatment and outcomes of patients with leptospirosis (N = 78)

Characteristic	N = 78
Treatment, n (%)	
Antibiotics	78 (100)
Corticosteroids	3 (3.8)
Intravenous immunoglobulin	1 (1.3)
Plasmapheresis	3 (3.8)
Hemodialysis (for acute kidney injury)	1 (1.3)
Mechanical ventilation/noninvasive ventilation	8 (10.3)
Length of hospital stay, days—median (IQR)	7 (5–9)
Outcome, n (%)	
Discharged	73 (93.6)
Died	2 (2.6)
Left against medical advice	3 (3.8)

AKI, acute kidney injury; IQR, interquartile range; NIV, noninvasive ventilation

of these infections in the region. Hepatitis A (6.4%) and enteric fever (6.4%) were also notable. The high rate of coinfections (11.5% had two, and 2.6% had three or more) underscores the complex diagnostic and clinical challenges in tropical febrile illnesses and is a unique contribution of this series.

Treatment and Outcomes

Table 3 highlights that all patients received antibiotics, reflecting the standard of care. Antibiotics included doxycycline, ceftriaxone, azithromycin, piperacillin–tazobactam, and meropenem, selected based on clinical severity and physician discretion. Antibiotic escalation was required in a subset of patients with worsening clinical status or suspected secondary infections. Adjunctive therapies were used selectively: corticosteroids (3.8%), intravenous immunoglobulin (IVIG) (1.3%), plasmapheresis (PLEX) (3.8%), and hemodialysis (1.3%). The three patients who required PLEX had diffuse alveolar hemorrhage, severe jaundice, and secondary thrombotic microangiopathy, respectively. Mechanical ventilation was required in 10.3% of patients. The median length of stay was 7 days (interquartile range 5–9). Outcomes were favorable overall, with 93.6% discharged, 2.6% mortality (2 deaths), and 3.8% leaving against medical advice. The low mortality rate suggests good clinical outcomes with timely management.

Icteric vs Anicteric Leptospirosis

Table 4 shows that patients with icteric disease (Weil's disease) were younger (median 30 vs 57.5 years, $p < 0.001$) and had fewer comorbidities (25 vs 63.6%, $p = 0.01$). Hepatic involvement was universal in the icteric group

Table 4: Comparison of patients with icteric vs anicteric leptospirosis (N = 78)

Characteristic	Icteric (n = 12)	Anicteric (n = 66)	p-value	OR (95% CI)
Age, years—median (IQR)	31.5 (23–58)	58 (43–68)	$<0.001^1$	–
Male gender—n (%)	7 (58.3)	34 (51.5)	0.76 ²	1.32 (0.38–4.56)
Rural background—n (%)	6 (50.0)	40 (60.6)	0.54 ²	0.65 (0.19–2.20)
Any comorbidity—n (%)	3 (25.0)	42 (63.6)	0.01 ²	0.19 (0.05–0.75)
Organ involvement—n (%)				
Hepatic	12 (100)	42 (63.6)	$<0.001^2$	14.4 (1.7–121) ³
Renal	6 (50.0)	20 (30.3)	0.20 ²	2.30 (0.66–7.98)
Respiratory	8 (66.7)	44 (66.7)	1.00 ²	1.00 (0.27–3.68)
Hematological	8 (66.7)	35 (53.0)	0.54 ²	1.77 (0.49–6.44)
Neurological	3 (25.0)	9 (13.6)	0.38 ²	2.11 (0.47–9.45)
Cardiac	3 (25.0)	8 (12.1)	0.36 ²	2.42 (0.53–11.0)
Rhabdomyolysis	2 (16.7)	3 (4.5)	0.15 ²	4.20 (0.62–28.5)
Uveitis	2 (16.7)	2 (3.0)	0.09 ²	6.40 (0.80–51.0)
HLH (secondary)	4 (33.3)	1 (1.5)	$<0.001^2$	32.5 (3.5–304)
Multi-organ dysfunction (≥ 2 organs)—n (%)	9 (75.0)	39 (59.1)	0.36 ²	2.08 (0.51–8.47)
Any ventilation (NIV/invasive)—n (%)	3 (25.0)	14 (21.2)	0.72 ²	1.24 (0.29–5.29)
Length of stay, days—median (IQR)	9.5 (7.5–13)	7 (5–9)	0.02 ¹	–
Mortality—n (%)	1 (8.3)	1 (1.5)	0.27 ²	5.91 (0.34–101)

CI, confidence interval; HLH, hemophagocytic lymphohistiocytosis; IQR, interquartile range; NIV, noninvasive ventilation; OR, odds ratio; ¹Mann–Whitney U test; ²Fisher's exact test; ³Odds ratio calculated using the Haldane–Anscombe correction because of a zero cell count

(100 vs 63.6%, $p < 0.001$), and secondary hemophagocytic lymphohistiocytosis (HLH) was far more frequent (33.3 vs 1.5%, $p < 0.001$).

Renal involvement was higher in icteric cases (50 vs 30.3%) but was not statistically significant. Icteric patients had longer hospital stays (10.5 vs 7 days, $p = 0.02$). Mortality was higher (8.3 vs 1.5%) but was not statistically significant. Overall, Weil's disease represents a more severe phenotype requiring prolonged care and monitoring for complications such as HLH.

Coinfected vs *Leptospira* Alone

Table 5 shows that coinfecting patients were significantly younger (median 44 vs 60 years, $p < 0.001$) and had fewer comorbidities (39 vs 78.4%, $p < 0.001$). Interestingly, they had less renal (22 vs 45.9%, $p = 0.03$), respiratory (56.1 vs 78.4%, $p = 0.04$), and neurological involvement (7.3 vs 24.3%, $p = 0.05$). They also required significantly less ventilatory support (7.3 vs 37.8%, $p = 0.001$). This suggests that coinfections may occur in a healthier, younger population but do not necessarily worsen organ dysfunction compared to *Leptospira* infection alone.

Dengue and Scrub Typhus Coinfections

Table 6 descriptively provides a detailed profile of patients with the two most common coinfections. Dengue-coinfecting

patients had universal hepatic and hematological involvement but no renal, neurological, or cardiac complications. Scrub typhus-coinfecting patients had more varied organ involvement, including renal (44.4%), respiratory (55.6%), and cardiac (22.2%) manifestations. Both groups had zero mortality, although the small sample sizes preclude firm conclusions. This table highlights the distinct clinical patterns associated with different coinfections.

Severe vs Nonsevere Leptospirosis

Table 7 reveals that severe disease (≥ 2 organ involvement) occurred in 61.5% of patients. The only predictor of severity was coinfection (56.3 vs 46.7%, $p = 0.48$, odds ratio 1.47), although this did not reach statistical significance. The icteric phenotype showed a strong trend (18.8 vs 3.3%, $p = 0.08$). Severe cases had significantly longer hospital stays (8 vs 5 days, $p < 0.001$), and both deaths occurred in the severe group. This table underscores that while severe disease prolongs hospitalization, mortality remains low with appropriate care. The low mortality rate may reflect early diagnosis, prompt initiation of appropriate antibiotics, and access to advanced supportive care, including intensive care unit (ICU) monitoring and organ support.

Table 5: Comparison of patients with any coinfection vs *Leptospira* alone (N = 78)

Characteristic	Coinfection (n = 41)	<i>Leptospira</i> alone (n = 37)	p-value	OR (95% CI)
Age, years—median (IQR)	44 (29–60)	60 (50–70)	<0.001 ¹	–
Male gender, n (%)	22 (53.7)	19 (51.4)	1.00 ²	1.10 (0.45–2.67)
Rural background, n (%)	23 (56.1)	23 (62.2)	0.65 ²	0.78 (0.31–1.94)
Any comorbidity, n (%)	16 (39.0)	29 (78.4)	<0.001 ²	0.17 (0.06–0.46)
Organ involvement, n (%)				
Hepatic	32 (78.0)	22 (59.5)	0.09 ²	2.42 (0.91–6.46)
Renal	9 (22.0)	17 (45.9)	0.03 ²	0.33 (0.12–0.90)
Respiratory	23 (56.1)	29 (78.4)	0.04 ²	0.36 (0.13–0.97)
Hematological	25 (61.0)	18 (48.6)	0.36 ²	1.65 (0.67–4.06)
Neurological	3 (7.3)	9 (24.3)	0.05 ²	0.24 (0.06–0.99)
Cardiac	3 (7.3)	8 (21.6)	0.10 ²	0.29 (0.07–1.20)
Rhabdomyolysis	1 (2.4)	4 (10.8)	0.18 ²	0.21 (0.02–1.95)
Uveitis	1 (2.4)	3 (8.1)	0.34 ²	0.28 (0.03–2.85)
Secondary HLH	4 (9.8)	1 (2.7)	0.36 ²	3.89 (0.41–36.5)
Multi-organ dysfunction (≥2 organs), n (%)	27 (65.9)	21 (56.8)	0.48 ²	1.47 (0.58–3.70)
Any ventilation (NIV/invasive), n (%)	3 (7.3)	14 (37.8)	0.001 ²	0.13 (0.03–0.50)
Length of stay, days—median (IQR)	7 (5–10)	7 (5–9)	0.65 ¹	–
Mortality, n (%)	1 (2.4)	1 (2.7)	1.00 ²	0.90 (0.05–14.9)

CI, confidence interval; HLH, hemophagocytic lymphohistiocytosis; IQR, interquartile range; NIV, noninvasive ventilation; OR, odds ratio;

¹Mann–Whitney U test; ²Fisher's exact test

Table 6: Clinical characteristics of patients with dengue and scrub typhus coinfections (N = 78)

Characteristic	Dengue coinfection (n = 11)	Scrub typhus coinfection (n = 9)	All patients (N = 78)
Age, years—median (IQR)	41 (36–51)	44 (28–60)	57 (41–68)
Male gender, n (%)	4 (36.4)	6 (66.7)	41 (52.6)
Rural background, n (%)	5 (45.5)	7 (77.8)	46 (59.0)
Any comorbidity, n (%)	3 (27.3)	4 (44.4)	45 (57.7)*
Organ involvement, n (%)			
Hepatic	11 (100)	8 (88.9)	54 (69.2)
Renal	0 (0)	4 (44.4)	26 (33.3)
Respiratory	4 (36.4)	5 (55.6)	52 (66.7)
Hematological	11 (100)	6 (66.7)	43 (55.1)
Neurological	0 (0)	1 (11.1)	12 (15.4)
Cardiac	0 (0)	2 (22.2)	11 (14.1)
Rhabdomyolysis	1 (9.1)	0 (0)	5 (6.4)
Uveitis	0 (0)	1 (11.1)	4 (5.1)
Secondary HLH	0 (0)	2 (22.2)	5 (6.4)
Multi-organ dysfunction (≥2 organs), n (%)	11 (100)	8 (88.9)	48 (61.5)
Any ventilation (NIV/invasive), n (%)	0 (0)	2 (22.2)	17 (21.8)
Length of stay, days—median (IQR)	7 (6–9)	9 (5–10)	7 (5–9)
Mortality, n (%)	0 (0)	0 (0)	2 (2.6)

HLH, hemophagocytic lymphohistiocytosis; IQR, interquartile range; NIV, noninvasive ventilation; Some patients had both dengue and scrub typhus (n = 1) and are counted in both columns; Any comorbidity denotes patients with at least one preexisting condition (refer to Table 1)

DISCUSSION

This study provides a comprehensive overview of acute leptospirosis in a tertiary care center in Rajasthan, highlighting its diverse clinical

spectrum and outcomes. The median age of 57 years and slight male predominance align with previous Indian and global reports demonstrating that leptospirosis commonly affects adults with a higher proportion of

male patients; systematic reviews from India have similarly noted male predominance and a wide age distribution in clinical cohorts.^{1,2}

Although leptospirosis has traditionally been considered a rural disease linked to agricultural exposures, the substantial proportion of urban patients (41%) in this cohort suggests a shift in epidemiology. Urban leptospirosis has been increasingly reported, including the influence of urban risk factors such as waterlogging and rodent exposure contributing to transmission.^{3,10} While common comorbidities such as diabetes and hypertension were observed, 42% of patients were previously healthy, emphasizing that leptospirosis affects individuals across health backgrounds.²

Clinically, anicteric presentations predominated (84.6%), consistent with numerous studies showing that nonjaundiced leptospirosis is the more frequent clinical form; the disease's spectrum ranges from mild febrile illness to severe multi-organ involvement.^{1,4} However, multi-organ involvement occurred in over 60% of cases in this cohort, underscoring the potential severity even in nonicteric patients. Gastrohepatic and pulmonary systems were often affected, reflecting the classic organ predilection of leptospiral infection.^{1,11} Fever remained the most universal symptom, with respiratory manifestations and breathlessness commonly reported, highlighting the disease's systemic nature.^{2,4}

A notable finding was the high rate of coinfections, present in more than half of the cohort, with dengue and scrub typhus

Table 7: Comparison of severe vs nonsevere leptospirosis (*N* = 78)

Characteristic	Severe (<i>n</i> =48)	Nonsevere (<i>n</i> =30)	<i>p</i> -value	OR (95% CI)
Age, years—median (IQR)	57 (41–68)	56 (40–66)	0.78 ¹	–
Male gender— <i>n</i> (%)	25 (52.1)	16 (53.3)	1.00 ²	0.95 (0.38–2.39)
Rural background— <i>n</i> (%)	28 (58.3)	18 (60.0)	1.00 ²	0.93 (0.36–2.40)
Any comorbidity— <i>n</i> (%)	30 (62.5)	15 (50.0)	0.35 ²	1.67 (0.65–4.26)
Icteric phenotype— <i>n</i> (%)	9 (18.8)	3 (10.0)	0.53 ²	2.08 (0.51–8.38)
Any coinfection— <i>n</i> (%)	27 (56.3)	14 (46.7)	0.48 ²	1.47 (0.58–3.70)
Length of stay, days—median (IQR)	8 (6–11)	5 (4–7)	<0.001 ¹	–
Mortality— <i>n</i> (%)	2 (4.2)	0 (0.0)	0.52 ²	–

Severe disease was defined as involvement of ≥ 2 organ systems; CI, confidence interval; IQR, interquartile range; OR, odds ratio; ¹Mann–Whitney *U* test; ²Fisher's exact test

being the most frequent. Systematic analyses in India report coinfection of scrub typhus and leptospirosis as an important clinical consideration due to overlapping seasonal and geographic distributions.^{5,8} Coinfections with dengue and leptospirosis occur globally, with pooled coinfection prevalence reported in meta-analytic studies, and can complicate diagnosis and management.^{2,6,7} In the present cohort, these coinfections occurred predominantly in younger, healthier patients and were associated with less severe renal, respiratory, and neurological involvement, suggesting that coinfecting patients may not necessarily develop more severe leptospirosis.^{7,10} However, this finding should be interpreted cautiously given the small subgroup size and lack of multivariate adjustment. The possibility of serological cross-reactivity, particularly in endemic settings, cannot be excluded and may have led to overestimation of coinfection rates. Therefore, these findings should be interpreted with caution.

Distinct clinical patterns were observed with specific coinfections. For instance, dengue coinfection primarily affected the hepatic and hematological systems, while scrub typhus coinfection showed broader organ involvement, reinforcing pathogen-specific vigilance in endemic regions.^{5,12,13} These findings are consistent with other acute febrile illness surveillance studies that show diverse organ involvement depending on the infectious agent.^{6,8}

Icteric leptospirosis (Weil's disease) represented a younger, more severely affected subgroup with universal hepatic involvement, a higher incidence of hemophagocytic lymphohistiocytosis (HLH), longer hospital stays, and a trend toward increased mortality. Severe leptospirosis marked by jaundice and organ dysfunction is well documented as a distinct and serious clinical phenotype with higher morbidity and variable mortality rates across settings.^{1,9}

Severe leptospirosis, defined by multi-organ involvement, was observed in over 60% of patients and was associated with

prolonged hospitalization, although mortality remained low (2.6%), highlighting the effectiveness of timely antibiotic therapy and supportive care in modern clinical settings.^{2,3,11} Despite this low mortality, global data indicate that severe forms, especially with pulmonary hemorrhage or renal failure, are associated with a significantly higher risk of death—up to 50% in some contexts without prompt care.^{1,9}

Overall, these findings underscore the heterogeneity of leptospirosis presentations, the importance of recognizing icteric and coinfecting subgroups, and the critical role of early diagnosis and comprehensive management in improving outcomes. Additionally, the study highlights evolving epidemiology, including increasing urban cases and high rates of coinfections, emphasizing the need for region-specific surveillance and clinical awareness to improve timely diagnosis and tailored therapeutic strategies in endemic and emerging settings.^{2,5,6,14} The findings of this study are broadly consistent with previous Indian studies demonstrating male predominance, multi-organ involvement, and the predominance of anicteric disease. However, compared to earlier reports, our study shows a higher proportion of urban cases and coinfections, suggesting evolving epidemiological patterns.

Strengths and Limitations

This study provides a comprehensive real-world evaluation of acute leptospirosis, including the clinical spectrum, organ involvement, coinfections, and outcomes in a tertiary care setting. Inclusion of only laboratory-confirmed cases and the use of predefined criteria enhance diagnostic reliability. The comparative analysis of icteric and anicteric phenotypes and the high burden of coinfections offer clinically relevant insights into disease heterogeneity and evolving epidemiology, including a notable urban contribution.

However, limitations include the retrospective, single-center design with potential selection bias and limited generalizability. The modest sample size and lack of multivariate analysis restrict the identification of independent predictors. Incomplete documentation limited the detailed assessment of some clinical parameters. Additionally, reliance on serology for coinfections raises the possibility of cross-reactivity. Despite these constraints, the study highlights important trends in the clinical profile of leptospirosis in an endemic setting.

CONCLUSION

Acute leptospirosis in adults demonstrates marked clinical heterogeneity with frequent multi-organ involvement and a substantial burden of coinfections in endemic settings. Icteric disease represents a distinct and more severe clinical phenotype associated with prolonged hospitalization and higher complication rates. Early diagnosis, vigilant monitoring for organ dysfunction, and timely supportive care are key determinants of favorable outcomes. Greater awareness of overlapping tropical infections is essential for improving diagnostic accuracy and management strategies in India.

LEARNING POINTS

Acute leptospirosis shows wide clinical variability, with frequent hepatic and respiratory involvement and multi-organ dysfunction in many hospitalized adults.

Anicteric disease is more common, while icteric (Weil's) disease represents a more severe phenotype with greater complications and longer hospital stays.

Coinfections, especially dengue and scrub typhus, are common but do not consistently worsen outcomes.

Early diagnosis and timely supportive management result in low mortality and favorable outcomes.

Urban cases of leptospirosis show a rising trend.

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REFERENCES

1. Rajapakse S, Fernando N, Dreyfus A, et al. Leptospirosis. *Nat Rev Dis Primers* 2025;11:32.
2. Gupta N, Yadav R, Kumar S, et al. Leptospirosis in India: a systematic review and meta-analysis of clinical profile, treatment and outcomes. *Infez Med* 2023;31(3):290–305.
3. Levett PN. Leptospirosis. *Clin Microbiol Rev* 2001;14(2):296–326.
4. Sicong Wang, Noel Dunn. *StatPearls. Leptospirosis*. NCBI Bookshelf. 2024.
5. Bhatia M, Puri O, Govekar S, et al. Scrub typhus-leptospirosis co-infection in India: systematic review and meta-analysis. *Trans R Soc Trop Med Hyg* 2025;119(2):97–106.
6. Veena RK, Prasad S, Kumar V, et al. Epidemiological analysis of leptospirosis, dengue, and co-infection rates among febrile illness cases in Dakshina Kannada, Karnataka. *Indian J Med Microbiol* 2024;51:100698.
7. Tiwari S, Singh A, Reddy P, et al. Prevalence of dengue and leptospirosis coinfection and associated mortality rates: systematic review and meta-analysis. *BMC Infect Dis* 2025;25:111.
8. Borkakoty B, Jakharia A, Biswas D, et al. Co-infection of scrub typhus and leptospirosis in patients with pyrexia of unknown origin in Arunachal Pradesh, India. *Indian J Med Microbiol* 2016;34(1):88–91.
9. Sethia M, Jain R, Singh SK, et al. A study of clinical profile of 100 icteric leptospirosis cases. *Med J DY Patil Vidyapeeth* 2023;16:611–616.
10. Kembhavi RS, Velhal GD, Shah AK, et al. Epidemiological determinants of leptospirosis in rural and urban districts of Maharashtra, India. *J Family Med Prim Care* 2021;10:3361–3367.
11. Sellors P, Watson RF, Bate R, et al. Clinical features and severity of leptospirosis cases reported in the Hawke's Bay Region of New Zealand. *J Trop Med* 2021;2021:5567081.
12. Tiwari S, Khatib MN, Mm R, et al. Prevalence of dengue and leptospirosis coinfection and associated mortality rates: a systematic review and meta-analysis. *BMC Infect Dis* 2025;25(1):111.
13. G M, V A, P G, et al. A case series and review of severe leptospirosis. *Int J Med Pharm Res* 2023;4(2).
14. Mishra D, Singh A, Shewale AD, et al. Prevention & control of leptospirosis in India: human health initiatives. *Epi-Dis-Phere (Publication of Health Resilience)* 2025;1(1):41–47.



Etiological Spectrum of Hyponatremia in Tuberculous Meningitis: Insights from Referral Institute in Northern India

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ABSTRACT

Background: Tuberculous meningitis (TBM) causes death or severe disability in 50% of afflicted patients. Among the various complications, such as hydrocephalus, hyponatremia, cranial nerve palsies, seizures, and myeloradiculopathy, hyponatremia occurs more frequently, affecting 35–65% of patients with central nervous system (CNS) tuberculosis.

Aim: To study the prevalence of hyponatremia in patients with TBM and its correlation with the clinical profile, severity of illness, and outcome.

Methodology: In suspected TBM patients with low sodium levels, serum and urine osmolality were measured by an osmometer [Advanced Instruments, Inc. (2020)] to evaluate the possible causes. Patients underwent brain imaging to look for hydrocephalus, vasculitic infarcts, and basal exudates. They were followed up with serum sodium levels until the completion of treatment and repeat brain imaging during follow-up to assess radiological recovery.

Results: A total of 100 suspected TBM patients with a mean age of 32.6 years and predominantly female (57%) were included. The most common symptoms were fever, headache, altered sensorium, and seizures. The VI cranial nerve was most frequently involved. A total of 31% of patients presented in stage III, with a significant association with mortality ($p = 0.002$). Hyponatremia was seen in 57% of patients. The GeneXpert Ultra-based polymerase chain reaction (PCR) test for tuberculosis was positive in 41% of patients. Basal exudates ($p = 0.001$) and tuberculomas ($p = 0.004$) on brain imaging had a significant association with mortality. On follow-up, 41% of patients had improvement, 35% expired, and 10% had a static condition. Repeat sodium levels along with brain imaging were assessed ($p = 0.001$).

Conclusion: There was a high prevalence of hyponatremia in TBM patients, as seen in 57% of patients, which occurred most frequently due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), followed by cerebral salt-wasting syndrome (CSWS), and was related to the severity of TBM.

Keywords: Basal exudates, Hyponatremia, Syndrome of inappropriate antidiuretic hormone secretion, Tuberculous meningitis.

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INTRODUCTION

Tuberculous meningitis (TBM) is a serious public health problem in developing countries, as it causes significant mortality and residual neurological sequelae. As per the Indian national guidelines for extrapulmonary tuberculosis (TB),¹ it constitutes 1% of all TB cases. In drug-resistant TB meningitis patients coinfecting with the retrovirus, the death rate is nearly 100%. Among chronic central nervous system (CNS) infections, CNS TB is the most common because of the high prevalence of TB in the community.

In 2020, worldwide, there was a substantial fall (18% drop) in the number of people newly diagnosed with TB and notified to health authorities compared with 2019, in contrast to the marked increase in notifications between 2017 and 2019.²

Globally, an estimated 10.6 million people suffered from TB in 2021. Among all TB cases, 6.7% were among people living

with human immunodeficiency virus (HIV). Geographically, most TB cases in 2021 were in the World Health Organization (WHO) regions of South-East Asia (45%), Africa (23%), and the Western Pacific (18%).³ When it comes to TBM, it has an incidence of 0.1 million every year and is the most devastating and disabling form, with >50% mortality or neurological sequelae among survivors.⁴

The Government of India launched the Pradhan Mantri TB Mukht Bharat Abhiyaan on 9th September 2022, which aimed at the early identification of cases from such population groups and the early initiation of treatment,⁵ as TB causes the largest number of deaths among all infectious diseases in India. India has 20% of the world's population but accounts for >25% of the total TB cases worldwide.

If untreated, TBM may lead to altered sensorium, coma, and death. In patients who survive TBM, neurological

sequelae, such as intellectual disability, hydrocephalus, sensorineural hearing loss, cranial nerve palsies, seizures, stroke-associated neurological deficits, and coma, occur.²

Intravascular volume disturbances are frequent in TBM. Among TBM patients, nearly 45% present with hyponatremia in the study by Misra et al.,⁶ and it can independently predict death or disability. In another study by Hieu et al.,⁷ the death rate among TBM patients was approximately one-third of cases.

Disability-free survival in TBM is not entirely dependent on the activity of antitubercular drugs. Brain infarction, severe hyponatremia, tuberculoma formation, and hydrocephalus are the most common life-threatening complications that can occur both before and during antituberculosis treatment. The need to distinguish between cerebral salt-wasting syndrome (CSWS) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) is important because the treatment of one might be detrimental to the other.

This study primarily emphasized the need for the early diagnosis of the cause of hyponatremia, which can significantly alter the neurological outcome of the patient.

METHODOLOGY

The study was conducted based on the collection of data from suspected TBM patients aged older than 12 years admitted to the Post Graduate Institute of Medical

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Education and Research (PGIMER), Chandigarh, India, during the study period from August 2021 to June 2023 after obtaining permission from the Institutional Ethics Committee vide INT/IEC/2021/SPL-1301 dated 14th September 2021. Suspected TBM patients who fulfilled the Lancet Consensus Criteria⁸ were enrolled in the study, and their cerebrospinal fluid (CSF) was collected. The collected CSF samples were analyzed using the polymerase chain reaction (PCR)-based GeneXpert Ultra method to diagnose TBM.

At the initial evaluation of patients, a detailed history, including symptoms of raised intracranial pressure, seizures, diarrhea, and vomiting, was recorded in the case record form. TBM severity [British Medical Research Council (BMRC)] was categorized, and the conscious level was also assessed using the Glasgow Coma Scale (GCS). Clinical examination was focused on hemodynamic assessment, such as hypotension, tachycardia, and dry mucous membranes, which helped differentiate between the major causes of hyponatremia in TB meningitis.

Biochemical Tests

All suspected TBM patients at the time of admission underwent routine blood investigations, such as complete hemogram, serum sodium and potassium levels, renal function tests, and liver function tests. Serum samples were analyzed on the random-access autoanalyzers Beckman Coulter (models AU5800 and AU480) and Cobas 8000 used in the emergency biochemistry laboratory. Serum and urine sodium level measurements were based on the potentiometry principle.

In patients with low sodium levels who were treatment-naïve for TBM, serum and urine osmolality were measured by an osmometer [Advanced Instruments, Inc. (2020)] using the freezing-point depression method to establish the type of hyponatremia and evaluate the possible causes.

Hyponatremia was categorized based on serum sodium levels into severe (<120 mEq/L), moderate (120–129 mEq/L), and mild (130–134 mEq/L) groups. In addition, a volume status assessment was performed to differentiate the common causes of hyponatremia in TBM, such as CSWS and SIADH.^{9,10}

Patients underwent brain imaging, such as noncontrast computed tomography (CT) of the head at admission, followed by magnetic resonance imaging (MRI) of the brain to look for hydrocephalus, vasculitic infarcts, basal exudates, and gyral enhancement.

Patients were followed up every 6 weeks, and serum sodium levels and liver function tests were measured until the completion of

treatment. They also underwent repeat MRI of the brain to assess radiological recovery.

Statistical Analysis

Data were entered into an Excel sheet after collection from the study participants. The cleaned data were exported to SPSS version 21 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows to carry out all statistical calculations.

Continuous data, including demographic details and clinical and laboratory parameters, were described in terms of mean $\pm$ standard deviation (SD) and range or median and interquartile range. Discrete categorical data to denote the prevalence of hyponatremia in TBM patients were estimated as percentages and presented as *n* (%) with a 95% confidence interval. For predictors of outcome compared between patients with hyponatremia and those without hyponatremia in the TBM study subjects, the Chi-square (χ^2) test and Fisher's exact test (<5) were performed. Comparison among etiologies, such as CSWS and SIADH, in TBM patients was also evaluated using the Chi-squared test. A probability value (*p*-value) of <0.05 was considered statistically significant.

RESULTS

Our study included 100 patients with TBM, of whom 43 (43%) were male and 57 (57%) were female. The mean age of the patients in our study was 32 years, with two-thirds of patients (67%) below 40 years of age. The age of the patients turned out to be a significant predictor of mortality (*p*-value = 0.015), whereas gender was not a significant predictor of mortality (*p*-value = 0.369).

Among the 100 patients, the most common presenting symptom was fever in 97 (97%), followed by headache in 81 (81%), altered mental sensorium in 73 (73%), and vomiting in 56 (56%) patients. In addition, 27 (27%) patients had seizures on presentation.

Hyponatremia was prevalent in 57% of the patients, among whom most were euvoletic (29%), 26% were hypovolemic, and 2% were hypervolemic. However, no significant association between the type of hyponatremia and the outcome was observed (*p*-value = 0.693).

Among the cranial nerve palsies, cranial nerve VI was affected most frequently in 18 (18%) patients, followed by cranial nerve III in eight (8%), cranial nerve IV in four (4%), and cranial nerve II in three (3%) patients; these findings were not statistically significant.

In this study, 41 (41%) patients had definitive cases, 48 (48%) were highly probable, and 11 (11%) had a possible diagnosis of TBM.⁸ The GeneXpert Ultra

test was positive in 41 (41%) patients, which accounted for a definitive diagnosis of TBM. Sixty (60%) patients had rifampicin-sensitive disease, two (2%) patients were rifampicin resistant, whereas 38 (38%) had indeterminate resistance, as highlighted in Table 1.

TBM patients presented with different clinical stages. Most patients, 40 (40%), were in stage II, 31 (31%) were in clinical stage III, and 29 (29%) were in stage I. Clinical stage had a significant association with mortality (*p*-value = 0.002).

On brain imaging, 57 (57%) patients had hydrocephalus, 38 (38%) had basal exudates, 24 (24%) had cerebral vasculitic infarcts, 17 (17%) had tuberculomas, 13 (13%) had arachnoiditis, and 11 (11%) patients had a miliary pattern on chest X-ray. Among these findings, only basal exudates (*p*-value = 0.01) and tuberculomas (*p*-value = 0.004) had a significant correlation with patient outcomes.

The clinical-radiological predictors of poor outcome in this study were low GCS at admission, the presence of altered mental sensorium, a higher clinical stage of TBM, and the presence of infarcts and exudates on MRI brain findings at the time of admission.

In our study, the probable etiology of hyponatremia was assessed based on volume status (clinical and laboratory parameters). Among the 57 (57%) patients with hyponatremia, 29 (29%) belonged to the SIADH group, and 26 (26%) belonged to the CSWS group. However, the etiology of hyponatremia in our study was not a predictor of mortality (*p*-value = 0.693). CSWS was more common in males, whereas SIADH was more common in females. Seizures occurred with almost equal frequency in both the CSWS and SIADH groups. Among the radiological parameters, hydrocephalus occurred with equal frequency in both groups. Exudates and infarcts appeared to be more common in the SIADH group (Fig. 1).

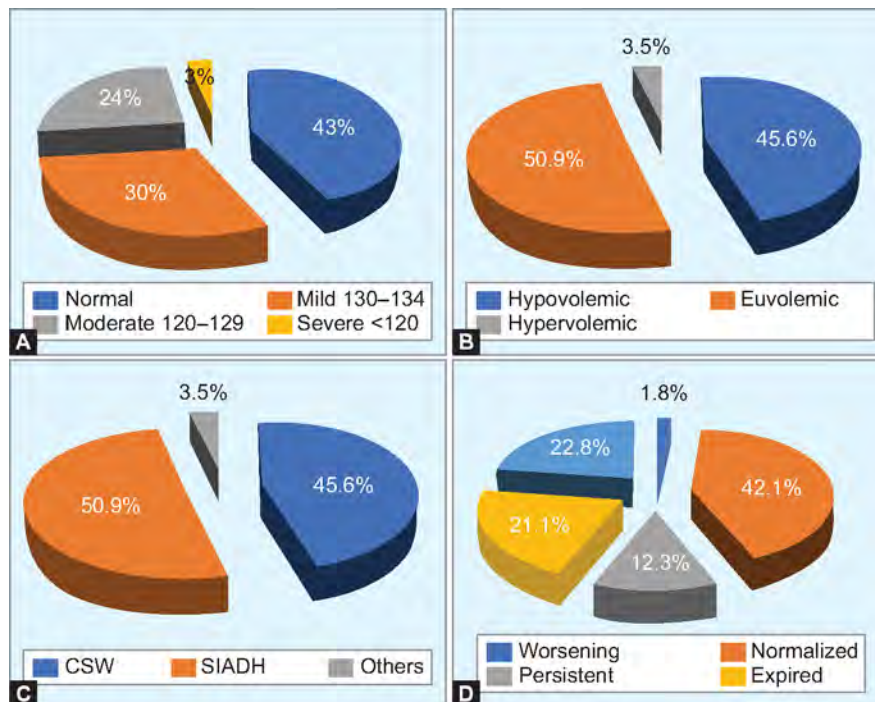
The Glasgow Coma Scale (GCS) score calculated at the time of admission was found to be a significant predictor of mortality (*p*-value = 0.001) (Fig. 2).

The occurrence of clinical parameters, such as hypotension, dry mucous membranes, and tachycardia, had a significant association when comparing the CSWS and SIADH groups (*p*-value = 0.001). However, the laboratory parameters, such as serum uric acid, urea, hematocrit, and albumin, did not have a significant association, whereas the occurrence of anemia in both groups had statistical significance (*p*-value = 0.039) (Table 2).

Modified antitubercular therapy (ATT) was started in 10 patients who had initially been started on first-line antitubercular therapy,

Table 1: Comparison of clinical, radiological parameters with and without Hyponatraemia in patients with Tubercular meningitis ($n = 100$)

Parameters	Total	Hyponatremia 57 (57%)	Without hyponatremia 43 (43%)	p-value
Age-group				0.151
<20 years	23 (23%)	15 (26.3%)	8 (18.6%)	
21–30	32 (32%)	17 (29.8%)	15 (34.9%)	
31–40	18 (18%)	12 (21.05%)	6 (14%)	
41–50	15 (15%)	7 (12.2%)	8 (18.6%)	
51–60	7 (7%)	3 (5.2%)	4 (9.3%)	
>60	5 (5%)	3 (5.2%)	2 (4.7%)	
Gender				0.67
Male	47 (47%)	27 (47.36%)	20 (46.5%)	
Female	53 (53%)	20 (35.08%)	23 (53.5%)	
Cerebral imaging				
Hydrocephalus	50 (50%)	30 (52.6%)	20 (46.5%)	0.709
Basal exudates	38 (38%)	27 (47.3%)	11 (25.6%)	5.97
Vasculitic infarcts	24 (24%)	16 (28.07%)	8 (18.6%)	1.43
Tuberculomas	17 (17%)	11 (19.29%)	6 (14%)	5.76
Arachnoiditis	13 (13%)	6 (10.52%)	7 (16.3%)	1.32


Fig. 1A to D: Pie-diagram illustrates various types of Hyponatraemia on basis of laboratory values of sodium (A), volume status (B), etiology of hyponatraemia (C), outcome of patients with hypo-natraemia (D)

and ventriculoperitoneal (VP) shunting was performed in 15 patients among the 50 patients with hydrocephalus. Neither of these parameters had a significant association with the final outcome (p -values = 0.2 and 0.5, respectively).

In terms of study outcomes, 48 (48%) patients showed improvement, 35 (35%) patients died, 10 (10%) patients remained in a static condition, and seven (7%) patients were lost to follow-up. Parameters that had a significant association with mortality included patient age, clinical stage, GCS, hydrocephalus, basal

exudates on MRI of the brain at presentation, follow-up MRI findings, and follow-up sodium levels (p -value = 0.001) (Table 3).

DISCUSSION

In India, the disease burden of tuberculosis (TB) is estimated at 2.6 million people contracting the disease, and approximately 4,00,000 people die every year.⁵ The enormous burden of the disease is faced by developing and underdeveloped countries because of

poverty, poor sanitation, overcrowding, and limited access to health care.

The present study included 100 patients, with 43 males and 57 females, and the mean age was 32 years. Most of the patients ($n = 32$) included in our study were between 21 and 40 years of age, and age was established as a significant predictor of mortality (p -value = 0.015), in contrast to the study by Hieu et al.,⁷ in which age was not a significant contributor to mortality.

In our study, 30% of patients had mild hyponatremia, 24% had moderate hyponatremia, while severe hyponatremia occurred in only 3% of cases, possibly because our institute provides tertiary care facilities to various northern states of India, especially for neurological illnesses, as the first point of contact, and patients came from far-flung areas with early referral for timely diagnosis and the excellent services provided by our institute (Figs 1 and 2).

About 30% of the patients with hyponatremia were hypovolemic, which was similar to the study by Misra et al.,⁶ as most of the admitted patients belonged to a lower socioeconomic status and were less educated, resulting in a poorer understanding of the disease process.

A total of 41 (41%) patients had a definitive diagnosis of TBM, which differed from the study by Misra et al.,¹¹ in which 23% of patients had a definitive diagnosis. This is attributed to the higher sensitivity of the CSF GeneXpert Ultra test¹² performed in comparison with previous studies, which primarily depended on GeneXpert. Among cranial nerve involvement, three (3%) patients had involvement of cranial nerve II, eight (8%) of cranial nerve III, four (4%)

Table 2: Comparison of clinical, laboratory, cerebral imaging, staging in different etiologies of Hypo-natraemia in patients with Tubercular meningitis (n = 57)

Parameters	CSWS (N = 26)	SIADH (N = 29)	Others (N = 2)	Total (N = 57)	p-value
Clinical					
Gender					
Male	15 (57.7%)	12 (41.4%)	0 (0%)	27	0.189
Female	11 (42.3%)	17 (58.6%)	2 (100%)	30	
Dry mucous membrane	24 (92.3%)	2 (6.9%)	0 (0%)	26	0.001
Tachycardia (HR >100)	26 (100%)	4 (13.8%)	1 (50%)	31	0.001
Weight loss	15 (57.7%)	17 (58.6%)	0 (0%)	32	0.265
Seizures	17 (65.4%)	18 (62.1%)	1 (50%)	36	0.896
Blood investigations					
Hemoglobin >11 gm/dL	26 (100%)	23 (79.3%)	2 (100%)	51	0.039
Hematocrit >30	18 (69.2%)	25 (86.2%)	2 (100%)	45	0.329
Urea >40 mg/dL	15 (57.7%)	16 (55.2%)	2 (100%)	33	0.462
Uric acid <4 mg/dL	2 (7.7%)	7 (24.1%)	1 (50%)	10	0.395
S. albumin >3 gm/dL	18 (69.2%)	18 (62.1%)	1 (50%)	37	0.727
Cerebral imaging					
Hydrocephalus	13 (50%)	13 (44.8%)	2 (100%)	28	0.318
Exudates	9 (34.6%)	17 (58.6%)	1 (50%)	27	0.204
Infarcts	5 (19.2%)	11 (37.9%)	0 (0%)	16	0.204
Tuberculomas	4 (15.4%)	7 (24.1%)	0 (0%)	11	0.557
Arachidionitis	3 (11.5%)	3 (10.3%)	0 (0%)	6	0.876
Stage III TBM	9 (34.6%)	11 (37.9%)	0 (0%)	20	0.532

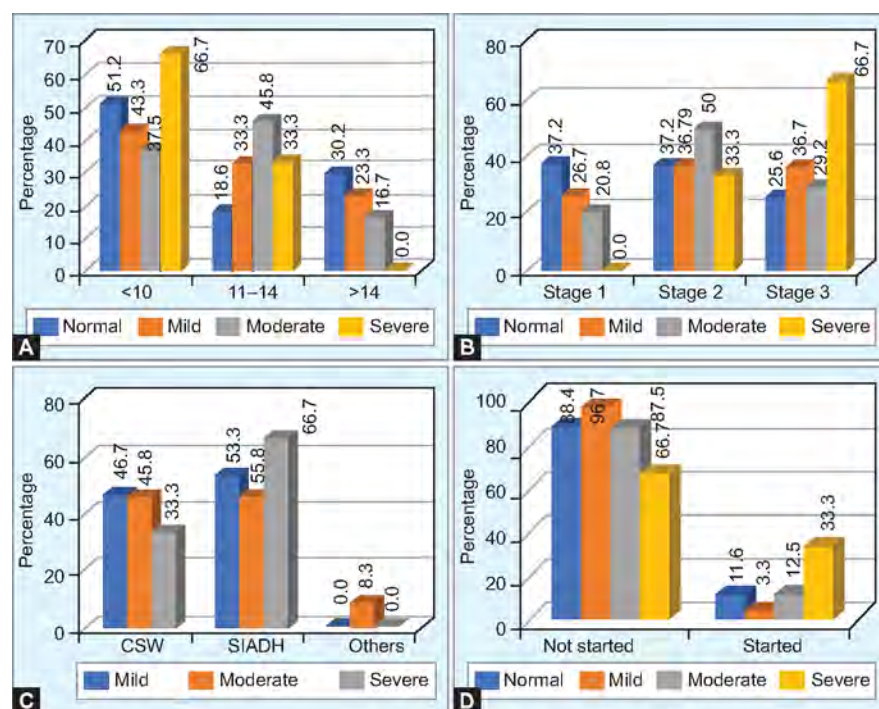


Fig. 2A to D: Patients with Hyponatraemia are categorized into mild, moderate, severe types on basis of sodium levels on Y-axis as constant. In different bar diagrams: (A) Comparison with level of consciousness with Glasgow coma scaling system (GCS) is established; (B) Comparison with various stages of TBM is described; (C) Various etiologies of Hyponatraemia like cerebral salt wasting, syndrome of inappropriate anti-diuretic hormone secretion is described; (D) Comparison is done with early initiation of anti-tubercular therapy versus late initiation with severity of Hypo-natraemia

of cranial nerve IV, two (2%) of cranial nerve V, and 18 (18%) of cranial nerve VI, but this did not predict mortality, in contrast to the study by Synmon and Kayal,¹³ in which a significantly

poor outcome was observed. The sixth cranial nerve was the most commonly involved in our study because of its longest intracranial course and basal brain predilection.

