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EDITORIAL

MASLD—A Gateway for ASCVD: A Call for Early Intervention and Multidisciplinary Care

Prabhash Chand Manoria[1*], Piyush Manoria[2]

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has emerged as a significant public health concern, affecting approximately 25% of the global population with its prevalence rising from 22% in 1991 to 37% in 2019.[1] While the hepatic consequences of MASLD, such as steatohepatitis, fibrosis, and cirrhosis, are well documented, its systemic implications are increasingly coming to light. While traditionally viewed as a hepatic disorder, growing evidence highlights MASLD as a multisystem disease with profound implications on cardiovascular health. Atherosclerotic cardiovascular disease (ASCVD) has now been recognized as the leading cause of mortality in patients with MASLD, surpassing liver-related complications. MASLD is present in up to 75% of patients with type 2 diabetes mellitus (T2DM). Notably, MASLD is linked to a higher risk of cardiovascular diseases (CVD), including arrhythmia, atherosclerotic heart disease, heart failure, and CVD-related mortality.[2] The association between MASLD and ASCVD is particularly alarming, positioning MASLD as a critical gateway for cardiovascular morbidity and mortality.

Metabolic dysfunction-associated steatotic liver disease and ASCVD share common pathophysiological underpinnings, including insulin resistance, chronic inflammation, dyslipidemia, and endothelial dysfunction. These overlapping mechanisms suggest that MASLD is not merely a liver-specific condition but a multisystem disorder with far-reaching consequences. Emerging evidence indicates that individuals with MASLD are at a significantly higher risk of developing ASCVD, independent of traditional cardiovascular risk factors.[3] This association underscores the need for a paradigm shift in how we perceive and manage MASLD, moving beyond hepatology to embrace a more holistic, multidisciplinary approach.

The MASLD–ASCVD Nexus: A Pathophysiological Continuum

The relationship between MASLD and ASCVD is bidirectional and synergistic. On one hand, MASLD exacerbates cardiovascular risk by promoting atherogenic dyslipidemia, systemic inflammation, and oxidative stress. On the other hand, the metabolic dysregulation driving ASCVD—such as obesity, type 2 diabetes, and hypertension—also fuels the progression of MASLD. This vicious cycle highlights the importance of early detection and intervention in MASLD to mitigate its cardiovascular sequelae.

Recent studies have demonstrated that the severity of liver fibrosis in MASLD is a strong predictor of cardiovascular outcomes.[4] Patients with advanced fibrosis are at a markedly increased risk of coronary artery disease, heart failure, and arrhythmias. These findings emphasize the need for risk stratification in MASLD patients, with a focus on identifying those at highest risk for ASCVD. A major concern is that MASLD often remains undiagnosed, as hepatic steatosis is frequently silent until advanced stages. This diagnostic gap results in a missed opportunity for early cardiovascular risk stratification and intervention. Given that MASLD affects nearly a quarter of the global population, the implications for ASCVD prevention are substantial.

Reframing MASLD as a Cardiovascular Risk Factor

Given the strong association between MASLD and ASCVD, it is imperative to incorporate hepatic health into cardiovascular risk assessment frameworks. Current guidelines emphasize traditional risk factors such as hypertension, diabetes, and dyslipidemia, but MASLD remains largely overlooked. Emerging data suggest that advanced MASLD, especially in the presence of fibrosis [metabolic dysfunction-associated liver fibrosis, or metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis], confers an independent risk for cardiovascular events.[3] A shift toward proactive screening strategies in high-risk individuals, such as those with type 2 diabetes, obesity, or metabolic syndrome, is warranted. Incorporating noninvasive tools like, liver stiffness measurements, and serum biomarkers into routine cardiovascular evaluations can aid in early risk identification.

A Call for Early Intervention and Integrated Management

Given the strong link between MASLD and ASCVD, early intervention is paramount. Lifestyle modifications, including weight loss, dietary changes, and increased physical activity, remain the cornerstone of MASLD management. These interventions not only improve liver health but also reduce cardiovascular risk. Pharmacological therapies targeting metabolic dysfunction show promise in addressing both MASLD and ASCVD offering a dual benefit. Drugs like Vitamin E, pioglitazone and saroglitazar has been used in treatment of MASLD for quiet sometime but recently Resmetirom and injectable semaglutide has also been approved for treatment of MASLD by US FDA. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have also shown encouraging results in its treatment. Moreover, the integration of cardiovascular risk assessment into the routine care of MASLD patients is essential. Hepatologists, cardiologists, endocrinologists, consultant physicians, and primary care providers must collaborate to develop comprehensive care plans that address both hepatic and extrahepatic manifestations of MASLD. Noninvasive tools, such as transient elastography and cardiovascular risk scores, can aid in risk stratification and guide therapeutic decisions.

The Role of Research and Public Health Initiatives

Despite the growing recognition of the MASLD–ASCVD connection, significant gaps remain in our understanding of the underlying mechanisms and optimal management strategies. Large-scale, longitudinal studies

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are needed to elucidate the causal pathways linking MASLD to ASCVD and to identify biomarkers that can predict cardiovascular outcomes in MASLD patients. Additionally, public health initiatives aimed at raising awareness of MASLD and its systemic implications are crucial for early detection and prevention.

Conclusion

Metabolic dysfunction-associated steatotic liver disease is no longer just a liver disease; it is a multisystem disorder with profound implications for cardiovascular health. The recognition of MASLD as a cardiovascular risk amplifier necessitates a paradigm shift in clinical practice. Moving beyond the liver-centric approach and integrating MASLD into ASCVD risk prediction models can significantly enhance preventive strategies. The strong association between MASLD and ASCVD underscores the need for early intervention, multidisciplinary care, and a renewed focus on research and public health initiatives. By addressing MASLD as a gateway for ASCVD, we can not only improve liver outcomes but also reduce the global burden of cardiovascular disease. The time has come to view MASLD not just as a hepatic disorder but as a sentinel warning of impending cardiovascular disease. By addressing this link proactively, we have the opportunity to mitigate ASCVD burden and improve long-term patient outcomes. The time to act is now, before the ripple effects of MASLD become a tidal wave of cardiovascular morbidity and mortality.

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References

1. Le MH, Yeo YH, Li X, et al. 2019 Global NAFLD prevalence: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2022;20:2809–2817.
2. Møller S, Kimer N, Hove JD, et al. Cardiovascular disease and metabolic dysfunction-associated steatotic liver disease: pathophysiology and diagnostic aspects. Eur J Prev Cardiol 2025:zwae306.
3. Zheng H, Sechi LA, Navarese EP, et al. Metabolic dysfunction-associated steatotic liver disease and cardiovascular risk: a comprehensive review. Cardiovasc Diabetol 2024;23(1):346.
4. Driessen S, Francque SM, Anker SD, et al. Metabolic dysfunction-associated steatotic liver disease and the heart. Hepatology 2023;82:487–503.

Living Will and Advance Care Planning: The Need of the Hour

Umesh Khanna[1*], Smriti Khanna[2]

What is Advance Care Planning and Why Does It Matter for Clinicians?

Advance care planning (ACP) refers to the process through which patients, their families, and healthcare providers discuss and record preferences for end-of-life care.[1] Internationally, ACP has been shown to reduce unnecessary interventions, align medical decisions with patient wishes, and provide dignity at the end-of-life. In India, however, structured ACP is virtually absent. Good end-of-life care is directly linked to the quality of death that Indians achieve, which has been consistently poor; in the 2021 Quality of Death Index report, India ranked 59 out of 81 countries that were studied.[2]

For physicians, the absence of ACP is more than an ethical dilemma; it is a daily practical challenge. Doctors are frequently caught between offering aggressive interventions that may be futile and the risk of being accused of negligence if they withdraw or withhold treatment. In a country where nearly 80% of deaths now occur in hospitals, ACP offers a path forward by documenting patient preferences. It gives doctors the confidence to respect autonomy while staying within legal and professional boundaries.

Definitions and Scope

Advance care planning is defined by the European Association of Palliative Care as planning that "enables individuals to define goals and preferences for future medical treatment and care, to discuss these goals and healthcare preferences with family and healthcare providers, and to record and review these preferences if appropriate."[1] The "umbrella" of ACP can include advanced medical directives (AMDs), designation of healthcare power of attorney, do not attempt resuscitation (DNAR) orders, and physicians' orders for limiting life-sustaining treatment (POLST). These terminologies are discussed in Table 1.[3]

Advanced Medical Directives: The History

The term living will was coined by Luis Kutner, a US-based human rights lawyer in 1969. The power of attorney was added to the living will in the 1980s–90s, so that individuals without capacity also had a way of ensuring their wishes were followed by appointing a designated healthcare representative.[4]

On March 9, 2018, the Supreme Court of India passed a judgment affirming the individual right to autonomy under Article 21. The judgment extended this autonomy to medical decision-making in the event of terminal illness by recognizing and laying down the process of creating AMDs. However, the administrative procedure required for the same was very tedious, and very few individuals were actually successful in creating their AMDs. This procedural complexity was addressed in a January 2023 Supreme Court amendment, which has given the procedure that we currently follow for creating an AMD. The Supreme Court has also retained a set of checks and balances, including a two-step medical board verification process and a shared decision-making model with the designated healthcare provider.[5]

In parallel, medical and nonmedical societies such as the Indian Society of Critical Care Medicine, the Indian Association of Palliative Care, and the Federation of Indian Chambers of Commerce and Industry have issued guidelines on good end-of-life care, incorporating DNAR orders and administrative procedures for medical institutions.[6,7]

The Living Will: Practical Aspects

The Indian ACP pathway has been outlined previously by Damani et al.,[8] which covers steps from creation to implementation of the living will. The Indian living will, as described in the Supreme Court judgment, has its scope limited to terminal illness.[5]

While an ACP discussion can be done by all healthcare professionals, including doctors, nurses, and social workers, it usually falls within the purview of doctors.[9] The first Living Will Clinic of India was launched at PD Hinduja Hospital, Mumbai, to give guidance and medical information about various aspects of the living will process.[10] Individuals present to the clinic to understand the various medical procedures that may be performed at the end-of-life and to discuss their preferences.

These individuals fall under three categories:

- Healthy individuals or individuals with stable long-term illnesses, for example, hypertension (HTN) and diabetes mellitus (DM).
- Individuals with serious illness who have required multiple medical interventions, for example, organ failure.
- Individuals in the last year of life, for example, end-stage organ disease and stage 4 cancer.

Table 1: List of terminologies falling under the ACP umbrella[3]

ACP terms	*Description*
Advanced care planning	Process of considering and communicating personal values and goals related to medical care over time
Designated healthcare representative	A person nominated to take healthcare decisions when the patient is incapacitated
Living will	A document that records patients' preferences about medical treatment
AMD	A document that (1) records patients' preferences about medical treatment and (2) designates a healthcare representative. In this document, the terms living will and AMD are used interchangeably
DNAR order	A documented decision to withhold cardiopulmonary resuscitation from a patient, taken with the consent of the patient. They are valid as per the ICMR guidelines on DNAR
Physician orders for life-sustaining treatment	Medical documents that translate patient preferences into physician directed order; not valid in India

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The discussion also includes decision-making about a designated healthcare representative who will be responsible for carrying out the patient's wishes once the living will gets activated. Once they have reflected on these aspects, they prepare their final document under supervision for notarization and submission. Patients are encouraged to discuss their medical preferences with their family. The hope is that ACP and Living Will Clinics in the country will enhance death literacy.

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References

1. Rietjens JAC, Sudore RL, Connolly M, et al. Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. Lancet Oncol 2017;18(9):e543–e551.
2. Butola S, Gursahani R. Advance care planning and the ethical obligation of death literacy as a public health initiative in India. Indian J Med Ethics 2024;9(4):308–312.
3. Mehta D, et al. End of Life Care and the Law in India: Addressing Common Concerns. Vidhi Centre for Legal Policy. New Delhi; 2025.
4. Sabatino CP. The evolution of health care advance planning law and policy. Milbank Q 2010;88(2):211–239.
5. Supreme Court of India. Common Cause v. Union of India, Miscellaneous Application 1699/2019 in Writ Petition (C) 215/2005. [Accessed on October 10, 2025]. Available from: https://indiankanoon.org/doc/184449972/
6. Mani RK, Bhatnagar S, Butola S, et al. Indian Society of Critical Care Medicine and Indian Association of Palliative Care Expert Consensus and Position Statements for End-of-life and Palliative Care in the Intensive Care Unit. Indian J Crit Care Med 2024;28(3):200–250.
7. End of Life Care in India Taskforce (ELICIT), Federation of Indian Chambers of Commerce & Industry. Improving End-of-life Care & Decision-making. Available from: https://www.scribd.com/document/727108801/FICCI-ELICIT-Guide-for-Doctors-and-Administrators. [Accessed on October 15, 2025].
8. Damani A, Ghoshal A, Rao K, et al. Enhancing advance care planning in India through a 12-step pathway. Indian J Crit Care Med 2025;29(4):301–307.
9. Martina D, Lin CP, Kristanti MS, et al. Advance care planning in Asia: a systematic narrative review of healthcare professionals' knowledge, attitude, and experience. J Am Med Dir Assoc 2021;22(2):349.e1–349.e28.
10. Iyer M. In a First, Mumbai Hospital Starts Clinic to Help Prepare Living Will. The Times of India; 2025. Accessed from: https://timesofindia.indiatimes.com/city/mumbai/in-a-1st-city-hosp-starts-clinic-to-help-prepare-living-will/articleshow/122146845.cms.

ORIGINAL ARTICLE

Knowledge, Attitudes, and Practices of Indian Cross-specialty Healthcare Professionals Managing Diabetes on Nondiarrheal Dehydration and Its Management in Persons with Diabetes

Manoj Chawla[1*], Sanjay Agarwal[2], Sanjay Kalra[3], L Sreenivasamurthy[4]

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Abstract

Background: Hydration plays a vital role in metabolic health, particularly in diabetes, where factors such as osmotic diuresis, polypharmacy, and comorbidities heighten the risk of dehydration. Effective management of fluid, electrolyte, and energy (FEE) deficits is crucial, yet gaps persist in current practices. This is the first study to assess the knowledge, attitude, and practices of cross-specialty healthcare professionals (HCPs) managing diabetes on such a unique issue in persons with diabetes.

Objectives: This study assessed the knowledge, attitudes, and practices (KAP) of 525 cross-specialty HCPs managing diabetes in India regarding FEE management in diabetic patients with acute nondiarrheal illnesses to identify gaps and inform interventions.

Materials and methods: An online cross-sectional survey evaluated physician perspectives on dehydration in diabetes using a 30-item questionnaire covering knowledge of dehydration in diabetes, attitudes toward the oral FEE formulations, and current practice.

Results: Most respondents (90%) identified osmotic diuresis as a key driver of dehydration in diabetes, with 75% highlighting Sodium–glucose cotransporter 2 (SGLT-2) inhibitors as a risk factor. Despite widespread recognition of the adverse effects of dehydration and energy deficits (86%), only 46.5% routinely assessed hydration status during acute illnesses in persons with diabetes. Slow-release carbohydrates, such as isomaltulose, D-tagatose, and trehalose, were favored by 68.9% of respondents for their metabolic benefits to address energy deficits. 84.2% of HCPs perceived ready-to-drink (RTD) FEE formulations supporting rehydration and enhanced recovery, with an average impact on recovery time of 4.1 days.

Conclusion: This study highlights the gaps in understanding the role of hydration in persons with diabetes. It also underscores the need for standardized oral FEE management guidelines and innovative solutions, such as RTD FEE drinks, to improve outcomes in diabetic care.

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Introduction

Water balance is critical for maintaining homeostasis and metabolic health, with optimal hydration supporting physiological processes and cellular equilibrium.[1] However, disruptions in water balance are common in diabetes due to inadequate fluid intake, increased losses, or underlying complications.[2] In India, approximately 77 million individuals live with diabetes, a number projected to exceed 134 million by 2045.[3] This highlights the need for effective hydration strategies tailored to this population.

Patients with diabetes face unique hydration challenges driven by factors such as hyperglycemia, diuretic use, complex drug regimens, and comorbid conditions.[4] Coexisting conditions, such as fever, nausea, vomiting, and infections, further compound these risks by disturbing fluid and electrolyte balance, increasing the likelihood of severe complications.[5]

Uncontrolled diabetes mellitus leads to osmotic diuresis, characterized by excessive urination (polyuria) and compensatory increased thirst (polydipsia).[6] This process results in substantial deficits in water, sodium, and potassium, leading to dehydration and electrolyte imbalances. Sodium–glucose cotransporter 2 (SGLT-2) inhibitors, one of the therapeutic interventions used in diabetes management, exacerbate these challenges by promoting glucosuria, osmotic diuresis, and natriuresis.[7]

Hyperglycemia-induced osmotic diuresis and associated electrolyte imbalances are central to the pathogenesis of dehydration in diabetes. Dehydration also raises plasma arginine vasopressin (AVP) levels, disrupting glucose homeostasis by stimulating glycogenolysis and gluconeogenesis through hepatic and neuroendocrine pathways.[8] These mechanisms not only worsen glycemic control but also contribute to metabolic instability.

Dehydration in diabetes presents symptoms such as fatigue, hypotension, and tachycardia, which can range from mild to life-threatening.[9] Despite its prevalence, dehydration is frequently underdiagnosed due to its nonspecific symptoms and the absence of universal diagnostic criteria. Furthermore, dehydration impairs immune function by disrupting aquaporin-mediated cellular processes critical for chemotaxis, phagocytosis, and overall immune response, potentially delaying recovery even in nondiarrheal conditions.[10]

Effective management of hydration in diabetes requires timely fluid and electrolyte therapy to restore fluid, electrolyte, and energy (FEE) balance and prevent complications. A daily total water intake (TWI) of at least 1.8 L is recommended to maintain metabolic health and avoid dehydration-related glycemic dysfunction.[11]

Traditional oral rehydration solutions (ORS) are effective for treating dehydration but may lack sufficient energy provision for nondiarrheal conditions.[12] Emerging evidence supports the use of ready-to-drink (RTD) FEE formulations enriched with sugar substitutes such as isomaltulose, D-tagatose, trehalose, and stevia (natural sweetener).[13,14] These alternatives provide glycemic control, improve insulin response, and reduce caloric intake while addressing hydration and energy needs.

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Although hydration strategies using RTD FEE supplements have shown potential in managing electrolyte imbalances, hyperglycemia, and comorbidities in diabetic patients, there is a lack of data on their application in the Indian context, where the diabetes burden is rapidly rising. To address this knowledge gap, we conducted a knowledge, attitude, and practice (KAP) study among cross-specialty healthcare professionals (HCPs) managing diabetes in India, focusing on the utilization of oral supplements in their diabetic patients. This study aims to identify prescription gaps and provide insights to improve patient outcomes, emphasizing the need for effective and accessible interventions for this vulnerable population.