In this study, mortality was high in both hypovolemic and euvoletic states, at 14 and 16%, respectively, while 14.3% mortality was observed in the hypervolemic state. In the present study, two patients (among the three patients) with severe hyponatremia died. As far as gender is concerned, although female patients had a predisposition for moderate and severe hyponatremia, no significant difference in terms of mortality was observed. The Chi-squared test did not demonstrate any significant association between the severity of hyponatremia and overall survival (p -value = 0.621). However, mortality with respect to the clinical stage of the disease had a significant association (p -value = 0.001), which is expected because patients with stage III disease had more severe illness and, thus, higher mortality.

Correction of hypovolemic hyponatremia requires close serial monitoring, as the correction rate is unpredictable in this category. In contrast, in hypervolemia or SIADH, water restriction with appropriate drugs is the mainstay of treatment for the correction of hyponatremia to induce negative water balance. In the management of SIADH, loop diuretics, plentiful oral salt, and vaptans augment free water excretion and help normalize sodium levels. Thus, hypotonic fluids must be administered carefully to hospitalized patients, as they can precipitate severe hyponatremia and carry a high mortality risk, as reported in earlier studies.^{6,11}

As the study was conducted during the coronavirus disease 2019 (COVID-19) pandemic, when access to tertiary health

Table 3: Comparison of clinical characteristics, radiological, staging of TBM between survivors and non survivors (n = 100)

Parameters	Total	Survivors (N = 73)	Nonsurvivors Mortality (N = 27)	p-value
Age				0.015
<20 years	23 (23%)	21 (28.8%)	2 (7.4%)	
21–30	32 (32%)	26 (35.6%)	6 (22.2%)	
31–40	18 (18%)	12 (16.4%)	6 (22.2%)	
41–50	15 (15%)	9 (12.3%)	6 (22.2%)	
51–60	7 (7%)	2 (2.7%)	5 (18.5%)	
>60	5 (5%)	3 (4.1%)	2 (7.4%)	
Gender				0.369
Male	47 (47%)	32 (43.8%)	15 (55.6%)	
Female	53 (53%)	41 (56.2%)	12 (44.4%)	
GCS group				0.001
<10	26	26 (35.6%)	20 (74.1%)	
11–14	23	23 (31.5%)	7 (25.9%)	
>14	24	24 (32.9%)	0 (0.0%)	
Hydrocephalus	50	31 (42.5%)	19 (70.4%)	0.023
Basal exudates	38	32 (43.8%)	6 (22.2%)	0.048
Vasculitic infarcts	24 (24%)	12 (16.4%)	12 (44.4%)	0.004
Tuberculomas	17 (17%)	16 (21.9%)	1 (3.7%)	0.036
Arachnoiditis	13 (13%)	11 (15.1%)	2 (7.4%)	0.505
Diagnosis				
Definitive	41	28 (38.4%)	13 (48.1%)	0.609
Clinical stage TBM				0.001
I	29 (29%)	27 (37%)	2 (7.4%)	
II	40 (40%)	31 (42.5%)	9 (33.3%)	
III	31 (31%)	15 (20.5%)	16 (59.3%)	
VP shunting	15	10 (13.7%)	5 (18.5%)	0.549
MRI status				0.001
Worsening	1	1 (1.4%)	0 (0.0%)	
Improvement	38	38 (52.1%)	0 (0.0%)	
Static	12	11 (15.1%)	1 (3.7%)	
LTFU	24	22 (30.1%)	2 (7.4%)	
Death	25	1 (1.4%)	24 (88.9%)	
Follow-up Na				0.001
Worsening	1	1 (1.4%)	0 (0.0%)	
Normalized	24	24 (32.9%)	0 (0.0%)	
Persistent	7	7 (9.6%)	0 (0.0%)	
Death	12	11 (15.1%)	1 (3.7%)	
LTFU	13	0 (0.0%)	13 (48.1%)	
Etiology of hyponatremia				0.693
CSWS	26	19 (26.0%)	7 (25.9%)	
SIADH	29	22 (30.1%)	7 (25.9%)	
Other causes	2	2 (2.7%)	0 (0.0%)	

Contd...

Contd...

Parameters	Total	Survivors (N = 73)	Nonsurvivors Mortality (N = 27)	p-value
Type of hyponatremia				0.693
Hypovolemic	26	19 (26.0%)	7 (25.9%)	
Euvolemic	29	22 (30.1%)	7 (25.9%)	
Hypervolemic	2	2 (2.7%)	0 (0.0%)	

services was jeopardized, more patients presented with stage III disease; therefore, patients presented in critical condition, leading to high mortality.

Hyponatremia in CNS infections can result from more than one mechanism, with SIADH and CSWS being the most common, as reported in a similar study by Misra et al.⁶

SIADH is a volume-expanded state because of antidiuretic hormone-facilitated renal water retention, in contrast to CSWS, in which there is reduced effective arterial blood volume secondary to renal salt wasting. Natriuretic peptides, including both brain natriuretic peptide and C-type natriuretic peptides, have been associated with the proposed mechanism in CSWS.¹

In our study, 57 (57%) of the patients had hyponatremia at admission, similar to the study by Anderson et al.¹⁴ Out of the 57 patients, the probable etiology of hyponatremia was SIADH in 29 (29%) patients and CSWS in 26 (26%) patients, in contrast to the study by Misra et al.,⁶ in which CSWS occurred in 17% of patients and SIADH in 13%.

CONCLUSION

There was a high prevalence (57%) of hyponatremia in TBM patients. Hyponatremia

in TBM occurred most frequently due to SIADH, followed by CSWS. There was high mortality (35%), and the predictors of outcome were patient age, clinical stage, GCS, the presence of hydrocephalus and exudates on MRI brain findings at presentation, improvement on follow-up MRI brain findings, and normalization of follow-up sodium levels, all of which were statistically significant parameters.

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REFERENCES

1. Vinny PW, Vishnu VY. Tuberculous meningitis: a narrative review. *J Curr Res Sci Med* 2019;5(1):13.
2. COVID-19 and TB [Internet]. [cited 2022 Dec 20]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/covid-19-and-tb>
3. Global Tuberculosis Report 2022 [Internet]. [cited 2022 Dec 20]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022>
4. World Health Organization. Global tuberculosis report 2020. Geneva: World. Health Organization; 2020.
5. Pradhan Mantri TB Mukta Bharat Abhiyaan: Central TB Division [Internet]. [cited 2022 Dec 23]. Available from: <https://tbcindia.gov.in/index1.php?lang=1&level=1&sublinkid=5630&lid=3670>
6. Misra UK, Kalita J, Tuberculous Meningitis International Research Consortium. Mechanism, spectrum, consequences and management of hyponatremia in tuberculous meningitis. *Wellcome Open Res* 2021;4:189.
7. Hieu TH, Hashan MR, Morsy S, et al. Hyponatremia in tuberculous meningitis: a systematic review and meta-analysis. *Indian J Tuberc* 2021;68(4):516–526.
8. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis* 2010;10(11):803–812.
9. Mount DB. Hyponatremia. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. *Harrison's Principles of Internal Medicine*, 20e. McGraw-Hill Education; 2018. bookid 2129§ionid=252877938
10. Kubre J, Goyal V, Saigal S, et al. Tuberculous meningitis presenting as cerebral salt wasting syndrome: a review of literature with clinical approach to hyponatremia. *Neurol India* 2021;69(1):190.
11. Misra UK, Kalita J, Bhoi SK, et al. A study of hyponatremia in tuberculous meningitis. *J Neurol Sci* 2016;367:152–157.
12. Donovan J, Cresswell FV, Thuong NTT, et al. Xpert MTB/RIF ultra for the diagnosis of tuberculous meningitis: a small step forward. *Clin Infect Dis* 2020;71(8):2002–2005.
13. Synmon B, Kayal A. Cranial nerve involvement: its role in intracranial tuberculosis. *Int J Res Med Sci* 2021;9:196–199.
14. Anderson NE, Somaratne J, Mason DF, et al. Neurological and systemic complications of tuberculous meningitis and its treatment at Auckland City Hospital, New Zealand. *J Clin Neurosci* 2010;17(9):1114–1118.



Prevalence of Diabetes Mellitus and Its Correlations with Body Mass Index, Neck Circumference, and Obstructive Sleep Apnea Risk among Adults in Kolkata, West Bengal

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ABSTRACT

Diabetes mellitus, a chronic metabolic disorder with the key feature of hyperglycemia, constitutes a significant global health threat due to the rising number of cases worldwide. This cross-sectional study was designed to examine the prevalence of diabetes mellitus and its connection with body mass index (BMI), neck circumference, and obstructive sleep apnea (OSA) risk among the adults of Kolkata, West Bengal.

The study included 1,016 adults between the ages of 41–70 years, with anthropometric measurements and fasting blood glucose levels recorded. The diabetes prevalence was 12.98% in males and 13.01% in females, which was highest in the age group of 51–60 years. A significant association was observed between BMI and diabetes, as higher prevalence rates were witnessed among overweight and obese individuals as opposed to those with normal or underweight BMIs. Moreover, neck circumference was positively correlated with the prevalence of diabetes. The larger the neck circumference, the higher the risk of diabetes. Besides, the prevalence of diabetes in high-risk subjects for OSA was higher than in low- and intermediate-risk participants, indicating a remarkable association between the risk for OSA and diabetes.

These findings draw attention to the need for public health interventions for the prevention and management of obesity, monitoring neck circumference, and addressing OSA in order to reduce the burden of diabetes in urban areas in India. Screening and intervention campaigns aimed at different age groups at high risk should focus on early detection and treatment of patients. The study overall helps in the understanding of the epidemiology in urban India, and such comprehensive approaches in diabetes management are also emphasized.

Keywords: Body mass index, Diabetes mellitus, Neck circumference, Obstructive sleep apnea, Urban India.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that arises from hyperglycemia due to insulin secretion defects, insulin action defects, or a combination of the two. It is one of the most significant global health risks that we have to face, and the cases have kept rising in the past few decades.¹ As per the International Diabetes Federation (IDF), the global prevalence of diabetes in 20–79 years old for 2021 was measured to be 10.5% (536.6 million people), which will continue to rise to 12.2% in the projection to 2045. The 2021 global health expenditures for diabetes-related diseases were about 966 billion USD and will be projected to grow to 1,054 billion USD by 2045. In India, there are 77 million people who are 18 years old and above and are diabetic (type 2), and almost 25 million people are others who are categorized as prediabetics (have a higher chance of developing diabetes soon).^{2,3} One of the main characteristics of type 2 diabetes mellitus (T2DM) is obesity, which is noted by high body mass index (BMI). Excess deposition of

adipose tissue is the main feature of obesity. It interferes with insulin metabolism, principally by making the body resistant to insulin, which means that T2DM is more likely to develop. The link between BMI and diabetes rates at population levels is well-known, pointing out a prevalent correlation between high BMIs and an increased risk of diabetes.⁴

Diabetes mellitus is common among adults, and it is essential to understand the relationship between its prevalence and BMI. This information can help in the development of public health planning and intervention programs to mitigate the burden of this chronic disease. The prevalence of diabetes and its association with BMI can be evaluated, which can later guide identifying high-risk populations, stimulating targeted prevention efforts, and improving optimal healthcare resource allocation.^{5,6}

In India, particularly in cities like Kolkata in West Bengal, the diabetes burden is increasing exponentially, posing a formidable challenge to the healthcare

sector and necessitating epidemiological studies for a comprehensive understanding of the disease prevalence and associated risk factors. The metropolitan city of Kolkata, famous for its rich heritage, culture, and busy landscapes, faces a double-edged sword of communicable and noncommunicable diseases, with diabetes being the major cause for the latter. Kolkata, like several other urban settings in India, has come under the spell of rapid urbanization and lifestyle transitions, which have changed food habits and physical activity levels and consequently affected the BMI distribution pattern among the adult population. Hence, looking into the link between BMI and diabetes along with other risk factors such as neck circumference and obstructive sleep apnea (OSA) in this vicinity is essential for designing helpful measures and promoting healthy lifestyles.^{7–10}

In this context, the present study intends to assess the current prevalence of diabetes mellitus among the adults of Kolkata, West Bengal, and also study the correlations with BMI, neck circumference, and OSA risk levels in this population. This study is poised to contribute to the larger discussion on preventing and managing noncommunicable diseases in urban India.

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MATERIALS AND METHODS

This cross-sectional study was carried out among 1,016 adults, aged 41–70 years; of these, males and females were 524 and 492, respectively, from 2023, November 11 to 14. The participants were selected through a simple random technique from the Baguihati area of Kolkata, West Bengal, India.

The participants were divided into three different age groups with 10-year intervals each to study the age trend of diabetes. Anthropometric measurements, such as stature and body weight, were measured using standard instruments and techniques given by Weiner and Lourie.¹¹ Measurements were taken on the subjects wearing minimal and light apparel. BMI ($\text{weight}/\text{height}^2$) was calculated and classified according to the proposed criteria of the World Health Organization (WHO) Asian-Pacific cutoff points (underweight $<18.5 \text{ kg}/\text{m}^2$, normal = $18.5\text{--}22.9 \text{ kg}/\text{m}^2$, overweight = $23.0\text{--}24.9 \text{ kg}/\text{m}^2$, and obese $\geq 25 \text{ kg}/\text{m}^2$).¹² Diabetes was taken as $<126 \text{ mg}/\text{dL}$. A value of $100\text{--}125 \text{ mg}/\text{dL}$ was classified as prediabetes. Nondiabetes was taken as $>100 \text{ mg}/\text{dL}$.¹³

Neck circumference was measured with a standard nonelastic tape. Measurements were classified into two groups: $<38 \text{ cm}$ and $\geq 38 \text{ cm}$. To measure the OSA risk levels, participants were categorized into three groups: low, intermediate, and high. The OSA risk levels were determined by using a standard OSA risk assessment tool considering data such as age, BMI, neck circumference, and sleep apnea symptoms.

Statistical software MedCalc (Version:20) was used to carry out statistical analysis. Descriptive statistics of mean and standard deviation were used to examine the collected data. Besides descriptive statistics, to test the differences between the age groups and the association between BMI, neck circumference, OSA risk levels, and diabetes, t-test and correlation analysis were done, respectively. $p < 0.05$ was taken as statistically significant.

RESULTS

The significance of the sex difference between various parameters is evident from Table 1. Mean values of age, stature, body weight, BMI, neck circumference and FBG were found

to be higher in males as compared with their female counterparts.

Table 2 shows the prevalence of diabetes according to age, sex, BMI categories, neck circumference and OSA risk levels among the study participants. A total of 1,016 suburban adults were included in this present study, of which 524 (51.57%) were males and 492 (48.43%) were females. The prevalence of diabetes among males and females is 12.98% (95% CI: 10.22–16.16) and 13.01% (95% CI: 10.16–16.31), respectively.

Of the total study population, the majority, 376 (37.01%), were in the age group 41–50 years, and the minimum number of participants was present in the age group 51–60 years (26.18%). The maximum prevalence (18.42%, 95% CI: 13.95–23.61) of diabetic adults was in the 51–60 years age group, whereas the minimum prevalence (7.75%, 95% CI: 5.25; 10.95) was in the 61–70 years age group.

Among the total study participants, 443 (43.61%) were overweight, and 56 (5.51%) were obese. The prevalence of diabetic adults with undernutrition and normal BMI category is 13.59% (95% CI: 7.63; 21.75) and 14.25% (95% CI: 11.03; 17.99), respectively. Besides this, the prevalence of diabetic adults with overweight and obese BMI categories is 12.64% (95% CI: 9.69; 16.10) and 5.36% (95% CI: 1.12; 14.87), respectively.

Furthermore, the study explored the neck circumference and the prevalence of diabetes among studied participants. It was notable that the mean neck circumference of the diabetic group ($39.2 \pm 3.5 \text{ cm}$) was significantly more than that of the nondiabetic group

Table 1: Significance of the sex difference between various parameters ($n = 1016$)

Parameters	Males (mean $\pm$ SD)	Females (mean $\pm$ SD)
Age (years)	56.35 $\pm$ 8.52	55.97 $\pm$ 8.68
Stature (cm)	156.97 $\pm$ 7.22	154.15 $\pm$ 7.07
Weight (kg)	55.19 $\pm$ 7.49	52.21 $\pm$ 8.02
BMI (kg/m^2)	22.42 $\pm$ 2.93	21.93 $\pm$ 2.87
Neck circumference (cm)	39.5 $\pm$ 3.7	37.8 $\pm$ 3.1
FBG (mg/dL)	105.41 $\pm$ 28.66	104.59 $\pm$ 23.01

Table 2: Prevalence of diabetes according to age, sex, BMI categories, neck circumference and OSA risk level ($n = 1016$)

Parameters	Number (%)	Diabetic (%)	Prevalence (%)	95% CI	p-value
Sex					
Male	524 (51.57)	68 (51.52)	12.98	10.22 to 16.16	0.9866
Female	492 (48.43)	64 (48.48)	13.01	10.16 to 16.31	
Age group (years)					
41–50	376 (37.01)	54 (40.91)	14.36	10.98 to 18.32	0.0002
51–60	266 (26.18)	49 (37.12)	18.42	13.95 to 23.61	
61–70	374 (36.81)	29 (21.97)	7.75	5.25 to 10.95	
BMI					
Undernutrition	103 (10.14)	14 (10.61)	13.59	7.63 to 21.75	0.2650
Normal	414 (40.74)	59 (44.69)	14.25	11.03 to 17.99	
Overweight	443 (43.61)	56 (42.42)	12.64	9.69 to 16.10	
Obese	56 (5.51)	3 (2.28)	5.36	1.12 to 14.87	
Neck circumference (cm)					
<38	668 (65.7)	60 (45.45)	8.98	6.84 to 11.91	0.0001
>38	348 (34.3)	72 (54.55)	20.69	17.13 to 24.52	
OSA risk levels					
Low	612 (60.2)	59 (43.39)	9.66	7.53 to 12.11	0.0003
Intermediate	286 (28.2)	54 (39.13)	18.88	14.58 to 24.28	
High	118 (11.6)	19 (17.96)	16.10	10.82 to 23.62	

Table 3: Correlation between body mass index, neck circumference, OSA risks and diabetes of participants (*n* = 1016)

BMI categories	Diabetic <i>n</i> (%)	Glycemic status		<i>p</i> -value	<i>r</i> -value
		Prediabetic <i>n</i> (%)	Nondiabetic <i>n</i> (%)		
Undernutrition	14 (10.61)	41 (10.91)	48 (9.45)	0.009	0.99
Normal	59 (44.69)	153 (40.69)	202 (39.76)		
Overweight	56 (42.43)	160 (42.55)	227 (44.68)		
Obese	3 (2.27)	22 (5.85)	31 (6.11)		
Neck circumference (cm)					
<38	60 (45.45)	173 (46.01)	435 (85.63)	0.0001	0.52
>38	72 (54.55)	203 (53.99)	73 (14.37)		
OSA risk levels					
Low	59 (43.39)	154 (40.96)	399 (78.57)	0.0003	0.48
Intermediate	54 (39.13)	141 (37.5)	91 (17.91)		
High	19 (17.96)	81 (21.54)	18 (3.52)		

(37.8 ± 3.0 cm). Statistical analysis revealed a significant positive correlation ($r = 0.52$, $p < 0.01$) between neck circumference and prevalence of diabetes.

In addition, the association between obstructive sleep apnea (OSA) risk levels and prevalence of diabetes was analyzed. Participants were categorized into low risk, intermediate risk, and high risk for OSA. The analysis revealed that participants with high OSA risk levels had a higher prevalence of diabetes (16.10%, 95% CI: 10.82; 23.62) compared to those with low (9.66%, 95% CI: 7.53; 12.11) and intermediate (18.88%, 95% CI: 14.58; 24.28) risk levels. A statistically significant correlation ($r = 0.48$, $p < 0.01$) was observed between OSA risk levels and prevalence of diabetes among studied participants.

Table 3 shows the correlation between BMI, neck circumference, and the prevalence of diabetes among studied participants. A statistically significant correlation was observed between body mass index and diabetes. The *r* value shows a significant correlation between body mass index and diabetes. Similarly, a significant correlation was found between neck circumference and the prevalence of diabetes.

DISCUSSION

The findings of this cross-sectional study provide essential information on the existence of diabetes mellitus among adults in Kolkata, West Bengal, and their link with body mass index (BMI), neck circumference, and Obstructive Sleep Apnea (OSA) risk levels. The observed prevalence rates of diabetes in this population (12.98% in males and 13.01% in females) mirror the worldwide trend of the diabetes burden rising, especially in urban areas where lifestyles shift rapidly. These

results reinforce the vital importance of implementing public health measures geared toward the prevention and management of diabetes in urban India, in particular, Kolkata.

The distribution of diabetes prevalence by age shows interesting trends; the greatest prevalence is registered in the age-group 51–60 years. The middle-aged group also included the highest proportion of participants, demonstrating that middle-aged adults are especially vulnerable to diabetes in this community. These results stress the need for targeted screening and intervention strategies that aim at different age groups, especially with the increasing prevalence of diabetes worldwide among the younger age cohorts.

This study provides evidence of the association between BMI and diabetes. Obesity was found to be related to diabetes in this study, confirming the role of obesity as an important risk factor for diabetes development. Diabetes was more common among people whose BMI was overweight or obese as compared to those with normal or underweight BMI categories. This is a testimony to the seriousness of obesity prevention and management strategies in solving the problem of diabetes in cities such as Kolkata.

The distribution of diabetic, prediabetic, and nondiabetic participants in various BMI categories reveals the importance of the need for targeted preventive measures. Programs aimed at promoting a healthy lifestyle that includes regular physical activity and balanced nutrition are the key to preventing obesity and diabetes in these people. Besides, the early identification of people who are prone to diabetes through routine screening using BMI will provide the chance for timely intervention and management, potentially avoiding the long-term complications associated with the disease.

Several studies have revealed that neck circumference is another important anthropometric measurement that is significantly associated with the prevalence of diabetes. The diabetic group showed greater neck circumference compared with their nondiabetic counterparts. This indicates that neck circumference can be one of the useful indicators for diabetes risk assessment, probably due to its association with upper body adiposity and insulin resistance.

This study further showed that there is a significant relationship between diabetes prevalence and the levels of OSA risk. The prevalence of diabetes among the participants at high risk for OSA was higher than among those either at low or intermediate risk. Such a correlation might indicate that OSA contributes to the development or worsening of diabetes risk via intermittent hypoxia and resultant metabolic disturbances. This strong positive association of risk between OSA and diabetes would, therefore, underline the imperative requirement for comprehensive screening and management strategies addressing the two conditions together.

In the context of prevention and management, it is not only weight management that will be important but also addressing sleep disorders to reduce the overall burden of diabetes. Public health interventions need to be age- and risk-profile-specific, with regular screening for diabetes and obesity, with OSA enabling early detection and effective management.

CONCLUSION

In conclusion, the data in this research illustrate the prevalence of diabetes mellitus and its relation with BMI, neck circumference, and

OSA risk levels among adults in Kolkata, West Bengal. The results highlight the urgent need for multifaceted public health approaches that include diabetes prevention and management in urban India, focusing on lifestyle modifications to deal with obesity-related risk factors. Appropriate interventions targeted at different age groups and BMI categories should be instrumental in reducing the diabetes burden and overall population health in this setting.

Further research is required to identify the additional risk factors for diabetes and also evaluate various integrated intervention programs for their effectiveness. Multifactorial interventions will be required for combating the rising prevalence of diabetes and improving public health in urban India.

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REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2009;32(Suppl 1):S62–S67.
2. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022;183:109119.
3. Kumar A, Gangwar R, Zargar AA, et al. Prevalence of diabetes in India: a review of IDF

Diabetes Atlas 10th edition. *Curr Diabetes Rev* 2024;20(1):e130423215752.

4. Wondmkun YT. Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications. *Diabetes Metab Syndr Obes* 2020;13:3611–3616.
5. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444(7121):840–846.
6. Ros Pérez M, Medina-Gómez G. Obesidad, adipogénesis y resistencia a la insulina [Obesity, adipogenesis and insulin resistance]. *Endocrinol Nutr* 2011;58(7):360–369.
7. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. *Indian J Ophthalmol* 2021;69(11):2932–2938.
8. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. *Australas Med J* 2014;7(1):45–48.
9. Li D, Zhao Y, Zhang L, et al. Association between neck circumference and diabetes mellitus: a systematic review and meta-analysis. *Diabetol Metab Syndr* 2023;15(1):133.
10. Abelleira R, Zamarrón C, Riveiro V, et al. Relationship between obstructive sleep apnea and type 2 diabetes mellitus. *Med Clin (Barc)* 2024;162(8):363–369.
11. Weiner JS, Lourie JA. Anthropometry. *Practical Human Biology*. New York: Academic Press; 1981. p. 27.
12. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363(9403):157–163.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33(Suppl 1):S62–S69.



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Etiology and Left Ventricular Function in Right Bundle Branch Block: A Prospective Observational Study



Rajeev Bhardwaj^{1*}, Rajesh Nandal², Subeg Singh³, Pramod Rawat⁴, Jaskiran Kaur⁵

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ABSTRACT

Purpose of study: Right bundle branch block (RBBB) is a common ECG finding. It may be caused by coronary artery disease, dilated cardiomyopathy, chronic obstructive lung disease, or degenerative disease of the conduction system of the heart. The purpose of the study was to find out the etiology and left ventricular function in patients with RBBB coming to a tertiary care hospital.

Materials and methods: All consecutive patients coming to our hospital on an outdoor or inpatient basis with ECG showing RBBB were studied. Detailed history and physical examination were done. All patients were subjected to echocardiography.

Results: 201 patients with RBBB were studied. Mean age was 61.01 ± 12.92 years. 157 were male (78.11%), and 44 (21.89%) were female. The most Common symptom was dyspnea in 81 patients (40.29%) and chest pain in 15 patients (7.46%). Four patients presented with syncope and were proved to have intermittent complete heart block. 95 persons (47.26%) with RBBB had no symptoms, 43 out of which had come for clearance for noncardiac surgery. On echocardiography, left ventricular hypertrophy was present in 32 patients (15.92%), regional wall motion abnormality in 45 patients (22.38%), and left ventricular global hypokinesia in 13 patients (6.46%). LV systolic dysfunction was present in 43 patients (21.39%), and 85 (42.28%) patients had a normal study.

Conclusion: The most common presentation in patients was dyspnea. About half of the patients were asymptomatic. Around 20% were detected to have RBBB when they came for clearance for noncardiac surgery. Common causes were coronary artery disease, dilated cardiomyopathy, and cor pulmonale.

Keywords: Echocardiography, Myocardial infarction, Right bundle branch block, Systolic dysfunction.

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INTRODUCTION

Right bundle branch block (RBBB) is an ECG diagnosis, and its true incidence in the population is difficult to find. It is caused by anatomical or functional conduction abnormality in the conduction through the RBB of the conduction system. So, conduction from the Bundle of His occurs through the left bundle branch (LBB) to the left ventricle (LV), and from there, the conduction occurs through the heart muscle to the right ventricle, thereby causing delayed activation of the right ventricle (RV). This results in abnormal and prolonged QRS duration. Criteria for diagnosis of RBBB are QRS duration more than 120 ms, a large R' wave in V1 and V2, and a broad and deep S wave in V5 and V6. We studied the LV functions in patients with ECG evidence of RBBB coming to a tertiary care unit.

MATERIALS AND METHODS

A total of 201 consecutive patients with ECG evidence of RBBB coming to our hospital on OPD or IPD basis were studied. The presenting symptoms were studied in detail. History of angina, dyspnea, wheeze, syncope, cyanosis, hypertension, diabetes,

and chest infection was taken. Special attention was given to ECG evidence of acute or old myocardial infarction, right ventricular volume or pressure overload. All patients were subjected to detailed echocardiography, with special attention to wall motion abnormalities, rheumatic heart disease, congenital heart disease, pulmonary artery hypertension, and ejection fraction. Acute myocardial infarction was diagnosed when there was a history suggestive of ischemic chest pain, ST changes, with typical rise and fall in biomarkers. Old MI was diagnosed when there was chest pain suggestive of MI in the past, abnormal Q waves, and regional wall motion abnormality on echocardiography. If required, coronary angiography and angioplasty were done.

Statistical Analysis

Descriptive statistics were used to present categorical variables as frequency (percentage), and continuous variables were described as mean with standard deviation (SD).

RESULTS

A total of 201 patients with RBBB were studied. Table 1 shows the clinical

characteristics of the patients. Mean age was 61.01 ± 12.92 years. 154 were male, and 47 were female. 61 were hypertensive, and 18 were diabetic. The most common symptom was dyspnea in 81 patients and chest pain in 15 patients. 4 patients presented with syncope and were proved to have intermittent complete heart block (CHB) and were implanted with a permanent pacemaker. 95 patients had no symptoms, out of which 43 had been referred to us for clearance for noncardiac surgery.

Table 2 shows the echocardiographic findings in patients with RBBB. Left ventricular hypertrophy was present in 32 patients, regional wall motion abnormality (RWMA) in 45 patients, and left ventricular global hypokinesia in 13 patients. Rheumatic heart disease (RHD) was present in 3 patients and congenital heart disease in 3 patients.

Table 1: Clinical characteristics of the patients

Total patients	201
Male	157 (78.11%)
Female	44 (21.89%)
Mean age (YEARS)	61.01 ± 12.92
Hypertensive	61 (30.34%)
Diabetic	18 (8.95%)
CKD	2 (0.99%)
Hypothyroidism	1 (0.49%)
Symptoms	
Dyspnea	81 (42.29%)
Chest pain	15 (7.46%)
Palpitation	6 (2.98%)
Syncope	4 (1.99%)
Asymptomatic	95 (47.26%)
Clearance for noncardiac surgery	43

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8 patients had cor pulmonale. LV systolic dysfunction was present in 43 patients (21.39%), mild in 8 patients, moderate in 19 patients, and severe in 16 patients. Out of 43 patients with LV systolic dysfunction, 31 had CAD, 11 had dilated cardiomyopathy (DCM), and one patient had chemotherapy-induced LV dysfunction. 41 patients had diastolic dysfunction. 85(42.28%) patients had a normal study.

Table 3 shows the age distribution of RBBB patients. It can be seen that RBBB is uncommon in younger age. Out of 201 patients, 165 (82.08%) were more than 50 years of age, and 153 patients were between 50 and 80 years of age.

Table 4 shows the age distribution of RBBB. It can be seen that CAD was more common after 40 years of age, COPD and CHB after 60 years of age, and DCM can be seen in any age group.

DISCUSSION

Isolated RBBB usually does not cause any symptoms, and hence its true incidence is not known. However, the prevalence of RBBB is estimated to be 1–3% in some studies.^{1,2} As the age goes on increasing, the incidence of RBBB goes on increasing.¹ In persons above the age of 80 years, the prevalence of RBBB is around 11%.

Blood supply to RBB comes mainly from left anterior descending artery. So RBBB may be seen in patients with anterior wall myocardial infarction. Due to same reason, 45 of our patients had evidence of old or acute myocardial infarction. Other causes of RBBB include DCM, myocarditis, valvular heart disease, cor pulmonale, pulmonary hypertension and congenital heart disease.^{1–4} It can also be caused by fibrosis and degenerative disease of conduction system,³ progression of which can lead to complete heart block. Four of our patients presented with syncope and were found to have intermittent CHB as a cause of syncope. Hypertension is a risk factor for RBBB. Patients with RBBB are more likely to have hypertension than those without RBBB.⁵ Almost one third of our patients had evidence of hypertension. Transient RBBB may develop during right heart catheterization due to irritation of RBBB by the catheter.⁵ RBBB resolves once the catheter is removed.⁶ Brugada syndrome should be suspected in a patient presenting with syncope and ECG suggestive of RBBB with ST segment elevation in lead V1, V2.⁷

Right bundle branch block in a healthy person does not cause any symptoms and is an incidental finding on ECG.¹ 95 of our patients were asymptomatic, out of which 43 were detected when they came for clearance for noncardiac surgery. In others, symptoms are not due to RBBB but due to an underlying cardiac condition. When found in a healthy person, RBBB is a benign condition and does not affect the long-term prognosis. However, in patients with underlying cardiac disease, the prognosis is mainly determined by the underlying condition. But RBBB does increase mortality in these conditions, especially in patients with CAD and DCM.¹ However, some patients, especially those with a prolonged PR interval on ECG, may progress to heart block.

About 21.93% of patients with RBBB had LV systolic dysfunction. In comparison, in our study with LBBB, 56.8% patients showed LV dysfunction,⁸ indicating that LBBB is a more serious condition compared to RBBB.

Table 2: Echocardiographic findings in patients with RBBB

Total patients	201
Left ventricular hypertrophy	32 (15.9%)
Diastolic dysfunction	41 (20.39%)
Regional wall motion abnormality	45 (22.38%)
Global hypokinesia of LV	13 (6.47%)
Rheumatic heart disease	3 (1.49%)
Mitral stenosis	2
Mitral regurgitation with PAH	1
Congenital heart disease	3 (1.49%)
ASD	2
AV canal defect	1
Precapillary PAH	8 (3.98%)
LV systolic dysfunction	43 (21.39%)
Mild	8
Moderate	19
Severe	16
CAD	31
DCM	11
Chemotherapy-induced	1

Table 3: Age distribution of RBBB patients

Age (in years)	Total cases	Male	Female
18–39	11	8	3
40–49	25	17	8
50–59	43	36	7
60–69	68	55	13
70–79	42	30	12
>80	12	11	1

Table 4: Distribution of etiologies according to age group in patients with RBBB

Etiology	18–39	40–49	50–59	60–69	70–79	>80
CAD	02	08	11	16	09	03
DCM	03	03	02	04	02	00
RHD	00	03	00	00	00	00
CHD	01	01	01	00	00	00
CHB	00	00	02	01	00	01
COPD	00	00	00	04	03	01

Though most of the patients with ECG do not have structural heart disease, they still require evaluation, mainly focusing on cardiac and lung diseases. X-ray of the chest and echocardiogram are the initial tools of investigation. Patients presenting with syncope with RBBB may require Holter recording and electrophysiological studies in some cases.

CONFLICT OF INTEREST

None.

REFERENCES

- Ikeda T. Right bundle branch block: current considerations. *Curr Cardiol Rev* 2021;17(1):24–30.
- Alventosa-Zaidin M, Guix Font L, Benitez Camps M, et al. Right bundle branch block: prevalence, incidence, and cardiovascular morbidity and mortality in the general population. *Eur J Gen Pract* 2019;25(3):109–115.
- Harkness WT, Hicks M. (2023). Right bundle branch block. *StatPearls* [online]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK507872/> [Last accessed July, 2026].
- Birnbaum Y, Nikus K. What should be done with the asymptomatic patient with right bundle branch block? *J Am Heart Assoc* 2020;9(19):e018987.
- Jeong JH, Kim JH, Park YH, et al. Incidence of and risk factors for bundle branch block in adults older than 40 years. *Korean J Intern Med* 2004;19(3):171–178.
- Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;74(7):932–987.
- Francis J, Antzelevitch C. Brugada syndrome. *Int J Cardiol* 2005;101(2):173–178.
- Bhardwaj R. Etiology and left ventricular functions in left bundle branch block: a prospective observational study. *J Assoc Physicians India* 2016;64:36–38.



Carotid Intimal Media Thickness as an Indicator of Ischemic Heart Disease in Male Patients with Type 2 Diabetes and Metabolic Syndrome

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ABSTRACT

Background: Metabolic syndrome (MetS) increases cardiovascular disease risk due to accelerated atherosclerosis. Carotid intima-media thickness (CIMT) is an effective, noninvasive screening tool for atherosclerosis. Hence, we sought to measure the CIMT of male patients with type 2 diabetes and MetS and attempted to correlate the CIMT values between patients with and without evidence of ischemic heart disease.

Materials and methods: This was a cross-sectional study conducted on diabetic patients who met the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for MetS (specified for the Indian population), aged 45–60 years. Each participant completed the Rose questionnaire and was grouped as either symptomatic or asymptomatic. Further, all patients were subjected to biochemical tests, electrocardiography (ECG), CIMT, echocardiography (ECHO), and ankle-brachial pressure index (ABPI). Those who showed no evidence of ischemia on ECG and ECHO were subjected to exercise stress testing (treadmill test). Abnormal ECG, ECHO, and treadmill test results indicating ischemic heart disease were used to group patients into ischemic and nonischemic groups.

Results: A total of 128 patients who met the inclusion criteria were recruited. The values of CIMT ranged from 0.62 to 0.76 mm. The CIMT values between the ischemic and nonischemic groups were found to be similar. However, CIMT values were consistently higher in patients with MetS compared to the general population CIMT values based on prior studies in India across all age-groups. The Rose questionnaire served as a good screening tool, with a negative predictive value of 86% for the detection of ischemia in asymptomatic patients. Among the other parameters, the critical value of ABPI was found to be higher in the ischemic group [1.1 (1–1.12) vs 1 (0.85–1.075), $p = 0.004$].

Conclusion: While CIMT was not a reliable indicator of ischemic heart disease in patients with MetS, its consistently elevated values compared to those of the general population suggest that it could serve as a valuable marker of atherosclerosis. The ankle-brachial pressure index (ABPI) has consistently proven to be a reliable and repeatable indicator of ischemia. Due to the high incidence of silent ischemia in this study group (12.9%), further research on early markers of ischemia and atherosclerosis is warranted.

Keywords: Atherosclerosis, Cardiology, Carotid intimal media thickness, Metabolic syndrome, Treadmill test.

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INTRODUCTION

Metabolic syndrome (MetS) is a complex of multiple atherosclerotic risk factors. The worldwide prevalence is estimated to be 30–35% among adults.¹ Over the years, insulin resistance and obesity have been repeatedly emphasized as the prerequisites of MetS. A chronic hyperglycemic milieu develops owing to insulin resistance, and diabetic vasculopathy develops. It can present with cardiovascular disease (CVD) due to advanced glycation end products, oxidative stress, and chronic low-grade inflammation.² Obesity adds to this by the deposition of cholesterol esters in vessel walls and endothelial dysfunction.³

The hazard ratio of cardiovascular risk is 1.2–1.6 in patients with diabetes and

nearly 1.9–2.2 in patients with uncontrolled hypertension,^{4,5} combined, projecting much higher numbers for cardiovascular mortality and morbidity attributed to MetS. Hence, the topic of early detection of MetS and, consequently, ischemic heart disease (IHD) has garnered a lot of interest in recent years.