Materials and Methods

Study Design

This was a research initiated by the Research Society for the Study of Diabetes in India (RSSDI). An online, cross-sectional survey evaluated physicians' KAP concerning the management of FEE deficits in acute nondiarrheal illnesses using oral FEE formulations.[15] The questionnaire was hosted on the RSSDI website, targeting cross-specialty HCPs managing diabetes (endocrinologists, Diabetologists (Diploma in Diabetology), general practitioners, and internal medicine physicians with diabetes practice) across India.

Study Questionnaire

The questionnaire included four domains: (1) knowledge of dehydration in persons with diabetes, FEE deficits, dehydration awareness, clinical challenges, signs, symptoms, and biomarkers; (2) attitudes toward FEE drink use in various clinical scenarios; (3) practices related to prescribing and recommending FEE drinks; and (4) perceived patient outcomes, focusing on oral FEE management's impact on recovery. The survey comprised 30 questions, provided as an appendix.

Study Outcomes

The study's primary outcome was to evaluate Indian cross-specialty HCPs managing diabetes's KAP regarding oral FEE management in diabetes, particularly with acute nondiarrheal illnesses. The secondary outcome assessed the perceived effectiveness of oral FEE strategies on recovery speed and overall health improvement in persons with diabetes.

Statistics

Results will be presented as mean ± standard deviation (SD), and knowledge scores will be summed to a maximum of 6. Correlation analysis will assess associations between knowledge scores, attitudes, practices, and perceived outcomes, with statistical tests performed at $\alpha = 0.05$ using R version 4.4.2 and RStudio version 2024.9.1.394.

Ethics Committee and Informed Consent

The study protocol was reviewed and approved by the Suraksha Ethics Committee on 26th June, 2024. Informed consent was obtained from all participating physicians.

Results

The online questionnaire was completed by 525 cross-specialty HCPs managing diabetes, and their demographics are provided in Table 1. The key findings related to the increased risk of dehydration, the influence of SGLT-2 inhibitors, diagnostic challenges in dehydration, the impact of dehydration and energy deficits, the role of slow-release carbohydrates, and the importance of hydration status assessment are provided in Table 2 and Figure 1.

Nearly 90% of diabetologists, consulting physicians, and endocrinologists agreed that dehydration and energy deficits in diabetes have a high impact on their recovery from acute nondiarrheal illnesses, as against 75% of general practitioners.

Interestingly, 67% consulting physicians and 82% diabetologists agreed that acute nondiarrheal illnesses (acute febrile illnesses/heat related illnesses/nausea vomiting) can further aggravate fluid electrolyte energy deficits due to insensible losses through the skin as sweat, through the lungs from respiration, sensible losses like vomiting as well as insufficient fluid intake while only 33% of general practitioners were aligned on same. This highlighted limited knowledge among general practitioners about mechanisms of FEE deficits in persons with diabetes and nondiarrheal conditions, while they see most of these patients in their practice.

Only 46% of general practitioners consider the high impact of chronic undetected dehydration on the health of persons with diabetes. 80–90% of all HCPs in the study agreed that oral formulations with the right balance of FEE content are vital to address FEE deficits in the recovery of persons with diabetes from acute nondiarrheal illnesses.

The findings related to the role of FEE management and the role of RTD FEE formulations are provided in Table 3 and Figure 2.

Interestingly, more general practitioners (44.2%) vs consulting physicians (15% and diabetologists (13%) agreed that RTD format electrolyte fluids with optimal glucose and sodium to facilitate glucose absorption with zero energy content will be most suitable to address the hydration needs of persons with diabetes.

About 86% consulting physicians, 89% diabetologists, and 92% endocrinologists agreed that RTD electrolyte drinks with an optimal concentration of sodium and glucose can provide rapid rehydration as compared to plain water in persons with diabetes.

Diabetologists (82.8%) and consulting physicians (90.6%) are more aligned than general practitioners (68.4%) on the fact that persons with diabetes have increased energy requirements during acute nondiarrheal illnesses. Similarly, a larger percentage of diabetologists and consulting physicians agreed that RTD FEE drinks based on slow-release carbohydrates such as isomaltulose, D-tagatose, and trehalose would form an efficient choice to restore rehydration and energy deficits in diabetic persons with acute nondiarrheal illnesses.

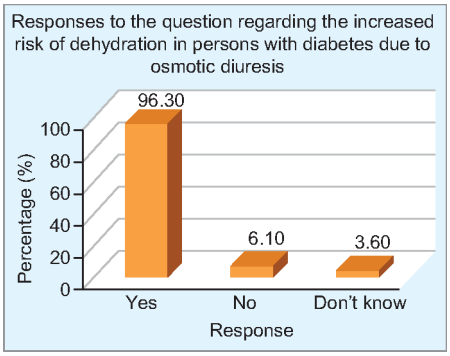

Fig. 1: Risk of dehydration in diabetic patients

Table 1: Survey participant demographics

Profession	*Number of physicians*	*Percentage (%)*
Diabetologist (diploma/fellowship in diabetology)	174	33.1
Consulting physician (MD/DNB internal medicine)	159	30.3
General practitioner (MBBS)	158	30.1
Nutritionist/dietitian	20	3.8
Endocrinologist (DM/DNB endocrinology)	14	2.7

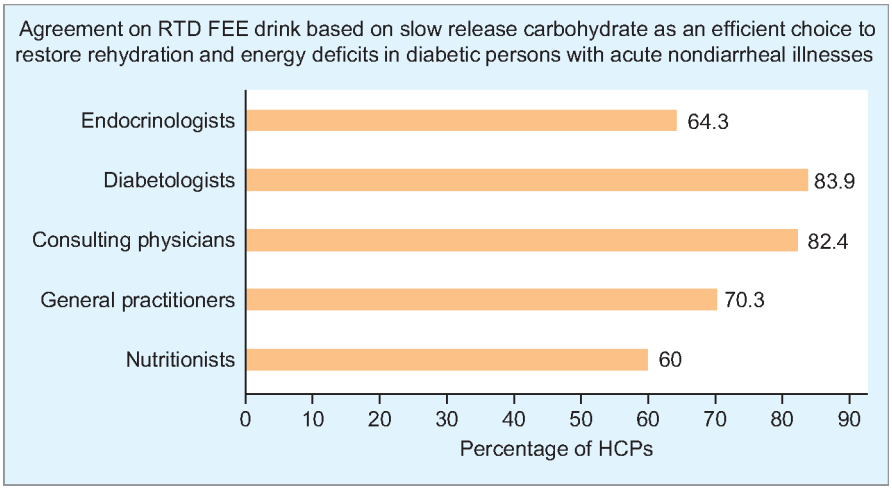

Fig. 2: Cross-specialty perceptions on the use of RTD FEE based on slow-release carbohydrate to restore FEE in diabetic persons with acute non-diarrheal illnesses

conditions as compared to non-RTD FEE drinks (Fig. 3).

The correlation between knowledge and attitude scores was evaluated using Spearman's rank correlation (ρ), yielding a moderate positive correlation (ρ = 0.476) among the respondents. This suggests that higher knowledge scores related to hydration and diabetes management are generally associated with more positive attitudes toward its importance, although the relationship is not perfectly consistent. The moderate strength of this correlation implies that increasing knowledge may influence attitudes positively, although other factors may also contribute to HCP' perceptions of the issue.

Table 4 provides the mean and median percent of diabetic patients in whom

Table 2: Key findings on the knowledge among cross-specialty HCPs managing diabetes related to hydration in their diabetic patients

Survey topic	*Finding*	*Percentage*
Increased risk due to osmotic diuresis	Acknowledgment of increased risk of dehydration due to osmotic diuresis	90.3%
Impact of SGLT-2 inhibitors	Link between SGLT-2 inhibitors and increased risk of dehydration	75%
Challenges in diagnosing dehydration	Absence of an international consensus on the definition and diagnosis	44.2%
	Non-specific clinical symptoms	51.6%
	Complex and variable pathophysiology	38.9%
	Lack of sensitive, objective biomarkers	37.7%
Impact of dehydration and energy deficits	Dehydration and energy deficits significantly impact recovery in acute nondiarrheal illnesses	85.9%
	Acute nondiarrheal conditions further aggravate fluid, electrolyte, and energy deficits	61.5%
Role of slow-release carbohydrates	Confirmation of role of slow-release carbohydrates such as isomaltulose, D-tagatose, and trehalose in stable glucose release and metabolic profile	68.9%
Hydration status Assessment	Importance of assessing hydration status in diabetic patients	93.7%

Table 3: Key survey results on FEE management

Survey topic	*Finding*	*Percentage (%)*
Importance of FEE	High and medium importance of FEE in diabetic individuals with acute non-diarrheal illnesses	92.6%
Adverse impact of chronic dehydration	High to medium adverse impact of chronic undetected dehydration on the health of diabetic patients	89.1%
Formulations for FEE deficits	Agreement that oral formulations with the right balance of fluid, electrolytes, and energy/calories are vital for FEE deficits recovery	88.0%
Physician perceptions on RTD fluids	Strong agreement that RTD electrolyte drinks with optimal sodium and glucose concentrations provide rapid rehydration	84.2%
Physician perceptions on RTD fluids (immune hydration)	Strong agreement that electrolytes and micronutrients can form an effective immune-hydration solution for diabetic patients	79.2%
Increased energy requirements in acute illness	Acknowledgement of increased energy requirements for diabetic patients during acute non-diarrheal illnesses	80.1%
RTD FEE with slow-release carbohydrates (isomaltulose, D-tagatose, trehalose)	Agreement that RTD FEE with slow-release carbohydrates can prevent blood glucose and insulin spikes, providing prolonged energy	77.9%
Use of natural sweeteners	Strong agreement that natural stevia is a healthy sweetener with zero caloric value and improved palatability	66.7%

Overall, only 28.1% of general practitioners assess hydration status in diabetic persons with acute nondiarrheal illnesses, as against 51.8% of consulting physicians and 60% of diabetologists. Similarly, only 30% of general practitioners, as against 50% of diabetologists, recommend oral FEE to eligible diabetic persons with acute nondiarrheal illnesses.

Importantly, 67% of general practitioners give formal (written/electronic) prescriptions of RTD fluids to >50% of my eligible diabetic patients who need hydration, as against 24.5% physicians and 40% of diabetologists. Nearly 75–80% of all specialties agreed that RTD FEE drinks can lead to faster recovery in diabetic persons with non-diarrheal

cross-specialty HCPs managing diabetes assess the hydration levels and use FEE supplements as a treatment approach. These physicians spend a mean of 14.6 minutes and a median of 10 minutes advising patients on hydration.

The results on approaches to managing hydration in diabetes patients are provided in Table 5.

General practitioners specify that RTD FEE drinks can shorten the recovery mean of 7.7 days in diabetic persons with acute nondiarrheal illnesses, as against a mean of 3.8 and 3.4 days specified by consulting physicians and diabetologists, respectively.

The correlation between knowledge scores and hydration practices in diabetes management was assessed using Spearman's rank correlation (ρ). The results revealed weak correlations, with ρ values ranging from −0.287 to 0.277. These findings suggest that while there is some degree of association between HCPs' knowledge of hydration and their actual hydration practices, the relationship is relatively weak. The weak correlations observed indicate that knowledge alone may not be a strong predictor of hydration practices in the context of diabetes management.

Discussion

Dehydration is a common yet often under-recognized condition, especially in diabetic patients, who are at higher risk due to factors such as osmotic diuresis and hyperglycemia-related electrolyte imbalances.[16] Despite its prevalence, proper fluid and electrolyte management in diabetes care remains an unmet need, and neglecting hydration can lead to delayed recovery and increased hospital readmissions.[17] Recent studies highlight the importance of oral FEE supplementation, with formulated fluids offering a viable solution for improving hydration and enhancing patient compliance.[18] Although FEE management has been shown to improve recovery, there is still a lack of well-documented guidelines on its use in diabetic patients with nondiarrheal dehydration.[15,19] This knowledge-practice gap underscores the need for further research and the development of standardized protocols to optimize hydration therapy and reduce adverse outcomes in diabetic patients suffering from dehydration.[20]

The findings from this survey provide a comprehensive overview of the existing knowledge, perceptions, practices, and challenges among HCPs regarding the management of dehydration and associated FEE deficits in persons with diabetes.

The survey highlights that a significant percentage of HCPs are aware of the heightened risk of dehydration in diabetic patients, with 90% of cross-specialty HCPs managing diabetes acknowledging the critical role osmotic diuresis plays in this risk, yet only 29.4% of doctors assess hydration levels in patients without acute illness. Despite the recognition of dehydration risks, the survey data show that only 43.8% of HCPs routinely provide recommendations for fluid, electrolytes, and energy/calorie management, reflecting a gap between awareness and proactive hydration guidance in daily diabetes care practices.

While 75% of respondents recognize that SGLT-2 inhibitors increase the risk of

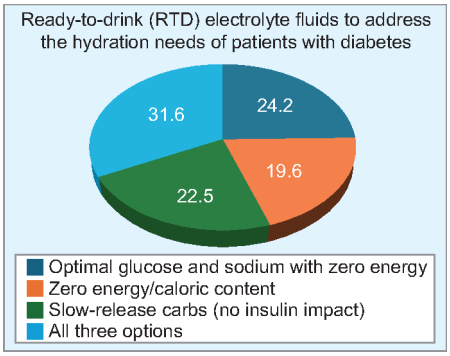

Fig. 3: Survey findings related to preferred RTD electrolyte fluids to address the hydration needs of patients with diabetes

Table 4: Assessment, management, and time spent advising for hydration in Diabetes patients

Survey category	*Mean (% of diabetic patients)*	*Median (% of diabetic patients)*
Assessment of hydration levels		
Without acute illness	29.4	20
With acute nondiarrheal illnesses	46.5	30
Recommendations		
For fluid, electrolytes, and energy/calorie	43.8	30

Table 5: Approaches to managing hydration in diabetes patients

Survey category	*Details*
Approaches to promoting hydration	
Formal prescriptions for ready-to-drink fluids	43.2%
Recommendation of homemade fluids	39.8%
General advice on increased fluid intake	12.4%
No hydration guidance included	1.7%
Referral to another healthcare professional	2.9%
Considerations for recommending packaged food	52% of healthcare professionals consider both glycemic index and glycemic load.
Types of oral fluids recommended	Clear homemade fluids, coconut water, and buttermilk, with a mean recommendation rate of 31.2%.
Reasons for recommending RTD fluids	Taste/palatability (47%) and convenience (43.4%) are the primary reasons.
Impact of fluid and electrolyte management	93.5% of healthcare professionals believe it improves overall outcomes in diabetic patients.
Immediate-release carbohydrates	61.9% consider using sucrose with fluids and electrolytes for managing deficits in diabetic patients.
FEE management recommendations	93.5% agree that oral fluid, electrolytes, and energy/calorie management improves outcomes.
Impact on glycemic control	73.1% believe oral fluid and electrolyte recommendations help maintain glycemic control.
RTD FEE drinks	78.1% perceive that RTD FEE drinks lead to faster recovery compared to non-RTD FEE drinks.
Impact of RTD FEE drinks on recovery	
Agreement on faster recovery with RTD FEE drinks	410 (78.1%) healthcare professionals agreed/strongly agreed.
Rehydration with RTD FEE drinks can shorten recovery time by	Mean: 4.10 days, Median: 3 days (n = 216)

dehydration, the survey reveals that only 46.5% of professionals assess hydration levels in patients with acute nondiarrheal illnesses, pointing to inconsistent monitoring when patients are under heightened risk.

Interestingly, the data show that 93.5% of HCPs agree that managing fluid and electrolyte intake positively impacts patient outcomes, yet only 43.2% prescribe RTD fluids, despite their convenience and higher palatability, which could enhance adherence to hydration recommendations. A lesser percentage of general practitioners are aware of mechanisms of fluid, electrolyte, and energy deficits in persons with diabetes and nondiarrheal illnesses, as well as their impact on recovery, compared to consulting physicians and diabetologists. This highlighted limited knowledge among general practitioners about mechanisms of FEE deficits in persons with diabetes and nondiarrheal conditions, while they see the bulk of these patients in their practice.

The diagnosis of dehydration remains a significant hurdle, as evidenced by the reported barriers, including nonspecific clinical symptoms (51.6%), the absence of an international consensus on diagnostic criteria (44.2%), and the lack of reliable biomarkers (37.7%). These challenges highlight an urgent need for standardized diagnostic frameworks and the development of sensitive, objective biomarkers to improve diagnostic accuracy.

A notable 86% of participants agreed that dehydration and energy deficits adversely affect recovery in diabetic patients during acute nondiarrheal illnesses. This emphasizes the dual burden of fluid and energy imbalances in exacerbating recovery delays, particularly in conditions such as febrile illnesses or heat-related illnesses. These insights underscore the importance of an integrated approach to managing both hydration and energy deficits in diabetic care.

The favorable reception of slow-release carbohydrates, such as isomaltulose, D-tagatose, and trehalose, by 68.9% of respondents underscores their promising role in managing blood glucose levels in diabetic patients. Their slower digestion and absorption compared to sucrose contribute to a more gradual increase in glucose concentrations, offering prolonged glycemia maintenance and minimizing postprandial insulin spikes. There seems to be a lack of awareness about the concept of slow-release carbohydrates and energy requirements amongst general practitioners, considering their lower agreement on RTD FEE drink based on slow-release carbohydrate to restore rehydration and energy deficits in diabetic persons with acute nondiarrheal illnesses.

By offering a more gradual increase in glucose levels and minimizing insulin spikes, slow-release carbohydrates such as isomaltulose, D-tagatose, and trehalose can complement hydration formulations, helping to maintain stable glycemic control while preventing dehydration-related complications.

Unlike high glycemic index (GI) carbohydrates, slow-release options such as isomaltulose, D-tagatose, and trehalose help minimize postprandial glucose spikes and reduce insulin demand. This further helps to support long-term energy requirements, making these carbohydrates a preferred choice for PWDs and other metabolic conditions. Isomaltulose stands out as a slow-release carbohydrate with benefits compared to trehalose and D-tagatose. The GI of D-tagatose is quite low, but it can provide only 1.5 kcal/gm, while trehalose has a high GI of 72.[13]

The survey reveals a near-universal agreement (92.6%) on the importance of addressing FEE deficits in diabetic patients with acute nondiarrheal illnesses. Chronic undetected dehydration was reported to have medium to high adverse impacts by 89.1% of respondents, emphasizing the need for routine hydration assessments. Additionally, 88% of respondents highlighted the critical role of oral formulations with balanced FEE content in patient recovery.

The preference for RTD fluids, cited by 84.2% of physicians, underscores their perceived efficacy in rapid rehydration compared to plain water. Physicians perceived the benefits of incorporating slow-release carbohydrates and micronutrients into these formulations, with 77.9% agreeing on their potential to prevent glycemic and insulin spikes. Moreover, 78.1% of respondents acknowledged the faster recovery associated with RTD FEE drinks in acute nondiarrheal conditions, with an estimated recovery time reduction of 4.10 days on average.