Carotid intima-media thickness (CIMT) has been a noninvasive screening tool for atherosclerosis for decades. Multiple studies have shown a significant correlation between CIMT values and the risk of CVD. The relative risk of CVD increases by 15% for every 0.1 mm increase in CIMT.⁶ This raises the hypothesis that increasing atherosclerotic risk factors will increase the CIMT and may help predict ischemia. Ischemia can be predicted by stress treadmill testing, which has a positive predictive value of >85% in high-risk groups,

such as patients with diabetes.⁷ Hence, in this study, we sought to measure the CIMT of male patients with type 2 diabetes and MetS and study its relationship with ischemia by comparing CIMT between patients with and without ischemia.

MATERIALS AND METHODS

Study Design

We conducted a cross-sectional study in which 132 patients were screened for eligibility, and 128 were recruited from the general medicine department of a tertiary care hospital. The study duration was 2.5 years.

The inclusion and exclusion criteria are given in Table 1.

Study Procedure

After enrollment based on the screening criteria, all consenting participants were administered the Rose questionnaire in their language of preference and were divided into those with and without angina. All participants were also subjected to biochemical tests, electrocardiography (ECG), CIMT, echocardiography (ECHO), and ABPI. Biochemical investigations were collected from each participant following a minimum of 8 hours of overnight fasting. Triglycerides and high-density lipoprotein (HDL) were measured. Glycated hemoglobin (HbA1c) and urine protein-creatinine ratio (PCR) were performed routinely as part of their outpatient department (OPD) diabetic workup. ECG was performed and analyzed for ischemic changes using the Minnesota Code and manual reading. Two-dimensional (2D)

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ECHO with color flow was performed to look for any regional wall motion abnormalities or thinning of wall segments suggestive of ischemia. ABPI was measured using a handheld Doppler.

Those who showed no evidence of ischemia on ECG and ECHO were subjected to exercise stress testing (treadmill test). During the stress test, patients were made to run for up to 9 minutes to the third stage of the standard Bruce protocol. Peak exercise on the treadmill test (TMT) was defined as the point at which the subject attained the predetermined heart rate (220—age in years) or exhaustion, whichever occurred earlier. TMT was considered inconclusive if the patient was unable to complete the second stage of TMT, was unable to achieve the target heart rate, or failed to achieve the minimum metabolic equivalents (METs). A positive TMT was defined as ≥ 2 mm rapidly up-sloping or ≥ 1 mm horizontal ST depression in concordant leads that persisted beyond stage III of the Bruce protocol. Based on the TMT results, patients were reclassified into ischemic and nonischemic groups.

The CIMT values were measured for all recruited patients. CIMT was measured in the distal 1 cm during diastole by ECG gating on the GE Color Doppler Vivid P3 system. The maximum and minimum values generated by the machine were noted on both sides and compared between the two groups.

Statistical Analysis

For sample size calculation, the software OpenEpi version 2.0 was used. The normality of the data was assessed using the Shapiro–Wilk test. The continuous data were expressed as the mean with standard deviation or the median with interquartile range, based on the distribution. Intergroup comparisons were performed using Student's *t*-test or the Kruskal–Wallis test, based on the number of groups. The categorical variables were assessed using the Chi-squared test. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), IBM SPSS version 28.

Figure 1 shows the key for the terms used in the recruitment flow diagram. This is followed by the recruitment flow diagram (Fig. 2).

OBSERVATIONS AND RESULTS

This study included 128 patients. The median age of the study population was 53.5 years, with an average duration of diabetes of 6 years and a median glycated hemoglobin (HbA1c) level of 8.7. Though the age bracket was 45–60 years, nearly half of the population was aged 54 years and above. Thirty-five percent of the patients had diabetes for <5 years, and 33.5% had diabetes for 5–10 years; hence, patients with

early diabetes comprised the majority of the participants. Among the 95 participants who had hypertension, 47.6% had been diagnosed <5 years earlier. Eighty percent of the study population had dyslipidemia, with triglycerides (TG) having a median value of 151.5 mg/dL and high-density lipoprotein (HDL) having a mean value of 39.42 mg/dL. The median ABPI was found to be 1.05. The baseline characteristics of all recruited patients are given in Table 2.

On comparison of the baseline characteristics between the two groups, four parameters showed statistically significant differences. Waist circumference and triglyceride levels were lower in the ischemic group, whereas the HbA1c and ABPI were higher in the ischemic group. Confounding factors for atherosclerotic ischemia, such as anemia and smoking, were also compared between the two groups, and there was no statistically significant difference. The proportion of silent ischemia was 12.9%. Plaques were present in 7.8% of the patients. A comparison of all characteristics studied between the ischemic and nonischemic groups is given in Table 3.

The higher values were consistently observed for the left CIMT, for both the maximum and average values, ranging from 0.62 to 0.76 mm. The median of the entire data set was 0.70 mm (0.60–0.825). There was a steady increase in the CIMT values as the number of criteria for MetS increased, but it was not statistically significant. Average CIMT values were higher than the general population values, 0.632 ± 0.156 mm vs 0.582 ± 0.08 mm, as reported in the SCORE-India trial.⁹

Table 1: Recruitment criteria

Inclusion criteria	Exclusion criteria
Males aged 45–60 years with type 2 diabetics with the presence of any 2 of the following four conditions: Increased waist circumference (males ≥ 90 cm and for females ≥ 80 cm) Hypertriglyceridemia ≥ 150 mg/dL Low HDL (male ≤ 40 mg/dL and for females ≤ 50 mg/dL) Elevated blood pressure (systolic blood pressure ≥ 130 mm hg and/or diastolic blood pressure ≥ 85 mm hg or Rx for hypertension)	Chronic kidney disease Connective tissue disorders Diagnosed cases of human immunodeficiency virus infection Intensive long-term statin therapy (≥ 20 mg/day Atorvastatin or 5 mg/day Rosuvastatin consistently for 1 year) ⁸ Prior diagnosis of acute coronary syndrome (unstable angina/ non-ST elevation myocardial infarction/ST elevation myocardial infarction)

Ischemic changes on ECG - Major Q waves, ST-T changes, New onset LBBB
Ischemic changes on ECHO -Regional Wall Motion Abnormalities (RWMA), thinned out segments, reduced ejection fraction
Unfit - Unable to complete 1st stage of TMT
Inconclusive - Unable to complete 2nd stage of TMT, inability to achieve target Heart Rate or minimum Metabolic Equivalents (METs)
Positive -> 2mm rapidly up-sloping or ≥ 1 mm horizontal ST depression in concordant leads that persist beyond stage III Bruce protocol.
Negative - No ST-T changes throughout the 9 minutes of Stress testing
F/U-Follow up

Fig. 1: Key to the flow diagram

Table 2: Baseline characteristics (all data sets are nonnormal in distribution except HDL and Hb)

Parameter	Mean $\pm$ SD/median (IQR)
Age (in years)	53.5 (47–57)
Duration of diabetes (in years)	6 (4–10)
Duration of hypertension (in years) (95)	3 (1–6)
Waist circumference (in cm)	98 (90–102)
TG (mg/dL) (115)	151.5 (115–247)
HDL (mg/dL) (116)	39.42 (± 10.39)
HbA1C (%) (98)	8.7 (7.4–10.3)
Urine PCR (81)	0.20 (0.14–0.55)
ABPI	1.05 (0.98–1.12)
Hb (mg/ dL) (83)	12.59 $\pm$ 2.385

Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; PCR, protein creatinine ratio; TAG, triacylglycerol

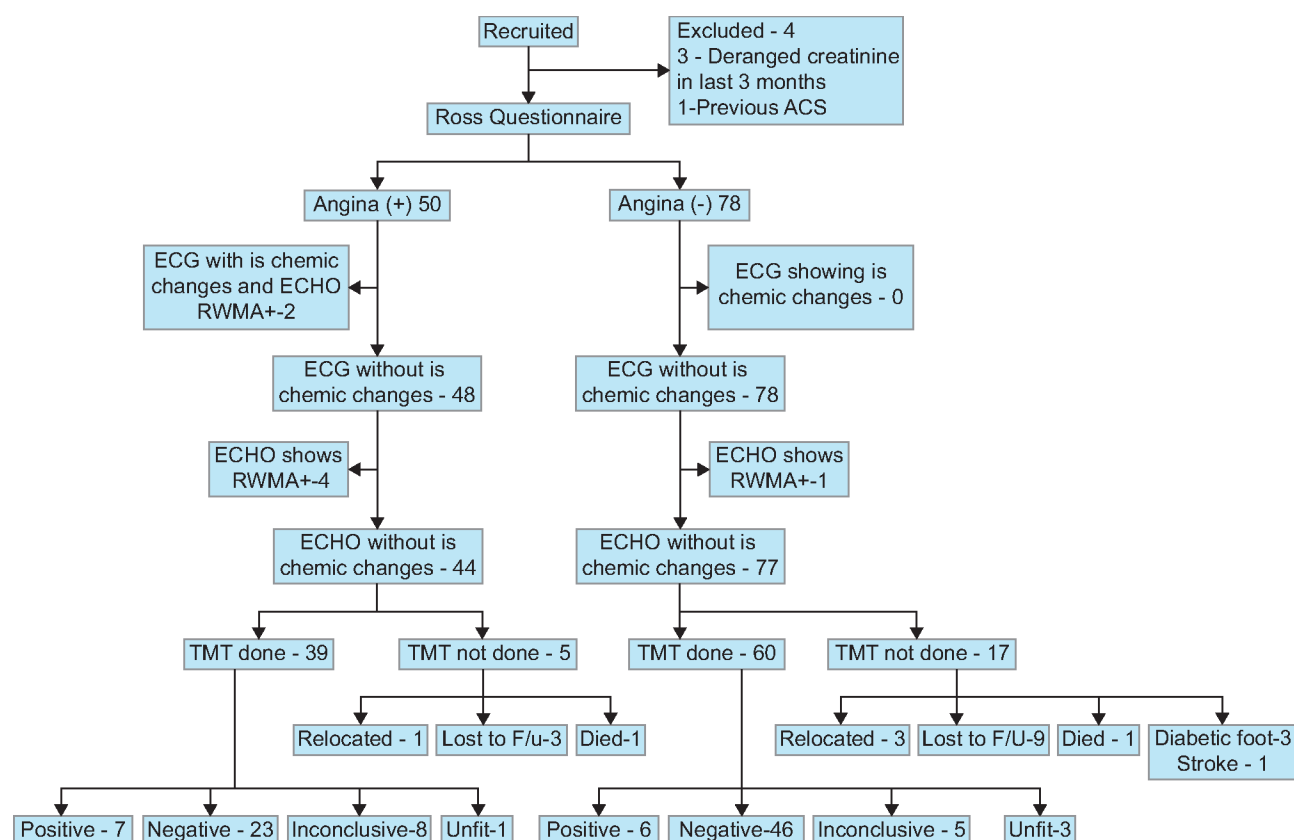


Fig. 2: Recruitment flow diagram

Table 3: Comparison of the baseline characteristics between the ischemic and nonischemic groups

Parameters	Nonischemic group	Ischemic-group	p-value
Age (in years)	53 (45–57)	53.5 (47.5–57)	0.3910
Duration of diabetes (in years)	6 (3–10)	6.5 (4–15)	0.372
Duration of hypertension (in years) (95)	1 (0–4)	1 (0–5.5)	0.87
Waist circumference (in cm)	99 (92–105)	92 (88.5–98)	0.005
TG (mg/dL) (74)	164 (119–274)	120 (95.5–158.5)	0.0158
HDL (mg/dL) (83)	40.34 ± 9.84	39.4 ± 11.88	0.64
HbA1C (%) (98)	8.3 (7.3–9.6)	10.1 (7.7–11.3)	0.044
Urine PCR (59)	0.2 (0.14–0.41)	0.14 (0.085–0.28)	0.13
ABPI	1.1 (1–1.12)	1 (0.85–1.075)	0.004
CIMT right average (mm)	0.62 (0.53–0.75)	0.61 (0.54–0.715)	0.742
CIMT right maximum (mm)	0.72 (0.6–0.87)	0.75 (0.62–0.8)	0.660
CIMT left average (mm)	0.66 (0.55–0.75)	0.655 (0.5–0.715)	0.423
CIMT left maximum (mm)	0.72 (0.64–0.88)	0.735 (0.65–0.84)	0.255
Ex/smokers (%)	22.2	20.0	1.00
Hb (63)	12.51 ± 2.53	13.12 ± 0.911	0.216

The sensitivity and specificity ranged between 45 and 55%, and the positive predictive value (PPV) was 25% for CIMT in predicting any evidence of ischemia. Given the rising burden of MetS and ischemic heart disease, these cutoff values may serve as credible screening tools; however, there was no statistically significant difference in CIMT values between the ischemic and nonischemic groups. Based on our data, the sensitivity of the Rose questionnaire as a screening tool for

evidence of ischemia was 65%, with a good negative predictive value of 86%. Additionally, the ABPI value differed significantly between the ischemic and nonischemic groups, with a good sensitivity of 90.65% for predicting ischemic heart disease at an absolute cutoff value of 0.9.

Figure 3 shows the receiver operating characteristic (ROC) curve for the CIMT cutoff value of 0.75 mm on the right side. Figure 4 shows the ROC curve for ABPI as an indicator

of ischemia, with a cutoff value of 0.9, where the ABPI curve demonstrates a high sensitivity of 90.6% for predicting ischemia.

DISCUSSION

Our study consisted of men aged 45–60 years with MetS, with ECG, ECHO, and treadmill test (TMT) as the predictors of ischemia. TMT has lower overall test accuracy for the identification of coronary artery disease and a

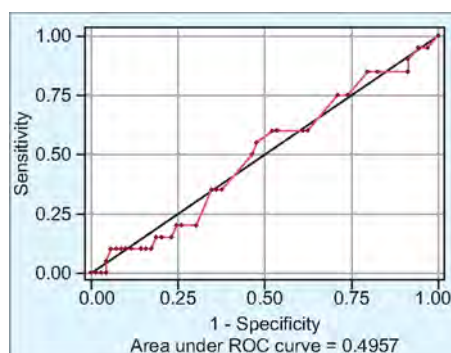


Fig. 3: Receiver operating characteristic (ROC) curve for CIMT cutoff of 0.75 mm at the right maximum values

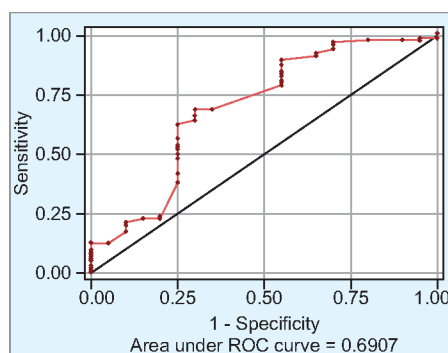


Fig. 4: Receiver operating characteristic (ROC) curve for ABPI as an indicator of ischemia, with a cutoff of 0.9 (sensitivity, 90.65%; specificity, 35%)

Table 4: Indian studies with CIMT values in MetS or diabetic patients

Study	Study population	CIMT values (mm)
PRISM study ¹⁵	338 diabetic males and females, evaluated for silent ischemia	0.7133 $\pm$ 0.022 in TMT positive vs 0.6624 $\pm$ 0.029 0.001 in TMT negative
Sethia et al. ¹⁶	200 males and females, case control between MetS and non-MetS	MetS 0.81 $\pm$ 0.23 non-MetS 0.66 $\pm$ 0.13 ($p < 0.005$)
Jose et al. ¹⁷	116 males and females in 45–60 years	MetS 0.699 $\pm$ 0.108 vs non-MetS 0.586 $\pm$ 0.083 ($p < 0.001$)
Abhishek et al. ¹⁸	100 males and females patients with MetS	0.90 (0.50–1.30)
Current study	128 male diabetics with MetS	MetS with ischemia (0.72) vs MetS without ischemia (0.735) ($p = 0.225$)

Table 5: Comparison of CIMT values in our study with the general population

Age (in years)	MetS patients	General population (SCORE study) ⁹
40–49 (45)	Average 0.632 $\pm$ 0.156	Maximum 0.752 $\pm$ 0.203
50–59 (83)	0.696 $\pm$ 0.192	0.808 $\pm$ 0.211
		0.646 $\pm$ 0.14

poor positive predictive value (PPV) in women; hence, women were excluded.^{10,11}

Among the various parameters assessed, four were found to be statistically significant between the ischemic and nonischemic groups. The glycated hemoglobin (HbA1c) levels were significantly higher in the ischemic group. The National Health and Nutrition Examination Survey (NHANES) study demonstrated that, among persons with known diabetes, the cardiovascular disease (CVD) risk increased progressively in concordance with HbA1c values.¹¹ The ABPI was statistically significant ($p < 0.004$) between the ischemic and nonischemic groups. This mirrors worldwide data, which state that a critical ABPI value doubles the 10-year cardiovascular mortality.¹² One peculiar finding was a statistically significant difference in the waist circumference and

triglyceride levels between the ischemic and nonischemic groups, with lower values in the ischemic group. This can be explained by the obesity paradox, given that CVD rates have been consistently demonstrated to be higher in normal-weight patients with diabetes compared to obese patients with diabetes.¹³ In fact, the PROactive study demonstrated that for every 1% body weight loss, the hazard ratio for CVD was 1.13.¹⁴

Carotid intima-media thickness values between the two groups, though not statistically higher, showed a PPV of 25% at a cutoff value of 0.75 mm for the detection of ischemia. Considering the high morbidity and mortality of the disease and the rising burden, this predictive value of CIMT may streamline the screening process for CVD and help in the early identification of a significant population. Our median CIMT values ranged from

0.62 to 0.76 mm. The CIMT values generated in various Indian studies for patients with MetS are given in Table 4.

The Seattle Heart Watch study stated that TMT in asymptomatic individuals was not predictive of combined adverse cardiovascular events; however, in patients with one or more risk factors and two or more abnormal features on exercise testing, there was a nearly 30-fold increase in CVD risk.¹⁹ Given that our study included men with diabetes aged 45 years and above, with at least two additional atherosclerotic comorbidities, all asymptomatic individuals with a positive TMT, as indicated by ischemic ST depressions at moderate metabolic equivalents (METs), had an increased risk of CVD and were initiated on lipid-lowering therapy. Table 5 shows a comparison of CIMT values in our study with those of the general population.

Our study had a few limitations. The major limitation of the study was the inability to classify the inconclusive TMT patients into ischemic and nonischemic groups. Further structured workup in the form of contrast computed tomography (CT) angiography or stress perfusion imaging could have been helpful. Also, a large number of patients were lost to follow-up owing to logistical reasons.

CONCLUSION

CIMT is a noninvasive, cost-effective screening tool for atherosclerosis, as our study consistently showed higher values in patients with MetS compared to the general population. However, it had a poor predictive value for ischemia (as evidenced by Q waves or ST-T changes on ECG, regional wall motion abnormalities on ECHO, or a positive TMT) in high-risk individuals, and there was no statistically significant difference between those with and without evidence of ischemia. ABPI showed a sensitivity of 90.65% for the screening of ischemia in this group. Further studies are needed to validate its utility and to identify earlier screening tools for ischemia.

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REFERENCES

1. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109(3):433–438.
2. Mathieu P, Pibarot P, Després JP. Metabolic syndrome: the danger signal in atherosclerosis. *Vasc Health Risk Manag* 2006;2(3):285–302.

3. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021;143(21):e984–e1010.
4. Ke C, Gupta R, Shah BR, et al. Association of hypertension and diabetes with ischemic heart disease and stroke mortality in India: the million death study. *Glob Heart* 2021;16(1):69.
5. Geldsetzer P, Manne-Goehler J, Theilmann M, et al. Diabetes and hypertension in India: a nationally representative study of 1.3 million adults. *JAMA Intern Med* 2018;178(3):363–372.
6. Onut R, Balanescu AP, Constantinescu D, et al. Imaging atherosclerosis by carotid intima-media thickness in vivo: how to, where and in whom? *Maedica* 2012;7(2):153–162.
7. Daphale A, Acharya S, Shukla S. Detection of asymptomatic coronary artery disease (CAD) in newly detected type 2 diabetes mellitus (DM) by exercise treadmill test. *Int J Contemp Med Res* 2017;4(11):2269–2275.
8. Hiro T, Kimura T, Morimoto T, et al. JAPAN-ACS Investigators. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome] study). *J Am Coll Cardiol* 2009;54(4):293–302.
9. Kasliwal RR, Bansal M, Desai N, et al. A Study to derive distribution of carotid intima media thickness and to determine its correlation with cardiovascular risk factors in asymptomatic nationwide Indian population (SCORE-India). *Indian Heart J* 2016;68(6):821–827.
10. Detry JM, Kapita BM, Cosyns J, et al. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. *Circulation* 1977;56(5):756–761.
11. Sketch MH, Mohiuddin SM, Lynch JD, et al. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. *Am J Cardiol* 1975;36(2):169–173.
12. Saydah S, Tao M, Imperatore G, et al. GHb level and subsequent mortality among adults in the U.S. *Diabetes Care* 2009;32:1440–1446.
13. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;300(2):197–208.
14. Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. *JAMA* 2012;308(6):581–590.
15. Prasad DS, Kabir Z, Revathi Devi K, et al. Prevalence and Risk factors for Silent Myocardial ischemia (PRISM): a clinico observational study in patients of type 2 diabetes. *Indian Heart J* 2019;71(5):400–405.
16. Sethia S, Acharya S, Shukla S, et al. Carotid intima media thickness (CIMT) in metabolic syndrome (MS) - a case control study. *J Evid Based Med Healthc* 2020;7(41):2336–2340.
17. Jose N, Hansdak S, Jose J, et al. Carotid intima media thickness in metabolic syndrome: an Indian perspective. *Indian J Appl Res* 2016;6(3).
18. Abhishek TG, Darshan A, Appajigol JS, et al. Association between carotid intima media thickness and metabolic syndrome. *Int J Adv Med* 2018;5(6):1503–1509.
19. Bruce RA, DeRouen TA, Hossack KF. Value of maximal exercise tests in risk assessment of primary coronary heart disease events in healthy men: five years experience of the Seattle Heart Watch Study. *Am J Cardiol* 1980;46:371–378.

Comprehensive Approach to Detect Liver Fibrosis by Indirect Serum Biomarkers



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ABSTRACT

Aim and objective: The diagnostic accuracy of three serum-derived markers—aspartate aminotransferase-to-platelet ratio index (APRI), Fibrosis-4 (FIB-4), and the aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio—was investigated as noninvasive alternatives in this study for assessing liver fibrosis severity and correlating these scores with FibroScan-derived liver stiffness measurements in patients with chronic liver disease (CLD).

Materials and methods: We enrolled 100 adult patients with a confirmed diagnosis of CLD for this cross-sectional analysis at GMC Kota. Consenting patients received clinical evaluations, ultrasound, and biochemical screenings [complete blood count (CBC), liver function tests (LFTs), glucose, and viral serology]. We staged liver stiffness (F0–F4) via FibroScan and computed indirect indices, including FIB-4, APRI, and AST/ALT, using validated equations.

Results: The average participant age was 47 years, with males comprising 67% of the study population. FibroScan showed that 73% of patients had F4 fibrosis, followed by F3 (10%), F2 (12%), and F0–F1 (5%). Etiologies included alcohol-related liver disease (34%), hepatitis B (15%), hepatitis C (4%), autoimmune hepatitis (2%), and diabetes-associated nonalcoholic fatty liver disease (NAFLD) (38%). Significant positive correlations were found between liver stiffness and the AST/ALT ratio ($r = 0.658$), APRI ($r = 0.639$), and FIB-4 ($r = 0.444$), all with $p < 0.0001$. Diagnostic thresholds revealed that lower cutoff values (e.g., APRI > 0.5 , FIB-4 ≥ 1) had high sensitivity, whereas higher cutoff values (e.g., AST/ALT > 1 , APRI ≥ 1 , FIB-4 ≥ 3.24) achieved excellent specificity. A stepwise diagnostic approach using these thresholds improved detection accuracy and reduced reliance on liver biopsy.

Significance: The study validates simple, cost-effective biomarkers as reliable tools for fibrosis detection. Their integration into clinical practice may enhance early diagnosis, optimize resource use, and improve outcomes in patients with CLD, especially in low-resource settings.

Keywords: Aspartate aminotransferase-to-platelet ratio index, Fibrosis-4 score, Liver fibrosis, Transient elastography (FibroScan).

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INTRODUCTION

Liver fibrosis is a major pathological consequence of sustained liver injury, marked by excessive extracellular matrix (ECM) deposition and progressive architectural distortion of hepatic tissue. The natural history of untreated fibrosis involves a high risk of progression toward cirrhosis and its complications, including hepatocellular carcinoma (HCC) and end-stage liver failure. The global landscape of chronic liver disease (CLD) is heavily impacted by the burden in India; as of 2015, nearly one-fifth (18.3%) of all liver-related fatalities occurred within the country.¹ In 2016, CLDs and cirrhosis were responsible for 2.1% of total deaths in India,² with nonalcoholic fatty liver disease (NAFLD) affecting 8–20% of urban populations. Early identification and staging of liver fibrosis are essential to prevent complications and reduce the burden of liver transplantation. Limitations surrounding liver biopsy, primarily its invasive nature and potential complications, have necessitated the shift toward developing reliable, noninvasive

assessment tools. This study aims to assess the diagnostic utility of indirect fibrosis markers and their correlation with FibroScan-derived liver stiffness measurements to promote safer, cost-effective fibrosis evaluation.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Government Medical College and Associated Group of Hospitals, Kota, from ethical approval until December 2024.

Inclusion Criteria

We enrolled patients with established CLD [viral, alcoholic, autoimmune, or nonalcoholic fatty liver disease (NAFLD)] in whom fibrosis or cirrhosis was previously documented via imaging [ultrasonography (USG)/FibroScan] or biopsy.

Age > 18 years.

Exclusion Criteria

Acute liver diseases or acute liver failure.

Decompensated liver disease with severe complications (e.g., hepatic encephalopathy, variceal bleeding).

Previous liver transplantation or current listing for transplantation.

Significant comorbidities or medical conditions that may interfere with the study or treatment outcomes.

Pregnancy or breastfeeding.

A total of 100 adult subjects with CLD were included, with diagnosis supported by imaging [ultrasonography (USG) or FibroScan] or liver biopsy findings.

Participants were enrolled from inpatient and outpatient settings after informed consent. Clinical evaluation and investigations, including complete blood count (CBC), liver function tests (LFTs), viral markers [hepatitis B virus (HBV), hepatitis C virus (HCV)], glucose, and USG, were conducted. Liver stiffness was measured using FibroScan with patients in a supine position and categorized into fibrosis stages F0–F4 based on kPa values. Blood samples were analyzed for aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin, platelets, and glucose. Indirect markers of hepatic fibrosis, including the aspartate aminotransferase-to-platelet ratio index (APRI), AST/ALT ratio, and Fibrosis-4 (FIB-4) index, were computed using established clinical formulas.

RESULTS

Our study group had an average age of 47 years, with a male predominance of 67%, while females comprised 33% of the cohort. A total of 100 patients underwent liver stiffness measurement using FibroScan, which revealed advanced fibrosis (F4) in 73%

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Table 1: Distribution of patients according to liver fibrosis stage

Fibrosis grade	Count	Percentage
F0-F1 (none to mild)	5	5.00%
F2 (moderate)	12	12.00%
F3 (severe)	10	10.00%
F4 (cirrhosis)	73	73.00%

Table 2: Correlation of serum fibrosis biomarkers with FibroScan-derived liver stiffness measurements

Scores	Pearson coefficient	Pearson <i>p</i> -value
AST/ALT	0.658	<0.0001
FIB4	0.444	<0.0001
APRI	0.639	<0.0001

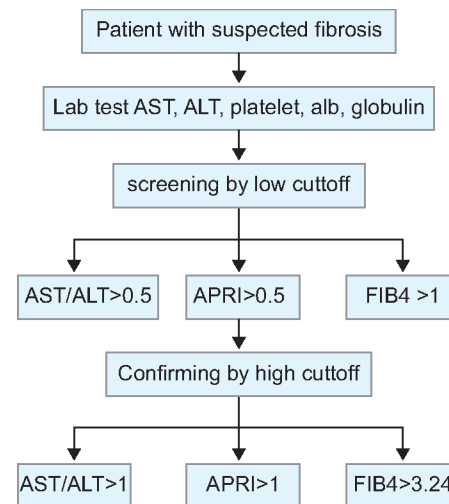
of patients, F3 fibrosis in 10%, F2 fibrosis in 12%, and minimal-to-mild fibrosis (F0–F1) in 5% (Table 1). The etiology of CLD varied, with 34% having alcohol-related liver disease, 15% being hepatitis B virus (HBV)-positive, 4% being hepatitis C virus (HCV)-positive, 2% showing an autoimmune association, and 38% having diabetes-associated nonalcoholic fatty liver disease (NAFLD). All three noninvasive indices [APRI, Fibrosis-4 (FIB-4), and the aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio] demonstrated a strong positive correlation with the stage of fibrosis, yielding highly significant results with $p < 0.0001$ (Table 2). Additionally, various cutoff values were assessed for each scoring system, and their respective sensitivity and specificity were calculated to evaluate diagnostic performance (Table 3). A stepwise diagnostic algorithm using these thresholds was applied to enhance diagnostic accuracy and refine the identification of patients with advanced fibrosis (Fig. 1).

DISCUSSION

Our study population spanned an age range of 18–78 years, with a calculated mean of 52.3 ± 12.7 years. A robust correlation emerged between age and fibrosis degree, identifying patient age as a key determinant in the longitudinal progression of CLD within our cohort. Our study was supported by the global meta-analysis by Singh et al.³ The overall cohort demonstrated a mean age of 55 ± 13 years, which is statistically comparable to the 52.3-year average found in our participants. A similar age was reported in studies by Trifan et al.⁴ and Fallatah et al.⁵ Similar results of male predominance were reported by Singh et al.,³ Sherazi et al.,⁶ and Alhankawi et al.⁷ However, the risk for females

Table 3: Diagnostic performance of AST/ALT ratio, APRI, and FIB-4 at different cutoff values

Index		Sensitivity	Specificity
AST/ALT	>0.5	0.989	0
	>1	0.736	1
FIB4	>1	0.989	0.889
	>3.24	0.44	1
APRI	0.5	0.956	0
	1	0.802	0.889

**Fig. 1:** Stepwise diagnostic algorithm for noninvasive assessment of liver fibrosis using AST/ALT ratio, APRI, and FIB-4

increases after menopause, as the loss of estrogen's antifibrotic role contributes to accelerated progression. This underscores the significance of gender-specific surveillance in liver disease management. In our study and all referenced studies, males consistently outnumbered females in terms of both disease prevalence and fibrosis severity.

Our results confirm that noninvasive markers, specifically the Fibrosis-4 (FIB-4), APRI, and AST/ALT ratio, closely track with liver stiffness measurements. A comparable relationship was documented by Fallatah et al.,⁵ emphasizing the reliability of these markers across different clinical cohorts. A positive statistical association was observed between participant age and the degree of fibrosis; conversely, hepatic stiffness values showed a significant decline as platelet counts increased. The diagnostic performance of these markers is further supported by Alhankawi et al.,⁷ who reported significant correlations with FibroScan results for the FIB-4 ($r = 0.472$), APRI ($r = 0.418$), and AST/ALT ratio ($r = 0.219$). Using a 7.5 kPa threshold for significant fibrosis, their study yielded area under the receiver operating characteristic curve (AUROC) values of 0.705, 0.644, and

0.643, respectively, which closely parallel the trends observed in our clinical data.

A study of 1,716 patients by Yen et al.⁸ showed a similar correlation of APRI and FIB-4 with fibrosis as our study. Chronic hepatocellular injury, especially due to alcohol or ongoing fibrosis, causes mitochondrial damage and vitamin B6 (pyridoxal phosphate) deficiency, leading to a disproportionately higher release of AST, which selectively reduces ALT activity. The development of thrombocytopenia in patients with advanced hepatic fibrosis is multifactorial. It typically involves impaired thrombopoietin synthesis by the liver, direct bone marrow suppression, and the entrapment of platelets within the spleen, a consequence of portal hypertension-induced splenomegaly. The FIB-4 index effectively reflects fibrosis severity because it integrates key biomarkers of hepatocellular damage, fibrotic progression, and portal hypertension.

CONCLUSION

Our analysis of 100 patients with CLD demonstrated that simple serum scores correlate well with fibrosis severity. The AST/ALT ratio showed the strongest linear association with FibroScan, followed by APRI and FIB-4. Lower cutoff values improved sensitivity for screening but reduced specificity, highlighting the importance of context-based threshold selection. A stepwise approach, starting with sensitive thresholds and confirming with specific ones, can reduce the need for biopsy, especially in resource-limited settings. Traditional clinical indicators, such as male sex, older age, elevated AST, and thrombocytopenia, also aligned with higher fibrosis stages. Despite their utility, these scores were less accurate at intermediate stages, reinforcing the role of elastography or biopsy in indeterminate cases. As affordable diagnostic adjuncts, the APRI, AST/ALT, and FIB-4 scores remain highly effective for the routine assessment and progression tracking of liver fibrosis.

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REFERENCES

1. Mokkad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries in between 1980 and 2010: a systemic analysis. *BMC Med* 2014;18:145.

2. India State-Level Disease Burden Initiative Collaborators. Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. *Lancet* 2017;390:2437–2460.
3. Singh S, Venkatesh SK, Wang Z, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. *Clin Gastroenterol Hepatol* 2015;13(3):440–451.e6.
4. Trifan A, Muzica CM, Nastasa R, et al. High prevalence of liver fibrosis among general population: a Romanian population-based study. *World J Gastroenterol* 2023;29(2):309–322.
5. Fallatah HI, Akbar HO, Fallatah AM. Fibroscan compared to FIB-4, APRI, and AST/ALT ratio for assessment of liver fibrosis in Saudi patients with nonalcoholic fatty liver disease. *Hepat Mon* 2016;16(7):e38346.
6. Sherazi A, Ali S, Goyal H, et al. Gender differences in cirrhosis: analysis of demographics, outcomes and healthcare utilization from a national database. *Am J Gastroenterol* 2021;116(Suppl):S562.
7. Alhankawi D, Kim HJ, Sharma S, et al. Transient elastography (FibroScan) compared to FIB-4, APRI, and AST/ALT ratio for assessment of liver significant fibrosis in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol* 2018;113(Suppl):S556.
8. Yen YH, Kuo FY, Kee KM, et al. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. *PLoS One* 2018;13(6):e0199760.

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References:

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

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

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A Retrospective Study of Clinical, Microbiological, and Ulcer Severity Patterns of Diabetic Foot Presenting to a Tertiary Care Hospital



Asif Dabeer Jafri^{1*}, Srikant Kumar Dhar², Muktesh Singh³, Ratender Kumar Singh⁴

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ABSTRACT

Background: Diabetic foot ulcers (DFUs) are a major complication of diabetes and are frequently associated with infection, antimicrobial resistance, and limb amputation. Regional Indian data on microbiological patterns and antimicrobial resistance remain limited.

Methods: This retrospective observational study evaluated 40 patients with DFUs presenting to a tertiary care hospital over a 12-month period. Clinical and laboratory parameters, including glycated hemoglobin (HbA1c), C-reactive protein (CRP), total leukocyte count (TLC), and serum albumin, were analyzed. Ulcer severity was graded using the Wagner classification, and wound cultures with antibiotic susceptibility testing were performed.

Results: Most patients were male (70%) and aged 40–60 years. Mean HbA1c was significantly higher in male than in female patients (13.99 ± 1.40 vs 10.45 ± 1.41 ; $p < 0.05$). Monomicrobial infections predominated, with Gram-negative organisms accounting for 70.3% of isolates, followed by Gram-positive bacteria (22.2%) and fungi (7.4%). Polymicrobial infections occurred in 12.5% of cases. Gram-negative isolates showed universal sensitivity to colistin, whereas *Acinetobacter* spp. demonstrated high resistance to other antibiotics. Higher Wagner grades were significantly associated with elevated HbA1c and CRP levels. All amputations occurred in male patients with polymicrobial infections.

Conclusion: Gram-negative pathogens predominated in DFUs in this setting, contrasting with the Gram-positive predominance reported in Western literature. Poor glycemic control and elevated inflammatory markers were associated with increasing ulcer severity and amputation risk.

Keywords: Amputation; Diabetes mellitus complications, Diabetic foot, Diabetic foot infections, Foot ulcer, Glycated hemoglobin.

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INTRODUCTION

Diabetic foot ulcers (DFUs) are among the most common long-term complications of poorly controlled diabetes and are frequently associated with inadequate glycemic control, peripheral vascular disease, neuropathy, poor foot care, and trauma. In diabetic people, the lifetime chance of getting a DFU is estimated to be 12 to 25%.^{1,2} Diabetes mellitus (DM) is now the most common cause of nontraumatic amputations in the world, and approximately 1% require amputation. Patients with DFU are approximately two to three times more likely to die than patients who do not have DFU.^{3,4} Therapy targeting recognized causal organisms can considerably improve outcomes and reduce infection-related morbidities.

The microbiological profile of Diabetic foot infections (DFIs) varies considerably across geographical regions. Studies from Western countries commonly report Gram-positive organisms, particularly *Staphylococcus aureus* and *Streptococci*, as the predominant pathogens.⁵ In contrast,

several studies from India and other developing countries have demonstrated a predominance of Gram-negative bacteria along with an increasing burden of multidrug-resistant (MDR) organisms. The choice of empirical antibiotics frequently relies on information from Western nations, which may not be suitable for application in these regions.⁶

Hyperglycemia impairs both innate and adaptive immune responses, increasing susceptibility to bacterial infections in patients with diabetes. DFIs are further promoted by peripheral neuropathy, vasculopathy, impaired circulation, and immunocompromised states.^{7,8} Inflammatory biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), total leukocyte count (TLC), and interleukin-6 (IL-6) have been associated with infection severity, lower-limb amputation, soft tissue infection, osteomyelitis, and sepsis in diabetic patients. Several clinical factors, including age, male gender, duration of diabetes, poor glycemic control, peripheral vascular disease, neuropathy, renal

dysfunction, osteomyelitis, gangrene, and elevated leukocyte count, have also been identified as predictors of amputation in patients with diabetic foot ulcers.^{9,10}

Despite the substantial burden of DFIs in India, region-specific data integrating microbiological spectrum, antimicrobial susceptibility patterns, ulcer severity, and biochemical markers remain limited. Therefore, the present study was undertaken to evaluate the microbiological profile and antimicrobial resistance patterns of diabetic foot infections and to assess their association with glycemic status, inflammatory markers, ulcer severity, and clinical outcomes, including amputation.

MATERIALS AND METHODS

Study Design and Ethical Considerations

This retrospective observational study was conducted in the Department of General Medicine at SUM Hospital, Bhubaneswar, India, over a 12-month period from 1 January 2025 to 1 January 2026. A total of 40 patients with diabetic foot ulcers were included in the analysis. Ethical approval for the study was obtained from the Institutional Ethics Committee-Clinical Research and Studies (IEC No. ECR/1604/Inst/OD/2021/03/01/2026). Owing to the retrospective nature of the study and the use of anonymized clinical data, the requirement for informed consent was waived by the Ethics Committee.

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Inclusion and Exclusion Criteria

Adults aged 20–80 years with diabetic foot ulcers were included in the study. Patients with nondiabetic foot ulcers, immunocompromised states, chronic inflammatory diseases, hemoglobinopathies, pregnancy, or chronic liver disease were excluded.

Clinical and Laboratory Assessment

Demographic details, duration of diabetes, associated comorbidities, and clinical findings were recorded for all patients. Ulcer severity was graded using the Wagner classification system. Peripheral neuropathy was assessed clinically using a 10-g Semmes–Weinstein monofilament, vibration perception testing with a 128 Hz tuning fork, ankle reflex testing, and temperature sensation assessment. Peripheral vascular disease was assessed clinically by pedal pulse examination.

Laboratory investigations included complete blood count (CBC), glycated hemoglobin (HbA1c), CRP, liver function tests, kidney function tests, serum albumin, and serum creatinine.

Microbiological Analysis

Wound exudate and pus samples were collected under sterile precautions for microbiological evaluation. Specimens were cultured using standard microbiological techniques, and isolates were identified according to Clinical and Laboratory Standards Institute (CLSI) guidelines (2023). Antibiotic susceptibility testing was performed using the modified Kirby–Bauer disk diffusion method and interpreted according to CLSI criteria. Methicillin resistance in *Staphylococcus aureus* was assessed using the cefoxitin disk diffusion test. Colistin susceptibility was confirmed by broth microdilution.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical data. Continuous variables were expressed as mean $\pm$ standard deviation (SD), while categorical variables were presented as frequencies and percentages. The chi-square test was used for categorical variables, and the independent *t*-test was applied for comparison of continuous variables between groups. One-way ANOVA was used to compare clinical parameters across age groups. Correlation analysis was performed using Pearson's correlation coefficient. A *p*-value < 0.05 was considered statistically significant.