Despite the well-documented benefits of proper hydration, hydration assessment practices in diabetes care remain suboptimal. Only 29.4% of diabetic patients without acute illness and 46.5% with acute nondiarrheal illness have their hydration levels assessed. Furthermore, while hydration is recognized as a critical component of diabetes management, the time spent providing hydration advice is limited, with an average of only 14.6 minutes per patient. The median time is even lower at 10 minutes, suggesting that HCPs may not be allocating enough time to adequately address hydration needs in diabetic patients. This gap highlights an area for improvement in routine clinical practice. Additionally, the weak correlations between knowledge scores and hydration practices suggest the need for targeted educational interventions to bridge this gap and translate knowledge into practice.

This study offers valuable insights, but has inherent limitations as a survey. The KAP questionnaire lacked psychometric validation, potentially affecting the reliability of latent variables such as attitude. Self-reported data may introduce biases, including socially desirable responses. Being a descriptive survey based on physician reports, it may not fully reflect patients' perspectives or outcomes. Other limitations include recall bias, missing data, and over reporting.

A key strength of this KAP survey is its generalizability, drawn from a large and diverse sample of 525 cross-specialty HCPs managing diabetes. The study highlights critical aspects of RTD FEE formulations and their applications, while also enhancing understanding of the various factors involved in managing hydration challenges in diabetic patients. Notably, as the first study to explore FEE management in nondiarrheal diabetic conditions, it lays a valuable foundation for future research and evidence generation.

Given the findings, several recommendations emerge: (1) the development of recommendations for evaluation of dehydration and management in persons with diabetes, (2) promoting the adoption of RTD fluids with slow-release carbohydrates and balanced FEE content, (3) increasing routine hydration assessments and advice in diabetic care, and (4) enhancing education and training to improve the translation of knowledge of hydration and energy requirements in diabetes into clinical practices.

In conclusion, this study highlights the critical role of effective hydration and energy management in improving outcomes for diabetic patients, particularly during acute illnesses. Despite the knowledge of increased risk of dehydration in persons with diabetes, the screening for dehydration and awareness of the impact of FEE deficits on recovery in nondiarrheal conditions is quite low, especially among general practitioners. Formal recommendations are required on oral fluid, electrolyte, and slow-release energy requirements in persons with diabetes and nondiarrheal conditions to support recovery.

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All authors contributed to the project confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors met ICMJE criteria, and those who fulfilled those criteria were enlisted as authors.

Supplementary Material

Supplementary files (appendix) are available with the author. Please connect with the author for the supplementary content.

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References

1. Thomas DR, Cote TR, Lawhorne L, et al. Understanding clinical dehydration and its treatment. J Am Med Dir Assoc 2008;9(5):292–301.
2. Uppara S, Narayanaswamy BS, Venkata RKA, et al. A study on serum electrolyte imbalance in type-2 diabetes mellitus - a hospital-based study. JEBMH 2020;7(48):2847–2851.
3. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol 2021;69(11):2932–2938.
4. Li S, Xiao X, Zhang X. Hydration status in older adults: current knowledge and future challenges. Nutrients 2023;15(11):2609.
5. Khan RN, Saba F, Kausar SF, et al. Pattern of electrolyte imbalance in type 2 diabetes patients: experience from a tertiary care hospital. Pak J Med Sci 2019;35(3):797–801.
6. Liamis G, Liberopoulos E, Barkas F, et al. Diabetes mellitus and electrolyte disorders. World J Clin Cases 2014;2(10):488–496.
7. Cianciolo G, De Pascalis A, Capelli I, et al. Mineral and electrolyte disorders with SGLT2i therapy. JBMR Plus 2019;3(11):e10242.
8. Carroll HA, James LJ. Hydration, arginine vasopressin, and glucoregulatory health in humans: a critical perspective. Nutrients 2019;11(6):1201.
9. Taylor K, Jones EB. Adult dehydration. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. [online] Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK555956/ [Last accessed November, 2025].
10. Vora A, Kalra S, Thakor P, et al. Connecting the dots: hydration, micronutrients, and immunity. J Assoc Physicians India 2024;72(6S):25–29.
11. Armstrong LE, Johnson EC. Water intake, water balance, and the elusive daily water requirement. Nutrients 2018;10(12):1928.
12. Aghsaeifard Z, Heidari G, Alizadeh R. Understanding the use of oral rehydration therapy: a narrative review from clinical practice to main recommendations. Health Sci Rep 2022;5(5):e827.
13. Sokołowska E, Sadowska A, Sawicka D, et al. A head-to-head comparison review of biological and toxicological studies of isomaltulose, D-tagatose, and trehalose on glycemic control. Crit Rev Food Sci Nutr 2022;62(21):5679–5704.
14. Peteliuk V, Rybchuk L, Bayliak M, et al. Natural sweetener *Stevia rebaudiana*: functionalities, health benefits and potential risks. EXCLI J 2021;20:1412–1430.
15. Malve H, Sathe P, Chakravarty P, et al. Knowledge, attitudes, and practices regarding oral fluid, electrolyte, and energy management in acute nondiarrheal illnesses among physicians in India. JAPI 2023;71(5):34–38.
16. Mohan V, Kalra S, Zargar AH, et al. Diabetes mellitus and fluid imbalance: the need for adequate hydration. J Assoc Physicians India 2024;72(6S):16–24.
17. Kalra S, Kapoor N, Jacob JJ, et al. Fluid imbalance in geriatrics: the need for optimal hydration. J Assoc Physicians India 2023;71(7):11–12.
18. Reddy BR, Nigam A, Gogia A, et al. Oral fluid, electrolytes, and energy management in various adult and geriatric illnesses beyond diarrhea: an Indian expert panel Delphi consensus recommendation. J Assoc Physicians India 2024;72(6S):39–56.
19. Sathe P, Chakravarty P, Tesado C, et al. Comparing the knowledge, attitude, and practices on oral fluids, electrolytes, and energy management in non-diarrheal illnesses across different physician specialties in India. J Assoc Physicians India 2023;71(10):19–30.
20. Reddy BR, Sreenivasamurthy L, Pal J, et al. Association of Physicians of India expert recommendations on oral fluid, electrolytes, and energy management during transition care and discharge for hospitalized patients with nondiarrheal illnesses. J Assoc Physicians India 2024;72(6S):57–66.

ORIGINAL ARTICLE

Comparative Assessment of Cardiac Biomarkers and APACHE II Score for Prognostication in Septicemic Patients at a Tertiary Care Hospital

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Abstract

Introduction: Cardiac dysfunction is one of the major causes of mortality in patients with sepsis. The acute physiology and chronic health evaluation II (APACHE II), quick sequential organ failure assessment (qSOFA), and other prognostic scores for sepsis have established data regarding their accuracy in predicting mortality. We have assessed the prognostic role of cardiac biomarkers [creatine phosphokinase-myocardial band (CPK-MB), troponin I (Trop I), and probrain natriuretic peptide (proBNP)] in patients with sepsis and compared it with the APACHE II score.

Materials and methods: A total of 126 patients (63 in each group) participated in this case–control study in a large tertiary care teaching hospital. Patients with sepsis who required hospitalization were enrolled in the case group and compared with another group of nonsepticemic patients. They were taken for detailed evaluation and investigation on day 1 and day 3. Our study included proBNP, CPK-MB, Trop I, and APACHE II score.

Results: Both the case and control groups comprised 63 patients each. It was observed that the cardiac biomarkers (proBNP, Trop I, CPK-MB) were markedly higher among cases than in controls. Similarly, these markers were also found markedly higher in fatal cases than survivors in the case group. Out of all three biomarkers, proBNP was correlated well with mortality as much as the APACHE II score. It was also observed that increasing trends in the levels of biomarkers depict prognosis more effectively than a single value.

Conclusion: We conclude that cardiac biomarkers can be routinely used as dynamic markers for the prediction of mortality and prognosis in patients with sepsis. ProBNP may be useful in predicting mortality in patients with sepsis.

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Introduction

Sepsis is an inflammatory reaction to infection that can result in organ failure and death.[1] Recent data showed that according to global estimates from 2017, sepsis affected approximately 48.9 million individuals and resulted in 11 million deaths, contributing to about 20% of total worldwide mortality.[2] This has led the World Health Organization (WHO) to acknowledge sepsis as a serious health concern and global health priority.

Circulatory impairment is a hallmark of severe sepsis and is exacerbated in septic shock. Complications of sepsis, such as cardiac dysfunction or septic organ dysfunction, most directly impacting the heart, can worsen the patient's health. Septic heart failure is widely acknowledged to increase the mortality risk in sepsis. What it looks like, how often it occurs, and what the long-term implications will be are all questions that remain unanswered.

Multiple pathways contribute to cardiac dysfunction in sepsis syndromes, including increased inflammation, energy loss, and reduced adrenergic signaling. Vascular permeability and endothelial dysfunction are both exacerbated by the activation of cytokines during the host immunological response to sepsis. These cytokines include interleukin-1 (IL-1), IL-8, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), IL-12, and IL-6.[3] The body's adrenergic response increases cardiac contractility and heart rate early in sepsis as a form of compensatory mechanism. In the long run, when oxidative stress levels rise, proapoptotic (β1 adrenergic receptors) and antiapoptotic (β2 adrenergic receptor) interactions become imbalanced, leading to overstimulation of β1 adrenergic receptors and subsequent myocardial damage and cell death.[4] The pathogenesis of sepsis-related cardiac dysfunction includes the energy imbalance of the organs brought on by sepsis. Because CD36, lipoprotein lipase, and lipoprotein remnant receptors are all downregulated, there is an increase in the quantity of lipoproteins in the blood that carry fatty acids and triglycerides.[5] Mitophagy also slows cardiac β-oxidation, leading to an accumulation of triglycerides intracellularly from unused fatty acids and ultimately a deficit in heart energetics.

Cardiac biomarkers in sepsis have been studied before, and many pathways leading to their appearance have been elucidated. Their association with mortality, cardiac dysfunction, and the progression of sepsis calls for additional studies, however. We compared the predictive ability of the acute physiology and chronic health evaluation II (APACHE II) score and three cardiac biomarkers in patients with septicemia: troponin I (Trop I), creatine phosphokinase-myocardial band (CPK-MB) isoform, and probrain natriuretic peptide (proBNP).

Materials and Methods

The present investigation was designed as a case–control study and was conducted in the Department of General Medicine at a tertiary care teaching hospital with a sample size of 126 patients (63 cases, 63 controls). Patients having sepsis who required hospitalization were enrolled in the cases group, while nonsepticemic patients were in the control group and evaluated accordingly. Participants were given a thorough explanation of the study's purpose, and after receiving their informed consent, the research was carried out.

Our study included CPK-MB, Trop I, proBNP, procalcitonin (PCT), and APACHE II scores. Other variables were hemoglobin, total leukocyte count (TLC), immature granulocytes (IG%), serum electrolytes, and serum creatinine. Patients were followed up for 28 days. Baseline cardiac biomarkers were done in cases and controls, and proBNP on day 3 was done in cases only.

For the statistical analysis, comparative analysis of quantitative data was performed

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using either the Mann–Whitney *U* test or the independent two-sample *t*-test, depending on data distribution. Categorical variables were evaluated using Fisher's exact test. All data were summarized as mean ± standard deviation (SD) or, when applicable, as percentages. Statistical significance was defined as a p-value < 0.05. The linear association between the APACHE II score and individual cardiac biomarkers was analyzed using the Pearson correlation coefficient.

Inclusion Criteria

Adults admitted to the hospital with sepsis.

Exclusion Criteria

Cardiothoracic events, long-term drug use, and pregnancy were all exclusion criteria. Patients with documented histories of chronic kidney disease, a systemic condition known to adversely affect heart performance, patients with fluid overload conditions such as severe anemia, or patients with central nervous system (CNS) disease who refused to participate in the study were excluded.

Observation and Results

Out of 63 cases, 35 (55.5%) were females and 28 (44.4%) were males, and out of 63 controls, 32 (50.7%) were males and 31 (49.2%) were females. Among 63 cases, the majority of individuals belonged to the 41–50-year age category, that is, 31 (49.21%). Among 63 controls, the majority of controls were in the age-group 41–50 years, that is, 27 (42.85%). There was a statistically significant difference in Trop I, CPK-MB, and proBNP levels on day 1 in cases and control groups (p-value 0.049, <0.0001, <0.0001, respectively) (Table 1).

Out of 63 patients in the cases group, 32 were nonsurvivors and 31 were survivors. The analysis demonstrated a statistically significant variation in the mean values of CPK-MB day 1 (p-value 0.0012), CPK-MB day 3 (<0.0001), proBNP day 1 (p-value 0.0350), and proBNP day 3 (p-value < 0.0001) in survivors and nonsurvivors among the cases group, while Trop I day 1 (p-value 0.2790) and day 3 (p-value 0.1065) were found nonsignificant (Table 2).

Pearson correlation analysis demonstrated significant positive associations between cardiac biomarkers and disease severity as measured by the APACHE II score. On day 1, Trop I (r = 0.234; p = 0.0649), CPK-MB (r = 0.507; p = 0.00002), and proBNP (r = 0.435; p = 0.0001) correlated with the APACHE II score. Similarly, on day 3, Trop I (r = 0.250; p = 0.0403), CPK-MB (r = 0.490; p = 0.00005), and proBNP (r = 0.727; p < 0.0001) maintained statistically significant correlations with the APACHE II score, with proBNP showing the strongest association.

A multivariate logistic regression model was applied to determine independent predictors of mortality among septicemic patients in the case group. The analysis revealed that elevated proBNP levels on day 1 (OR = 1.0001; p = 0.0511) and day 3 (OR = 1.0003; p = 0.0001), higher CPK-MB concentrations (OR = 1.0435; p = 0.0054), and increased APACHE II scores on day 1 (OR = 1.3413; p = 0.0001) and day 3 (OR = 1.3424; p = 0.0001) were significant predictors of mortality. These findings suggest that both biochemical markers and physiological scoring systems contribute meaningfully to mortality prediction in sepsis (Table 3).

With the exception of Trop I, all markers had area under the curves (AUCs) between 0.741 and 1 and were useful in identifying survivors from nonsurvivors on each day. The proBNP on day 3 was the best diagnostic measure for predicting nonsurvivors (AUC = 0.915) out of the five variables. The optimal cutoffs for proBNP day 1 were >2795, proBNP day 3 >3824, and CPK-MB >40.7. Correct prediction of nonsurvivors was achieved with a sensitivity of 84.4, 88.9, and

Table 1: Cardiac biomarkers among cases and controls

	Cases		*Controls*		*p-value*
	Mean	*SD*	*Mean*	*SD*	
Trop I	0.03	0.08	0.01	0.00	0.0494
CPK-MB	48.92	30.73	30.33	16.22	<0.0001
ProBNP (day 1)	7575.16	8445.52	255.73	140.82	<0.0001

Table 2: Cardiac biomarkers and APACHE II among survivors and nonsurvivors

	Nonsurvivors (N = 32)		*Survivors (N = 31)*		*p-value*
	Mean	*SD*	*Mean*	*SD*	
Trop I (day 1)	0.04	0.10	0.02	0.02	0.2790
Trop I (day 3)	0.04	0.10	0.01	0.02	0.1065
CPK-MB (day 1)	60.90	36.46	36.55	16.35	0.0012
CPK-MB (day 3)	57.62	22.6	34.66	15.23	<0.0001
ProBNP (day 1)	9770.44	9280.04	5309.06	6926.20	0.0350
ProBNP (day 3)	15456.67	10557.52	2389.65	3258.93	<0.0001
APACHE II (day 1)	33.44	5.29	27.00	3.92	<0.0001
APACHE II (day 3)	35.63	6.69	21.90	5.12	<0.0001

Table 3: Logistic regression analysis to predict predictors of mortality

Variable	*Coeff*	*Std err*	*p*	*OR*
ProBNP (day 1)	0.0001	0	0.0511	1.0001
ProBNP (day 3)	0.0003	0.0001	0.0001	1.0003
CPK-MB (day 1)	0.0425	0.0153	0.0054	1.0435
Trop I (day 1)	0.2658	12.0323	0.3936	2.29411
APACHE II score (day 1)	0.2936	0.0763	0.0001	1.3413
APACHE II score (day 3)	0.2945	0.0691	0.0001	1.3424

71.9% at these thresholds, while specificity ranged from 80.6 to 67.7% (Table 4).

The proBNP on day 3 was the best diagnostic measure for predicting nonsurvivors (AUC = 0.915) in cases out of the five variables (Fig.1).

Other significant variables included in our study are as follows—the mean arterial pressure (MAP) in cases is 70.29 and in controls 94.03. There was a highly significant difference in MAP between cases and controls ($p < 0.0001$), as well as between survivors and nonsurvivors ($p < 0.0001$). The mean APACHE II score demonstrated a reduction from 30.27 on day 1 to 27.39 on day 3, with a statistically significant difference between both groups ($p = 0.0289$). Moreover, within the case group, nonsurvivors had significantly higher mean APACHE II scores compared with survivors on both day 1 ($p < 0.0001$) and day 3 ($p < 0.0001$), indicating the strong prognostic value of this scoring system. In cases and controls, there is a statistically significant difference in mean TLC and IG% ($p < 0.0001$), while among survivors and nonsurvivors in the case group there is no statistically significant difference: TLC ($p = 0.4839$) and IG% ($p = 0.1249$).

A highly significant difference in serum PCT concentrations was observed between cases and controls ($p < 0.0001$), indicating its strong association with disease status, while among survivors and nonsurvivors there is no statistically significant difference.

Discussion

Sepsis still has a high fatality rate, comparable to that of myocardial infarction despite advances in treatment. Due to the elevated mortality observed in septic shock, cardiovascular dysfunction represents a characteristic and clinically significant manifestation among patients with severe sepsis. The cornerstone of sepsis care is, as always, early diagnosis and treatment.

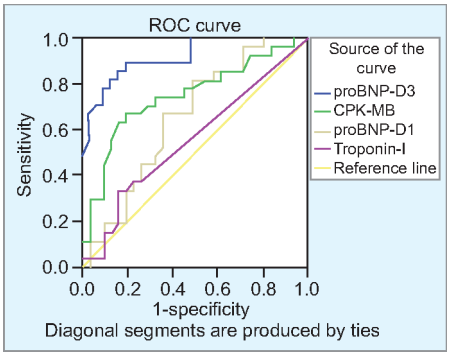

Fig. 1: ROC curve for APACHE II score and cardiac biomarkers

Raja et al.[6] conducted a study, "Cardiac biomarkers and myocardial dysfunction in septicemia." In the study, it was observed that troponin T (Trop T), CPK-MB, and NT proBNP were significantly elevated in patients with sepsis—mean values of 0.23 ± 0.8, 9.9 ± 13.4, and 5988.62 ± 13.7 pg/mL, respectively. In our study, similar results were seen; cardiac biomarkers were significantly elevated in cases as compared to controls—mean values of Trop I, CPK-MB, proBNP day 1, and proBNP day 3 are 0.03, 48.92, 7575.16, and 8472.57, respectively.