RESULTS

A total of 40 patients with DFUs were included in the study, comprising 28 males

(70%) and 12 females (30%). The majority of patients belonged to the 40–60 years of age group. Mean HbA1c levels were higher in males than females across all age groups and were significantly elevated in the 40–60 years age group ($p < 0.001$), as shown in Table 1.

The mean HbA1c level of the study population was 12.93%, indicating poor glycemic control. Mean CRP and TLC values were elevated, suggesting active inflammation and infection, while lower hemoglobin and serum albumin levels reflected poor nutritional status (Fig. 1).

Male patients demonstrated significantly higher HbA1c levels than females, while hypertension, neuropathy, chronic kidney disease, and peripheral vascular disease were more frequent among males (Table 2).

Microbiological analysis revealed monomicrobial growth in 67.5% ($n = 27$) of cultures, polymicrobial growth in 12.5% ($n = 5$), and no growth in 20% ($n = 8$). Gram-negative organisms predominated (70.3%), followed by Gram-positive organisms (22.2%) and

fungi (7.4%). The most common isolates were *Pseudomonas* spp., *Escherichia coli*, *Klebsiella* spp., and *Acinetobacter* spp., while methicillin-resistant *Staphylococcus aureus* (MRSA) was the predominant Gram-positive organism. Polymicrobial infections were more frequent in males (Table 3).

Gram-negative isolates demonstrated high resistance to β -lactams, cephalosporins, and fluoroquinolones, whereas colistin retained activity against most isolates. *Acinetobacter* spp. exhibited the highest multidrug resistance. Among Gram-positive organisms, vancomycin and linezolid showed good activity. *Candida albicans* was isolated in 5% of cases, with resistance to fluconazole observed in all isolates (Table 4).

Higher Wagner grades showed significant associations with HbA1c, CRP, and albumin levels (Table 5).

Debridement was the most commonly performed procedure across Wagner grades. Amputations were observed only in male patients with grade III and grade V ulcers

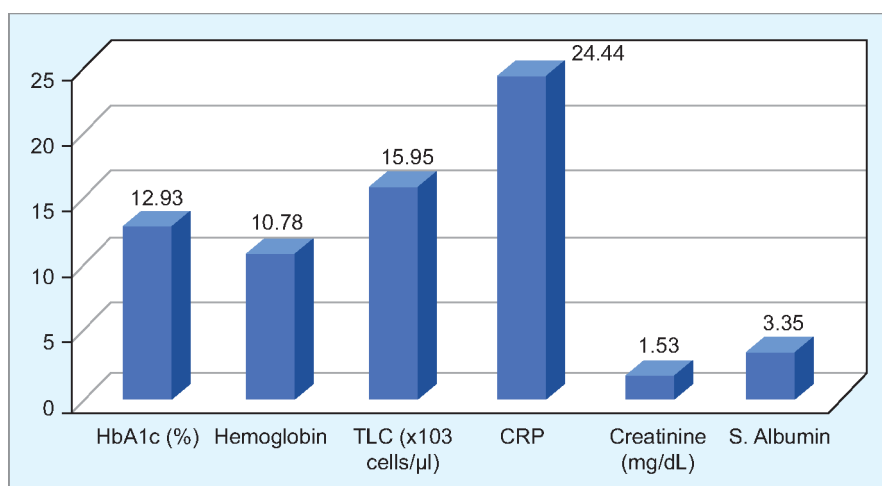


Fig. 1: Mean values of the laboratory parameters

Table 1: HbA1c levels across various age groups for both genders

Age in years	Male (n = 28)	Female (n = 12)	p-value	HbA1c male	HbA1c female	p-value
<40	7 (25%)	3 (25%)	0.99	13.98 $\pm$ 1.55	10.53 $\pm$ 1.35	0.010
40–60	15 (53.5%)	8 (66.7%)	0.48	13.80 $\pm$ 1.42	10.31 $\pm$ 1.58	<0.001
>60	6 (21.4%)	1 (8.4%)	0.652	14.48 $\pm$ 1.31	11.30	0.075

Table 2: Comparison of clinical variables in males and females

Variables	Male (n = 28)	Female (n = 12)	p-value
HbA1c (mean)	13.99 $\pm$ 1.40	10.45 $\pm$ 1.41	<0.001
Hypertension	16 (57.2%)	5 (41.7%)	0.369
Neuropathy	13 (46.5%)	5 (41.7%)	0.781
Chronic kidney disease	7 (25%)	1 (8.4%)	0.462
Peripheral vascular disease	4 (14.3%)	0 (0%)	0.168

and were associated with poor glycemic control and polymicrobial infections (Fig. 2).

DISCUSSION

The microbiological profile and antibiotic sensitivity of DFIs vary significantly across

regions, largely due to differences in antibiotic use and healthcare practices. Male sex and poor glycemic control have consistently been identified as important risk factors for infected and non-healing DFUs.¹¹ In our study, male patients demonstrated poorer glycemic control and a higher frequency

of severe infections, which is consistent with previous reports. Lacopi et al. also reported that male patients with diabetic foot disease tend to have more severe clinical presentations, higher rates of comorbidities, and increased risks of minor and major amputations.¹² Similar findings have been reported in European DFI studies, where male predominance and uncontrolled diabetes were commonly observed among patients with severe DFIs.^{11,13,14}

Bacteriological patterns of DFIs demonstrate considerable regional variation. While Western studies frequently report Gram-positive predominance,^{15,16} several Indian studies have documented a higher prevalence of Gram-negative organisms.^{17–19} Our findings are consistent with these observations, with Gram-negative bacteria accounting for the majority of isolates. Previous antibiotic exposure and chronic ulceration may contribute to the predominance of Gram-negative organisms in severe DFIs. *Acinetobacter* and *Klebsiella* species, which were commonly isolated in our study, have also been associated with increased risk of major amputations.²⁰ In addition, severe DFIs in our cohort were predominantly polymicrobial, whereas mild-to-moderate infections were mainly monomicrobial, similar to findings from earlier studies.^{21,22} Gram-negative infections, particularly *Pseudomonas aeruginosa*, are associated with greater severity, antibiotic resistance, tissue damage, and higher amputation risk.^{23,24}

The emergence of multidrug-resistant organisms (MDROs) in DFIs represents a major therapeutic challenge. Factors such as ischemia, ulcer severity, osteomyelitis, previous antibiotic exposure, and repeated hospitalizations contribute to the development of antimicrobial resistance.²⁵ In the present study, Gram-negative organisms exhibited high resistance to β -lactams, cephalosporins, and fluoroquinolones, whereas colistin retained good activity against most isolates. Among Gram-positive organisms, vancomycin and linezolid remained highly effective. *Candida* isolates were also

Table 3: Culture results of diabetic foot ulcers (DFUs) (n = 40)

Type of growth	Organism	Frequency (%)	Male (n = 28)	Female (n = 12)
Monomicrobial	<i>Acinetobacter</i>	3 (7.5)	2	1
	<i>Klebsiella pneumoniae</i>	3 (7.5)	2	1
	<i>Pseudomonas</i>	5 (12.5)	3	2
	<i>Citrobacter</i>	2 (5)	1	1
	<i>Candida</i>	2 (5)	2	0
	<i>Enterococcus</i>	2 (5)	2	0
	MRSA	3 (7.5)	2	1
	<i>E. coli</i>	4 (10)	3	1
	MSSA	1 (2.5)	1	0
Polymicrobial	<i>Proteus mirabilis</i>	2 (5)	2	0
	<i>Acinetobacter</i> + <i>Klebsiella</i>	1 (2.5)	1	0
	<i>Klebsiella</i> spp. + <i>Proteus</i>	1 (2.5)	1	0
	<i>Pseudomonas</i> + <i>Acinetobacter</i>	1 (2.5)	1	0
	<i>E. coli</i> + <i>Pseudomonas</i>	1 (2.5)	1	0
	<i>E. coli</i> + <i>Klebsiella</i>	1 (2.5)	0	1
No growth	–	8 (20)	6	2

Table 4: Major antimicrobial resistance patterns among isolates from diabetic foot infections

Organism	Predominant Resistance Pattern	Antibiotics with Highest Sensitivity
<i>Acinetobacter</i> spp. (n = 5)	High resistance to cephalosporins, fluoroquinolones, and β -lactams	Colistin
<i>Klebsiella</i> spp. (n = 6)	Resistant to third-generation cephalosporins and β -lactams	Colistin, meropenem
<i>Proteus</i> spp. (n = 3)	High resistance to cephalosporins and β -lactams	Meropenem, colistin
<i>Pseudomonas aeruginosa</i> (n = 7)	Resistant to cephalosporins and fluoroquinolones	Colistin
<i>Escherichia coli</i> (n = 6)	High resistance to cephalosporins and β -lactams	Colistin, meropenem
<i>Citrobacter</i> spp. (n = 2)	Multidrug resistance to β -lactams and cephalosporins	Colistin
MRSA (n = 3)	Resistant to oxacillin, levofloxacin, and clindamycin	Vancomycin, linezolid
<i>Enterococcus</i> spp. (n = 2)	Resistant to amoxiclav and doxycycline	Vancomycin, linezolid
<i>Candida albicans</i> (n = 2)	Resistant to fluconazole	Caspofungin, micafungin, amphotericin B

Table 5: Association between Wagner ulcer grading and selected biochemical and hematological parameters. Values are expressed as mean $\pm$ standard deviation (SD) for each Wagner ulcer grade (I–V). *p*-values represent the statistical significance of differences across Wagner grades

Wagner grading	I	II	III	IV	V	<i>p</i> -value
HbA1c (mean $\pm$ SD)	10.22 $\pm$ 1.12	12.90 $\pm$ 0.53	14.27 $\pm$ 0.37	15.20 $\pm$ 0.07	15.95 $\pm$ 0.43	0.001
CRP (mg/L)	16.83 $\pm$ 7.25	23.16 $\pm$ 17.03	16.68 $\pm$ 9.66	14.60 $\pm$ 30.92	44.50 $\pm$ 31.9	0.026
TLC ($\times 10^3/\mu\text{L}$)	10.92 $\pm$ 4.40	17.00 $\pm$ 10.78	14.71 $\pm$ 3.14	21.60 $\pm$ 12.06	23.00 $\pm$ 8.83	0.057
Albumin (gm/dL)	3.73 $\pm$ 0.38	3.21 $\pm$ 0.71	3.42 $\pm$ 0.73	3.28 $\pm$ 0.76	2.57 $\pm$ 0.67	0.045
Hemoglobin (gm/dL)	11.42 $\pm$ 1.35	10.68 $\pm$ 1.85	11.27 $\pm$ 1.59	9.92 $\pm$ 1.50	9.40 $\pm$ 1.90	0.174
Creatinine (mg/dL)	0.96 $\pm$ 0.71	1.86 $\pm$ 1.09	1.45 $\pm$ 0.71	1.64 $\pm$ 0.74	2.30 $\pm$ 1.51	0.092

HbA1c, glycated hemoglobin; CRP, C-reactive protein; TLC, total leukocyte count; SD, standard deviation

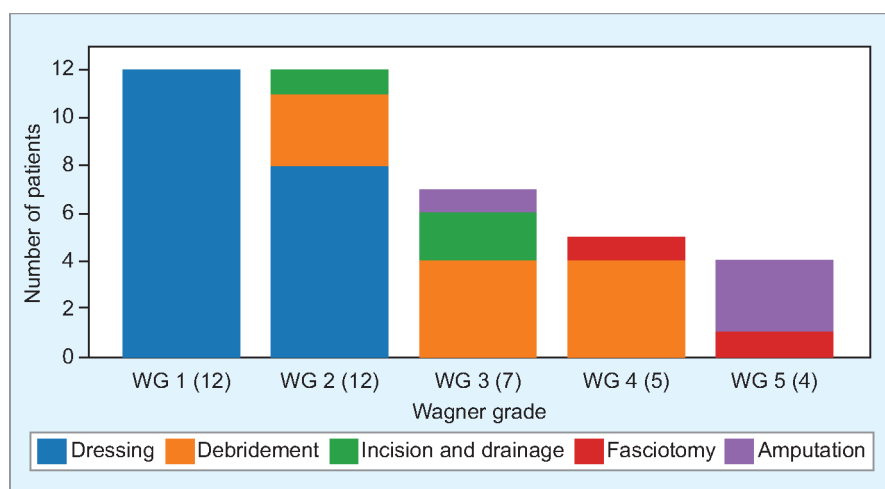


Fig. 2: Treatment modalities according to Wagner grade in patients with diabetic foot ulcers. The stacked bar chart illustrates the distribution of treatment modalities across Wagner grades I-V. Dressing was the predominant treatment in grade I ulcers, whereas debridement was most commonly performed in grades II-IV. Amputations were observed only in grades III and V, reflecting the association between advanced ulcer severity and limb loss

identified, highlighting the possibility of fungal superinfection in chronic DFIs.

Inflammatory and biochemical markers are important indicators of infection severity and prognosis in DFUs. Elevated CRP, TLC, and HbA1c levels in our study correlated with increasing Wagner grades and severity of infection, consistent with previous meta-analyses.^{26,27} Poor glycemic control was strongly associated with severe infection and amputation risk. In addition, reduced serum albumin and hemoglobin levels were associated with advanced ulcer severity, reflecting the impact of nutritional status on wound healing and clinical outcomes. Similar associations between hypoalbuminemia, elevated inflammatory markers, and increased amputation risk have been reported previously.²⁸

Overall, our findings highlight the predominance of Gram-negative and multidrug-resistant organisms in DFIs in this region and emphasize the importance of early microbiological evaluation, appropriate antimicrobial selection, and optimal glycemic control in reducing ulcer progression and amputation risk.

LIMITATIONS

The small sample size and single-center retrospective design limit the generalizability of the findings. Wound swab cultures were used instead of deep tissue biopsy, which may not reliably distinguish colonization from true infection. Anaerobic cultures and prior antibiotic exposure data were unavailable. The limited number of severe cases and amputations also precluded multivariate analysis. Therefore, these

findings should be considered preliminary and require validation in larger prospective multicenter studies.

CONCLUSION

This study demonstrates a predominance of Gram-negative organisms in DFIs, with a notable burden of multidrug-resistant pathogens. Poor glycemic control and abnormal inflammatory and nutritional markers were associated with increasing ulcer severity and adverse outcomes. These findings emphasize the importance of early microbiological evaluation and consideration of broader Gram-negative coverage when initiating empirical therapy in similar clinical settings.

CONFLICT OF INTEREST

None.

SOURCE OF FUNDING

None.

AUTHORS' CONTRIBUTIONS

Conceptualization: ADJ, SKD, MS, RKS; Methodology: ADJ; Software: ADJ; Validation: ADJ, SKD, MS, RKS; Formal analysis: ADJ, SKD; Investigation: ADJ, SKD; Resources: ADJ; Data curation: ADJ, SKD; Writing—original draft preparation: ADJ; Writing—review and editing: ADJ, SKD, MS, RKS; Visualization: ADJ, SKD, MS, RKS; Supervision: ADJ, SKD; Project administration: SKD.

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REFERENCES

- Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* 1999;22(3):382–387.
- Ledoux WR, Shofer JB, Smith DG, et al. Relationship between foot type, foot deformity, and ulcer occurrence in the high-risk diabetic foot. *J Rehabil Res Dev* 2005;42(5):665–672.
- Mouluk PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care* 2003;26(2):491–494.
- Walsh JW, Hoffstad OJ, Sullivan MO, et al. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. *Diabet Med* 2016;33(11):1493–1498.
- Dang CN, Prasad YD, Boulton AJ, et al. Methicillin-resistant *Staphylococcus aureus* in the diabetic foot clinic: a worsening problem. *Diabet Med* 2003;20(2):159–161.
- Nelson SB. Management of diabetic foot infections in an era of increasing microbial resistance. *Curr Infect Dis Rep* 2009;11(5):375–382.
- Frydrych LM, Fattahi F, He K, et al. Diabetes and sepsis: risk, recurrence, and ruination. *Front Endocrinol (Lausanne)* 2017;8:271.
- Chastain CA, Klopfenstein N, Serezani CH, et al. A clinical review of diabetic foot infections. *Clin Podiatr Med Surg* 2019;36(3):381–395.
- Dmitriyeva M, Kozhakhmetova Z, Urazova S, et al. Inflammatory biomarkers as predictors of infected diabetic foot ulcer. *Curr Diabetes Rev* 2022;18(6):e280921196867.
- Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a meta-analysis. *PLoS One* 2020;15(9):e0239236.
- Shakil S, Khan AU. Infected foot ulcers in male and female diabetic patients: a clinico-bioinformative study. *Ann Clin Microbiol Antimicrob* 2010;9:2.
- Iacopi E, Pieruzzi L, Riitano N, et al. The weakness of the strong sex: differences between men and women affected by diabetic foot disease. *Int J Low Extrem Wounds* 2023;22(1):19–26.
- Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIAB Study. *Diabetologia* 2008;51(5):747–755.
- Sivanmaliappan TS, Sevanan M. Antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* from diabetes patients with foot ulcers. *Int J Microbiol* 2011;2011:605195.
- Mendes JJ, Marques-Costa A, Vilela C, et al. Clinical and bacteriological survey of diabetic foot infections in Lisbon. *Diabetes Res Clin Pract* 2012;95(1):153–161.
- Citron DM, Goldstein EJ, Merriam CV, et al. Bacteriology of moderate-to-severe diabetic foot infections and in vitro activity of antimicrobial agents. *J Clin Microbiol* 2007;45(9):2819–2828.
- Elamurugan TP, Jagdish S, Kate V, et al. Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis. *Int J Surg* 2011;9(3):214–216.
- Gadepalli R, Dhawan B, Sreenivas V, et al. A clinico-microbiological study of diabetic foot ulcers in an Indian tertiary care hospital. *Diabetes Care* 2006;29(8):1727–1732.
- Bansal E, Garg A, Bhatia S, et al. Spectrum of microbial flora in diabetic foot ulcers. *Indian J Pathol Microbiol* 2008;51(2):204–208.

20. Cardoso NA, Cisneiros LDL, Machado CJ, et al. Bacterial genus is a risk factor for major amputation in patients with diabetic foot. *Rev Col Bras Cir* 2017;44(2):147–153.
21. Goldstein EJ, Citron DM, Nesbit CA. Diabetic foot infections: bacteriology and activity of 10 oral antimicrobial agents against bacteria isolated from consecutive cases. *Diabetes Care* 1996;19(6):638–641.
22. Ramakant P, Verma A, Misra R, et al. Changing microbiological profile of pathogenic bacteria in diabetic foot infections: time for a rethink on which empirical therapy to choose? *Diabetologia* 2011;54(1):58–64.
23. Sugandhi P, Prasanth DA. Microbiological profile of bacterial pathogens from diabetic foot infections in tertiary care hospitals, Salem. *Diabetes Metab Syndr* 2014;8(3):129–132.
24. Roberts W, Roessler C, Francis PJ, et al. Post-surgical gangrene with *Pseudomonas luteola* resulting in limb amputation: a case review. *Cureus* 2018;10(10):e3441.
25. Dai J, Jiang C, Chen H, et al. Assessment of the risk factors of multidrug-resistant organism infection in adults with type 1 or type 2 diabetes and diabetic foot ulcer. *Can J Diabetes* 2020;44(4):342–349.
26. Kishore S, Upadhyay AD, Jyotsna VP. Awareness of foot care among patients with diabetes attending a tertiary care hospital. *Natl Med J India* 2015;28(3):122–125.
27. Wang YT, Zhang LX, Li Y, et al. Inflammatory markers in diabetic foot infection: a meta-analysis. *Wounds* 2023;35(12):425–432.
28. Sun JH, Tsai JS, Huang CH, et al. Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner classification. *Diabetes Res Clin Pract* 2012;95(3):358–363.



ANNOUNCEMENT

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Candidemia in ICU and Non-ICU Settings: Species Distribution and Antifungal Resistance Patterns from a Tertiary Care Center in India with Reference to ICMR AMR 2024

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ABSTRACT

Background: Candidemia is a major cause of invasive fungal bloodstream infections associated with significant morbidity and mortality. An increase in bloodstream infections caused by nonalbicans *Candida* species is concerning because it has different epidemiological characteristics and antifungal susceptibility compared to *C. albicans*. Resistance to antifungal agents, particularly azoles, complicates treatment.

Materials and methods: This retrospective hospital-based observational study was carried out in the Department of Microbiology, Saveetha Medical College, Chennai, from January 2025 to December 2025. Blood samples were collected and loaded into the BACT/ALERT automated system for microbial detection. Identification and antifungal susceptibility testing (AFST) were performed using the VITEK 2 automated system. CLSI M60 guidelines were used for interpreting the results.

Results: *Candida* species were isolated in 68/1207 (5.6%) positive blood cultures; 38/68 (55.9%) from ICU and 30/68 (44.1%) from non-ICU settings. Males (27/38, 71.1%) predominated in ICU, whereas females (18/30, 60%) predominated in non-ICU. The most commonly isolated species in the non-ICU setting was *C. auris* (11/30, 36.7%), whereas in the ICU setting it was *C. tropicalis* (13/38, 34.2%). *C. albicans* and *C. glabrata* showed 100% susceptibility, whereas *C. auris* demonstrated high resistance to azoles with variable resistance to echinocandins. Diabetes mellitus was the most common risk factor in both settings. Mortality was higher in ICU patients (9/38, 23.7%) than non-ICU patients (5/30, 16.7%); however, this difference was not statistically significant ($p = 0.47$).

Conclusion: Candidemia remains a significant source of bloodstream infections with a notable trend toward nonalbicans species and emerging antifungal resistance. Continuous surveillance and appropriate infection control practices are essential.

Keywords: Antifungal resistance, *Candida auris*, *Candida duobushaemulonii*, *Candida utilis*, Candidemia, Indian Council of Medical Research.

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INTRODUCTION

Candida species-related bloodstream infections (BSI) are the most common invasive fungal diseases globally and are linked to significant morbidity and mortality.¹ Candidemia is a significant public health issue due to adverse patient outcomes, extended hospitalizations, elevated healthcare expenditures, and mortality rates ranging from 5% to 58%.^{2,3} Due to several risk factors such as central venous catheterization, mechanical ventilation, total parenteral nutrition, renal replacement therapy, immunosuppression, and extended exposure to broad-spectrum antibiotics, patients admitted to intensive care units are especially vulnerable to candidemia. But candidemia is not limited to critical care units; more cases are being recorded from non-ICU wards, which is indicative of the growing number of patients with impaired immune systems and the complexity of contemporary medical care.

Currently, over 200 species of *Candida* have been reported, of which only 10% are known to cause human infections.⁴ *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* are typically responsible for the majority of invasive *Candida* infections. *C. auris* has become a significant nosocomial pathogen of concern that causes candidiasis in recent times.^{5,6}

The rising cases of BSI with nonalbicans *Candida* species are alarming because they have a distinct epidemiological profile and antifungal susceptibility patterns compared to *C. albicans* and also can exhibit varying acquired and innate susceptibility to antifungal drugs.⁷⁻⁹ The increasing resistance to conventional antifungal drugs, especially azoles, makes diagnosis and treatment of *Candida* infections more difficult.¹⁰ There is ample evidence of fluconazole resistance in *C. albicans*, which is often linked to drug exposure.¹¹ Fluconazole resistance may be more common in some nonalbicans species than in *C. albicans*, such as *C. glabrata* and

C. parapsilosis, while *C. krusei* is naturally resistant to fluconazole, further complicating its outcomes.⁷⁻⁹

National statistics on the distribution of *Candida* species and patterns of antifungal susceptibility are provided in the ICMR AMR 2024 report;¹² however, resistance trends are not separated by ICU and non-ICU settings; therefore, institution-based research is required to assess local epidemiology and antifungal resistance patterns. Additionally, comparing institutional data with the ICMR AMR report allows for the evaluation of local resistance trends and the development of targeted antifungal stewardship initiatives.

The purpose of this study was to compare pooled resistance data with the results of the ICMR AMR 2024 national monitoring and to ascertain the species distribution and antifungal resistance trends of *Candida* bloodstream isolates in ICU and non-ICU settings at a tertiary care hospital in India. This study is primarily descriptive in nature and aims to provide a single-center epidemiological snapshot rather than establish causal relationships or definitive comparative conclusions.

MATERIALS AND METHODS

Study Design and Setting

This retrospective hospital-based observational study was carried out in the Department of Microbiology, Saveetha Medical College, Chennai, from January 2025 to December 2025 after obtaining approval from the Institutional Scientific Committee (730/01/2026/SRB/SMCH). As it

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was a retrospective study, a waiver certificate was obtained from the Institutional Ethical Committee.

Inclusion Criteria

Intensive care unit and non-ICU patients with laboratory-confirmed candidemia, defined as at least one positive blood culture for *Candida* species in the presence of clinical features of infection such as fever, hypotension, or signs of sepsis.

Only the first episode per patient was included in the analysis, and duplicate isolates from the same patient were excluded.

Exclusion Criteria

- Colonization-related cases without a clinical connection.
- Inadequate clinical records.

Specimen Collection and Transport

Blood samples were collected under aseptic precautions from hospitalized patients and inoculated directly into BACT/ALERT blood culture bottles (bioMérieux, France). Bottles were transported immediately to the microbiology laboratory and loaded into the automated BACT/ALERT blood culture system for continuous monitoring.¹³

Sample Processing

Blood cultures flagged as positive by the automated system were followed by Gram-staining and subcultured onto blood agar and CHROMagar for growth and species differentiation. The VITEK 2 automated system was used for identification (ID card: VITEK® 2 YST) and antifungal susceptibility testing (AST card: VITEK® 2 AST-YS08), and results were interpreted in accordance with CLSI M60 (2024) guidelines using clinical breakpoints or epidemiological cutoffs wherever applicable.¹⁴ It is acknowledged that automated identification systems such as VITEK 2 may have limitations in accurately identifying rare or emerging species such as *C. auris*, and confirmatory methods (e.g., MALDI-TOF MS) were not available.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using OpenEpi software version 3.01, an open-source epidemiological statistics tool. Categorical variables were expressed as frequencies and percentages. The chi-square test was used for comparison when expected cell counts were ≥ 5 ; otherwise, Fisher's exact test was applied. Due to the small sample size, odds ratios and confidence intervals were interpreted cautiously. All statistical tests were two-tailed, and a p -value < 0.05 was considered statistically significant.

Given the limited sample size and small subgroup counts, multivariate analysis was not performed, and findings were interpreted as exploratory. Species with ≤ 3 isolates were excluded from inferential statistical comparisons and described descriptively.

RESULTS

A retrospective analysis of blood culture data from the study period showed 1,207 positive blood cultures. Of these, 310 (26%) were from ICU patients while 897 (74%) were from non-ICU patients. *Candida* species were isolated in 68 cases (30 non-ICU cases and 38 ICU cases), accounting for 5.6% of all positive blood cultures.

Demographic Profile of Candidemia

Sex-wise Distribution

Males (71.1%) constituted the majority of candidemia cases in ICU, whereas females (60%) made up a larger percentage of cases in the non-ICU group. Overall, candidemia was more common in male patients. A statistically significant difference in sex distribution was noted between ICU and non-ICU patients ($p = 0.014$). Male patients had higher odds of ICU admission compared to females (OR 3.68; 95% CI 1.34–10.13) (Table 1).

Age-wise Distribution

The most common age group affected was 41–60 years in the ICU group, whereas in the non-ICU group, the 61–80 years age group predominated. There was no statistically significant difference in age distribution between ICU and non-ICU groups ($p = 0.265$) (Table 2).

Species Distribution of *Candida*

The most commonly isolated species in the non-ICU setting was *C. auris*, followed by *C. parapsilosis*, *C. tropicalis*, *C. albicans*, *C. glabrata*, *C. guilliermondii* and *C. utilis*.

In ICU, *C. tropicalis* was most commonly isolated, followed by *C. auris*, *C. albicans*, *C. glabrata*, *C. duobushaemulonii*, *C. parapsilosis*, *C. lusitanae* and *C. utilis*.

Among the *Candida* species, only *C. parapsilosis* ($p = 0.018$) showed a statistically significant difference between ICU and non-ICU settings. No statistically significant differences were observed for other species (all $p > 0.05$). Species with ≤ 3 isolates (*C. guilliermondii*, *C. duobushaemulonii*, *C. lusitanae* and *C. utilis*) were categorized as rare *Candida* species and are presented descriptively without inferential statistical comparison (Table 3).

Species-wise Antifungal Resistance Pattern of *Candida* Isolates

Antifungal resistance patterns are presented as the number of resistant isolates over total isolates tested (n/N) along with percentages. *Candida albicans* showed complete susceptibility to all antifungal agents tested in both ICU and non-ICU settings (0/6 and 0/1, respectively).

In ICU settings, *C. auris* showed resistance in 5/8 isolates (62.5%) to fluconazole, 8/8 isolates (100.0%) to voriconazole, 4/8 isolates (50.0%) to itraconazole, 2/8 isolates (25.0%) to clotrimazole, 5/8 isolates (62.5%) to micafungin and 3/8 isolates (37.5%) to amphotericin B, while all isolates were susceptible to caspofungin (0/8).

In non-ICU settings, *C. auris* showed resistance in 7/11 isolates (63.6%) to fluconazole, 11/11 isolates (100.0%) to voriconazole, 7/11 isolates (63.6%) to itraconazole, 3/11 isolates (27.3%) to clotrimazole and 7/11 isolates (63.6%) to amphotericin B, while all isolates were susceptible to caspofungin and micafungin (0/11).

In ICU settings, *C. duobushaemulonii* showed resistance in 2/3 isolates (66.7%) to fluconazole, 1/3 isolates (33.3%) to voriconazole, and 1/3 isolates (33.3%) to

Table 1: Sex-wise distribution of *Candida* species

Sex	Non-ICU [n (%)]	ICU [n (%)]	Total [n (%)]
Male	12 (40%)	27 (71%)	39 (57%)
Female	18 (60%)	11 (29%)	29 (43%)
Total	30 (100%)	38 (100%)	68 (100%)

Table 2: Age-wise distribution of *Candida* species

Age (years)	Non-ICU [n (%)]	ICU [n (%)]	Total [n (%)]
0–20	7 (23.33)	10 (26)	17 (25)
21–40	4 (13.34)	4 (11)	8 (12)
41–60	7 (23.33)	16 (42)	23 (34)
61–80	12 (40)	8 (21)	20 (29)
Total	30 (100)	38 (100)	68 (100)

Table 3: Species distribution of *Candida* isolates

Species	Non-ICU [n (%)]	ICU [n (%)]	Total [n (%)]	p-value
<i>C. albicans</i>	1 (3.3)	6 (15.8)	7 (10.3)	0.12
<i>C. tropicalis</i>	7 (23.3)	13 (34.2)	20 (29.4)	0.42
<i>C. glabrata</i>	1 (3.3)	4 (10.5)	5 (7.4)	0.37
<i>C. parapsilosis</i>	8 (26.7)	2 (5.3)	10 (14.7)	0.01
<i>C. auris</i>	11 (36.7)	8 (21.1)	19 (27.9)	0.18
<i>C. guilliermondii</i>	1 (3.3)	0	1 (1.5)	–
<i>C. duobushaemulonii</i>	0	3 (7.9)	3 (4.4)	–
<i>C. lusitaniae</i>	0	1 (2.6)	1 (1.5)	–
<i>C. utilis</i>	1 (3.3)	1 (2.6)	2 (2.9)	–

p-values were calculated using Fisher's exact test; $p < 0.05$ was considered statistically significant

amphotericin B, while all isolates were susceptible to caspofungin (0/3).

C. glabrata showed complete susceptibility to all antifungal agents tested in both ICU and non-ICU settings (0/4 and 0/1, respectively).

In ICU settings, *C. lusitaniae* showed complete susceptibility to all antifungal agents tested (0/1).

In ICU settings, *C. parapsilosis* showed complete susceptibility to all antifungal agents tested (0/2). In non-ICU settings, *C. parapsilosis* showed resistance in 3/8 isolates (37.5%) to fluconazole, 2/8 isolates (25.0%) to voriconazole, 2/8 isolates (25.0%) to itraconazole, and 3/8 isolates (37.5%) to amphotericin B, while all isolates were susceptible to caspofungin and micafungin (0/8).

In non-ICU settings, *C. guilliermondii* showed complete susceptibility to all antifungal agents tested (0/1).

In ICU settings, *C. tropicalis* showed resistance in 2/13 isolates (15.4%) to voriconazole, 4/13 isolates (30.8%) to itraconazole, 1/13 isolates (7.7%) to caspofungin, and 3/13 isolates (23.1%) to micafungin, while all isolates were susceptible to fluconazole and amphotericin B (0/13). In non-ICU settings, *C. tropicalis* showed resistance in 1/7 isolates (14.3%) to fluconazole, 2/7 isolates (28.6%) to voriconazole, 2/7 isolates (28.6%) to itraconazole, 5/7 isolates (71.4%) to micafungin, and 3/7 isolates (42.9%) to amphotericin B, while all isolates were susceptible to caspofungin (0/7).

C. utilis showed complete susceptibility to all antifungal agents tested in both ICU and non-ICU settings (0/1 each) (Table 4).

RISK FACTORS AND OUTCOMES OF THE PATIENTS WITH CANDIDEMIA

The most frequently observed risk factors included diabetes mellitus and dialysis, with no statistically significant differences observed between ICU and non-ICU groups ($p > 0.05$).

Other risk factors such as preterm status, prolonged antibiotic use, chemotherapy, and radiotherapy were observed in the non-ICU group, while mechanical ventilation, polytrauma, steroid use, and systemic lupus erythematosus were observed in the ICU group. No statistically significant differences were observed for any of the evaluated risk factors (all $p > 0.05$).

Mortality was numerically higher among ICU patients (23.7%) compared to non-ICU patients (16.7%); however, this difference was not statistically significant ($p = 0.47$) (Table 5).

ANTIFUNGAL RESISTANCE AMONG CANDIDA BLOODSTREAM ISOLATES IN ICU AND NON-ICU SETTINGS WITH REFERENCE TO ICMR AMR 2024 NATIONAL SURVEILLANCE DATA

Antifungal resistance patterns observed in the present study are presented alongside ICMR AMR 2024 surveillance data for reference. *C. albicans* in our study showed 100% susceptibility to fluconazole, voriconazole, caspofungin and micafungin, while the ICMR AMR 2024 report documented resistance rates of 2.1% to fluconazole, 2.8% to voriconazole, 2.8% to caspofungin and 2.7% to micafungin.

C. auris showed an overall resistance rate of 63.2% to fluconazole, 100% to voriconazole, 26.3% to micafungin, and 100% susceptibility to caspofungin in our study, while the ICMR AMR 2024 report documented a resistance rate of 50% to fluconazole, 84% to voriconazole, 10.1% to caspofungin, and 2.8% to micafungin.

C. glabrata showed 100% susceptibility to fluconazole and voriconazole in our study; ICMR AMR 2024 documented resistance rates of 2% to fluconazole and 3.5% to voriconazole.

C. parapsilosis showed overall 20% resistance to fluconazole, 20% resistance to voriconazole, and 100% susceptibility to micafungin and caspofungin in our study, while the ICMR AMR 2024 report documented

a resistance rate of 19.1% to fluconazole, 4.3% to voriconazole, 1.4% to caspofungin, and 0.4% to micafungin.

C. tropicalis showed an overall resistance rate of 5% to fluconazole, 20% to voriconazole, and 100% susceptibility to caspofungin and micafungin in our study, while the ICMR AMR 2024 report documented a resistance rate of 6.2% to fluconazole, 5.3% to voriconazole, 0.7% to caspofungin, and 1.4% to micafungin.

These differences may reflect local epidemiological variation rather than true population-level differences (Table 6).

DISCUSSION

The present study highlights the burden, demographic trends, species distribution, and antifungal resistance pattern. In our study, *Candida* species constituted about 5.6% of all positive blood cultures, indicating that fungal bloodstream infections are an important contributor to morbidity, particularly among hospitalized and critically ill patients, which is in concordance with several other studies.^{15,16} The larger patient base in general wards may account for the higher candidemia cases; however, ICU patients usually have more predisposing risk factors such as extended hospital stays, invasive procedures, and immunosuppression, which increase susceptibility to invasive fungal infections.¹⁷

The demographic study revealed a gender-based variation in the incidence of candidemia. In ICU settings, the majority of cases were male, whereas in non-ICU settings, females were most commonly affected. Generally, the incidence of candidemia was found to be higher in males.¹⁸ A significant male predominance was noted among ICU patients ($p = 0.014$); however, this association should be interpreted with caution given the limited sample size. This is consistent with a number of studies that have shown a slightly higher incidence of bloodstream infections in males, potentially due to greater exposure to comorbid conditions.¹⁸

Based on the age distribution, candidemia affected a broad range of patients. The 61–80 years age group was most commonly affected in the ICU group, while the 41–60 years age group predominated in the non-ICU group. In general, both elderly and middle-aged populations were greatly impacted. The higher incidence in older age groups is mainly due to chronic illnesses, a weakening immune system, and frequent exposure to healthcare facilities.¹⁹

Diabetes mellitus is a well-established risk factor for candidemia, as hyperglycemia impairs immune function and promotes fungal proliferation; recent studies have

Table 4: Species-wise antifungal resistance pattern of *Candida* isolates

Species	Antifungal drugs	ICU R (%) (N/N)	Non-ICU R (%) (N/N)
<i>C. albicans</i>	Fluconazole	0% (0/6)	0% (0/1)
	Voriconazole	0% (0/6)	–
	Itraconazole	0% (0/6)	0% (0/1)
	Caspofungin	0% (0/6)	0% (0/1)
	Micafungin	0% (0/6)	0% (0/1)
	Amphotericin B	0% (0/6)	0% (0/1)
<i>C. auris</i>	Fluconazole	62.5% (5/8)	63.6% (7/11)
	Voriconazole	100% (8/8)	100% (11/11)
	Itraconazole	50% (4/8)	63.6% (7/11)
	Clotrimazole	25% (2/8)	27.3% (3/11)
	Caspofungin	0% (0/8)	0% (0/11)
	Micafungin	62.5% (5/8)	0% (0/11)
<i>C. duobushaemulonii</i>	Amphotericin B	37.5% (3/8)	63.6% (7/11)
	Fluconazole	66.7% (2/3)	–
	Voriconazole	33.3% (1/3)	–
	Caspofungin	0% (0/3)	–
<i>C. glabrata</i>	Amphotericin B	33.3% (1/3)	–
	Fluconazole	0% (0/4)	0% (0/1)
	Itraconazole	0% (0/4)	0% (0/1)
	Voriconazole	0% (0/4)	0% (0/1)
	Clotrimazole	0% (0/4)	0% (0/1)
<i>C. lusitaniae</i>	Amphotericin B	0% (0/4)	0% (0/1)
	Fluconazole	0% (0/1)	–
	Voriconazole	0% (0/1)	–
<i>C. parapsilosis</i>	Amphotericin B	0% (0/1)	–
	Fluconazole	0% (0/2)	37.5% (3/8)
	Voriconazole	0% (0/2)	25% (2/8)
	Itraconazole	0% (0/2)	25% (2/8)
	Caspofungin	0% (0/2)	0% (0/8)
<i>C. guilliermondii</i>	Micafungin	0% (0/2)	0% (0/8)
	Amphotericin B	0% (0/2)	37.5% (3/8)
	Fluconazole	–	0% (0/1)
	Voriconazole	–	0% (0/1)
	Caspofungin	–	0% (0/1)
<i>C. tropicalis</i>	Micafungin	–	0% (0/1)
	Amphotericin B	–	0% (0/1)
	Fluconazole	0% (0/13)	14.3% (1/7)
	Voriconazole	15.4% (2/13)	28.6% (2/7)
	Itraconazole	30.8% (4/13)	28.6% (2/7)
<i>C. utilis</i>	Caspofungin	7.7% (1/13)	0% (0/7)
	Micafungin	23.1% (3/13)	71.4% (5/7)
	Amphotericin B	0% (0/13)	42.9% (3/7)
	Fluconazole	0% (0/1)	0% (0/1)
	Voriconazole	0% (0/1)	0% (0/1)
	Itraconazole	0% (0/1)	0% (0/1)
	Amphotericin B	0% (0/1)	0% (0/1)

‘–’ indicates that no isolates were available for testing

consistently identified diabetes as one of the most common comorbidities associated with candidemia.²⁰ In both ICU and non-ICU groups, other risk factors such as dialysis, long-

term antibiotic usage, chemotherapy and preterm status were noted; however, none of these factors showed a statistically significant association between ICU and non-ICU groups.

Despite having a substantially higher mortality rate (23.7% vs 16.7%) than non-ICU patients, this difference was not statistically significant and should be interpreted cautiously.