Papanikolaou et al.[7] conducted a study, "New insights into the mechanisms involved in BNP elevation and its role as an independent prognostic indicator in sepsis." The study demonstrated that the severity of sepsis was primarily associated with BNP elevation. A sustained elevation of BNP above 500 pg/mL provided a more reliable prediction of mortality than single-point BNP assessments. The inability to decrease BNP levels below 500 pg/mL was significantly associated with 28-day mortality, yielding an area under the receiver operating characteristic curve (AUROC) of 0.74 (95% CI: 0.55–0.93; $p = 0.03$), indicating moderate discriminatory accuracy. In our study, it was observed that out of three cardiac biomarkers, proBNP is the best diagnostic measure to predict nonsurvivors (AUC = 0.915, $p < 0.0001$, 95% CI: 0.84–0.98).

Yucel et al.,[8] in their study titled "The prognostic value of atrial and brain natriuretic peptides, Trop I and C-reactive protein in patients with sepsis," reported that BNP and APACHE II scores (AUC = 1.0) were the strongest diagnostic indicators for predicting nonsurvivors throughout the study period. On the 1st day, optimal cutoff values for BNP, cardiac troponin I (cTnI), and APACHE II were >32.1 pg/mL, >0.03 gm/L, and >23, respectively. On the 2nd day, the corresponding thresholds were >23.9 pg/mL, >0.03 gm/L, and >20, while on the final day, optimal cutoff values were >20.1 pg/mL, >0.03 gm/L, and >17, respectively. The diagnostic performance analysis demonstrated sensitivity rates of 100, 85, and 100% for accurate identification of nonsurvivors, accompanied by specificity rates of 100, 95, and 100% on respective study days. In our study, we observed the level of cardiac biomarkers and APACHE II scores on day 1 and day 3 of admission. With the exception of Trop I, all markers had AUCs between 0.741 and 1 and were useful in identifying survivors from nonsurvivors on each day. Among all observation days, the proBNP level measured on day 3 exhibited the greatest diagnostic efficacy for predicting mortality among septic patients out of the five variables (AUC = 0.915). The optimal cutoffs for proBNP day 1 were >2795, proBNP day 3 >3824, and CPK-MB >40.7. Correct prediction of nonsurvivors was achieved with a sensitivity of 84.4, 88.9, and 71.9% at these thresholds, while specificity ranged from 80.6 to 67.7%.

Witthaut et al.,[9] through their investigation "Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of IL-6 and sepsis-associated left ventricular dysfunction," were the first to demonstrate a significant elevation in plasma BNP levels among patients with septic shock, suggesting a potential link between inflammatory mediators and cardiac dysfunction in sepsis. In our study, it was observed that high proBNP levels were associated with hospital stays of long duration and mortality.

Mehta et al.[10] conducted a study "Cardiac troponin-I predict myocardial dysfunction and adverse outcome in septic shock." The study included 37 consecutive patients who had septic shock. At study enrollment and 24 and 48 hours later, serum cTnI levels were assessed. Elevated serum cTnI was associated with a significantly higher dependence on inotropic and vasopressor agents, higher APACHE II score, regional wall motion abnormalities, lower ejection fraction, and higher mortality. Multivariate analysis revealed that serum cTnI, APACHE II score, anion gap, and serum lactate independently predicted both mortality and duration of intensive care unit (ICU) stay. Receiver operating characteristic curve analysis further confirmed the prognostic

Table 4: Calculated cutoff, sensitivity, specificity, and AUC values discharge/death

	AUC	*p-value*	*CI 95*	*Cutoff*	*Sensitivity*	*Specificity*
Trop I	0.597	0.185	0.456–0.738	0.025	38.4	83.9
CPK-MB	0.741	0.001	0.616–0.866	40.7	71.9	67.7
ProBNP (day 1)	0.701	0.006	0.572–0.830	2795	84.4	51.6
ProBNP (day 3)	0.915	<0.0001	0.844–0.986	3824	88.9	80.6

significance of serum cTnI as a reliable indicator of death in patients with septic shock. In our study, the receiver operating characteristics of Trop T were least significant with AUC (0.597); sensitivity and specificity of 38.4 and 83.9, respectively.

Berendes et al.,[11] in their work "Differential secretion of atrial and brain natriuretic peptide in critically ill patients," explored the secretion profiles of atrial and brain natriuretic peptides in individuals admitted to the ICU following major surgical interventions. Their findings indicated elevated plasma levels of these peptides among critically ill patients; however, no significant relationship was found between peptide concentrations and clinical outcomes. Conversely, Yin et al.,[12] in their retrospective study "Female-specific association of plasma N-terminal probrain natriuretic peptide (NT-proBNP) with organ dysfunction and prognosis in sepsis," demonstrated that elevated NT-proBNP levels were significantly associated with the occurrence of septic shock and increased 30-day mortality, particularly among female patients, suggesting a potential sex-specific prognostic value. In our study, it was observed that 28-day mortality was strongly associated with rising trends of proBNP rather than single-day value.

Perman et al.,[13] in their study "Relationship between B-type natriuretic peptide and adverse outcome in patients with clinical evidence of sepsis presenting to the emergency department," analyzed 825 patients and found that BNP had an AUC of 0.69 for predicting a triple composite outcome. The optimal predictive cutoff for BNP was identified as 49 pg/mL. Subjects with BNP concentrations above this threshold exhibited significantly higher rates of mortality, severe sepsis, and septic shock compared to those with lower levels. In our study, it was observed that except Trop I, proBNP and CPK-MB can be used as a diagnostic measure to predict nonsurvivors; AUC = 0.74 and 0.9, respectively. The sensitivity of CPK-MB was 71.9% (95% CI: 61–86%); specificity 67.7%. The sensitivity of proBNP on day 1 and day 3 was 84.4 and 88.9% (95% CI: 57–83 and 84–98%), respectively.

Chen and Li,[14] in their work "Prognostic significance of brain natriuretic peptide obtained in the emergency department in patients with systemic inflammatory response syndrome (SIRS) or sepsis," demonstrated that BNP positivity and 28-day mortality differed significantly between SIRS and non-SIRS groups. BNP levels correlated positively with APACHE II scores across all study groups. Furthermore, a BNP threshold >113 pg/mL emerged as an independent predictor of death among septic patients. In our study, it was observed that cardiac biomarkers were raised in cases as compared to controls, and there is a statistically significant Pearson correlation between Trop I ($r = 0.250$; p-value = 0.0403), CPK-MB ($r = 0.490$; p-value = 0.00005), and proBNP D1 ($r = 0.727$; p-value < 0.0001) and APACHE II score at day 3. Rising trends of BNP were more associated with an increased risk of mortality than any single value.

A study conducted by Amman et al.[15] entitled "Elevation of troponin I in sepsis and septic shock" measured cTnI levels in patients diagnosed with SIRS, sepsis, and septic shock. Elevated cTnI concentrations were found in 85% of the study cohort—comprising three patients with SIRS and nine with sepsis—while no elevation was detected among control participants (median 0.57 µg/L; range 0.17–15.4). In our study, cTnI levels were within the normal range in controls, while out of 63 cases, only 13 (5 survivors; 8 nonsurvivors) had raised cTnI levels.

Conclusion

In ICU settings, cardiac biomarkers (CPK-MB, proBNP, Trop I) show promise as a predictor of illness severity and mortality. ProBNP is the most reliable predictor of cardiac outcomes among the three biomarkers currently available. Time-series trends in proBNP are more informative than single readings, and it correlates as strongly with mortality as the APACHE II score does. It can be utilized as a dynamic marker of sepsis and is a cheap, quick test for diagnosis and prognosis in sepsis patients.

References

1. Sepsis and septic shock. Harrison's Manual of Medicine, 21st edition. pp. 2241–2249.
2. Global Report on the Epidemiology and Burden of Sepsis: Current Evidence, Identifying Gaps and Future Directions. Geneva: World Health Organization; 2020. pp 6–37.
3. Schulz R, Panas DL, Catena R, et al. The role of nitric oxide in cardiac depression induced by interleukin-1β and tumour necrosis factor-α. Br J Pharmacol 1995;114(1):27–34.
4. de Montmollin E, Aboab J, Mansart A, et al. Bench-to-bedside review: beta-adrenergic modulation in sepsis. Crit Care 2009;13(5):230.
5. Drosatos K, Drosatos-Tampakaki Z, Khan R, et al. Inhibition of c-Jun-N-terminal kinase increases cardiac peroxisome proliferator-activated receptor alpha expression and fatty acid oxidation and prevents lipopolysaccharide-induced heart dysfunction. J Biol Chem 2011;286(42):36331–36339.
6. Raja DC, Mehrotra S, Agrawal A, et al. Cardiac biomarkers and myocardial dysfunction in septicemia. J Assoc Physicians India 2017;65(12):14–19.
7. Papanikolaou J, Makris D, Mpaka M, et al. New insights into the mechanisms involved in B-type natriuretic peptide elevation and its prognostic value in septic patients. Crit Care 2014;18(3):R94.
8. Yucel T, Memiş D, Karamanlioglu B, et al. The prognostic value of atrial and brain natriuretic peptides, troponin I and C-reactive protein in patients with sepsis. Exp Clin Cardiol 2008 Winter;13(4):183–188.
9. Witthaut R, Busch C, Fraunberger P, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. Intensive Care Med 2003;29(10):1696–1702.
10. Mehta NJ, Khan IA, Gupta V, et al. Cardiac troponin I predicts myocardial dysfunction and adverse outcome in septic shock. Int J Cardiol 2004;95(1):13–17.
11. Berendes E, van Aken H, Raufhake C, et al. Differential secretion of atrial and brain natriuretic peptide in critically ill patients. Anesth Analg 2001;93(3):676–682.
12. Yin S, Zhang Y, Guo Y, et al. Female-specific association of plasma N-terminal pro-brain natriuretic peptide with organ dysfunction and prognosis in sepsis: a retrospective study. Crit Care Explor 2021;3(5):e0392.
13. Perman SM, Chang AM, Hollander JE, et al. Relationship between B-type natriuretic peptide and adverse outcome in patients with clinical evidence of sepsis presenting to the emergency department. Acad Emerg Med 2011;18(2):219–222.
14. Chen Y, Li C. Prognostic significance of brain natriuretic peptide obtained in the ED in patients with SIRS or sepsis. Am J Emerg Med 2009;27(6):701–706.
15. Ammann P, Fehr T, Minder EI, et al. Elevation of troponin I in sepsis and septic shock. Intensive Care Med 2001;27(6):965–969.