The antifungal resistance patterns in our study help in understanding the regional susceptibility trends. *C. albicans* demonstrated complete susceptibility to all the antifungal drugs tested in this study, which is in line with global trends that show that *C. albicans* resistance is still relatively low compared to nonalbicans species.²¹ However, in both ICU and non-ICU settings, *C. auris* demonstrated high resistance rates to azoles, particularly fluconazole and voriconazole.^{22,23} Resistance to amphotericin B was also notable. The elevated resistance observed in *C. auris*, especially to azoles and echinocandins, may be attributed to intrinsic mechanisms such as ERG11 gene mutations and efflux pump overexpression, as reported in previous studies. Although molecular characterization was not performed in the present study, these findings may indicate the presence of resistant clades and underscore the need for further genomic surveillance. These observations highlight the importance of periodic antifungal susceptibility testing and careful selection of empirical antifungal therapy.

C. tropicalis showed considerable resistance to azoles and echinocandins, which suggests changing resistance trends, especially in non-ICU settings.²⁴ *C. parapsilosis* showed variable resistance to fluconazole and Amphotericin B in non-ICU patients, which is important from a clinical point of view as this species is commonly associated with catheter-related bloodstream infections. *C. glabrata*, *C. lusitaniae*, *C. utilis* and *C. guilliermondii* had overall lower resistance rates; however, these findings should be interpreted cautiously due to the small number of isolates.

The findings in our study reveal both agreement and discrepancies when compared to the ICMR 2024 national surveillance data.¹² In our study, the fluconazole resistance rate in *C. auris* was higher than the ICMR report, which may reflect local or regional variation. *C. auris* may require focused attention in antimicrobial stewardship programs, as the resistance rate of micafungin in *C. auris* was higher than that reported in national surveillance data. On the other hand, compared to the national data, *C. albicans* and *C. glabrata* had a lower rate of resistance, which indicates that these species are still susceptible to the commonly used antifungal drugs.

The increasing number of cases of nonalbicans *Candida* species and the trend of antifungal resistance make it necessary

Table 5: Risk factors and outcomes of the patients with candidemia

Risk factors/comorbidities	ICU (%)	Non-ICU	p-value
Dialysis	6 (15.8)	5 (16.7)	0.90
Prolonged antibiotic use	1 (2.6)	2 (6.7)	0.60
Chemotherapy	1 (2.6)	2 (6.7)	0.60
Diabetes mellitus	15 (39.5)	10 (33.3)	0.59
Preterm	4 (10.5)	6 (20)	0.32
Radiotherapy	0 (0)	1 (3.3)	0.44
Mechanical ventilation	4 (10.5)	0 (0)	0.06
Polytrauma	3 (7.9)	0 (0)	0.11
Steroid	2 (5.3)	0 (0)	0.20
SLE	1 (2.6)	0 (0)	0.36
Outcome			
Dead	9 (23.7)	5 (16.7)	0.47
Recovered	29 (76.3)	25 (83.3)	0.47

p values were calculated using Fisher's exact test; $p < 0.05$ was considered statistically significant

Table 6: Antifungal resistance among *Candida* bloodstream isolates in ICU and non-ICU settings with reference to ICMR AMR 2024 national surveillance data

Species	Antifungal drugs	ICU + Non-ICU settings	ICMR AMR 2024
<i>C. albicans</i>	Fluconazole	0% (0/7)	2.1%
	Voriconazole	0% (0/7)	2.8%
	Caspofungin	0% (0/7)	2.8%
	Micafungin	0% (0/7)	2.7%
<i>C. auris</i>	Fluconazole	63.2% (12/19)	50%
	Voriconazole	100% (19/19)	84%
	Caspofungin	0% (0/19)	10.1%
	Micafungin	26.3% (5/19)	2.8%
<i>C. glabrata</i>	Fluconazole	0% (0/5)	2%
	Voriconazole	0% (0/5)	3.5%
<i>C. parapsilosis</i>	Fluconazole	20% (2/10)	19.1%
	Voriconazole	20% (2/10)	4.3%
	Caspofungin	0% (0/10)	1.4%
	Micafungin	0% (0/10)	0.4%
<i>C. tropicalis</i>	Fluconazole	5% (1/20)	6.2%
	Voriconazole	20% (4/20)	5.3%
	Caspofungin	0% (0/20)	0.7%
	Micafungin	0% (0/20)	1.4%

to identify the species early and perform susceptibility testing.^{25,26} The use of antifungal agents should be appropriate and timely to reduce the mortality rate due to candidemia. Infection control practices play an important role in the prevention of nosocomial fungal infections, particularly in ICUs. The development and spread of resistance can be prevented by strictly adhering to aseptic practices and antimicrobial stewardship programs.

LIMITATIONS

The study has some limitations in the form of being a retrospective study done at a single center, which might have implications in terms of generalization of the study. Secondly, the study has a small sample size

in general, and some of the *Candida* species have very few isolates, which might have implications in terms of the robustness of the statistical analysis and the interpretation of the results. In addition, the study has relied on VITEK 2 for species identification, and it might have implications in terms of the absence of advanced technology in the form of MALDI-TOF mass spectrometry for species identification, especially for rare species of *Candida*. In addition, the absence of molecular typing of the isolates and the lack of longitudinal data are some of the limitations.

CONCLUSION

Candidemia is an important cause of bloodstream infections with an increasing

trend of nonalbicans species of *Candida* and increased resistance to antifungal agents. *C. tropicalis* and *C. auris* were the most common pathogens, with *C. auris* demonstrating higher resistance to antifungal agents. There is an urgent need to monitor, perform antifungal susceptibility testing, and use antifungal agents judiciously along with infection control measures to combat the rising threat of candidemia, both in ICU and non-ICU settings.

AUTHOR CONTRIBUTIONS

Praveetha C: Conceptualization, data curation, formal analysis, investigation, methodology, software, supervision, validation, visualization, writing—original draft, and writing—review and editing. Rithvika Vetrivel: Data curation, supervision, validation, visualization, and writing—review and editing.

ETHICAL APPROVAL

The study was approved by the Institutional Scientific Committee (approval no. 730/01/2026/SRB/SMCH). As this was a retrospective study, a waiver of informed consent was obtained from the Institutional Ethics Committee.

PATIENT CONSENT STATEMENT

Not applicable. The study was reviewed by the Institutional Ethics Committee, which determined that ethical approval was not required due to the retrospective nature of the study using anonymized data.

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REFERENCES

- Ye N, Liu Z, Tang W, et al. Systematic characterization of epidemiology, antifungal susceptibility, risk factors and outcomes of candidaemia: a six-year Chinese study. *Infect Drug Resist* 2022;15:4887–4898.
- Matos T, Lejko Zupanc T, Skofljanc A, et al. Candidaemia in Central Slovenia: a 12-year retrospective survey. *Mycoses* 2021;64(7):753–762.
- Al-Musawi TS, Alkhalifa WA, Alasaker NA, et al. A seven-year surveillance of *Candida* bloodstream infection at a university hospital in KSA. *J Taibah Univ Med Sci* 2021;16(2):184–190.
- Alkharashi N, Aljohani S, Layqah L, et al. *Candida* bloodstream infection: changing pattern of occurrence and antifungal susceptibility over 10 years in a tertiary care Saudi hospital. *Can J Infect Dis Med Microbiol* 2019;2019:2015692.
- Lockhart SR. Current epidemiology of *Candida* infection. *Clin Microbiol News* 2014;36(17):131–136.
- Rudramurthy SM, Chakrabarti A, Paul RA, et al. *Candida auris* candidaemia in Indian ICUs: analysis of risk factors. *J Antimicrob Chemother* 2017;72(6):1794–1801.
- Pappas PG, Kauffman CA, Andes DR, et al. Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the

- Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):409–417.
8. Casalini G, Giacomelli A, Antinori S. The WHO fungal priority pathogens list: a crucial reappraisal to review the prioritisation. Lancet Microbe 2024;5(7):717–724.
 9. Rogers TR, Verweij PE, Castanheira M, et al. Molecular mechanisms of acquired antifungal drug resistance in principal fungal pathogens and EUCAST guidance for their laboratory detection and clinical implications. J Antimicrob Chemother 2022;77(8):2053–2073.
 10. Berkow EL, Lockhart SR. Fluconazole resistance in *Candida* species: a current perspective. Infect Drug Resist 2017;10:237–245.
 11. Yadav SK, Himanshu D, Gupta P, et al. Multidrug-resistant *Candida* in bloodstream infections: a growing concern in Indian healthcare. Cureus 2025;17(6):e85420.
 12. Indian Council of Medical Research. Annual Report, 2024: ICMR Antimicrobial Resistance Research & Surveillance Network (AMRSN), 8th edition. New Delhi: Indian Council of Medical Research; 2025.
 13. Balaji L, Manoharan H, Prabhakaran N, et al. Time-to-positivity for *Candida* in bloodstream infections: prognostic implications for mortality. Cureus 2024;16(8):e66364.
 14. Clinical and Laboratory Standards Institute. Performance Standards for Antifungal Susceptibility Testing of Yeasts, 3rd edition. CLSI supplement M27M44S. Wayne, PA: Clinical and Laboratory Standards Institute; 2022.
 15. Bassetti M, Merelli M, Righi E, et al. Epidemiology, species distribution, antifungal susceptibility, and outcome of candidemia across five sites in Italy and Spain. J Clin Microbiol 2013;51(12):4167–4172.
 16. Lamoth F, Lockhart SR, Berkow EL, et al. Changes in the epidemiological landscape of invasive candidiasis. J Antimicrob Chemother 2018;73(Suppl 1):i4–i13.
 17. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med 2015;373(15):1445–1456.
 18. Rajput A, Rajput M, Parveen C, et al. Prevalence of *Candida* infections and their resistance profile among patients at tertiary care hospitals, North India. Int J Pharm Res Technol 2025;15(2):1107–1117.
 19. Saeed NK, Almusawi S, Al-Beltagi M. Candidemia chronicles: retrospective analysis of candidemia epidemiology, species distribution, and antifungal susceptibility patterns in Bahrain. World J Virol 2024;13(4):98839.
 20. Preece G, Bhola S, Davidson A, et al. Epidemiology, management and outcome of candidaemia in patients with diabetes. J R Coll Physicians Edinb 2022;52(4):292–297.
 21. Prasanna Kumar KP, Tejashree A. Genotyping of *Candida albicans* and comparison of its antifungal resistance pattern in the South Indian region. J Pure Appl Microbiol 2022;16(3):2123–2130.
 22. Deshkar S, Patil N, Amberkar S, et al. Identification and antifungal drug susceptibility pattern of *Candida auris* in India. J Glob Infect Dis 2022;14(4):131–135.
 23. World Health Organization. WHO Fungal Priority Pathogens List to Guide Research, Development and Public Health Action. Geneva: World Health Organization; 2022.
 24. Paul S, Shaw D, Joshi H, et al. Mechanisms of azole antifungal resistance in clinical isolates of *Candida tropicalis*. PLoS One 2022;17(7).
 25. Umamaheshwari S, Sumana MN. Retrospective analysis on distribution and antifungal susceptibility profile of *Candida* in clinical samples: a study from Southern India. Front Public Health 2023;11:1160841.
 26. Kumar A, Singh N, Das A, et al. Analyzing the distribution and antifungal susceptibility profile of *Candida* in various clinical samples: a retrospective study from a tertiary care hospital in North India. Cureus 2025;17(8).



Optimizing Catheter Removal in Amebic Liver Abscess: A Simplified Protocol for Faster Recovery

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ABSTRACT

Introduction: Percutaneous catheter drainage (PCD) is widely used in the management of large amebic liver abscesses (ALA). However, considerable variation exists in catheter removal practices, and concerns regarding residual cavities often result in prolonged catheterization and hospital stay. This study assessed whether an early catheter removal strategy could improve clinical outcomes without increasing complications.

Methods: In this prospective observational study, 40 adult patients with uncomplicated ALA requiring percutaneous drainage were enrolled. Catheter removal was attempted after 72 hours in patients demonstrating sustained clinical improvement, defined by resolution of fever and abdominal pain, declining leukocyte counts, and at least a 50% reduction in abscess cavity volume on ultrasonography. Patients were followed clinically and with serial ultrasound examinations to assess outcomes and the behavior of residual cavities.

Results: The study population was predominantly male (90%), with 62.5% having abscesses larger than 10 cm and 75% involving the right hepatic lobe. Early catheter removal was successfully achieved in 36 patients (90%) without procedure-related complications or mortality. The median duration of catheterization and hospital stay was 3 days each. Residual cavities were frequently observed on follow-up imaging (87.5% at 2 weeks and 82.5% at 1 month) but showed progressive reduction in size over time, decreasing from a mean of 6.5 ± 3.3 cm at discharge to 3.0 ± 1.7 cm at 1 month. Clinical recovery was rapid, with median resolution times of 2 days for fever and 3 days for abdominal pain.

Conclusion: Early removal of percutaneous catheters in patients with uncomplicated amebic liver abscess is safe and effective, significantly reducing catheter duration and length of hospitalization without increasing adverse outcomes. Although residual cavities are common, they regress gradually and do not justify prolonged catheter retention.

Keywords: Amebic liver abscess, Catheter drainage, Residual cavities.

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INTRODUCTION

Amebic liver abscess (ALA) represents the predominant extraintestinal manifestation of invasive amebiasis and continues to contribute significantly to morbidity in endemic regions.¹⁻⁶ Most patients respond well to antiamebic therapy, with nitroimidazoles such as metronidazole, tinidazole, and satranidazole forming the backbone of treatment.^{3,7} A particularly severe complication of amebic liver abscess is rupture into the pleural, peritoneal, or pericardial cavities, a situation that may necessitate surgical intervention or insertion of an intercostal chest drain.

Although uncomplicated and smaller abscesses are typically managed with pharmacotherapy alone, a notable proportion of patients require concurrent abscess drainage.⁷ Drainage is generally indicated in selected clinical scenarios such as left-lobe involvement, features suggestive of impending rupture, inadequate response to medical therapy, or diagnostic

uncertainty. Image-guided percutaneous interventions constitute the mainstay of abscess decompression, with percutaneous needle aspiration (PNA) generally reserved for smaller cavities and percutaneous catheter drainage (PCD) preferred for larger collections (>5 cm).⁸⁻¹¹

Considerable heterogeneity exists in catheter removal protocols, with proposed criteria ranging from sustained low daily drainage volumes to near-complete radiological resolution of the abscess cavity. The mean duration of PCD in these studies was 7–10 days.⁸⁻¹²

Persistent cavities are commonly identified on follow-up ultrasonography or computed tomography, leading to uncertainty regarding their clinical relevance. The exact prevalence of these residual cavities is unclear, and there is no standardized approach to their management.⁸ Prolonged catheter use may lead to complications such as catheter slippage, leakage, and fistula

formation and also increases the duration of hospitalization and costs.

We hypothesized that removing the PCD catheter as early as 3 days after clinical improvement and a 50% reduction in abscess volume would be effective in managing most cases of large, uncomplicated amebic liver abscesses (ALA). This approach may offer prompt symptomatic relief while minimizing the risk of complications.

The present study was designed to assess the safety and efficacy of early PCD removal in such patients and to evaluate the nature and clinical significance of any residual cavities.

METHODS

This was a single-center, prospective observational study carried out in the Department of Gastroenterology at Sawai Man Singh Medical College and Hospital, Jaipur, over a 14-month period spanning January 2024 to February 2025.

Adults aged 18 years or older with radiologically confirmed uncomplicated ALA who fulfilled predefined indications for drainage were consecutively enrolled. The diagnosis of amebic liver abscess (ALA) was established using a combination of clinical presentation (including fever, right upper quadrant pain, and tender hepatomegaly), characteristic imaging

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findings on ultrasonography or contrast-enhanced computed tomography, gross appearance of aspirated material, and supportive serological evidence of amebic infection, where available.

Percutaneous drainage was undertaken in patients with features suggestive of impending rupture, left-lobe abscesses, cavity size exceeding 5 cm, or persistent symptoms despite at least 72 hours of antiamebic therapy.

Patients were excluded if they had abscesses that did not require drainage or presented with complications such as pleural, bronchial, or pericardial fistulization, or peritonitis at initial assessment. Other exclusion criteria included uncorrectable coagulopathy, pregnancy, pyogenic liver abscess, human immunodeficiency virus (HIV) infection, or failure to provide informed consent.

Approval for the study protocol was obtained from the institutional ethics committee, and written informed consent was secured from all participants before enrollment. At admission, a detailed clinical history and physical examination were documented. Laboratory investigations included hemoglobin concentration, creatinine, total white blood cell count, markers of inflammation including C-reactive protein and erythrocyte sedimentation rate, as well as liver function tests, coagulation profile, blood glucose levels, viral serology, and amebic serology. Baseline abdominal ultrasonography was performed in all patients, with contrast-enhanced computed tomography obtained when clinically indicated, to define the number, location, and size of abscess cavities. The size of the abscess was assessed by measuring two perpendicular dimensions, and the cavity volume was subsequently calculated using a conventional geometric formula.¹³

All patients received oral or intravenous metronidazole at a dose of 40 mg/kg/day in three divided doses, along with concomitant injectable ofloxacin 200 mg twice daily. Antibiotic therapy was administered for a minimum of 7 days or until removal of the PCD catheter, whichever was longer, after obtaining at least one set of blood cultures. Metronidazole was continued for a total duration of 14 days.

Ultrasonography-guided Percutaneous Drainage of the Abscess

Ultrasonography-guided PCD was performed under aseptic conditions by the radiology team using a standard wire-

guided catheter insertion technique. An 8–12 French Malecot drainage catheter was positioned within the abscess cavity. Aspirated material was submitted for Gram staining, bacterial culture, and antibiotic susceptibility testing. The catheter was attached to a closed drainage system, and routine catheter maintenance protocols were followed. Following drainage, patients were monitored daily for clinical improvement (resolution of fever and abdominal pain) and for trends in inflammatory markers. Drain output was recorded every 24 hours.

Criteria for Catheter Removal

An attempt at catheter removal was made after a dwell time of 72 hours when patients showed sustained symptomatic improvement (defined by resolution of fever and abdominal pain) with falling leukocyte counts, and ultrasonography demonstrated a reduction of $\geq 50\%$ in cavity volume compared with baseline. Notably, persistence of a residual cavity on follow-up ultrasonography was not considered a contraindication to catheter removal, and no additional catheter manipulation or aspiration was performed. Patients not meeting removal criteria underwent repeat ultrasonographic assessment every 48 hours until eligibility for catheter removal was achieved. Potential complications, including bile leak or secondary infections, were actively evaluated and managed appropriately.

Follow-up and Assessment of Residual Cavities

Patients were discharged once clinically stable and afebrile, tolerating oral intake, and once PCD had been removed. Outpatient follow-up visits were scheduled at 1, 2, and 4 weeks after discharge. Ultrasonography was performed at each visit to document the evolution of residual cavities.

Statistical Analysis

Categorical variables describing demographic characteristics and clinical findings were expressed as percentages. Continuous variables were summarized using the mean with standard deviation or the median with interquartile range, depending on the distribution of the data. Changes in abscess size over time (at discharge, 2 weeks, and 4 weeks) were analyzed using the Friedman test for repeated measures. Data analysis was performed using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). A two-sided p -value < 0.05 was considered statistically significant.

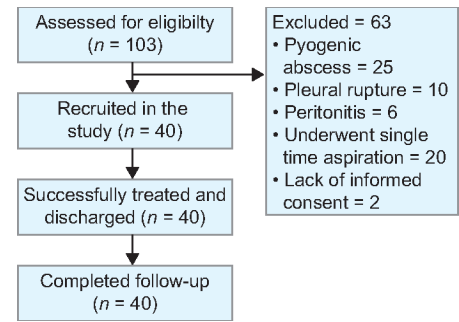


Fig. 1: Enrollment flowchart

RESULTS

During the study period, 103 patients were evaluated for eligibility, 63 were excluded for various reasons (Fig. 1), and 40 patients were ultimately enrolled. Most patients were male (36/40), and a substantial proportion (65%) had a history of significant alcohol use disorder. The mean age was 46.6 ± 10.5 years. Fever and tender hepatomegaly were almost universally present (95 and 100%, respectively). The majority of patients (80%) had solitary abscesses, while 8 (20%) had multiple abscesses (Table 1).

The indications for abscess drainage were impending rupture (8/40), left-lobe abscess (10/40), failure to respond to medical therapy after 72 hours (22/40), and >1 indication (30/40). Twenty-five patients (62.5%) had a baseline abscess diameter >10 cm, while only four patients (10%) had an abscess diameter <5 cm. In this subgroup, indications for abscess drainage included impending rupture (2 patients), left-lobe involvement (2 patients), and failure to respond to medical therapy after 72 hours (1 patient).

The majority of patients (38/40) underwent 1 PCD placement, and only 2 patients required 2 PCD placements. Their hospital stay was not significantly prolonged compared to that of patients who required only 1 PCD placement.

Catheter drainage was successfully performed in all patients without any major intraprocedural or immediate postprocedural complications. However, 2 patients experienced moderate-to-severe pain at the catheter site following the procedure and required intravenous analgesia. None of the catheter aspirate cultures demonstrated bacterial growth.

The time to resolution of fever and abdominal pain is detailed in Table 2. Most patients (36/40; 90%) demonstrated rapid clinical improvement, with normalization of symptoms occurring within 3 days of PCD insertion. In the remaining 4 patients (10%), symptom resolution occurred beyond 3 days following catheter placement. All patients

Table 1: Baseline characteristics

Variables	N = 40
Age (years) [#]	46.6 ± 10.5
Males, n (%)	36 (90%)
Alcoholics, n (%)	26 (65%)
Clinical features	
Fever, n (%)	38 (95%)
Duration of fever (days)*	10.0 (4.8–13.2)
Abdominal pain, n (%)	40 (100%)
Duration of pain (days)*	10.0 (5.0–16.0)
Diarrhea, n (%)	6 (15%)
Anorexia, n (%)	22 (55%)
Tender hepatomegaly, n (%)	40 (100%)
Comorbidities	
Diabetes mellitus, n (%)	4 (10.0%)
Investigations (at admission)	
Hemoglobin (gm/dL)*	9.2 (7.2–11.2)
Total leukocyte count (number/ μ L)*	13.8 (11.8–15.7)
Erythrocyte sedimentation rate (mm after 1 hour)*	50.0 (34.0–64.0)
C-reactive protein (mg/L)*	33.5 (18.0–53.3)
Bilirubin (mg/dL)	1.4 (1.3–2.1)
Abscess characteristics	
Single abscess, n (%)	32 (80%)
Multiple abscesses, n (%)	8 (20%)
Right lobe location, n (%)	30 (75%)
Left lobe location, n (%)	4 (10%)
Both lobe location, n (%)	6 (15%)
Mean abscess size (cm)*	10.0 (5.8–13.0)
Baseline abscess size >10 cm, n (%)	25 (62.5%)
Indication of abscess drainage	
Left lobe abscess, n (%)	10 (25.0%)
Impending rupture, n (%)	8 (20%)
Size >5 cm, n (%)	36 (90%)
Lack of response to medical therapy, n (%)	22 (55%)
>1 indication, n (%)	30 (75%)

*Median (interquartile range); [#]Mean ± standard deviation

who improved within the initial 3-day period had an uncomplicated hospital course and were discharged without adverse events.

Patients with delayed clinical improvement underwent further assessment for potential local or systemic complications. A persistent biliary leak was identified in 1 patient and was successfully managed with endoscopic retrograde cholangiopancreatography, sphincterotomy, and placement of a temporary plastic stent. The remaining 3 patients continued to have fever, with abscess volume failing to decrease by >50% from baseline. All 3 patients subsequently improved with continued drainage and medical therapy, without the need for any additional invasive intervention.

Early percutaneous catheter removal was therefore successful in 36 patients (90%). The

median time to catheter removal was 3 days [interquartile range (IQR), 2–5 days], and the median length of hospital stay was 3 days (IQR, 2–7 days). Notably, all patients who underwent successful early catheter removal demonstrated a drainage output of <20 mL on day 3.

Residual abscess cavities were commonly observed, with 38 of 40 patients (95%) having residual cavities at the time of PCD removal. Serial imaging revealed that residual cavities persisted in the majority of patients, with 87.5% (35/40) showing persistent cavities at the 2-week follow-up and 82.5% (33/40) at 1 month. However, there was a significant and progressive reduction in abscess size over time, from a mean of 6.5 ± 3.3 cm at discharge to 4.9 ± 2.7 cm at 2 weeks and further to 3.0 ± 1.7 cm at 1 month ($p < 0.001$).

No patients were lost to follow-up, and none showed an increase in abscess size after PCD removal. There were no catheter site-related complications, no rehospitalizations, and no deaths. No patient developed a percutaneous fistula after catheter removal, and no patient developed concomitant gastrointestinal (GI) bleeding. No patient required repeat drainage, catheter reinsertion, or surgical intervention at any point.

DISCUSSION

Amebic liver abscess constitutes the predominant extraintestinal presentation of amebiasis.¹³ In North India, the disease predominantly affects males from lower socioeconomic strata, with a strong association with chronic alcohol consumption.¹⁴ Management of amebic liver abscess (ALA) is largely medical in nature, with treatment predominantly based on nitroimidazole therapy.^{3,7} Recent studies indicate that, in uncomplicated amebic liver abscess, nitazoxanide demonstrates therapeutic effectiveness comparable to metronidazole, while being better tolerated and providing the additional advantage of concurrent luminal eradication, which may help lower recurrence rates.¹⁵

While the criteria for initiating percutaneous drainage in ALA are relatively well defined, there remains no consensus on the most appropriate timing for catheter removal or on how residual cavities identified on imaging should influence management decisions. Several earlier studies, largely involving patients with ALA, have proposed differing criteria to guide catheter removal. Rajak et al. proposed catheter removal only after patients demonstrated sustained clinical recovery, improvement in inflammatory parameters, persistently low drain output, and near-total radiological resolution of the abscess cavity. Using this approach, catheter duration ranged from 3 to 15 days, with hospitalization extending up to 24 days.⁹

Similarly, a comparative study from North India by Singh et al. advised maintaining catheter drainage until output had ceased for several days, with repeated ultrasonographic assessments guiding further management. Residual cavities prompted saline flushing, aspiration, and catheter manipulation when loculations were present, resulting in a mean time to clinical relief of more than 8 days and a mean hospital stay exceeding 20 days.⁸ A study from Punjab and a large liver unit series by Jindal et al. adopted comparable drainage-based criteria, recommending catheter removal after sustained clinical improvement accompanied by minimal daily output.^{12,16}

Table 2: Outcomes

Variables	N = 40
Time until the normalization of	
Fever (days)*	2.0 (1.0–3.0)
Abdominal pain (days)*	3.0 (2.0–5.0)
Quantity of fluid drained (mL)*	287.5 (75.0–752.5)
Time until the pigtail removal (days)*	3.0 (2.0–5.0)
Complications	
No complication seen, n (%)	38 (95.0%)
Moderate-to-severe pain at catheter site, n (%)	2 (5%)
Continuous bile leak, n (%)	1 (2.5%)
Catheter removal status at 72 hours	
Met predefined criteria for catheter removal, n (%)	36 (90%)
Did not meet criteria at 72 hours, n (%)	4 (10%)
Reasons for delayed eligibility	
Bile leak, n (%)	1 (2.5%)
Persistent fever with <50% volume reduction, n (%)	3 (7.5%)
Duration of hospitalisation (days)*	3.0 (2.0–7.0)
Residual abscesses	
At the time of pigtail removal, n/N (%)	38/40 (95%)
Follow-up at 2 weeks after discharge, n/N (%)	35/40 (87.5%)
Follow-up at 1 month after discharge, n/N (%)	33/40 (82.5%)

*Median (interquartile range)

Despite this, reported catheter duration and hospital stay remained longer than in the present study.^{12,16}

More recently, a multicenter prospective study by Goyal et al. evaluated catheter removal using a composite of sustained clinical recovery and low drainage output, rather than complete radiological resolution.¹⁷ Using this framework, catheter removal was achieved after a median of 5 days, even though residual cavities persisted in the majority of patients. This observation supports the broader principle that residual imaging abnormalities, in isolation, should not mandate prolongation of catheter drainage.¹⁷

In contrast, our study employed a simplified, clinically driven protocol that prioritized early symptomatic improvement combined with a predefined reduction in abscess volume, without requiring a minimum period of negligible drain output or radiological resolution. Using this approach, the median catheter duration was limited to only 3 days, which is substantially shorter than that reported in earlier studies.^{8,9,12,16,17} In our experience, the majority of drainage occurs within the first few days of PCD placement, after which output declines sharply despite the persistence of residual cavities. This observation led us to question the physiological necessity of prolonged catheter retention and to systematically evaluate the safety and outcomes of an early catheter removal strategy.

This streamlined strategy translated into a markedly shorter median hospital stay of 3 days, compared with the 9–20 day range reported in the meta-analysis by Cai et al.¹⁸ Early discharge was feasible because decisions regarding catheter removal and hospitalization were guided by clinical recovery rather than persistence of residual cavities on imaging, allowing safe transition to outpatient follow-up once patients stabilized.

Notably, none of the patients in our cohort required catheter manipulation or repositioning, even in the presence of multiloculated cavities. Prior studies have demonstrated that single-catheter drainage is often sufficient in multiloculated ALA, with internal septations representing necrotic inflammatory stroma rather than true compartmentalization.^{19,20} Our observations further support this concept, indicating that aggressive interventional strategies are rarely necessary in uncomplicated disease.

Residual cavities were frequently observed in our cohort but proved to be clinically insignificant. Serial ultrasonography demonstrated progressive regression of these cavities without any increase in size or recurrence of symptoms. At 1-month follow-up, approximately 15% of patients showed complete radiological resolution, while the remaining 85% continued to demonstrate gradual reduction in cavity size. The mean abscess diameter decreased significantly from 6.5 ± 3.3 cm at discharge

to 4.9 ± 2.7 cm at 2 weeks and further to 3.0 ± 1.7 cm at 1 month ($p < 0.001$). Some residual cavities may eventually evolve into simple hepatic cysts that can persist indefinitely.²¹

Importantly, support for using partial radiological resolution as a clinically meaningful endpoint also comes from earlier prospective observations on the natural history of amebic liver abscess. In a large longitudinal cohort, clinical and hematological recovery occurred rapidly, whereas sonographic resolution was substantially delayed and often incomplete for several months.²² A subset of patients demonstrated an early reduction in cavity volume to approximately 50% of baseline, followed by a prolonged phase of slow radiological regression without relapses or the need for additional therapy. These findings indicate that once a critical reduction in abscess volume is achieved, subsequent cavity resolution follows a benign course, thereby providing biological justification for the 50% volume reduction threshold used in our protocol.

Given that ALA is predominantly a medically managed condition, the primary role of drainage is to accelerate clinical recovery and prevent complications such as impending rupture.^{3,7} Complete radiological resolution is therefore not essential for successful management. In this context, the threshold of a 50% reduction in cavity volume used in our protocol was sufficient to ensure safety, particularly in patients with larger abscesses.

Key strengths of this study include its prospective design, exclusive inclusion of confirmed ALA cases, and complete follow-up, which minimized heterogeneity seen in earlier studies that included abscesses of mixed or uncertain etiology. In addition, catheter removal was guided primarily by clinical improvement rather than radiological resolution. Despite residual cavities in most patients, there was no need for rehospitalization, repeat drainage, or surgery, and hospital stay was short.

However, certain limitations must be acknowledged. The relatively small sample size and lack of a comparator group limit generalizability, as our protocol was not directly contrasted with alternative catheter management strategies. Additionally, as a tertiary referral center, many patients had received antibiotics prior to presentation, which may have influenced outcomes.²³ Larger multicenter randomized controlled trials are therefore required to validate the routine use of early catheter removal in the management of amebic liver abscess.

CONCLUSION

In conclusion, early removal of percutaneous catheters in patients with uncomplicated ALA was safe and effective in most cases, facilitated earlier discharge, and reduced the length of hospitalization. Residual cavities were frequently present at the time of catheter removal but followed a benign clinical course and did not require additional intervention.

INFORMED CONSENT

Informed consent was obtained prior to enrollment from the included patients.

ETHICAL APPROVAL

Ethical approval was obtained from the institutional review board prior to initiation of patient enrollment.

REFERENCES

1. Ravdin JI. Prevalence of *Entamoeba histolytica* infection. In: Ravdin JI, editor. *Amebiasis: Human Infection by Entamoeba histolytica*. New York: Wiley-Liss; 1988. pp. 93–105.
2. Stanley SL Jr. *Amoebiasis*. *Lancet* 2003;361(9362):1025–1034.
3. Haque R, Huston CD, Hughes M, et al. Amebiasis. *N Engl J Med* 2003;348:1565–1573.
4. Salles JM, Moraes LA, Salles MC. Hepatic amebiasis. *Braz J Infect Dis* 2003;7:96–110.
5. Kantor M, Abrantes A, Estevez A, et al. *Entamoeba histolytica*: updates in clinical manifestation, pathogenesis, and vaccine development. *Can J Gastroenterol Hepatol* 2018;2018:4601420.
6. Ghosh S, Sharma S, Gadpayle AK, et al. Clinical, laboratory, and management profile in patients of liver abscess from northern India. *J Trop Med* 2014;2014:142382.
7. Salles JM, Salles MJ, Moraes LA, et al. Invasive amebiasis: an update on diagnosis and management. *Expert Rev Anti Infect Ther* 2007;5:893–901.
8. Singh O, Gupta S, Moses S, et al. Comparative study of catheter drainage and needle aspiration in management of large liver abscesses. *Indian J Gastroenterol* 2009;28:88–92.
9. Rajak CL, Gupta S, Jain S, et al. Percutaneous treatment of liver abscesses: needle aspiration versus catheter drainage. *AJR Am J Roentgenol* 1998;170:1035–1039.
10. Stain SC, Yellin AE, Donovan AJ, et al. Pyogenic liver abscess. Modern treatment. *Arch Surg* 1991;126:991–996.
11. Zerem E, Hadzic A. Sonographically guided percutaneous catheter drainage versus needle aspiration in the management of pyogenic liver abscess. *AJR Am J Roentgenol* 2007;189:W138–W142.
12. Jindal A, Pandey A, Sharma MK, et al. Management practices and predictors of outcome of liver abscess in adults: a series of 1630 patients from a liver unit. *J Clin Exp Hepatol* 2021;11(3):312–320.
13. Juimo AG, Gervéz F, Angwafo FF. Extraintestinal amebiasis. *Radiology* 1992;182:181–183.
14. Dhaked GK, Agarwal VK, Dhaked S, et al. Demographic, clinical, laboratory and management profile in patients of amoebic liver abscess from Northern India. *Trop Gastroenterol* 2022;43(1):25–31.
15. Goel V, Jain A, Sharma G, et al. Evaluating the efficacy of nitazoxanide in uncomplicated amoebic liver abscess. *Indian J Gastroenterol* 2021;40:55–60.
16. Singh P, Tapasvi C, Kaur R, et al. Prospective randomized comparison of ultrasound-guided percutaneous needle aspiration with percutaneous catheter drainage of liver abscesses. *J Med Sci* 2019;39.
17. Goyal A, Dhaliwal HS, Nampoothiri RV, et al. Percutaneous catheter drainage of uncomplicated amoebic liver abscess: prospective evaluation of a clinical protocol for catheter removal and the significance of residual collections. *Abdom Radiol (NY)* 2021;46(7):2855–2864.
18. Cai YL, Xiong XZ, Lu J, et al. Percutaneous needle aspiration versus catheter drainage in the management of liver abscess: a systematic review and meta-analysis. *HPB (Oxford)* 2015;17:195–201.
19. Baijal SS, Agarwal DK, Roy S, et al. Complex ruptured amoebic liver abscesses: the role of percutaneous catheter drainage. *Eur J Radiol* 1995;20:65–67.
20. Bernardino ME, Berkman WA, Plemmons M, et al. Percutaneous drainage of multiseptated hepatic abscess. *J Comput Assist Tomogr* 1984;8:38–41.
21. Ralls PW, Quinn MF, Boswell WD Jr, et al. Patterns of resolution in successfully treated hepatic amoebic abscess: sonographic evaluation. *Radiology* 1983;149:541–543.
22. Sharma MP, Dasarathy S, Sushma S, et al. Long-term follow-up of amebic liver abscess: clinical and ultrasound patterns of resolution. *Trop Gastroenterol* 1995;16(3):24–28.
23. Khim G, Em S, Mo S, et al. Liver abscess: diagnostic and management issues found in the low resource setting. *Br Med Bull* 2019;132:45–52.

Understanding Obesity through a Public Health Lens

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ABSTRACT

Obesity is a complex and chronic public health challenge that reflects deep-rooted social, economic, and environmental determinants rather than solely individual choices. Its global prevalence has risen sharply over recent decades, affecting more than one in eight people worldwide, with a growing burden in low- and middle-income countries. This paper explores obesity as a complex and growing public health challenge that extends beyond individual behavior. It highlights the social, economic, and environmental factors driving the epidemic, with a focus on the Indian context where undernutrition and overnutrition coexist. Recent research, population data, and policy reports were reviewed to analyze current trends, determinants, and the limitations of traditional measures such as the body mass index (BMI). Particular attention was given to South Asian populations, who are prone to obesity-related diseases at lower BMI thresholds. Global obesity rates have risen sharply, now affecting more than one in eight people, with a marked increase in low- and middle-income countries. In India, urbanization, sedentary lifestyles, and the easy availability of ultraprocessed foods have accelerated the problem across all age groups. The COVID-19 pandemic worsened the situation through reduced physical activity, stress, and food-system disruptions. Conventional BMI measures underestimate true metabolic risk in South Asians, underscoring the need for more nuanced diagnostic approaches. Obesity adds significantly to the burden of noncommunicable diseases and demands multisectoral action through healthier food policies, physical activity promotion, and early prevention. Integrating these strategies into health systems is vital to reduce its long-term impact.

Keywords: Body mass index, Noncommunicable diseases, Nutrition transition, Obesity, Public health.

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INTRODUCTION

The escalating prevalence of obesity worldwide necessitates a fundamental reevaluation of its underlying causes and appropriate public health responses. For too long, the discourse surrounding obesity has narrowly focused on individual dietary choices and physical activity levels, implicitly assigning blame to those affected. However, a critical public health perspective reveals that obesity is far more complex than a simple matter of personal willpower. The World Health Organization (WHO) defines obesity as “abnormal or excessive fat accumulation that may impair health.”¹ This definition, while foundational, must be understood within a broader context that recognizes obesity as a “complex, heterogeneous, chronic, and progressive disease.” However, obesity is a complex, chronic disease driven by systemic issues economic, social, and political rather than merely a consequence of individual choices.²

The global burden of obesity presents an alarming trajectory. In 2016, over 1.9 billion adults were classified as overweight, with 650 million of these categorized as obese. Projections indicate that by 2030, more than 1 billion people worldwide will be obese.³ More recent data suggest that obesity

now affects more than one in eight people globally.^{1,4} A particularly concerning aspect of this epidemiological shift is the rapid increase in low- and middle-income countries (LMICs). This trend is accompanied by significant disparities in prevalence across different socioeconomic strata, notably affecting women more profoundly.⁵ The prevalence of childhood obesity has also surged, with an estimated 39 million children under five being overweight or obese in 2022. Alarming, obesity rates among adolescents have quadrupled since 1980.^{6,7} According to the National Family Health Survey (NFHS-5, 2019–21), 24% of women and 22.9% of men aged 15–49 years were overweight or obese, a notable increase from previous surveys in India.⁸ The Comprehensive National Nutrition Survey (CNNS) of children and adolescents further revealed that approximately 5% of children aged 5–19 years were obese.⁹

This nutritional duality, where undernutrition and overnutrition coexist within the same communities and even households, creates a highly intricate policy environment. Interventions designed to address one form of malnutrition could inadvertently worsen the other if not meticulously planned and implemented. For instance, strategies focused on increasing

calorie availability to combat undernutrition might inadvertently exacerbate obesity if they promote access to cheap, unhealthy, calorie-dense but nutrient-poor foods. This situation demands highly nuanced, integrated nutrition policies that address both ends of the malnutrition spectrum simultaneously. The focus must shift toward ensuring access to nutrient-dense, healthy food for all, rather than merely focusing on calorie sufficiency. Such integrated strategies are crucial for developing effective and sustainable responses to India's unique public health landscape.

MATERIALS AND METHODS

A systematic and comprehensive search of the literature was conducted across major electronic databases, including PubMed and Google Scholar, to capture gray literature and policy documents. The search covered studies published between 2010 and 2025, ensuring inclusion of contemporary perspectives shaped by recent developments such as urbanization, lifestyle changes, and the COVID-19 pandemic. Keywords and combinations such as “obesity,” “public health,” “determinants,” “India,” “policy response,” and “epidemiology” were used. Reference lists of key papers were also screened to identify additional relevant sources.

Studies were included if they addressed obesity from a population or policy perspective, examined determinants such as diet, physical activity, environment, or socioeconomic context, or discussed frameworks for prevention and management. Articles focusing solely on pharmacological or surgical interventions, or those unrelated to human populations, were excluded.

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RESULTS

Critical Examination of Obesity Definition and Diagnosis

Body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters (kg/m^2), remains the most commonly used indicator for classifying overweight and obesity, with a BMI of $\geq 30 \text{ kg}/\text{m}^2$ generally considered obese.¹⁰ For South Asians, the cut-off values for central obesity and related anthropometric indicators are generally lower due to their higher risk of cardiometabolic diseases at lower body fat levels. The recommended values are as follows:¹¹

- Stage 1 obesity is characterized by increased adiposity ($\text{BMI} \geq 23 \text{ kg}/\text{m}^2$) without noticeable impairment of organ function or limitations in daily activities. Stage 2 obesity represents a more advanced state with generalized and abdominal fat accumulation, adversely affecting physical and organ functions, leading to restrictions in day-to-day activities and the development of comorbid conditions.¹²
- The classification of stage 2 obesity requires a $\text{BMI} \geq 23 \text{ kg}/\text{m}^2$ (as per South Asian cut-offs, where $\geq 23 \text{ kg}/\text{m}^2$ indicates overweight and $\geq 25 \text{ kg}/\text{m}^2$ indicates obesity), along with at least one of the following indicators of excess adiposity:
 - Waist circumference (WC): $\geq 90 \text{ cm}$ for men, $\geq 80 \text{ cm}$ for women.
 - Waist-to-hip ratio (WHR): >0.90 for men, >0.80 for women.
 - Body fat percentage: $>25\%$ in men, $>32\%$ in women.

Additionally, the presence of one or more symptoms reflecting functional limitations in daily activities or one or more obesity-related comorbidities is required to support the diagnosis of stage 2 obesity.

Body mass index is a simple and widely used tool to classify individuals based on weight relative to height, but it has several limitations. BMI cut-offs were originally developed based on European populations and may not accurately capture obesity-related risks in other ethnic groups, such as South Asians, who face higher health risks at lower BMI levels. It also overlooks factors like age, sex, body composition, and fitness level, limiting its effectiveness as a standalone tool for assessing individual health risk. The primary weakness in BMI measurement is that it does not differentiate between fat mass and muscle mass, which can lead to misclassification—muscular individuals may be labeled as overweight or obese, while people with high body fat but low muscle mass (e.g., in sarcopenic obesity) may fall within a “normal” BMI range. BMI also does not reflect

fat distribution, particularly harmful visceral fat around internal organs, which is more strongly associated with metabolic risks. This is particularly relevant for non-White populations, such as Asians, who may experience obesity-related health consequences at lower BMI ranges due to higher visceral fat accumulation, a phenomenon known as the Yajnik-Yudkin (Y-Y) paradox.¹³

To overcome the primary weakness of BMI as an assessment tool for obesity, assessing body compartments through multi- or compartmental models is essential for accurately understanding and managing obesity, far beyond what simple metrics such as BMI can reveal. Classic two-compartment models distinguish between fat mass and fat-free mass, but they often mask key differences in the distribution of water, bone, and protein. More advanced models such as the six-compartment model using *in vivo* neutron activation analysis offer the precision necessary to evaluate total body fat more reliably, serving as a gold standard for comparing other methods (Fig. 1).¹⁴

The redefinition of treatment success is a profound implication of this new diagnostic paradigm. The primary goal of care when treating obesity is health gain, with weight loss serving as a surrogate marker of treatment effectiveness. This means that success in management should be assessed by the improvement or reversal of signs and symptoms, and the regaining or improvement of functions, rather than solely by measures of weight loss.¹⁵ If health systems continue to prioritize BMI reduction as the sole measure of success, they risk overlooking meaningful health improvements in patients who do not achieve large weight losses, or conversely, failing to address underlying health issues in those who lose weight but still experience organ dysfunction.

Evolving Diagnostic Paradigms: Toward Clinical and Preclinical Obesity

Recognizing the limitations of BMI, a more accurate and clinically relevant approach to diagnosing obesity is emerging.¹⁶ A new diagnostic paradigm proposed by the Lancet Diabetes and Endocrinology Commission moves beyond BMI to focus on other measures of body fat and objective signs and symptoms of ill health. This new approach introduces two distinct categories: preclinical and clinical obesity. Preclinical obesity is a condition where an individual has excess body fat but does not yet show signs of illness or organ dysfunction. These individuals can carry out daily activities normally, but they are at a higher risk of progressing to clinical obesity and developing conditions such as cardiovascular disease, type 2 diabetes, and certain cancers. In contrast, clinical obesity is recognized as a chronic disease in which obesity itself causes noticeable symptoms and reduced organ or tissue function. People with clinical obesity may experience breathlessness, joint pain, or metabolic abnormalities, and may have dysfunctions in systems such as the heart, lungs, kidneys, or reproductive organs, impacting their quality of life and daily functioning. This distinction is vital for tailoring interventions and resource allocation more effectively.

Table 1 visually demonstrates how relying on BMI alone can lead to misclassification, either overdiagnosing individuals with high muscle mass or underdiagnosing those with excess fat but a lower BMI. It clearly illustrates the two new categories - preclinical and clinical obesity and how they are determined by both body fat and health status. However, there is another paradigm is metabolically healthy obesity (MHO). It refers to a condition in which individuals classified as obese

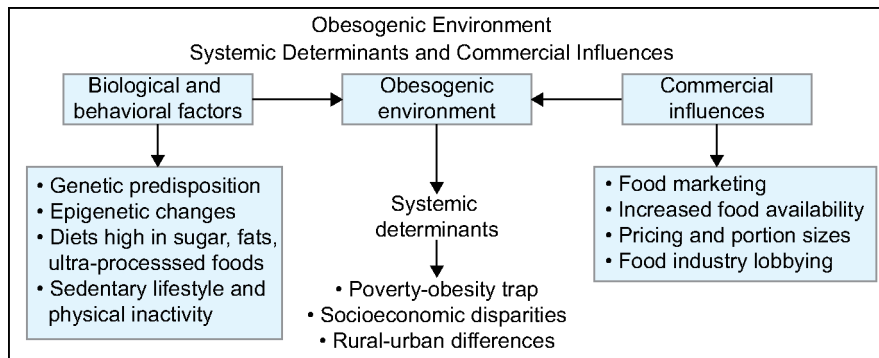
One compartment model	Body weight					
Two compartment model	Fat mass (FM)		Fat free mass (FFM)			
Three compartment model*	Fat mass (FM)	Total body water (TBW)	Fat free dry mass (FFDM) (BMC + metabolic tissue)			
Three compartment model**	Fat mass (FM)	Bone mineral content (BMC)	Lean tissue mass (LTM) (TBW + metabolic tissue)			
Four compartment model	Fat mass (FM)	Total body water (TBW)	Bone mineral content (BMC)	Metabolic tissue		
Five compartment model	Fat mass (FM)	Total body water (TBW)	Bone mineral content (BMC)	Soft tissue mineral	Residual tissue	
Six compartment model	Fat mass (FM)	Total body water (TBW)	Bone mineral content (BMC)	Soft tissue mineral	Glycogen	Protein

Fig. 1: Body compartment model for obesity assessment¹⁴. *Siri model; **DXA model

Table 1: Traditional vs new clinical obesity diagnosis¹⁶

	BMI (kg/m ²)	Excess body fat	Muscle mass	Signs/symptoms?*	Old diagnosis	New diagnosis
1	28.2	Yes	Normal/Low	No	Overweight	Underdiagnosis of obesity (Preclinical obesity)
2	30.1	No	High	No	Obesity	Overdiagnosis of obesity (No obesity)
3	36.2	Yes	Normal/Low	No	Obesity	Preclinical obesity
4	36.2	Yes	Normal/Low	Yes	Obesity	Clinical obesity
5	23.7	No	Normal/High	No	No obesity	No obesity
6	28.8	No	Normal	No	Overweight	No obesity
7	28.8	Yes	Normal/Low	No	Overweight	Preclinical obesity
8	32.4	No	High	No	Obesity	No obesity
9	39.2	Yes	Normal/Low	No	Obesity	Preclinical obesity
10	39.2	Yes	Normal/Low	Yes	Obesity	Clinical obesity

*Signs and symptoms of organ dysfunction due to excess body fat

**Fig. 2:** Obesogenic environment (Illustrated based on the text)

based on body mass index (BMI) or body fat percentage do not exhibit the typical metabolic abnormalities associated with obesity, such as insulin resistance, high blood pressure, dyslipidemia, or elevated blood glucose levels. These individuals generally have a favorable metabolic profile, including normal insulin sensitivity, healthy lipid levels, and absence of metabolic syndrome, and may possess less visceral fat despite having overall high adiposity. However, MHO is considered a transient and potentially unstable state, as many individuals may transition to a metabolically unhealthy status over time. It signals a necessary shift in how obesity is identified and managed at a population level, moving toward a more precise and health-outcome-oriented approach.

Obesogenic Environment: Systemic Determinants and Commercial Influences

While environmental and systemic factors play a dominant role in the obesity epidemic, biological and behavioral elements provide a foundational context. Obesity has a strong genetic component, with twin, family, and adoption studies estimating that 40–70% of variation in BMI is heritable.^{17–19} Furthermore, epigenetic changes, particularly those occurring *in utero* due to maternal obesity

or malnutrition (as posited by the Barker hypothesis), can predispose individuals to obesity and related metabolic diseases later in life. Sedentary behavior, excessive screen time, irregular sleep patterns, and stress-related eating are significant contributors. Diets rich in sugar, saturated fats, and ultraprocessed foods are prevalent in both urban and rural settings.^{20,21}

Socioeconomic status (SES) profoundly influences the prevalence and trajectory of obesity. While historically associated with affluence, obesity rates are now increasingly observed in lower-income and rural populations, often due to the greater availability and affordability of cheap, unhealthy foods. This creates a paradox where poverty, traditionally linked to undernutrition, now also drives obesity, forming a “poverty-obesity trap.”²² This is particularly evident in LMICs, where more than half of the global rise in mean BMI between 1985 and 2017 was attributed to increases in rural areas, with BMI rising faster in rural than urban settings (Fig. 2).²³

The food industry’s aggressive marketing of calorie-dense, nutrient-poor products, particularly targeting children through digital media, is a major concern. These commercial determinants include increased food availability, strategic food marketing, pricing

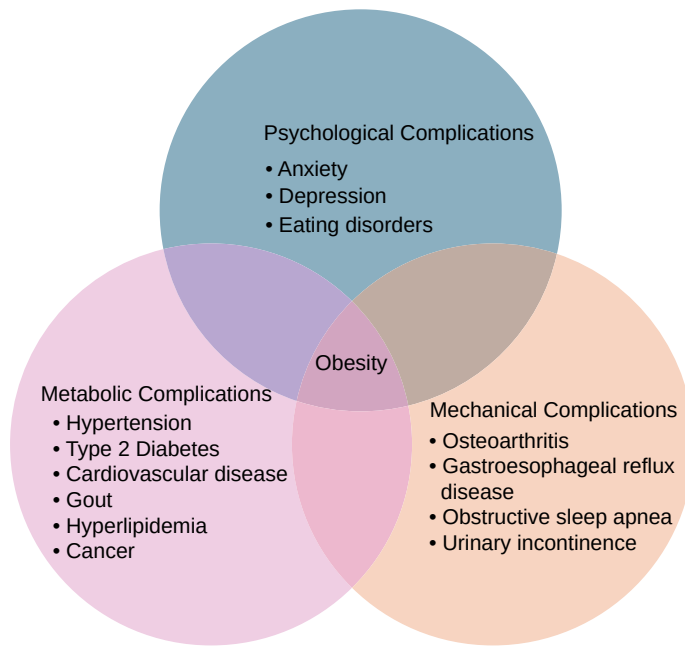
strategies that favor unhealthy options, ever-expanding portion sizes, high energy density, and the widespread ultraprocessing of foods and artificial sweeteners.^{24–26} The influence of large commercial interests extends beyond marketing to actively shape the policy environment. “Food industry lobbying against regulations” is identified as a significant challenge.²⁷ This consistent emphasis across multiple authoritative sources indicates that commercial entities are not just influencing individual choices but are actively shaping the obesogenic environment and hindering effective public health policy.

Childhood and Adolescent Obesity: A Public Health Catastrophe

Childhood and adolescent obesity represent an urgent public health concern due to its rapid escalation and profound long-term implications for future generations. The rates of obesity among adolescents have quadrupled since 1980.²⁸ This trend is particularly alarming because overweight children are highly likely to remain obese into adulthood, leading to the earlier onset of chronic diseases typically associated with adult obesity. The factors contributing to childhood obesity are complex, involving a mix of genetic susceptibility, poor dietary habits, insufficient physical activity, and adverse socio-environmental influences. Early-life exposures play a critical role; for instance, epigenetic changes occurring *in utero* due to maternal obesity or malnutrition (as posited by the Barker hypothesis) can predispose individuals to obesity later in life. Maternal health, including prepregnancy weight, gestational diabetes, and nutritional status, plays a crucial role in shaping fetal metabolism and future obesity risk. In infancy, breastfeeding, timely and appropriate complementary feeding, and avoiding rapid weight gain are protective. As children grow, dietary habits, physical activity levels, screen

Table 2: Levels of prevention in obesity as per Leavell and Clark model

Level of prevention	Goal	Key strategies
Primordial prevention	Prevent the development of obesity risk factors	Urban planning for walkability and cycling, exclusive breastfeeding, food policy reforms (e.g., sugar tax, trans-fat ban, front-of-pack labeling), strict regulation of food advertising (especially to children)
Primary prevention	Prevent the onset of obesity in healthy individuals	Community awareness campaigns, school-based physical activity and nutrition programs
Secondary prevention	Detect early risk and prevent progression to clinical obesity	Routine/opportunistic screening for high BMI, waist circumference, and early signs of metabolic disorders
Tertiary prevention	Manage established obesity and prevent complications	Pharmacotherapy, bariatric surgery, clinical management to improve quality of life

**Fig. 3:** Complications of obesity

time, and family and school environments significantly influence their weight trajectory. During adolescence, hormonal changes, increased autonomy, peer influence, mental health issues, and body image concerns further impact behaviors related to food and physical activity.^{29–31} Since obesity during childhood and adolescence often tracks into adulthood, leading to chronic diseases such as diabetes and cardiovascular conditions, early and sustained interventions are vital.

Impact of COVID-19 on Obesity

The COVID-19 pandemic significantly worsened the global obesity crisis. Lockdowns, school closures, and restrictions on movement led to reduced physical activity and increased sedentary behavior, especially among children and adolescents. Simultaneously, increased stress, anxiety, and disrupted routines contributed to emotional eating and greater consumption of unhealthy, processed foods. Limited access to fresh produce, irregular meal patterns, and screen-time overload further fueled

weight gain.³² Health services were diverted toward pandemic response, disrupting routine obesity prevention, screening, and management efforts. Moreover, people with obesity faced higher risks of severe COVID-19 outcomes, including hospitalization, ICU admission, and mortality, highlighting the need for integrated obesity care in future health preparedness strategies.

Consequences of Obesity

Obesity significantly contributes to the global burden of noncommunicable diseases, increasing the risk of type 2 diabetes, hypertension, heart disease, stroke, MASLD, and chronic kidney disease. Visceral fat promotes insulin resistance and inflammation, while excess weight stresses joints, leading to osteoarthritis. Obesity also impacts reproductive health, causing PCOS, infertility, and pregnancy complications. Beyond physical health, obesity affects mental well-being, with stigma and discrimination contributing to depression, anxiety, and low self-esteem. This bidirectional relationship

between obesity and depression highlights its profound impact on both physical and psychological health, ultimately reducing overall quality of life (Fig. 3).^{33–37}

The economic burden of obesity is substantial, imposing significant strain on healthcare systems and national economies worldwide. Beyond direct medical expenditures, there are considerable indirect costs, including loss of productivity due to illness, disability, and premature mortality. Globally, the current estimated economic costs of obesity are approximately 2.8% of the world's gross domestic product (GDP). In low-resource settings, such as India, the financial impact is particularly severe, as out-of-pocket expenditure for healthcare services further exacerbates financial stress on individuals and families.³⁸

Prevention of Obesity

Obesity prevention requires early and sustained efforts through healthy eating, regular physical activity, behavior change, and supportive environments. In children, family-based dietary changes, reduced screen time, and daily exercise are essential, while adults benefit from portion control, whole foods, and consistent physical activity. Promoting lifelong healthy habits is key to reducing obesity risk.³⁹ Breastfeeding plays a critical role in preventing childhood obesity, offering both immediate and long-term protective effects.⁴⁰ Exclusive breastfeeding for the first six months, as recommended by the WHO and UNICEF, and continued breastfeeding along with appropriate complementary foods, has been shown to lower the risk of obesity and related metabolic disorders later in childhood and adolescence (Table 2).^{41,42}

Various national and global initiatives have been launched to combat obesity. In India, programs such as Poshan Abhiyaan (combating malnutrition through awareness), Eat Right India (promoting healthy eating and food safety), Fit India Movement (encouraging physical activity), and Khelo India (enhancing sports infrastructure) represent significant efforts. Globally, frameworks such as the WHO

Table 3: Government initiatives to combat obesity in India

Program/initiative	Ministry/agency	Focus area
NP-NCD (formerly NPCDCS)	Ministry of Health and Family Welfare	Prevention, early detection, and management of NCDs
Fit India Movement (2019)	Ministry of Youth Affairs and Sports	Promoting physical fitness and active lifestyle
Poshan Abhiyaan	Ministry of Women and Child Development	Improving nutritional outcomes among children and women
School Health Program	MoHFW and MoE (under Ayushman Bharat)	Health education, screening, and promotion in schools
Eat Right India Movement	FSSAI	Safe, healthy, and sustainable food choices
Khelo India Program	Ministry of Youth Affairs and Sports	Sports infrastructure and fitness programs for youth
Yoga and Wellness Initiatives	Ministry of AYUSH	Promotion of yoga and traditional wellness practices

“Best Buys,” Global Syndemic Commission recommendations, and the WHO Acceleration Plan to Stop Obesity provide evidence-based policy guidelines, emphasizing multisectoral and equity-centered approaches (Table 3).⁴³

Despite these initiatives and the existence of comprehensive prevention strategies, a critical assessment reveals a significant gap between policy recommendations and real-world impact. Low awareness about the health risks of obesity and resistance to behavior change are significant barriers, often compounded by cultural norms and family practices.⁴⁴ The pervasive influence of the food industry through lobbying and dissemination of misleading information complicates public understanding and policy enforcement. A unique challenge in countries like India is the coexistence of undernutrition and obesity, representing a double burden of malnutrition that requires nuanced, context-specific approaches.⁴² A comprehensive public health approach to obesity requires interventions across multiple levels of prevention.³⁹

CONCLUSION AND RECOMMENDATIONS

The global obesity epidemic is not merely a matter of individual responsibility or a cosmetic concern; it is a complex societal issue deeply rooted in globalization, systemic inequity, and profoundly unhealthy environments. This chronic disease drives a large proportion of the global noncommunicable disease burden, posing a significant threat to economic development, healthcare sustainability, and the overall quality of life worldwide. Healthcare systems must be strengthened to integrate obesity prevention and management within national NCD programs, especially at the primary care level through routine screening and counseling. Training frontline health workers and addressing weight bias in medical education are essential to ensure empathetic, evidence-based care for obesity as a chronic disease. Governments must implement strong food policy reforms such as sugar taxes, trans-fat bans, front-of-pack

labeling, and restrictions on digital marketing to children to reduce exposure to unhealthy products. Additionally, subsidies should shift from harmful commodities to nutritious foods and sustainable infrastructure to combat the Global Syndemic.

AUTHOR CONTRIBUTIONS

BKP conceptualized the review topic, provided overall supervision, and guided the intellectual framework of the manuscript. SR contributed to the study design, supervised the literature search and evidence synthesis, and critically reviewed the manuscript for important intellectual content. PR conducted the comprehensive literature search, screening, data extraction, and drafted the initial manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

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REFERENCES

- World Health Organization. (2025) Obesity [online]. Available from: <https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity> [Last accessed July, 2026].
- The Lancet. (2026). Obesity [online]. Available from: <https://www.thelancet.com/clinical/diseases/obesity> [Last accessed July, 2026].
- World Health Organization. (2025). Obesity and overweight [online]. Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> [Last accessed July, 2026].
- World Obesity Federation. (2022). Prevalence of obesity [online]. Available from: <https://www.worldobesity.org/about/about-obesity/prevalence-of-obesity> [Last accessed July, 2026].
- Popkin BM, Slining MM. New dynamics in global obesity facing low- and middle-income countries. *Obes Rev* 2013;14(Suppl 2):11–20.
- Sanyaolu A, Okorie C, Qi X, et al. Childhood and adolescent obesity in the United States:

a public health concern. *Glob Pediatr Health* 2019;6:2333794X19891305.

- World Health Organization. (2025). Noncommunicable diseases: childhood overweight and obesity [online]. Available from: <https://www.who.int/news-room/questions-and-answers/item/noncommunicable-diseases-childhood-overweight-and-obesity> [Last accessed July, 2026].
- National Family Health Survey. (2017). NFHS [online]. Available from: <https://www.nfhsips.in/nfhsuser/nfhs5.php> [Last accessed July, 2026].
- Ministry of Health and Family Welfare, Government of India. (2026). Comprehensive National Nutrition Survey 2016–2018. [online]. Available from: <https://nhm.gov.in/WriteReadData/18925/1405796031571201348.pdf>
- Zierle-Ghosh A, Jan A. Physiology, body mass index. In: StatPearls [online]. StatPearls Publishing; 2025. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK535456/> [Last accessed July 20, 2025].
- Lopez-Jimenez F, Miranda WR. Diagnosing obesity: beyond BMI. *AMA J Ethics* 2010;12(4):292–298.
- Misra A, Vikram NK, Ghosh A, et al. Revised definition of obesity in Asian Indians living in India. *Diabetes Metab Syndr* 2025;19(1):102989.
- Yajnik CS, Yudkin JS. The Y-Y paradox. *Lancet* 2004;363(9403):163.
- Müller MJ, Braun W, Pourhassan M, et al. Application of standards and models in body composition analysis. *Proc Nutr Soc* 2016;75(2):181–187.
- Rodrigues Silva Sombra L, Anastasopoulou C. Pharmacologic therapy for obesity. In: StatPearls [online]. StatPearls Publishing; 2025. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK562269/> [Last accessed July, 2026].
- Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol* 2025;13(3):221–262.
- Lee A, Carde M, Donahoe WT. Social and environmental factors influencing obesity. In: Feingold KR, Ahmed SF, Anawalt B, et al. (Eds). *Endotext*. MDText.com, Inc 2000.
- Yadav HM, Jawahar A. Environmental factors and obesity. In: StatPearls [online]. StatPearls Publishing; 2025. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK580543/> [Last accessed July, 2026].
- Kahan LG, Mehrzad R. Environmental factors related to the obesity epidemic. In: Mehrzad R (Ed). *Obesity*. Elsevier; 2020. pp. 117–139.
- Affenito SG, Franko DL, Striegel-Moore RH, et al. Behavioral determinants of obesity: research findings and policy implications. *J Obes* 2012;2012:150732.
- Rennie KL, Johnson L, Jebb SA. Behavioural determinants of obesity. *Best Pract Res Clin Endocrinol Metab* 2005;19(3):343–358.
- Capoccia D, Milani I, Colangeli L, et al. Social, cultural and ethnic determinants of obesity: from pathogenesis to treatment. *Nutr Metab Cardiovasc Dis* 2025;35(6):103901.
- NCD Risk Factor Collaboration. Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature* 2019;569(7755):260–264.
- Story M, French S. Food advertising and marketing directed at children and adolescents in the US. *Int J Behav Nutr Phys Act* 2004;1:3.

25. Omoruyi AJ, Durojaye E. Misleading marketing of unhealthy foods and beverages to children in South Africa as a consumer protection issue. *J Consum Policy* 2025;48:105–131.
26. Edwards M. The Barker hypothesis. In: *Handbook of Famine, Starvation, and Nutrient Deprivation*. Cham: Springer; 2017. pp. 1–21.
27. The Sumner M Redstone Global Center for Prevention and Wellness. (2026). Report. Lancet Commission examines the “global syndemic”: the interplay of obesity, undernutrition and climate change, co-chaired by Bill Dietz [online]. Available from: <https://redstone.publichealth.gwu.edu/report-lancet-commission-examines-global-syndemic-interplay-obesity-undernutrition-climate-change> [Last accessed July, 2026].
28. Centers for Disease Control and Prevention. (2024). Childhood obesity facts [online]. Available from: <https://www.cdc.gov/obesity/childhood-obesity-facts/childhood-obesity-facts.html> [Last accessed July, 2026].
29. Pérez-Escamilla R, Kac G. Childhood obesity prevention: a life-course framework. *Int J Obes Suppl* 2013;3(Suppl 1):S3–S5.
30. Sahoo K, Sahoo B, Choudhury AK, et al. Childhood obesity: causes and consequences. *J Family Med Prim Care* 2015;4(2):187–192.
31. Xu S, Xue Y. Pediatric obesity: causes, symptoms, prevention and treatment. *Exp Ther Med* 2016;11(1):15–20.
32. Nour TY, Altıntaş KH. Effect of the COVID-19 pandemic on obesity and its risk factors: a systematic review. *BMC Public Health* 2023;23:1018.
33. Safaei M, Sundararajan EA, Driss M, et al. A systematic literature review on obesity: understanding the causes and consequences of obesity and reviewing various machine learning approaches used to predict obesity. *Comput Biol Med* 2021;136:104754.
34. World Health Organization. (2024). Obesity: health consequences of being overweight [online]. Available from: <https://www.who.int/news-room/questions-and-answers/item/obesity-health-consequences-of-being-overweight> [Last accessed July, 2026].
35. Djalalinia S, Qorbani M, Peykari N, et al. Health impacts of obesity. *Pak J Med Sci* 2015;31(1):239–242.
36. Centers for Disease Control and Prevention. (2022). Causes and consequences of childhood obesity [online]. Available from: <https://www.cdc.gov/obesity/basics/consequences.html> [Last accessed July, 2026].
37. Sarwer DB, Polonsky HM. The psychosocial burden of obesity. *Endocrinol Metab Clin North Am* 2016;45(3):677–688.
38. Okunogbe A, Nugent R, Spencer G, et al. Economic impacts of overweight and obesity: current and future estimates for eight countries. *BMJ Glob Health* 2021;6(10):e006351.
39. Johns Hopkins Medicine. (2024) Obesity prevention [online]. Available from: <https://www.hopkinsmedicine.org/health/conditions-and-diseases/obesity/preventing-obesity> [Last accessed July, 2026].
40. Harvard Health Publishing. (2018). The real link between breastfeeding and preventing obesity [online]. Available from: <https://www.health.harvard.edu/blog/the-real-link-between-breastfeeding-and-preventing-obesity-2018101614998> [Last accessed July, 2026].
41. World Health Organization. (2023). Exclusive breastfeeding to reduce the risk of childhood overweight and obesity [online]. Available from: <https://www.who.int/tools/elena/interventions/breastfeeding-childhood-obesity> [Last accessed July, 2026].
42. Harvard TH Chan School of Public Health. (2017). Obesity [online]. Available from: <https://hsph.harvard.edu/news/obesity/> [Last accessed July, 2026].
43. Press Information Bureau, Government of India. (2025). Toward a fit and healthy India: combating obesity through collective action [online]. Available from: <https://www.pib.gov.in/www.pib.gov.in/Pressreleaseshare.aspx?PRID=2107179> [Last accessed July, 2026].
44. Unnikrishnan AG, Chowdhury S, Pedersen SD, et al. Perceptions, attitudes and barriers to effective obesity care among people with obesity and health care professionals in India. *Diabetes Obes Metab* 2024;26(10):4791–4794.

Real-world Challenges and Predictors of Success in Glucagon-like Peptide-1 Receptor Agonist Therapy



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ABSTRACT

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have revolutionized the management of type 2 diabetes mellitus (T2DM) and obesity, demonstrating robust efficacy in landmark trials for glycemic control, weight reduction, and cardiovascular protection. However, real-world discontinuation rates exceed trial-reported rates, highlighting a gap between clinical efficacy and practical outcomes.

Objective: This review synthesizes evidence from 2018 to 2024, including trial data, population studies, and registry analyses, to identify and contextualize major real-world barriers. High rates of gastrointestinal side effects, substantial out-of-pocket costs, and patient aversion to injectable formulations often result in 1-year discontinuation rates ranging from 27 to 41%. These challenges are compounded by heterogeneity in patient response, with predictors of successful long-term use including higher baseline HbA1c, elevated body mass index (BMI), absence of severe gastrointestinal disorders, and robust early response to therapy.

Methods: A proposed clinical scoring model is presented to improve patient selection and predict adherence, while digital health tools and emerging combination therapies offer additional avenues to enhance persistence and outcomes. Despite promising advances such as dual- and triple-incretin agents and oral GLP-1 RA formulations, cost and access remain major hurdles.

Results: Key factors, including baseline HbA1c >8.0%, BMI >30 kg/m², absence of severe gastrointestinal (GI) disorders, and prior adherence success, correlate strongly with higher persistence. Real-world data reveal that discontinuation rates for GLP-1 receptor agonists remain high, with 1-year discontinuation ranging from approximately 28% to around 41%, depending on the patient population and indication. Discontinuation is more common among patients using GLP-1 RAs for obesity without diabetes, reaching rates above 50% in some cohorts. The primary reasons for stopping therapy include gastrointestinal side effects, reported in over 25% of discontinuations, high medication costs, and issues with insurance coverage or medication access. Persistence is generally higher among patients with T2DM, those with higher baseline BMI, and those who experience greater early weight loss or favorable tolerability, while frequent adverse effects and logistical barriers contribute to poorer long-term adherence. Although emerging clinical tools and digital health interventions are proposed to help address these barriers, further prospective data are needed to quantify their impact on persistence at scale.

Conclusion: Bridging trial evidence with real-world practice requires proactive candidate profiling and side-effect management. Combining predictive scoring, artificial intelligence (AI)-supported adherence tools, and emerging dual-incretin agents may transform GLP-1 RA therapy from short-term use to durable metabolic benefit.

Keywords: Glucagon-like peptide-1 receptor agonists, Glycated hemoglobin, Obesity, Predictive success, Type 2 diabetes mellitus.

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INTRODUCTION: THE PROMISE AND CHALLENGES OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Type 2 diabetes mellitus (T2DM) and obesity are major global health concerns, with their prevalence continuing to rise despite advances in therapeutic options. Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have emerged as a cornerstone in the management of these conditions, offering benefits that extend beyond glycemic control to include significant weight loss and cardiovascular protection.

Drugs such as semaglutide, liraglutide, and dulaglutide have demonstrated efficacy in landmark clinical trials such as LEADER, SUSTAIN, and AWARD-7, reinforcing their role in reducing major adverse cardiovascular events and improving metabolic health.^{1,2}

Despite their strong evidence base, translating these benefits from controlled clinical trials to real-world practice presents substantial challenges. Discontinuation rates for GLP-1 RAs is consistently higher than trial dropout rates, because of a combination of gastrointestinal side effects, high costs, and patient reluctance toward injectable formulations.³⁻⁵ Additionally, variability in

patient response, driven by factors such as baseline glycemic control, visceral adiposity, and comorbid conditions, further complicates their widespread adoption.

This review critically examines the real-world challenges of GLP-1 RA therapy, proposes a predictive framework for identifying ideal candidates, and explores emerging solutions, including the integration of digital health tools and novel combination therapies. By addressing these limitations, health care providers can enhance adherence, improve long-term outcomes, and ensure more effective utilization of these potent therapies.

CHALLENGES IN REAL-WORLD GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

While GLP-1 RAs have demonstrated significant efficacy in clinical trials, their real-world application is hindered by several challenges. These issues span patient adherence, drug tolerability, financial accessibility, and the presence of comorbid conditions that may limit eligibility. Understanding and addressing these barriers are critical to optimizing the long-term success of GLP-1 RA therapy.

Adherence and Persistence: The Dropout Problem

Adherence to GLP-1 RAs in real-world settings is significantly lower than in clinical trials. Studies report discontinuation rates of up to 28% within 6 months and poor 1-year persistence, with only 59% of patients continuing therapy.^{3,6} The main reasons for this include:

Gastrointestinal side effects: Nausea, vomiting, and diarrhea are the most common

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adverse events, occurring in 20–30% of patients and often leading to premature discontinuation.^{4,7}

Cost and insurance coverage: GLP-1 RAs are expensive, with out-of-pocket costs acting as a major deterrent. A cost-effectiveness analysis indicated that oral semaglutide was unlikely to be cost-effective unless prices were significantly reduced.⁵ Insurers remain hesitant to cover these medications, especially for obesity treatment alone.

Injection aversion: Despite the availability of oral semaglutide, many patients remain reluctant to start or continue injectable GLP-1 RAs.

Dosing frequency: Weekly formulations such as semaglutide and dulaglutide show better adherence compared with daily regimens, with 12-month persistence rates of approximately 55–60%.³

Addressing these issues requires patient education, gradual dose titration, and the use of digital health tools to track adherence and reinforce treatment benefits.

Tolerability Issues: Managing Side Effects to Improve Persistence

The most frequently reported side effects, nausea, vomiting, diarrhea, and abdominal pain, are linked to GLP-1 receptor activation in the gastrointestinal tract, leading to delayed gastric emptying.^{4,7} Strategies to improve tolerability include:

Gradual dose escalation: Starting with a lower dose and titrating upward over 4–8 weeks significantly reduces gastrointestinal side effects.⁷

Proactive patient education: Patients who are informed about expected side effects and management strategies (e.g., taking the medication with food and avoiding large meals) are less likely to discontinue treatment prematurely.

Individualized therapy selection: Patients with a history of gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), or gastroparesis are at a higher risk of experiencing intolerable gastrointestinal (GI) symptoms and may not be ideal candidates for GLP-1 RAs.⁷

Patient Selection: Who Benefits the Most?

The response to GLP-1 RA therapy is not uniform across all patients. Studies suggest that outcomes are influenced by baseline metabolic characteristics, including:

Baseline HbA1c: Higher HbA1c levels (>8.0%) predict greater glycemic benefit from GLP-1 RAs.

Body mass index (BMI): Patients with BMI >30 kg/m² tend to have a more pronounced

weight loss response, making them ideal candidates for this therapy.

Visceral adiposity: Patients with central obesity often experience better metabolic outcomes than those with peripheral adiposity.

Comorbidities: The presence of advanced chronic kidney disease (CKD) or severe gastrointestinal disorders may limit therapy options.²

The AWARD-7 trial demonstrated dulaglutide's renal benefits in patients with diabetes and CKD, making it a preferred option in this subgroup.² However, patients with gastroparesis, GERD, or IBS face a higher risk of symptom exacerbation and therapy discontinuation.

PREDICTING SUCCESS IN GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS THERAPY—A SCORING MODEL FOR CLINICAL DECISION-MAKING

Given the variability in patient response, a predictive framework can help clinicians identify ideal candidates for GLP-1 RA therapy and mitigate risks associated with discontinuation. The proposed scoring system in Table 1 incorporates metabolic, psychological, and gastrointestinal factors to estimate treatment success.

Interpretation

Score $\geq 7 \rightarrow$ High likelihood of successful therapy. Strong candidate for GLP-1 RA therapy.

Score 4–6 $\rightarrow$ Moderate benefit expected. Requires patient education and close monitoring for side effects.

Score 0–3 $\rightarrow$ Low likelihood of success. Alternative therapies should be considered.

Score $\leq -1 \rightarrow$ High risk of adverse effects and treatment failure. Strong recommendation for alternative treatment strategies.

Strengthening the Predictive Model with Real-world Evidence

While the above framework is based on clinical experience and trial data, its real-world application needs further validation through observational studies. Potential areas for improvement include:

Longitudinal tracking of patients to assess real-world persistence beyond 6 months.

Digital health integration, using artificial intelligence (AI)-driven models to refine predictions based on patient adherence data.⁹

Incorporating genetic and gut microbiome profiling, which may provide additional insights into therapy responsiveness.

The Role of Digital Health in Enhancing Glucagon-like Peptide-1 Receptor Agonists Therapy

Emerging evidence supports the use of digital health tools to improve adherence and treatment outcomes. These include:

Real-time glucose monitoring [continuous glucose monitoring (CGM)]—Helps track glycemic trends and ensures early intervention.

AI-driven patient support apps (MySugr, Carb Manager)—Provide tailored dietary and lifestyle recommendations.

Telemedicine and virtual coaching—Address patient concerns, encourage

Table 1: GLP-1 RA therapy success score

Factor	Score (–2 to +2)	Rationale
Baseline HbA1c >8.0%	+2	Greater glycemic improvement potential
BMI >30 kg/m ²	+2	Stronger weight loss benefits, better metabolic outcomes
Visceral adiposity presence	+1	Correlates with enhanced response to GLP-1 RAs
No prior GLP-1 RA failure	+1	Higher adherence likelihood if no past discontinuation due to intolerance
No severe GI disorders (GERD, IBS, gastroparesis)	+2	Lower dropout risk due to GI side effects ⁷
No history of eating disorders	+1	Reduces psychological barriers to adherence ⁸
No severe anxiety/depression	+1	Improved adherence and persistence ⁸
History of severe GI disorders	–2	Increased risk of treatment discontinuation
History of eating disorders	–1	Increased risk of poor adherence and negative psychological impact
Severe depression or anxiety	–2	Higher risk of therapy discontinuation ⁸

adherence, and enable dose titration without frequent clinic visits.

Bio-wearables—Devices such as Fitbit and Apple Watch monitor metabolic parameters to assess therapy effectiveness.⁹

By integrating predictive models with digital health, clinicians can proactively adjust treatment plans and ensure better long-term success for GLP-1 RA therapy.

FUTURE DIRECTIONS AND CONCLUSION

Emerging Therapies: The Next Generation of Glucagon-like Peptide-1-based Treatments

While GLP-1 RAs have proven highly effective, the next wave of metabolic treatments is poised to further enhance efficacy, tolerability, and accessibility.

Dual- and Triple-Incretin Therapies

Tirzepatide [glucose-dependent insulintropic polypeptide (GIP)/GLP-1 RA]: Clinical trials suggest greater HbA1c and weight reduction than semaglutide, making it a promising alternative.¹⁰

GLP-1/GIP/glucagon RAs: Early research indicates that adding glucagon receptor activity may improve energy expenditure and fat metabolism, potentially overcoming weight-loss plateaus.

Oral and Long-acting Injectable Formulations

Oral semaglutide: Despite improving adherence in injection-averse patients, its cost-effectiveness remains a concern.⁵

Ultra-long-acting GLP-1 RAs: Agents with biweekly or monthly dosing could enhance persistence and reduce dropout rates.

Personalized and Precision Medicine Approaches

Pharmacogenomics and microbiome research may help predict which patients respond best to GLP-1 therapy.

Artificial intelligence (AI) integration can optimize dosing schedules based on real-time metabolic data.⁹

Cost-effectiveness and Healthcare System Implications

The widespread adoption of GLP-1 RAs is hindered by cost considerations,

particularly in regions where insurance coverage is limited. Economic analyses suggest:

Cost per quality-adjusted life year (QALY): GLP-1 RAs become cost-effective when reducing hospitalization rates and cardiovascular events.¹¹

Comparative cost-effectiveness: Tirzepatide's enhanced efficacy may justify its cost premium over semaglutide.¹²

Health policy impact: Expanding insurance coverage and negotiating drug prices are crucial for improving access to these life-changing therapies.

Key Takeaways: Translating Clinical Success into Real-world Impact

To maximize the success of GLP-1 RA therapy in routine practice, the following strategies must be prioritized:

Optimized patient selection—Using predictive models to ensure that the right patients receive GLP-1 RAs, improving outcomes and cost-effectiveness.

Proactive side effect management—Employing dose-titration protocols and patient education to mitigate nausea and discontinuation rates.

Integration of digital health tools—Leveraging real-time glucose monitoring, AI-driven coaching, and telemedicine to enhance adherence.

Emerging therapies and personalized medicine—Preparing for the future of multi-incretin therapy and utilizing genetic and metabolic profiling to personalize treatments.

Addressing cost barriers—Advocating for insurance reimbursement policies and alternative pricing models to improve affordability.

CONCLUSION

GLP-1 RAs represent one of the most transformative developments in the management of T2DM and obesity, offering unparalleled benefits in glycemic control, weight loss, and cardiovascular protection. However, real-world challenges such as high discontinuation rates, tolerability concerns, and cost barriers necessitate a comprehensive, patient-centered approach.

By integrating predictive scoring models, digital health interventions, emerging combination therapies, and policy-driven

affordability strategies, health care providers can optimize treatment success and ensure that GLP-1 RAs fulfill their potential as a cornerstone therapy for metabolic disease.

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REFERENCES

1. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844.
2. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018;6:605–617.
3. Ulrich FS, Napoli N, Nielsen MF, et al. Real-world persistence and dose titration of GLP-1 receptor agonists in type 2 diabetes: a UK population-based cohort study by obesity and cardiovascular disease status. *Diabetes Obes Metab* 2026;28(4):3386–3395.
4. Xie X, Yang S, Deng S, et al. Comparative gastrointestinal adverse effects of GLP-1 receptor agonists and multi-target analogs in type 2 diabetes: a Bayesian network meta-analysis. *Front Pharmacol* 2025;16:1613610.
5. Feng Z, Tong WK, Zhang X, et al. Cost-effectiveness analysis of once-daily oral semaglutide versus placebo and subcutaneous glucagon-like peptide-1 receptor agonists added to insulin in patients with type 2 diabetes in China. *Front Pharmacol* 2023;14:1226778.
6. Polonsky WH, Gamble C, Iyer N, et al. Exploring why people with type 2 diabetes do or do not persist with glucagon-like peptide-1 receptor agonist therapy: a qualitative study. *Diabetes Spectr* 2021;34(2):175–183.
7. Nauck MA, Quast DR, Wefers J, et al. GLP-1 receptor agonists in the treatment of type 2 diabetes — state-of-the-art. *Mol Metab* 2021;46:101102.
8. Świątoniowska-Lonc N, Tański W, Polański J, et al. Psychosocial determinants of treatment adherence in patients with type 2 diabetes — a review. *Diabetes Metab Syndr Obes* 2021;14:2701–2715.
9. World Economic Forum. How biowearables are transforming diabetes and patient care [Internet]. 2025 Jan [cited 2026 Jul 14]. Available from: www.weforum.org/stories/2025/01/how-biowearables-are-transforming-diabetes-care-and-empowering-patients/
10. Friás JP, Davies MJ, Rosenstock J, et al; SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503–515.
11. Yang CY, Chen YR, Ou HT, et al. Cost-effectiveness of GLP-1 receptor agonists versus insulin for the treatment of type 2 diabetes: a real-world study and systematic review. *Cardiovasc Diabetol* 2021;20:20.
12. Zhang X, McAdam-Marx C. Short-term cost-effectiveness analysis of tirzepatide for the treatment of type 2 diabetes in the United States. *J Manag Care Spec Pharm* 2023;29(3):276–284.



Updates in Rhinitis: A Comprehensive Review of Recent Advances

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ABSTRACT

Rhinitis is a common inflammatory condition of the nasal mucosa. It significantly impacts a person's health and quality of life. Traditionally, it is categorized as allergic rhinitis (AR) or nonallergic rhinitis (NAR). Recent advancements have led to a more nuanced understanding of its pathophysiology, classification, and management. This review emphasizes key updates over the last decade. The focus is on evolving concepts in phenotyping and endotyping, novel insights into disease mechanisms, advancements in diagnosis, and emerging therapeutic strategies, including biologics and targeted nerve interventions. The recognition of local allergic rhinitis (LAR), the role of innate immunity and epithelial barrier dysfunction, and the increasing array of precision medicine options underscore a paradigm shift toward personalized management. Despite these newer advances, challenges remain in fully characterizing NAR and optimizing therapeutic guidelines. This review aims to provide an overview of these transformative developments, guiding clinicians and researchers toward more effective and tailored approaches to treat rhinitis.

Keywords: Allergic rhinitis, Biologics, Diagnosis, Endotypes, Immunotherapy, Local allergic rhinitis, Nonallergic rhinitis, Phenotypes, Rhinitis, Treatment.

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INTRODUCTION

Rhinitis, characterized by symptoms of sneezing, rhinorrhea, nasal itching, and congestion, affects a substantial portion of the global population, with prevalence estimates varying between 10% and 40%.¹ Beyond its perceived benign nature, rhinitis significantly impacts quality of life, sleep, cognitive function, and productivity, and is frequently comorbid with asthma, conjunctivitis, and chronic rhinosinusitis.^{2,3} For decades, rhinitis has been broadly classified into allergic rhinitis (AR), triggered by IgE-mediated reactions to allergens, and nonallergic rhinitis (NAR), encompassing various subtypes without a clear allergic etiology.⁴

The past decade has witnessed a rapid evolution in our understanding of rhinitis, driven by advances in molecular biology, immunology, and therapeutic development. This review aims to consolidate the most significant updates in rhinitis within the last ten years, covering re-evaluation of classification, unraveling of new pathophysiological insights, refinement of diagnostic methods, and the emergence of innovative treatment modalities, including the burgeoning field of biologics and targeted nerve therapies. This synthesis provides a comprehensive overview for healthcare professionals navigating the complexities of modern rhinitis management.

UPDATES IN CLASSIFICATION, PHENOTYPES, AND ENDOTYPES

Traditional classification of rhinitis, primarily differentiating AR from NAR, has been increasingly recognized as insufficient to capture the intricate heterogeneity of the disease. The current trend emphasizes phenotyping (observable characteristics) and endotyping (mechanistic pathways) to guide personalized treatment strategies.^{5,6}

Local Allergic Rhinitis

One of the most significant advances in rhinitis classification is the widespread acceptance and characterization of local allergic rhinitis (LAR).⁷ LAR presents with classic AR symptoms triggered by allergens, but patients show negative results on standard skin prick tests and serum-specific IgE tests. Diagnosis relies on positive nasal provocation tests (NPT) with relevant allergens, demonstrating local IgE production within the nasal mucosa.⁸ Studies have elucidated the local immune response in LAR, involving mast cells, eosinophils, and T-helper 2 (Th2) cytokines, mirroring systemic AR but confined to the nasal cavity. The recognition of LAR is crucial as it accounts for a substantial proportion of patients previously misdiagnosed as NAR, enabling appropriate allergen-specific interventions.^{7,8}

Nonallergic Rhinitis Subtypes Refined

Nonallergic rhinitis remains a heterogeneous group, but recent efforts have aimed at a more granular classification with prognostic and therapeutic implications.⁹ Key subtypes gaining clearer definition include:

- *Nonallergic rhinitis with eosinophilia syndrome (NARES)/eosinophilic nonallergic rhinitis (ENAR):* Characterized by significant eosinophilia (typically >20%–25%) in nasal cytology, without systemic IgE sensitivity. ENAR is often associated with nasal polyps, asthma, and aspirin-exacerbated respiratory disease (AERD), suggesting a type 2 inflammatory endotype.¹⁰
- *Vasomotor rhinitis (VMR)/noneosinophilic nonallergic rhinitis (NENAR):* This is characterized by prominent congestion and rhinorrhea triggered by nonspecific stimuli (e.g., temperature changes, strong odors) without evidence of inflammation or allergy. Recent research highlights neurogenic inflammation and autonomic dysregulation as key drivers.^{9,11}
- *Other NAR forms:* Gustatory rhinitis, drug-induced rhinitis (e.g., from ACE inhibitors), hormonal rhinitis, atrophic rhinitis, and occupational rhinitis continue to be recognized based on specific etiologies.

ADVANCEMENTS IN PATHOPHYSIOLOGICAL INSIGHTS

The understanding of rhinitis pathophysiology has moved beyond a simple IgE-mast cell paradigm for AR and vague autonomic dysfunction for NAR. Recent research highlights the intricate interplay of genetic, environmental, immunological, and neurological factors.⁶

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Epithelial Barrier Dysfunction

Emerging evidence suggests that impaired epithelial barrier function in the nasal mucosa plays a crucial role in both AR and NAR.¹² Damaged tight junctions can lead to increased permeability, allowing allergens, irritants, and microbial products to penetrate the mucosa, initiating or exacerbating inflammatory responses. This concept has opened new avenues for therapeutic interventions targeting barrier integrity.

Innate Immunity and Alarmins

The role of innate immune responses, particularly through epithelial-derived cytokines known as alarmins (e.g., IL-33, TSLP, IL-25), has gained prominence in type 2 inflammatory rhinitis.¹³ These alarmins are released upon epithelial damage and drive the differentiation and activation of type 2 innate lymphoid cells (ILC2s), contributing to the characteristic type 2 immune response (eosinophilia, IgE production). This deeper understanding has directly informed the development of biologic therapies.

Neurogenic Inflammation

For NAR, especially VMR, renewed focus is on the role of neurogenic inflammation.¹¹ Dysregulation of sensory nerves (trigeminal nerve), release of neuropeptides (e.g., substance P, calcitonin gene-related peptide), and altered autonomic tone contribute to symptoms such as hypersecretion and congestion. This insight underpins the development of targeted nerve interventions.

Microbiome Influence

The nasal microbiome's influence on rhinitis development and progression is an active area of research.¹⁴ Dysbiosis, characterized by an imbalance in bacterial communities, may modulate immune responses, potentially contributing to inflammation and allergen sensitization. While still in early stages, this area holds promise for future diagnostic and therapeutic strategies.

CONTEMPORARY DIAGNOSTIC APPROACHES

While clinical history and physical examination remain fundamental, contemporary diagnostic approaches are integrating more refined tools to support phenotyping and guide treatment.

Advanced Allergy Diagnostics

Beyond traditional skin prick tests and serum-specific IgE, molecular allergology (component-resolved diagnostics [CRD]) has become more accessible.¹⁵ CRD allows for the identification of specific allergen molecules (e.g., profilins, PR-10

proteins, storage proteins), providing a more precise risk assessment for cross-reactivity, severity, and the potential efficacy of allergen immunotherapy.

Nasal Provocation Tests

Nasal provocation tests (NPT), particularly with allergens, are increasingly recognized as a vital diagnostic tool for LAR, as previously mentioned.⁸ Nonallergen NPTs (e.g., with histamine or methacholine) can assess nasal hyperactivity, aiding in the diagnosis of NAR.

Nasal Cytology

Microscopic examination of nasal secretions for inflammatory cells (eosinophils, neutrophils, mast cells) is gaining traction as a simple, non-invasive tool for phenotyping.¹⁰ Detection of high eosinophil counts can differentiate ENAR from other NAR subtypes and guide the use of intranasal corticosteroids or potentially biologics.

Biomarkers

Research into biomarkers is accelerating, aiming to identify objective measures of disease severity, response to treatment, and specific endotypes.¹⁶ While not routinely used in clinical practice, promising candidates include:

- *Exhaled nitric oxide (eNO)*: Nasal eNO levels can reflect Type 2 inflammation.
- *Tear/nasal fluid cytokines*: Levels of IL-4, IL-5, IL-13, TSLP, IL-33, and eotaxin are under investigation as indicators of type 2 inflammation.
- *Serum biomarkers*: Periostin, IgE, and eosinophil counts provide systemic indicators.

THERAPEUTIC ADVANCEMENTS

The therapeutic landscape for rhinitis has greatly expanded, particularly for severe and refractory cases, with a move toward personalized and targeted interventions.

Pharmacotherapy Updates

Intranasal Corticosteroids (INCS)

Remain the cornerstone of AR and inflammatory NAR treatment, with new formulations offering improved patient adherence and reduced systemic absorption.¹⁷ Combinations of INCS and intranasal antihistamines (e.g., azelastine/fluticasone) have demonstrated superior efficacy for moderate-to-severe AR compared to monotherapy.¹⁸

Antihistamines

Newer generation oral antihistamines (e.g., rupatadine, bilastine) offer effective symptom control with minimal sedation.¹⁹ Intranasal

antihistamines provide rapid onset of action, particularly useful for "on-demand" relief.

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists (LTRAs) continue to be an option, particularly for patients with coexisting asthma, but generally less effective than INCS for nasal symptoms alone.²⁰

Allergen Immunotherapy

Allergen immunotherapy (AIT), available as subcutaneous (SCIT) and sublingual (SLIT) routes, remains the only disease-modifying treatment for AR. Recent updates include:

- *Expansion of SLIT indications*: SLIT tablets are now approved for several common allergens (e.g., grass, ragweed, dust mites), offering a convenient home-based option.²¹
- *Improved protocols*: Ultra-rush and modified rush protocols for SCIT aim for faster desensitization while maintaining safety.²²
- *Real-world evidence*: Numerous studies reinforce the long-term efficacy of AIT in reducing AR symptoms, medication use, and preventing asthma development.²³

Biologic Therapies

A game changer: The most transformative development in severe rhinitis and its comorbidities has been the advent of biologic agents, primarily targeting type 2 inflammation. While most are approved for comorbid conditions such as severe asthma or chronic rhinosinusitis with nasal polyps (CRSwNP), their beneficial effects on severe AR and NAR with type 2 features are increasingly recognized.

Omalizumab (Anti-IgE): Approved for severe allergic asthma, omalizumab has shown efficacy in reducing symptoms and medication use in patients with severe AR, particularly those with high serum IgE levels.²⁴ Its role in patients with concurrent severe AR and chronic urticaria is also being explored.

Dupilumab (anti-IL-4Ra): A groundbreaking biologic targeting the common alpha subunit of the IL-4 and IL-13 receptors, dupilumab is approved for severe asthma, atopic dermatitis, and CRSwNP. For CRSwNP patients, dupilumab significantly reduces nasal polyps, improves sense of smell, and alleviates nasal congestion, with concomitant benefits for AR symptoms where present.²⁵ Its potential role in severe, refractory AR without CRSwNP is under investigation.

Mepolizumab and reslizumab (anti-IL-5): Primarily indicated for severe eosinophilic asthma and CRSwNP with eosinophilia, these anti-IL-5 agents also reduce nasal eosinophilia and improve nasal symptoms in patients with type 2 rhinitis and CRSwNP.²⁶

Benralizumab (anti-IL-5Ra): Targets the IL-5 receptor alpha expressed on eosinophils, leading to direct eosinophil depletion. Similar to anti-IL-5 antibodies, it is approved for severe eosinophilic asthma and shows promise in CRSwNP and Type 2 rhinitis.²⁷

Tezepelumab (anti-TSLP): A novel biologic targeting thymic stromal lymphopoietin (TSLP), an upstream alarmin crucial for initiating type 2 inflammation. Approved for severe asthma, tezepelumab has shown broad efficacy across various type 2 inflammatory conditions and holds significant promise for patients with severe AR, including those with nontype 2 asthma or AR features.²⁸

Targeted Nerve Interventions for Nonallergic Rhinitis

For refractory NAR, particularly VMR with prominent rhinorrhea and congestion, targeted nerve interventions represent a significant advance.

Posterior Nasal Nerve (PNN) Ablation/ Cryoablation

Procedures such as cryotherapy (e.g., RhinAer®) or radiofrequency ablation target the PNN, which supplies secretomotor and vasomotor innervation to the nasal mucosa. By disrupting these nerves, symptoms of chronic rhinorrhea and congestion are significantly reduced, offering a minimally invasive alternative for patients unresponsive to conventional medical therapy.²⁹

Vidian Neurectomy

A more invasive surgical procedure that ablates the vidian nerve, historically performed for severe rhinorrhea, is now rarely used due to significant side effects, but its principle informs newer PNN interventions.

Other Emerging Therapies

Nasal Barrier Sprays

Containing cellulose powder or polymers, these sprays aim to create a protective barrier on the nasal mucosa, preventing allergen and irritant penetration.³⁰

Probiotics

While still primarily investigational, some studies suggest that oral or intranasal probiotics may modulate immune responses and alleviate AR symptoms, though more robust evidence is needed.³¹

Immunomodulators

Research on compounds modulating specific immune pathways, beyond biologics, continues, but none have reached widespread clinical use for rhinitis.

CONCLUSION AND FUTURE DIRECTIONS

The landscape of rhinitis diagnosis and management has undergone a remarkable transformation over the past decade. The shift from a binary AR/NAR classification to a more nuanced understanding of phenotypes and endotypes, particularly the recognition of LAR and the refined characterization of NAR subtype, marks a significant step towards precision medicine. Our understanding of pathophysiology has deepened, highlighting the crucial roles of epithelial barrier function, innate immunity, and neurogenic inflammation.

Diagnostic tools are becoming more sophisticated, allowing for better identification of specific patient subsets, while the therapeutic arsenal has expanded dramatically. The introduction of biologic agents, initially for comorbid conditions but increasingly recognized for their broader benefits in severe type 2 rhinitis, represents a paradigm shift for patients with refractory disease. Furthermore, targeted nerve interventions offer new hope for those suffering from chronic, treatment-resistant NAR.

Despite these advances, challenges remain. A clearer understanding of the underlying mechanisms of all NAR subtypes is still needed to develop more targeted therapies. The high cost of biologics necessitates careful patient selection and economic evaluation. Further research is required to identify reliable and accessible biomarkers for routine clinical practice to guide personalized treatment decisions for all forms of rhinitis.

Future directions in rhinitis research will likely focus on:

- Developing more predictive biomarkers for response to specific therapies, especially biologics.
- Exploring novel targets beyond type 2 inflammation for non-responders or nontype 2 endotypes.
- Investigating the role of the nasal microbiome and its manipulation in disease prevention and treatment.
- Refining immunotherapy approaches for broader allergen coverage and improved safety profiles.
- Integrating artificial intelligence and machine learning to analyze complex patient data for personalized management algorithms.
- Ultimately, the goal is to move towards a stratified, patient-centric approach to rhinitis care, optimizing treatment selection based on an individual's specific endotype, thereby improving clinical outcomes and enhancing quality of life for millions affected by this pervasive condition.

CONFLICT OF INTEREST

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REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update. *Allergy* 2008;63(Suppl 86):8–160.
2. Nur Husna SM, Tan HTT, Md Shukri N, et al. Allergic rhinitis: a clinical and pathophysiological overview. *Front Med (Lausanne)* 2022;9:874114.
3. Tidke M, Borghare PT, Pardhekar P, et al. Recent advances in allergic rhinitis: a narrative review. *Cureus* 2024;16(9):e68607.
4. Greiner AN, Hellings PW, Rotiroti G, et al. Allergic rhinitis. *Lancet* 2011;378(9809):2112–2122.
5. Gu Y, Shu LL, Lu T, et al. Current insights into individualized diagnosis and treatment of allergic rhinitis based on phenotype and endotype. *World J Otorhinolaryngol Head Neck Surg* 2026;12(1):124–135.
6. Mullol J, Del Cuvillo A, Lockey RF. Rhinitis phenotypes. *J Allergy Clin Immunol Pract* 2020;8(5):1492–1503.
7. Rondón C, Fernandez J, Canto G, et al. Local allergic rhinitis: concept, clinical manifestations, and diagnostic approach. *J Invest Allergol Clin Immunol* 2010;20(5):364–371.
8. Mortada MM, Kurowski M. Challenges in local allergic rhinitis diagnosis, management, and research: current concepts and future perspectives. *Medicina (Kaunas)* 2023;59(5):929.
9. Settupane RA, Kaliner MA. Chapter 14: nonallergic rhinitis. *Am J Rhinol Allergy* 2013;27(Suppl 1):S48–S51.
10. Gelardi M, Fiorella ML, Russo C, et al. Role of nasal cytology. *Int J Immunopathol Pharmacol* 2010;23(Suppl 1):45–49.
11. Leader P, Geiger Z. Vasomotor rhinitis. In: StatPearls [online]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK547704/> [Last accessed July, 2026].
12. Hellings PW, Steelant B. Epithelial barriers in allergy and asthma. *J Allergy Clin Immunol* 2020;145(6):1499–1509.
13. Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol* 2015;16(1):45–56.
14. Che Y, Wang N, Ma Q, et al. Microbial characterization of the nasal cavity in patients with allergic rhinitis and non-allergic rhinitis. *Front Cell Infect Microbiol* 2023;13:1166389.
15. Eirringhaus K, Renz H, Matricardi P, et al. Component-resolved diagnosis in allergic rhinitis and asthma. *J Appl Lab Med* 2019;3(5):883–898.
16. Ogulur I, Pat Y, Ardicli O, et al. Advances and highlights in biomarkers of allergic diseases. *Allergy* 2021;76(12):3659–3686.
17. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis: revised edition 2017; first edition 2007. *Clin Exp Allergy* 2017;47(7):856–889.

18. Ridolo E, Montagni M, Melli V, et al. A role for the intranasal formulation of azelastine hydrochloride/ fluticasone propionate in the treatment of allergic rhinitis. *Ther Deliv* 2015;6(6):653–659.
19. Bousquet J, Bindslev-Jensen C, Canonica GW, et al. The ARIA/EAACI criteria for antihistamines: an assessment of the efficacy, safety, and pharmacology of desloratadine. *Allergy* 2004;59(Suppl. 77):4–16.
20. Moinuddin R, deTineo M, Maleckar B, et al. Comparison of the combinations of fexofenadine-pseudoephedrine and loratadine-montelukast in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2004;92(1):73–79.
21. Ji Z, Jiang F. Efficacy and safety of sublingual immunotherapy for allergic rhinitis: a network meta-analysis. *Front Immunol* 2023;14:1144816.
22. Lee SH, Kim ME, Shin YS, et al. Safety of ultra-rush schedule of subcutaneous allergen immunotherapy with house dust mite extract conducted in an outpatient clinic in patients with atopic dermatitis and allergic rhinitis. *Allergy Asthma Immunol Res* 2019;11(6):846–855.
23. Jutel M, Kosowska A, Smolinska S. Allergen immunotherapy: past, present, and future. *Allergy Asthma Immunol Res* 2016;8(3):191–197.
24. Cavaliere C, Begvarfaj E, Incorvaia C, et al. Long-term omalizumab efficacy in allergic rhinitis. *Immunol Lett* 2020;227:81–87.
25. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;394(10209):1638–1650.
26. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021;9(10):1141–1153.
27. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomized, multicenter, placebo-controlled phase 3 trial. *Lancet* 2016;388(10056):2115–2127.
28. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med* 2021;384(19):1800–1809.
29. Desai V, Sampieri G, Namavarian A, et al. Cryoablation for the treatment of chronic rhinitis: a systematic review. *J Otolaryngol Head Neck Surg* 2023;52(1):37.
30. Nehrig J, Grosse N, Hohenfeld IP, et al. Efficacy and safety of a drug-free, barrier-forming nasal spray for allergic rhinitis: randomized, open-label, crossover noninferiority trial. *Int Arch Allergy Immunol* 2023;184(2):111–121.
31. Luo C, Peng S, Li M, et al. The efficacy and safety of probiotics for allergic rhinitis: a systematic review and meta-analysis. *Front Immunol* 2022;13:848279.



ANNOUNCEMENT

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Risk Factors and Emerging Therapies for Immune Checkpoint Inhibitor-related Myocarditis: A Narrative Review

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) represent a groundbreaking development in immunotherapy, offering significant promise in the treatment of various malignancies previously considered incurable. However, despite their potential benefits, the increasing use of ICIs is associated with a spectrum of immune-related adverse events (irAEs). Myocarditis is a rare and potentially underestimated complication that represents the highest mortality rate among irAEs.

Objective: The review aims to evaluate the current understanding of ICI-myocarditis (ICI-M) through providing a detailed overview of diagnostic challenges, screening strategies, and, in particular, the risk factors and evolving treatment agents beyond corticosteroids.

Materials and methods: A comprehensive literature review was conducted on PubMed, analyzing data from relevant clinical studies, case reports, preclinical models, and expert consensus guidelines. In addition, data from one ongoing clinical trial (ATRIUM trial) not yet indexed in PubMed were included to reflect emerging therapeutic developments.

Results: Despite the low incidence of ICI-M (0.06%–1%), which is likely underestimated, the mortality rate is the highest among irAEs; the most identifiable risk factors include combination therapy with ICI agents (anti-PD1 and anti-CTLA-4), preexisting cardiovascular and autoimmune diseases, use of ICIs alongside other anticancer treatments, certain tumor types, older age, and female sex. Diagnosis of the condition is faced with challenges such as nonspecific clinical features and often requires multimodal evaluation including biomarkers, imaging, and biopsy. High-dose corticosteroids remain the first-line treatment; however, steroid-refractory cases are increasingly reported. Promising second-line options include mycophenolate mofetil, antithymocyte globulin, abatacept, and tacrolimus; however, there is a lack of prospective data to support their efficacy. Studies conducted on various preclinical models highlight potential therapeutic targets such as CXCR3.

Conclusion: ICI-M poses a significant challenge in cardio-oncology practice due to its underestimation, high mortality rate, and lack of robust clinical data evaluating standardized screening protocols and second-line treatment measures. Although several second-line agents show promise, the evidence supporting their usage is largely on the basis of expert consensus and case reports, hence representing a strong need for prospective studies offering direct comparisons. Likewise, preclinical studies show great promise in identifying the pathophysiology and potential therapeutic targets for ICI-M; however, translational studies are necessary to validate these findings.

Keywords: Immune checkpoint inhibitors, Immunotherapy, Myocarditis.

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INTRODUCTION

With cancer prevalence rising, one of the most groundbreaking advancements in cancer treatment is immunotherapy, which harnesses the body's immune system to target and eliminate malignancies. A key component of this approach is immune checkpoint inhibitors (ICIs), which have demonstrated significant promise in improving patient outcomes.¹

The US Food and Drug Administration approved ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, in 2011, marking its first authorization for melanoma therapy.² This was followed in 2014 by the approval of nivolumab, a programmed cell death protein-1 (PD-1) inhibitor, with additional

agents targeting PD-1 and its ligand PD-L1 introduced in subsequent years.^{3,4}

Although immunotherapy is a recent advance in the field of oncology, the concept goes back in time by more than a century. A documented example was the concept of immunosurveillance that was proposed by Ehrlich, postulating that commonly produced malignant cells only progress to develop into clinically significant disease when immunity is compromised.³

The anti-CTLA-4 antibody ipilimumab, along with anti-PD-1 agents such as nivolumab and pembrolizumab, has significantly transformed the management of advanced malignancies including metastatic melanoma, lung cancer, and renal cell carcinoma. Despite these therapeutic advances, their mechanism of enhancing immune activation has been

associated with a unique spectrum of toxicities termed immune-related adverse events (irAEs). These commonly manifest as gastrointestinal, hepatic, dermatologic, and endocrine complications, including diarrhea, colitis, hepatitis, skin reactions, hypophysitis, and thyroid dysfunction.⁵ An increasing number of cases of immune checkpoint inhibitor-related cardiotoxicity began to be reported, with complications ranging from cardiogenic shock to sudden death.⁶ A contemporary review of clinical cases noted that the median interval between initiation of ICI therapy and the onset of the first adverse event was 21 days, with the majority of patients receiving treatment with corticosteroids such as prednisolone or methylprednisolone.⁷ Due to limited understanding of the disease, there remains a paucity of a standardized treatment protocol.⁸

Due to the lack of awareness of the condition, its nonspecific clinical presentation, overlap with other cardiac and medical pathologies, and diagnostic challenges, the incidence of immune checkpoint inhibitor-related myocarditis (ICI-M) is likely underestimated, which brings us to the point that it is crucial to exercise caution with this manifestation of ICI.⁶ Reports suggest an estimated incidence of 0.04%–1.14% among the irAEs,^{9,10} and the highest mortality rates among all irAEs of 20–50%.¹¹

Not many risk factors contributing to the disease have been identified so far, hence necessitating further review of the topic considering its risk of rapid progression and high mortality rate.^{6,10} ICI combination therapy, other anticancer treatment, female sex, preexisting cardiovascular disease, certain tumor types, underlying

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autoimmune pathology, and diabetes mellitus are considered to be contributing factors to the pathogenesis of ICI-M.^{12–16} In this review, we primarily focus on the risk factors contributing to the occurrence of ICI-M and various treatment strategies that extend beyond conventional steroid therapy, while also highlighting the current screening and diagnostic methods.

PATHOPHYSIOLOGY

Immune checkpoint inhibitors comprise monoclonal antibodies that block suppressive signaling pathways controlling T-cell activity—most notably PD-1/PD-L1 and CTLA-4—thereby strengthening T-cell-mediated antitumor immune responses.¹⁷

Although the pathophysiology of ICI-M remains unclear, suggested mechanisms include a shared antigen between the tumor and myocardium, T-cell receptor cross-reactivity with a homologous muscle antigen, or T-cell receptors recognizing distinct, unrelated antigens.¹⁸

Histological findings through cardiac biopsy and autopsy of patients who developed myocarditis following therapy with ICI often reveal skeletal and myocardial T-cell infiltrates showing CD4+, CD8+, and CD68+ cells, with CD20+ B cells being absent. The presence of a shared antigen between the tumor and striated muscle is evidenced by the expression of muscle-specific transcripts in the tumor.¹⁹

CLINICAL FEATURES

The clinical features of ICI-M can vary over a wide spectrum ranging from patients being asymptomatic to life-threatening presentations.¹¹

Patient presentations can be nonspecific with symptoms and signs like chest pain, dyspnea, elevated troponin and creatine kinase levels, ST-segment elevation, cardiac arrhythmia, and other electrocardiographic abnormalities.²⁰

DISCUSSION

Risk Factors

Treatment-related Risk Factors

- *ICI combination therapy:* In a recent review, Yousif et al. highlight the four most prominent risk factors for cardiovascular irAEs. Among them, ICI combination therapy stands out as a major contributor to ICI-M, although shown to successfully overcome cases of primary and secondary resistance to ICIs.¹² Ipilimumab and nivolumab have individually shown

remarkable strides in improving survival in melanoma patients, with their combination being an even more successful treatment strategy.^{21–24} However, it is the combination of these two agents that is associated with increased reports of adverse effects rather than monotherapy with either one.²³ This is proven by several studies, one of which highlights the difference in incidence of myocarditis in the combined anti-PD1/anti-CTLA4 antibodies group compared to the anti-PD-1 monotherapy group, at 2.4% and 0.5%, respectively.¹⁶ A retrospective study from 2018 utilizing the World Health Organization's (WHO) global database found that myocarditis was reported in 0.41% of cases involving anti-PD-1/PD-L1 therapies (such as nivolumab and atezolizumab), compared to 0.07% for anti-CTLA-4 therapy (such as ipilimumab).²⁵

- *Other anticancer treatment:* Other treatment strategies targeting malignancies, including chemotherapy, radiotherapy and tyrosine kinase inhibitors, are being employed to enhance the efficacy of immunotherapy. Nevertheless, their combined use alongside ICIs has proven to increase the likelihood of cardiovascular irAEs.¹² A meta-analysis found that the incidence of cardiovascular irAEs was higher in patients treated with a combination of ICIs and chemotherapy, compared to those receiving ICIs or chemotherapy alone, with incidence rates of 3.7%, 3.1%, and 2.5%, respectively.²⁶

Cancer-specific Susceptibility

Tumor Type

Cardiovascular irAEs have been reported more often in patients with melanoma or lung cancer, indicating that the risk of developing these adverse effects might depend on the particular type of tumor. A study involving patients with several cancer types who received at least one cycle of ICIs revealed that the most frequently observed cancer types were lung (35.7%) and melanoma (33.7%). Patients who experienced cardiovascular irAEs within 1 year of starting ICI therapy were more likely to have lung cancer (42.3% vs 34.7%) and less likely to have liver cancer (2.8% vs 6.6%) than those who did not. However, this may represent the more common use of ICIs in these particular types of cancers, potentially leading to over-reporting associated with these malignancies.^{27,28}

Host-related Risk Factors

Age and Sex

A recent literature review identifies advancing age (over 64 years) and a high BMI (greater

than 28) as possible contributing risk factors of this rare adverse event.²⁹ Overall, males tend to have a higher risk of developing viral or non-ICI-related myocarditis, while females are generally more prone to autoimmune diseases, indicating a potential susceptibility to ICI-M or cardiovascular irAEs.³⁰ This observation is further supported by a retrospective study that focused on identifying cardiac complications postinitiation of ICI therapy, where female sex emerged as one of the strongest risk factors, showing a higher overall incidence of cardiovascular irAEs, including cases of pericarditis (2.2%) and atrial fibrillation (2.0%).³¹

Preexisting Autoimmune Disease

Patients with a history of autoimmune disease are generally not included in clinical trial populations, mostly due to fear of exacerbating an already dysregulated immune system.¹⁴ However, the studies that were carried out in this specific cohort have revealed higher occurrences of exacerbations of preexisting autoimmune conditions or irAEs.^{15,32,33} It has been hypothesized that patients with preexisting autoimmune diseases involving the heart such as systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, and Dressler's syndrome may be at a heightened risk for developing cardiovascular irAEs.³⁴

Preexisting Cardiovascular Disease

Another notable risk factor in cancer patients undergoing ICI therapy is preexisting cardiovascular disease. According to a meta-analysis, a significant proportion (40%) of individuals who developed cardiovascular irAEs had existing cardiovascular risk factors, with the most common ones being myocardial infarction, peripheral artery disease, and hypertension.²⁶ A review of the Mayo Clinic database for all patients with cancer who received ICIs evaluated the association of cardiovascular disease with clinical outcomes, and found that 2.4% of the patients developed cardiovascular irAEs. History of heart failure, acute coronary syndrome, and those above the age of 80 years were identified to be factors associated with an increased risk of developing ICI-M.³⁵

Metabolic and Inflammatory Conditions

Metabolic disorders such as diabetes mellitus have proven to be independent risk factors that may act as facilitators rather than direct triggers of ICI-M, potentially through mechanisms of chronic inflammation and impaired immune regulation. The logistic regression analysis in a retrospective analysis involving 1,047 participants revealed that

diabetes mellitus [odds ratio (OR): 1.96, 95% confidence interval (CI): 1.05–3.65, $p = 0.034$] was an independent risk factor for ICI-related cardiotoxicity.³⁶

Screening Methods

Although no robust monitoring protocol has been standardized for patients receiving immunotherapy, baseline ECG assessment and weekly troponin testing during the first 3 weeks for those receiving combination immunotherapy have been implemented in clinical practice.¹⁸ While it is common to see a rise in cardiac biomarkers (e.g., increased serum troponin levels) secondary to heart tissue damage, nearly 50% of patients exhibit preserved systolic function.¹⁶ Meanwhile, cardiac arrhythmias such as atrial fibrillation, ventricular arrhythmias, and conduction abnormalities are frequently observed, sometimes leading to sudden death.^{16,37} ECG and echocardiography can help detect those at risk by flagging up signs such as widening of the QRS complex and narrowing of global longitudinal strain.¹⁷ The simultaneous occurrence of myasthenia gravis and rheumatic and musculoskeletal immune-related adverse events (RMS-irAE) such as myositis after ICI therapy should raise suspicion of myocarditis.^{38,39}

Diagnosis

Most cases present with raised troponin levels and abnormal ECGs. Meanwhile, LVEF may be normal.¹⁶

The diagnosis of ICI-M relies on a multimodal approach due to the variability in its presentation. A definitive diagnosis is based on a combination of the presence of clinical signs, laboratory evidence of myocardial injury, and imaging or histological evidence, while ruling out alternative diagnoses such as ACS and acute infectious myocarditis (Fig. 1).³⁹

Cardiac troponin: Elevated levels of troponin are observed in most cases of ICI-M (46–97%), with evidence suggesting that troponin I is more specific to myocardial injury than troponin T.¹⁰

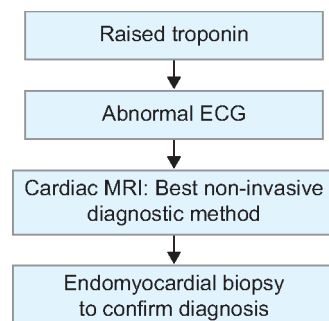


Fig. 1: Flowchart depicting diagnostic methods

Associated symptoms: The onset of new cardiac symptoms alongside musculoskeletal symptoms such as myositis warrants suspicion of ICI-M, possibly due to shared antigenic targets between cardiac and skeletal muscles.¹¹

Endomyocardial Biopsy

Endomyocardial biopsy provides a definitive diagnosis of ICI-M, particularly in uncertain cases. EMB typically reveals a characteristic pathology of a T-cell–predominant lymphocytic infiltrate, including CD8+ and CD4+ T cells, along with macrophages, with evidence of nonischemic necrosis occasionally present.⁴⁰ However, despite its diagnostic accuracy, EMB is not performed routinely due to its invasive nature and the inherent procedural risks, including cardiac tamponade and myocardial perforation. Moreover, EMB in ICI-M is prone to sampling errors due to the patchy appearance of inflammation in the condition, leading to false negatives when unaffected areas are sampled in the biopsy.¹¹ To mitigate the risk of false-negative results, recent expert consensus suggests collecting at least three samples of each approximately 1–2 mm and the utilization of preprocedural imaging to guide biopsy location.⁴⁰

Cardiac Imaging

Echocardiogram: ICI-M often presents with new-onset left ventricular impairment. The echocardiogram is widely used as a first-line test in the assessment of left ventricular failure, and while it may aid in the initial evaluation of ICI-M, various studies reveal that LVEF may be preserved in a large proportion of cases of ICI-M, hence limiting its sensitivity as a diagnostic tool.^{16,34}

Cardiovascular magnetic resonance: For noninvasive evaluation of myocarditis, cardiac magnetic resonance (CMR) imaging is widely accepted as the reference standard. It is highly valuable in the diagnosis of ICI-M owing to its high tissue specificity and minimal procedural risk, allowing detection of myocardial edema and nonischemic patterns of myocardial injury, including necrosis and scarring.⁴¹

The updated 2018 Lake Louise (LL) criteria underpin the CMR diagnosis of ICI-M, necessitating evidence of myocardial edema on T2-weighted imaging alongside a T1-based feature of nonischemic injury [late gadolinium enhancement (LGE) or increased extracellular volume (ECV)].⁴²

In one internal registry, the criteria reflecting nonischemic myocardial injury (T1-based markers, including LGE, T1, or ECV elevation) were met by 95% of patients with proven ICI-M, whereas only 51% of patients

met the T2-based criteria for myocardial edema.⁴³

In a more recent cohort study, LGE, which represents nonischemic patterns of myocardial injury, was observed far more frequently in ICI-M patients when compared to pre-ICI-M control groups (82% vs 10%). However, LGE was detected less frequently in ICI-M when compared to viral myocarditis (82% vs 100%). Conversely, T2 mapping results, which represent myocardial edema, were only present in 24% of patients.

Notably, ICI-M exhibits distinct patterns of LGE localization in the septal and midwall layers, in contrast to viral myocarditis. In the same study, 48% of ICI-M patients showed septal LGE compared to 29% of those with viral myocarditis, while midwall LGE was observed in 33% and 2%, respectively. The presence of septal LGE in particular is associated with an increased incidence of major adverse cardiovascular events.

Although CMR is the best noninvasive diagnostic modality for ICI-M, patients with ICI-M show a lower rate of fulfillment of the 2018 LL criteria, with only 61% of patients with ICI-M meeting both criteria.⁴⁴ Given the unique imaging patterns and diagnostic limitations of LL in ICI-M, specialized CMR criteria may be necessary, and patients should be treated for ICI-M if any single criterion is met in the context of high clinical suspicion.

Treatment

First-line Treatment

Despite its relative rarity, the mortality associated with ICI-M is an astounding 50%, warranting the need for more effective treatment regimens in place.⁴⁵

Specific treatments for ICI-M are rare, and there are no definitive treatment protocols in place. The American College of Cardiology recommends immediate discontinuation of the ICI and initiation of high-dose intravenous methylprednisolone (1 gm daily) for 3 days followed by tapering to oral prednisolone (1–2 mg/kg/day) for confirmed or suspected ICI-M.⁴⁶

Steroid-resistant and Steroid-refractory ICI-myocarditis

Steroid-refractory ICI-M refers to ICI-M which fails to demonstrate clinical improvement or biochemical response to high-dose corticosteroids within 24–72 hours of its commencement. Steroid-resistant is sometimes used as an interchangeable term with steroid refractory but mostly refers to ICI-M which initially responds to corticosteroids but relapses or worsens during the phase of steroid tapering.⁸ The high

incidence of steroid-refractory and steroid-resistant cases of ICI-M suggests that isolated steroid therapy alone is not sufficient in the effective treatment of ICI-M.

Second-line Immunosuppressive Agents

Mycophenolate mofetil: It is considered a reasonable option for steroid-resistant or steroid-refractory ICI-M on the basis of expert consensus and its efficacy in other immune-related cardiac conditions. Mycophenolate Mofetil inhibits inosine monophosphate dehydrogenase, thereby blocking *de novo* purine synthesis in T and B lymphocytes, hence inhibiting lymphocyte proliferation.⁴⁷ A prospective cohort study by Blagova et al., evaluating the role of a combination of mycophenolate mofetil with steroids in the treatment of lymphocytic myocarditis, revealed a high efficacy comparable to the standard combination of steroids and azathioprine, but with improved tolerance levels and far fewer infectious complications. Extrapolating the findings of this study would suggest its potential therapeutic benefits in the treatment of ICI-M.⁴⁸

Tacrolimus: A calcineurin inhibitor that acts on IL-2 expression and inhibits T-cell differentiation and growth; it has proven to be efficacious in the instance of corticosteroid-refractory ICI-M in a few case studies; it is often combined with IVIG, which plays a role in T-cell downregulation (via IL-33 and prostaglandin E-2).⁴⁴

Antithymocyte globulin (ATG): ATG is a second-line T-cell-depleting immunosuppressive agent which is recommended based on expert consensus by the American Heart Association for steroid-refractory/resistant ICI-M. The rationale for its use is supported by the pathophysiological similarities between ICI-M and acute cellular rejection in cardiac transplantation, in which T-cell-targeted therapies such as ATG are employed. The use of ATG is associated with an increased risk of infection and should ideally be supervised by a cardiac transplant team.⁴⁹

Case reports and case series have revealed successful use of ATG in fulminant steroid-refractory ICI-M and are a promising therapeutic avenue, particularly in hemodynamically unstable patients.^{50,51}

IVIG and Plasmapheresis

Plasmapheresis and IVIG therapy are beneficial options in patients presenting with associated neuromuscular complications such as myasthenia gravis.⁵² The American College of Cardiology in its 2024 Expert Consensus Decision Pathway states that IVIG may be considered in autoimmune myocarditis, including ICI-M, when viral infections have

been excluded by endomyocardial biopsy of samples.⁴⁶

Biologic Agents

TNF-alpha Antagonists

TNF-alpha antagonists, such as infliximab, are recommended for refractory or steroid-resistant myocarditis based on anecdotal evidence; however, the empirical evidence base supporting their use remains weak. Infliximab is typically contraindicated in moderate to severe heart failure, and Liu et al. reported clinical data from 18 cases where infliximab was used; while 66.7% of patients experienced improvement, 55.6% died (22.2% from cardiovascular causes), hence suggesting concerns regarding its safety profile in patients with heart failure. However, the evidence is insufficient to conclude that infliximab definitively worsens heart failure in ICI-M.⁵³

Abatacept

Abatacept is a CTLA-4 Ig Fusion Protein which targets T-cell costimulation and has shown promising outcomes in preclinical models and case reports.⁵³

In particular, it is noted to be efficacious in myocarditis associated with myositis; however, there is a potential risk of tumor relapse noted with the usage of abatacept, as described in the instance of two patients who

developed tumor relapse following treatment with abatacept. Hence, prospective clinical trials are necessary to evaluate its overall efficacy and safety profile.

The ATRIUM trial is a phase 3, randomized, placebo-controlled study evaluating abatacept (10 mg/kg IV at baseline, 24 hours, and day 14, with an optional dose at day 28) in hospitalized patients with ICI-M, with the primary endpoint being reduction in major adverse cardiac events (MACE). The trial is actively recruiting and has not released interim or final results (Table 1).⁵⁴

Other Biologic Agents

Other biologic agents that target T-cells, such as alemtuzumab (CD52 antibody) and tocilizumab (IL-6 inhibitor), are also currently promising investigative second-line options that are potentially effective in ICI-M. However, the use of other biologic agents requires further RCTs to substantiate their mortality and morbidity benefits.^{52,53,55}

Promising Therapeutic Avenues in Preclinical and Translational Models

CXCR3-CXCL9/10

An animal model study conducted in 2020 evaluated the role of immunoproteasome in the development of ICI-M and provided translational evidence that immunoproteasome inhibitors such as ONX

Table 1: Treatment modalities beyond steroids

Agent	Mechanism/rationale for use	Evidence
Mycophenolate mofetil (MMF)	A selective Inhibitor of Inosine Monophosphate dehydrogenase, essential for B and T cell proliferation	Use supported by efficacy in cardioallograft rejection and virus-negative lymphocytic myocarditis ^{47,48}
Tacrolimus	T-cell targeted immunosuppressive agent, often used in conditions such as giant cell myocarditis	Used successfully in two steroid-refractory cases of ICI-M alongside IVIG ⁴⁵
Abatacept (CTLA-4 agonist)	CTLA-4 immunoglobulin fusion protein that binds to CD80/CD86 leading to T-cell anergy	Successfully used in steroid-refractory cases, particularly those with concurrent myositis. ³⁰ ATRIUM trial currently ongoing ⁵²
Infliximab (TNF-α Inhibitor)	Blocks TNF-α, a pro-inflammatory cytokine	Recommended by guidelines such as ASCO, typically contraindicated in moderate to severe heart failure. The existing evidence based on case series is insufficient to conclude that infliximab worsens heart failure in ICI-M ⁵⁵
Antithymocyte globulin (ATG)	Targets T-cells by depletion and inducing apoptosis	Successfully used in cases of fulminant myocarditis refractory to steroids. Carries inherent risk of infectious disease. ^{50,51}
Intravenous immunoglobulin (IVIG)	Immunomodulatory effects including neutralizing pro-inflammatory cytokines	Used successfully in cases of steroid-refractory ICI-M along with Tacrolimus. ⁴⁵ Considered to be efficacious in patients with concurrent neuromuscular toxicities ⁵⁴

0914 are able to mitigate autoimmune cardiac damage and are a potential therapeutic option beyond corticosteroids and could serve a role in the cases of refractory myocarditis due to ICIs. The study identified the CXCR3-CXCL9/10 axis as a key therapeutic target; hence, blockade of CXCR3 or depletion of these macrophages reduced pathogenic T-cell infiltration and, hence, disease outcomes.⁵⁶

IL-15 supplementation:

A study by Yu et al. in 2024 used both human samples and an in vivo mouse model to evaluate the roles of IL-15 supplementation and CD4⁺ T cells in the treatment and pathogenesis of ICI-M. They observed in the human samples that ICI-M was associated with a marked reduction in CD4⁺ TCM and that as myocarditis severity increased, there was a corresponding decrease in IL-15 levels. The animal model of mice with ICI-M also revealed evidence of decreased CD4⁺ TCM cells and associated cardiac fibrosis. Supplementation with IL-15 in mice resulted in increased CD4⁺ TCM cells and a reduction in cardiac fibrosis.⁵⁷

CONCLUSION

Although ICIs are revolutionizing cancer therapy, they come with their own set of adverse side effects, one of the most fatal being myocarditis, which is probably underestimated and shown to have the highest mortality rates among all irAEs. We identified a paucity of robust clinical data evaluating standardized screening protocols and second-line treatment measures. Risk factors dependent on the type of cancer treatment include the use of ICI combination therapy and use of other anticancer therapy, with the former being the most recognized contributor to the pathology. Other important factors posing risk that are patient-specific include preexisting cardiovascular disease, preexisting autoimmune disease, and the tumor type. For steroid-resistant or refractory cases of ICI-M, second-line agents have shown positive outcomes, but use of these is dependent on expert consensus and individual case reports, hence indicating a stronger need for prospective studies offering direct comparisons. At the same time, pre-clinical studies have been successful in identifying potential therapeutic targets for ICI-M while still needing validation from translational studies.

ETHICAL STATEMENT

This study is a narrative review based on previously published literature and does not involve any new studies with human participants or animals. Hence, approval

from an institutional ethics committee and a protocol number are not applicable. The manuscript complies with relevant ethical standards.

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REFERENCES

- Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015;33(17):1974–1982.
- Decker WK, da Silva RF, Sanabria MH, et al. Cancer immunotherapy: historical perspective of a clinical revolution and emerging preclinical animal models. *Front Immunol* 2017;8:829.
- Fares CM, Van Allen EM, Drake CG, et al. Mechanisms of resistance to immune checkpoint blockade: why does checkpoint inhibitor immunotherapy not work for all patients? *Am Soc Clin Oncol Educ Book* 2019;39:147–164.
- Dobosz P, Dzieciatkowski T. The intriguing history of cancer immunotherapy. *Front Immunol* 2019;10:2965.
- Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev* 2016;44:51–60.
- Ganatra S, Neilan TG. Immune checkpoint inhibitor-associated myocarditis. *Oncologist* 2018;23(8):879–886.
- Zotova L. Immune checkpoint inhibitors-related myocarditis: a review of reported clinical cases. *Diagnostics (Basel)* 2023;13(7):1243.
- Man X, Wang H, Chen C, et al. Efficacy of high-dose steroids versus low-dose steroids in the treatment of immune checkpoint inhibitor-associated myocarditis: a case series and systematic review. *Front Immunol* 2025;16:1455347.
- Makunts T, Saunders IM, Cohen IV, et al. Myocarditis occurrence with cancer immunotherapy across indications in clinical trial and post-marketing data. *Sci Rep* 2021;11(1):17324.
- Dong H, Qi Y, Kong X, et al. PD-1/PD-L1 inhibitor-associated myocarditis: epidemiology, characteristics, diagnosis, treatment, and potential mechanism. *Front Pharmacol* 2022;13:835510.
- Jiménez-Alejandre R, Ruiz-Fernández I, Martín P. Pathophysiology of immune checkpoint inhibitor-induced myocarditis. *Cancers (Basel)* 2022;14(18):4494.
- Yousif LI, Screever EM, Versluis D, et al. Risk factors for immune checkpoint inhibitor-mediated cardiovascular toxicities. *Curr Oncol Rep* 2023;25(7):753–763.
- Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;378(2):158–168.
- Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. *Cancer* 2017;123(11):1904–1911.
- Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol* 2016;2(2):234–240.
- Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71(16):1755–1764.
- Vergara A, De Felice M, Cesaro A, et al. Immune-checkpoint inhibitor-related myocarditis: where we are and where we will go. *Angiology* 2024;75(10):909–920.
- Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375(18):1749–1755.
- Ibraheim H, Perucha E, Powell N. Pathology of immune-mediated tissue lesions following treatment with immune checkpoint inhibitors. *Rheumatology (Oxford)* 2019;58(Suppl 7):vii17–vii28.
- Golpour A, Patriki D, Hanson PJ, et al. Epidemiological impact of myocarditis. *J Clin Med* 2021;10(4):603.
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363(8):711–723.
- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372(4):320–330.
- Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;373(1):23–34.
- Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med* 2015;372(21):2006–2017.
- Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018;19(12):1579–1589.
- Rubio-Infante N, Ramírez-Flores YA, Castillo EC, et al. Cardiotoxicity associated with immune checkpoint inhibitor therapy: a meta-analysis. *Eur J Heart Fail* 2021;23(10):1739–1747.
- Li C, Bhatti SA, Ying J. Immune checkpoint inhibitors-associated cardiotoxicity. *Cancers (Basel)* 2022;14(5):1145.
- Shalata W, Abu-salman A, Steckbeck R, et al. Cardiac toxicity associated with immune checkpoint inhibitors: a systematic review. *Cancers (Basel)* 2021;13(20):5218.
- Otto SM, Martinez AL, Dains JE. Risk factors for immune checkpoint inhibitor-related myocarditis: an integrative review. *J Adv Pract Oncol* 2024;15(2):111–123.
- Fairweather DL, Cooper LT, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol* 2013;38(1):7–46.
- Brumberger ZL, Branch ME, Klein MW, et al. Cardiotoxicity risk factors with immune checkpoint inhibitors. *Cardiooncology* 2022;8(1):3.
- Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* 2017;28(2):368–376.
- Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. *J Clin Oncol* 2018;36(19):1905–1912.
- Lyon AR, Yousaf N, Battisti NML, et al. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol* 2018;19(9):e447–e458.
- Oren O, Yang EH, Molina JR, et al. Cardiovascular health and outcomes in cancer patients receiving immune checkpoint inhibitors. *Am J Cardiol* 2020;125(12):1920–1926.
- Chen X, Jiang A, Zhang R, et al. Immune checkpoint inhibitor-associated cardiotoxicity in solid tumors: real-world incidence, risk factors, and prognostic analysis. *Front Cardiovasc Med* 2022;9:882167.
- Escudier M, Cautela J, Malissen N, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. *Circulation* 2017;136(21):2085–2087.
- Anquetil C, Salem JE, Lebrun-Vignes B, et al. Immune checkpoint inhibitor-associated myositis: expanding the spectrum of cardiac complications of the immunotherapy revolution. *Circulation* 2018;138(7):743–745.
- Allenbach Y, Anquetil C, Manouchehri A, et al. Immune checkpoint inhibitor-induced myositis, the earliest and most lethal complication among rheumatic and musculoskeletal toxicities. *Autoimmun Rev* 2020;19(8):102586.
- Moslehi J, Lichtman AH, Sharpe AH, et al. Immune checkpoint inhibitor-associated myocarditis:

- manifestations and mechanisms. *J Clin Invest* 2021;131(5):e145186.
41. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;34(33):2636–2648.
42. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018;72(24):3158–3176.
43. Thavendiranathan P, Zhang L, Zafar A, et al. Myocardial T1 and T2 mapping by magnetic resonance in patients with immune checkpoint inhibitor-associated myocarditis. *J Am Coll Cardiol* 2021;77(12):1503–1516.
44. Cadour F, Cautela J, Rapacchi S, et al. Cardiac MRI features and prognostic value in immune checkpoint inhibitor-induced myocarditis. *Radiology* 2022;303(3):512–521.
45. Sakaguchi H, Nanjo S, Sato S, et al. Effectiveness of additional immunosuppressive drugs for corticosteroid-refractory immune checkpoint inhibitor-induced myocarditis: two case reports. *Intern Med* 2025;64(8):1205–1210.
46. Drazner MH, Bozkurt B, Cooper LT, et al. 2024 ACC expert consensus decision pathway on strategies and criteria for the diagnosis and management of myocarditis: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2025;85(4):391–431.
47. Hood KA, Zarembski DG. Mycophenolate mofetil: a unique immunosuppressive agent. *Am J Health Syst Pharm* 1997;54(3):285–294.
48. Blagova O, Rud' R, Kogan E, et al. Comparative efficacy and safety of mycophenolate mofetil and azathioprine in combination with corticosteroids in the treatment of lymphocytic myocarditis. *J Clin Med* 2023;12(15):4913.
49. Kociol RD, Cooper LT, Fang JC, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation* 2020;141(6):e69–e92.
50. Tay RY, Blackley E, McLean C, et al. Successful use of equine anti-thymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy. *Br J Cancer* 2017;117(7):921–924.
51. Barry T, Gallen R, Freeman C, et al. Successful treatment of steroid-refractory checkpoint inhibitor myocarditis with globulin derived-therapy: a case report and literature review. *Am J Med Sci* 2021;362(4):424–432.
52. Liu S, Chan J, Brinc D, et al. Immune checkpoint inhibitor-associated myocarditis with persistent troponin elevation despite abatacept and prolonged immunosuppression. *JACC CardioOncol* 2020;2(5):800–804.
53. Liu X, Wu W, Fang L, et al. TNF- α inhibitors and other biologic agents for the treatment of immune checkpoint inhibitor-induced myocarditis. *Front Immunol* 2022;13:922782.
54. Reynolds KL, Zlotoff DA, Mooradian M, et al. Abatacept for immune checkpoint inhibitor associated myocarditis (ATRIUM): phase 3, investigator-initiated, randomized, placebo-controlled study to evaluate the efficacy and safety of abatacept compared to placebo in hospitalized patients with immune checkpoint inhibitor associated myocarditis. *J Clin Oncol* 2023;41(16_suppl):TPS2680.
55. Mohammad KO, Fanous H, Vakamudi S, et al. Refractory right ventricular myocarditis induced by immune checkpoint inhibitor despite therapy cessation and immune suppression. *Cardiooncology* 2023;9(1):15.
56. Bockstahler M, Fischer A, Goetzke CC, et al. Heart-specific immune responses in an animal model of autoimmune-related myocarditis mitigated by an immunoproteasome inhibitor and genetic ablation. *Circulation* 2020;141(23):1885–1902.
57. Yu J, Long B, Li Z, et al. Central memory CD4+ T cells play a protective role against immune checkpoint inhibitor-associated myocarditis. *Cardiovasc Res* 2024;120(12):1442–1455.



Efficacy vs Effectiveness: What Truly Matters to the Practicing Clinician?

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In clinical practice, very few decisions are made in ideal circumstances. The patients we treat rarely resemble the precisely selected participants enrolled in randomized controlled trials (RCTs), although RCTs are the gold standard in evaluating the effects of treatments.¹

As clinicians, we frequently depend on data from RCTs to guide prescribing decisions. These trials typically evaluate efficacy and safety to determine whether a drug works under ideal, highly controlled conditions with strict inclusion and exclusion criteria. However, the patient sitting in front of us rarely represents those ideal conditions. This is where effectiveness becomes critically important.²

UNDERSTANDING THE DIFFERENCE

Efficacy trials (often RCTs) are designed to determine whether an intervention works under ideal circumstances. They use strict inclusion and exclusion criteria, closely monitor adherence, control co-interventions, and aim to maximize internal validity. The goal is to determine if the drug produces the intended effect.³⁻⁷

Clinical trials move step by step, with each phase answering a different clinical question. Phase I studies are small and focus mainly on safety, helping researchers understand the safe dose range and identify important adverse effects. Phase II trials involve more patients and look at whether the drug actually works while continuing to monitor safety and refine the dose. Phase III trials expand to larger populations to confirm efficacy, compare the new treatment with standard therapy or placebo, and generate the robust data needed for regulatory approval. Once approved, phase IV or postmarketing studies track long-term safety and real-world effectiveness, often identifying rare adverse events and assessing use in broader patient groups.⁸

In contrast, effectiveness trials evaluate how an intervention performs in real-world settings. These studies often include broader patient populations, allow variations in practice, and reflect everyday clinical

behavior. Their strength lies in external validity. They answer a different but equally important question: does the drug work in routine clinical care?³⁻⁷

Real-world data refer to health information collected outside traditional randomized trials, including electronic health records, insurance claims, registries, and even wearable devices. When analyzed systematically, it generates real-world evidence (RWE) that shows how treatments actually perform in routine clinical practice. Unlike controlled trial settings, this approach reflects diverse patient populations, comorbidities, and everyday prescribing patterns. It helps clinicians and researchers understand effectiveness, long-term safety, outcomes in specific subgroups, and even cost implications. Because it is often faster and more economical than large trials, it has become an important complement to randomized studies. Regulatory bodies such as the US Food and Drug Administration also use RWE for postmarketing safety surveillance and selected regulatory decisions.⁹

WHY EFFICACY MATTERS

For clinicians, efficacy data provide assurance. They confirm that the intervention has intrinsic therapeutic value. Regulatory approvals depend on such evidence. Guidelines are often constructed upon it. Without efficacy trials, clinical medicine would lack a scientific foundation.³⁻⁸ For example, when evaluating a new antidiabetic drug, tightly controlled glycated hemoglobin (HbA1c) reductions under standardized conditions confirm that the molecule works. In early decision-making, efficacy is essential. It establishes biological plausibility and therapeutic potential. It gives us confidence that the intervention has intrinsic value. However, efficacy alone is not enough.

THE CLINICAL REALITY

The patients we see daily often differ substantially from those enrolled in efficacy trials. They are older. They have multiple

comorbidities. They take several concomitant medications. Their adherence varies. Social determinants influence outcomes. Renal and hepatic functions are not always ideal. Follow-up is inconsistent. In such settings, the controlled environment of efficacy trials begins to feel distant.³⁻⁸

An antidiabetic drug that lowers HbA1c by 0.7% in a tightly selected trial population may show a smaller effect in real-world patients with variable adherence. This is where effectiveness evidence becomes more relevant.

EFFECTIVENESS SPEAKS TO CLINICIANS^{7,8,10}

Effectiveness trials reflect routine care. They include heterogeneous populations, typical adherence patterns, and pragmatic outcomes. Their findings often align more closely with what clinicians actually observe.

From a clinician's standpoint, effectiveness answers practical questions:

- Will this drug work in my patient population?
- How will it perform alongside multiple comorbidities?
- What is the true magnitude of benefit outside research settings?
- Does it remain beneficial when adherence is imperfect?

These questions shape real prescribing decisions. While efficacy demonstrates that a drug can work, effectiveness demonstrates whether it does work in usual practice.

As clinicians, we should avoid viewing efficacy and effectiveness as competing concepts. They are complementary. Efficacy establishes the foundation. Effectiveness determines applicability.¹⁰ Evidence-based medicine requires integrating both. In chronic diseases such as diabetes, cardiovascular disease, or inflammatory conditions,

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effectiveness evidence often better informs long-term management strategies.

WHICH IS MORE RELEVANT FOR CLINICIANS?^{8,10}

If forced to choose, effectiveness may be more directly relevant for day-to-day clinical practice. It mirrors the reality in which clinicians operate.

However, the ideal approach is sequential interpretation:

1. First, confirm the drug works under controlled conditions.
2. Then, evaluate how it performs in real-world settings.
3. Finally, individualize the decision for the patient in front of you.

Efficacy provides scientific assurance. Effectiveness provides clinical confidence.

THE WAY FORWARD

With increasing emphasis on pragmatic trials, RWE, and large observational datasets,

modern research is moving toward bridging this gap. Clinicians should welcome this shift. It aligns evidence generation more closely with clinical realities. At the bedside, decisions are rarely binary. They involve patient preferences, comorbidities, costs, and system factors. In such complexity, effectiveness evidence often carries greater practical weight. Yet without efficacy trials, there would be no foundation to build upon.

CONCLUSION

Efficacy demonstrates potential. Effectiveness determines practice. For clinicians, both forms of evidence are essential. Efficacy tells us whether a drug can work. Effectiveness tells us whether it will work for the patients we actually treat. The art of clinical medicine lies in understanding this distinction and applying it thoughtfully.

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REFERENCES

1. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet* 2005;365:82–93.
2. Gartlehner G, Hansen RA, Nissman D, et al. Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006. Technical Reviews, No. 12. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK44024/>
3. Fritz JM, Cleland J. Effectiveness versus efficacy: more than a debate over language. *J Orthop Sports Phys Ther* 2003;33:163–165.
4. Streiner D, Norman G. Efficacy and effectiveness trials. *Community Oncol* 2009;6:472–474.
5. Selker HP, Gorman S, Kaitin KI. Efficacy-to-effectiveness clinical trials. *Trans Am Clin Climatol Assoc* 2018;129:279–300.
6. Costa ML, Griffin XL, Parsons N, et al. Efficacy versus effectiveness in clinical trials. *Bone Joint J* 2017;99-B(4):419–420.
7. Kim SY. Efficacy versus effectiveness. *Korean J Fam Med* 2013;34(4):227.
8. Trailokya A, Srivastava A, Mukaddam Q, et al. Phase IV studies: what clinicians need to know! *J Assoc Physicians India* 2024;72(1):85–87.
9. Trailokya AA, Srivastava A, Mukaddam Q, et al. Real-world evidence simplified for clinicians. *J Assoc Physicians India* 2025;73(2):78–80.
10. Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. *Clin Transl Gastroenterol* 2014;5(1):e45.

Atlantoaxial Dislocation Presenting with Quadriplegia after Local Neck Massage Therapy: A Unique Presentation



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A hypertensive man in his early 60s was brought to the emergency department with the chief complaints of sudden-onset inability to move the extremities and altered mentation. He had a history of chronic neck pain for the last 3–4 years with an exacerbation of the pain, for which he was recommended by his physiotherapist to undergo flexion, extension, rotation, and lateral flexion maneuver under medical supervision, but the patient went to a local salon and underwent a neck massage after a haircut, following which he developed hiccups and dysphagia to solids more than liquids, followed by slurring of speech. He gradually started developing weakness on the right side of the body, which progressed to quadriplegia over a period of 3 days.

He presented to the hospital conscious and alert, with spontaneous eye opening and response to all verbal commands but had hypotonia and 0/5 power in all extremities. He was intubated in view of poor mentation and later underwent a tracheostomy and was continued on mechanical ventilation. Computed tomography images of the brain showed extra-axial hemorrhage at the craniovertebral junction level impinging upon

medulla, with widening of the atlantodental interval. Magnetic resonance imaging (MRI) of the brain and spine was done for further characterization. It revealed atlantoaxial dislocation, extra-axial hematoma impinging upon medulla, and edema involving pons, medulla, and cervical spine up to the C5–C6 IV disc level (Fig. 1).

The patient underwent bilateral C1–C2 transpedicular screw fixation and placement of bone graft from the iliac crest at C1–C2 joint titanium implant fixation. This case clinches the need for the physician to think out of the box and consider the possibility of atlantoaxial dislocation and associated extra-axial hemorrhage,¹ causing brainstem compression in an elderly patient with no preexisting disease presenting with quadriparesis as the vital centers of respiration and circulation are located there and hence the need for urgent neurosurgical intervention.

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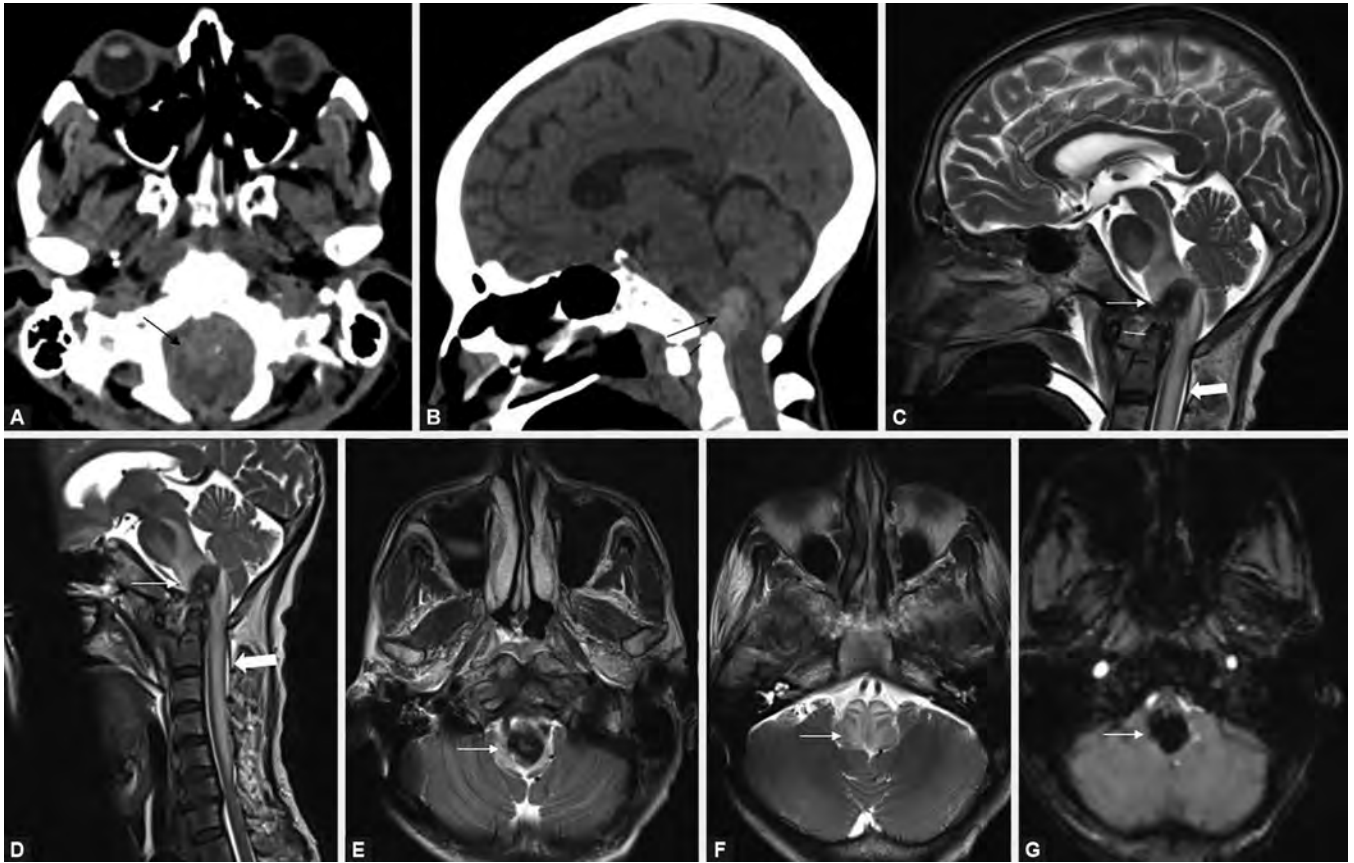
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1. Yin P, Gao N, Wu J, et al. Adverse events of massage therapy in pain-related conditions: a systematic review. *Evid Based Complement Alternat Med* 2014;2014:480956.

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Figs 1A to G: (A) Axial computed tomography image at the level of craniocervical junction showing extra-axial hematoma around odontoid process of C2 vertebra (shown by thin black arrow); (B) Sagittal multiplanar reformatted computed tomography image showing extra-axial hematoma (shown by thin black arrow) at base of skull impinging upon medulla oblongata, widening of atlantodental interval (shown by thin black line) suggestive of atlantoaxial dislocation; (C) Sagittal T2W MRI image of the brain showing T2 hypointense extra-axial hematoma (shown by thin white arrow) at base of skull impinging upon medulla oblongata with T2 hyperintensity representing edema (shown by thick white arrow) in pons, medulla, and cervical spinal cord, widening of atlantodental interval (shown by thin white line) suggestive of atlantoaxial dislocation; (D) Sagittal T2W MRI image of cervical spine showing T2 hypointense extra-axial hematoma (shown by thin white arrow) at base of skull impinging upon medulla oblongata with T2 hyperintensity representing edema (shown by thick white arrow) in pons, medulla, and cervical spinal cord extending up to C5–C6 intervertebral disc level; (E) Axial T2W MRI image at the level of C2 vertebra showing extra-axial hematoma (shown by thin white arrow); (F) Axial T2W MRI image at the level of pons showing diffuse intramedullary T2 hyperintensity representing edema (shown by thin white arrow); (G) Axial SWI phase image showing significant blooming at the level of C2 vertebra representing hemorrhage (shown by thin white arrow)

Reappraisal of Comparison of the Efficacy and Safety of Biosimilar Adalimumab with Innovator Adalimumab in Ankylosing Spondylitis



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Keywords: Adalimumab injection, Ankylosing spondylitis, Efficacy.

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Dear Editor,

We read with interest an article titled "Comparison of the Efficacy and Safety of Biosimilar Adalimumab Injection with Innovator Adalimumab in Subjects with Active Ankylosing Spondylitis," published in the *Journal of the Association of Physicians of India*.¹ We have the following comments to offer:

- While the introduction provides a solid pharmacological and socioeconomic context, there is an absence of a clearly stated hypothesis and primary outcomes. The rationale is regulatory rather than scientific, and the flow prematurely introduces methodological details that should appear later.²
- The Methods section is demonstrated very well. However, key methodological details are missing: justification for noninferiority margin and 2:1 allocation, incomplete blinding description, lack of missing data handling, and absence of recruitment timeline. These omissions limit full reproducibility and transparency, which are essential for validating noninferiority randomized controlled trials (RCTs).³

- While the Results section is statistically detailed and transparent about efficacy equivalence, it falls short on several parameters such as missing temporal and flow details (recruitment dates and attrition causes), lack of structured adverse event (AE) tables and graphical clarity, overuse of *p*-values instead of confidence intervals, incomplete analysis report, and missing data handling.⁴
- The unusually high response rates compared to global trials, the short 12-week duration, and sponsor involvement limit interpretability. Larger, longer, and independently funded multicenter studies across diverse populations are required to confirm long-term equivalence and safety.⁵

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REFERENCES

1. Chandrashekara S, Parida JR, Sonawale A, et al. Comparison of the efficacy and safety of biosimilar adalimumab injection with innovator adalimumab in subjects with active ankylosing spondylitis. *J Assoc Physicians India* 2025;73(9):e21–e27.
2. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010;63(8):834–840.
3. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308(24):2594–2604.
4. Bass AR, Stratton KR, Kumova OK, Rosenberg D (Eds). Evidence Review of the Adverse Effects of COVID-19 Vaccination and Intramuscular Vaccine Administration. National Academies Press; 2024.
5. Xu H, Li Z, Wu J, et al. IBI303, a biosimilar to adalimumab, for the treatment of patients with ankylosing spondylitis in China: a randomised, double-blind, phase 3 equivalence trial. *Lancet Rheumatol* 2019;1(1):e35–e43.

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References: 1. Singhal S, et al. Evaluation of safety and efficacy of pantoprazole and domperidone combination in patients with gastroesophageal reflux disease. *Internet J Gastroenterol.* 2006;4(2):1-5. 2. Sakamoto Y, et al. Effects of domperidone on gastric emptying: a crossover study using a continuous real-time 13C breath test (BreathID system). *Hepatogastroenterology.* 2011;58(106):637-641. 3. Karamanolis GP, et al. Current management of functional dyspepsia: impact of Rome III subdivision. *Ann Gastroenterol.* 2012;25(2):96-99.

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Listing of the Affective Domain in the AETCOM Module: An Issue Requiring Attention from the National Medical Commission of India



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Keywords: Affective domain, Competency-based medical education, Medical education.

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The Attitudes, Ethics, and Communication (AETCOM) module¹ was published in 2018 by the Medical Council of India (MCI) and later also adopted by the National Medical Commission (NMC) in the Competency-based Medical Education (CBME) curriculum. The inclusion of AETCOM skills in medical education is vital in India to cultivate compassionate, ethical, and patient-centered healthcare professionals who can build trust and effectively address the sociocultural complexities of the healthcare system.²⁻⁴ This was a praiseworthy attempt by the regulators of medical education in the country, NMC, to include the affective domain by listing core competencies which need to be addressed in the undergraduate training such as communicating with patients, professionalism, and ethics, among others. The AETCOM module has been created as a roadmap to help instructors and institutions construct a long-term program that will assist students in developing the requisite communication, ethical, and attitude skills. It provides a framework for the competencies that students need to master.¹ Appendix 1 of the AETCOM module (pages 78–84) lists the core and noncore competencies with the primary domain and the level to which the competency in question should be attained. There are 39 core and 15 noncore

competencies listed in this appendix. Out of the 39 core competencies, 21 are in the knowledge (cognitive) domain and 18 are in the skills (psychomotor) domain; out of the 15 noncore competencies, 5 are in knowledge and 10 are in the skills domain. Not a single competency is listed under the affective domain. All the competencies such as empathy, altruism, commitment to lifelong learning, or scholarship are listed under knowledge or skills. In a module that is almost entirely focused on the affective domain, not listing a single competency under the affective domain is a major *faux pas* and the NMC should address this at once since choosing the appropriate teaching-learning methods for a given competency to be taught and assessed depends largely on correctly identifying the educational domain.⁵ It is concerning to observe that certain significant oversights have persisted without rectification, even 6 years after the publication of the AETCOM module and addressing them would greatly enhance its impact.

SUPPLEMENTARY MATERIAL

Appendix 1 is available online at the journal website. https://www.nmc.org.in/wp-content/uploads/2020/01/AETCOM_book.pdf

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REFERENCES

1. Medical Council of India (2018). Attitude, ethics and communications competencies for the Indian Medical Graduate. Available at: https://www.nmc.org.in/wp-content/uploads/2020/01/AETCOM_book.pdf [Last accessed July, 2026].
2. Nissilä S, Karjalainen A, Koukkari M. It is the shared aims, trust and compassion that allow people to prosper: teacher educators. *lifelong learning in competence-based education*. *Eur J Educ Res* 2022;11(2):965–980.
3. Lal S, Sehgal P. Integration of attitude, ethics, and communication competencies into competency-based UG curriculum. *Indian J Community Med* 2022;47(1):4–7.
4. Pagatpatan CP Jr, Valdezco JAT, Lauron JDC. Teaching the affective domain in community-based medical education: a scoping review. *Med Teach* 2020;42(5):507–514.
5. Amin Z, Khoo HE. *Basics in Medical Education*. Singapore: World Scientific; 2009.

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Stroke-like Episodes in MELAS are not Caused by Cerebral Vasculopathy

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Keywords: m.3243A>G, MELAS, mtDNA, MT-TL1, Stroke-like episode.

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Dear Editor

We reviewed the article by Goel et al. on a 19-year-old male with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) due to the m.3243A>G variant in MT-TL1, who presented with seizures (for 5 years), hypoacusis (for 4 years), basal ganglia calcification, cognitive decline, short stature, hypogonadism, and a stroke-like episode (SLE) with visual field defects, migraine-like headaches, and vomiting.¹ The antiepileptic drug was switched from valproic acid to levetiracetam, and a mitochondrial cocktail was added.¹ The study is interesting, but some points should be discussed.

The first point is that the tissue in which the m.3243A>G variant was detected was not mentioned.¹ It is crucial to know whether the MT-TL1 variant was found in the blood, oral mucosal cells, urinary epithelial cells, muscle cells, hair follicles, or skin fibroblasts, as some of these tissues may be clinically affected while others are clinically unaffected. There is also no information on heteroplasmy rates, mtDNA copy number, haplotype, mutations in nDNA, tissue distribution, and environmental factors, all of which strongly influence the phenotype. To establish a genotype–phenotype correlation, it is crucial to know these influencing factors.

The second point relates to the identification of a stroke-like lesion (SLL), the morphological equivalent of an SLE, in multimodal MRI.¹ SLLs can be hyperintense not only on T2/FLAIR, but also on diffusion-weighted images (DWI) and perfusion-

weighted images (PWI).² They are hypointense on oxygen extraction fraction (OEF) MRI and hypometabolic on FDG positron emission tomography (PET).¹ SLLs are not confined to a vascular area and typically enlarge over several days until they reach a nadir, after which they regress and eventually end up as normal brain tissue, cyst, laminar cortical necrosis, focal atrophy, white matter lesion, or toenail sign.¹ Therefore, other critical MRI modalities should have been described, and long-term follow-up MRI results should have been provided.

The third point relates to the discrepancy between the high serum lactate levels (11.6 mmol/L) and the “unremarkable” muscle biopsy findings. Since lactate usually originates from muscles or blood cells,³ it should be explained whether the high serum lactate originated from the brain, myocardium, or other tissue. It should also be explained why the patient had elevated creatine kinase levels but normal muscle biopsy findings.¹ Was the biopsy examined only by light microscopy or also by immunohistochemistry or electron microscopy?

The fourth point is that cerebrospinal fluid (CSF) findings were reported as normal, but it was not mentioned whether CSF lactate was measured or not. Since the magnetic resonance spectroscopy found an increased lactate peak, it is conceivable that the CSF lactate was also increased.

The fifth point is that we disagree with the notion that SLEs are due to cerebral vasculopathy.¹ Since SLLs are not confined

to a vascular territory, they cannot originate from vasculopathy. More likely, SLLs are due to metabolic breakdown with consecutive spreading of the metabolic defect. Seizures are also unlikely to be the universal trigger of SLL, as there are SLEs in the absence of seizures.⁴

Finally, no reference limits were reported for the serum levels of parameters shown in the list of the case description. Without reference limits, it is difficult to interpret which of the parameters was increased, decreased, or normal. It is also not conceivable that the 19-year-old index patient could decline genetic testing of his siblings. Was the index patient the guardian of his siblings?

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REFERENCES

1. Goel K, Sinha N, Singh D, et al. Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes: a masquerader of young-onset stroke. *J Assoc Physicians India* 2025;73(115):24–26.
2. Finsterer J. Characteristics of stroke-like lesions on cerebral imaging. *Ideggyogy Sz* 2023;76(1–2):5–10.
3. Rabinowitz JD, Enerbäck S. Lactate: the ugly duckling of energy metabolism. *Nat Metab* 2020;2(7):566–571.
4. Mickelsson N, Hirvonen J, Martikainen MH. Clinical features and treatment of stroke-like episodes in mitochondrial disease: a cohort-based study. *J Neurol* 2024;272(1):47.

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Efficacy and Tolerability of Tenofovir/Lamivudine/ Dolutegravir among Antiretroviral Therapy Naive Human Immunodeficiency Virus Infected Patients of a Tertiary Care Center in Eastern India



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In the published article entitled "Efficacy and Tolerability of Tenofovir/Lamivudine/Dolutegravir among Antiretroviral Therapy Naive Human Immunodeficiency Virus Infected Patients of a Tertiary Care Center in Eastern India," the designations of the first two authors were interposed.¹ The correct designations of the authors are as follows:

1. Debroop Sengupta, Junior Resident, Department of General Medicine, IPGMER & SSKMH, Kolkata, West Bengal, India
2. Sandip Ghosh*, Associate Professor, Department of General Medicine, IPGMER & SSKMH, Kolkata, West Bengal, India
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REFERENCE

1. Sengupta D, Ghosh S, Pain S, et al. Efficacy and tolerability of tenofovir/lamivudine/dolutegravir among antiretroviral therapy naive human immunodeficiency virus infected patients of a tertiary care center in Eastern India. *J Assoc Physicians India* 2023;71(9):72-74.

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*Anjana RM et al. Lancet Diabetes Endocrinol.2023 Jul; 11(7) : 474 - 489



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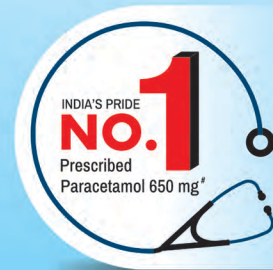
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