ORIGINAL ARTICLE

Correlation of Conventional and Extended Lipid Profiles with Plaque Burden in Statin-naïve Patients with Acute Coronary Syndrome: A Prospective Observational Study from South India

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Abstract

Background: Traditional lipid parameters like low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (TC) are commonly used in evaluating cardiovascular risk. Recently, emerging biomarkers such as apolipoprotein B (ApoB) and apolipoprotein A1 (ApoA1) are proposed to provide improved accuracy in assessing atherosclerotic risk. This study examined the association between conventional and novel lipid parameters and plaque burden in statin-naïve acute coronary syndrome (ACS) patients.

Methodology: We enrolled 81 statin-naïve patients with ACS. Each underwent both standard and extended lipid profiling. Coronary angiograms were evaluated using the Gensini score to quantify plaque burden. All participants were followed for 28 days to monitor for major adverse cardiac events (MACE).

Results: The average age was 51 years, with males comprising 77%. The ST-segment elevation myocardial infarction (STEMI) was observed in 58% of cases, non-ST-segment elevation myocardial infarction (NSTEMI) in 31%, and unstable angina in 11%. There was a significant correlation between the Gensini score and TC/HDL ratio ($r = 0.35$), LDL/HDL ratio ($r = 0.31$), and ApoB levels ($r = 0.24$). LDL and the ApoB/ApoA1 ratio did not exhibit significant associations with plaque burden. STEMI patients had higher LDL/HDL and TC/HDL ratios compared to those with NSTEMI or unstable angina. MACE occurred in 16% of participants, with no significant difference across ACS subtypes.

Conclusion: The ratios of TC/HDL, LDL/HDL, and ApoB levels were positively associated with coronary plaque burden. While conventional lipid parameters continue to serve well in cardiovascular risk assessment (CRA), ApoB presents a promising standalone marker for identifying atherogenic risk and may serve as a practical alternative in clinical practice.

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Introduction

Cardiovascular diseases account for 31% of deaths worldwide and 27% of deaths in India.[1] The incidence of acute coronary syndrome (ACS) is rising in the Indian population and has started to occur at a younger age. On the contrary, the resources for percutaneous interventions remain limited. Smoking, diabetes, dyslipidemia, and obesity are the modifiable risk factors for atherosclerotic cardiovascular diseases. Of these, dyslipidemia is often overlooked.[2]

Cholesterol is carried through the bloodstream by lipoproteins. Very low-density lipoprotein (VLDL) is responsible for delivering triglycerides and cholesterol from the liver to various body tissues. In the process, it gradually loses triglycerides and cholesterol, transforming first into intermediate-density lipoprotein (IDL) and eventually into low-density lipoprotein (LDL). High-density lipoprotein (HDL) helps protect against atherosclerosis by facilitating reverse cholesterol transport—carrying cholesterol from peripheral tissues back to the liver.[3] To evaluate dyslipidemia, fasting lipid profile parameters such as LDL, HDL, VLDL, and total cholesterol (TC) are commonly assessed. Additionally, lipid ratios like LDL/HDL, TC/HDL, and non-HDL/HDL are useful indicators for identifying individuals at increased risk of cardiovascular diseases.

The protein component of lipoprotein is called apolipoprotein. Apolipoprotein B (ApoB) is the major apolipoprotein in LDL. An LDL particle can carry a variable amount of cholesterol but has only one ApoB. ApoB is present in IDL and VLDL as well. So, measuring ApoB levels gives a better estimate of the number of atherogenic lipoproteins.[4] Conversely, apolipoprotein A1 (ApoA1) is the primary apolipoprotein in the antiatherogenic HDL.[5] The ApoB/ApoA1 ratio reflects the balance between lipoproteins that promote atherosclerosis and those that protect against it. An elevated ApoB/ApoA1 ratio is associated with an increased risk of acute coronary events.[6,7] However, evidence regarding its ability to predict the severity and extent of atherosclerosis remains limited. Lipoprotein(a) [Lp(a)] is a modified form of the LDL particle, distinguished by the presence of an additional protein, apolipoprotein(a), which enhances its atherogenic potential.[8]

Coronary angiography (CAG) is done to diagnose and treat ACS patients. Based on the location and percentage of coronary artery stenoses identified on CAG, the Gensini score is calculated, and it quantifies the extent of myocardial injury.[9] This scoring system provides better information on the severity of atherosclerosis rather than classifying it as single-, double-, or triple-vessel disease.

This study aimed to find whether these conventional and newer lipid parameters correlate with Gensini scores in ACS patients.

Methodology

The study was carried out from October 2022 to July 2024 after obtaining clearance from the Institutional Ethics Committee. We included ACS patients aged 18–65 years who were admitted to the departments of Medicine or Cardiology and were scheduled for CAG. Patients with known heart, kidney, or liver disease, as well as pregnant patients, were excluded. Since statin therapy affects lipid parameters earlier than coronary artery plaque, this study excluded patients who had been on statin therapy for >1 month.[10]

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Data Collection

Demographic information of the patients was recorded, and clinical history included detailed questions related to the symptoms and risk factors associated with ACS. All patients underwent a comprehensive clinical examination and baseline laboratory investigations, including hemograms, renal and liver function tests. Electrocardiogram (ECG) findings, cardiac biomarkers (troponin T or CK-MB), and echocardiogram reports were also collected.

Lipid Profile

A fasting lipid profile (TC, LDL, HDL, VLDL, and triglyceride) was performed within 48 hours of admission. In addition, a 5 mL fasting blood sample was collected within 48 hours, centrifuged at 3,000 rpm for 15 minutes to isolate the serum, which was then stored at −80°C. These stored serum samples were later analyzed to determine levels of ApoB, ApoA1, and Lp(a) using enzyme-linked immunosorbent assay (ELISA) kits.

Gensini Score Calculation

Once the study participants underwent CAG as part of routine care, their angiographic data were collected. A cardiologist assessed the location and percentage of stenoses in coronary arteries and collateral circulation.[9,11] Based on these findings, a severity score was allotted to each lesion, and the total score was obtained by adding the severity scores assigned to each coronary lesion.

Follow-up

All patients were monitored throughout their hospital stay and followed up for up to 28 days to monitor major adverse cardiac events (MACE).

Sample Size

We assumed that if a lipid parameter caused a 10% variation in the Gensini score, it was considered clinically significant. For this, the correlation coefficient (*r*) had to be 0.32. Assuming a 95% confidence level and 80% power, the estimated sample size required to detect a correlation significantly different from zero was 74. Assuming a 10% attrition rate, 81 participants were recruited in this study.

Statistical Analysis

Depending on the distribution of the data, continuous variables were expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR). Correlation analyses were carried out to explore the relationship between the Gensini score and lipid markers, including the LDL/HDL ratio, TC/HDL ratio, Lp(a), ApoB, and the ApoB/ApoA1 ratio. Differences in the ApoB/ApoA1 ratio across patients with unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) were evaluated using analysis of variance (ANOVA).

Definitions

ST-segment Elevation Myocardial Infarction

ST-segment elevation myocardial infarction is defined as "new ST-segment elevation at the J-point in at least two adjacent leads. The threshold is ≥1 mm in all leads except V2 and V3. In leads V2–V3, the cutoff is ≥2 mm in men aged 40 years or older, ≥2.5 mm in men younger than 40, and ≥1.5 mm in women."[12]

Non-ST-segment Elevation Myocardial Infarction

Non-ST-segment elevation myocardial infarction is defined as "the presence of horizontal or downsloping ST-segment depression of ≥0.5 mm in at least two contiguous leads, or T-wave inversion of >1 mm with a prominent R wave or an R/S ratio >1, along with elevated cardiac biomarkers indicating myocardial injury."[12]

Unstable Angina

Unstable angina is diagnosed "when there is chest pain at rest lasting >20 minutes, new-onset angina that significantly restricts physical activity, or worsening angina that is more frequent, prolonged, or occurs with less exertion compared to previous episodes. It may be accompanied by significant ST-segment depression and T-wave inversion but without a rise in cardiac biomarkers."[12]

Gensini Score

A severity score is assigned based on the percentage of stenoses and adjusted according to collaterals. This severity score is multiplied by a factor based on stenosis location. The total Gensini score is obtained by adding the severity scores assigned to each coronary lesion.

Gensini score = [Severity score based on degree of stenosis – adjustment for collaterals] × multiplication factor based on the location of stenosis[11]

Major Adverse Cardiac Events

Recurrent MI, heart failure, cardiogenic shock, cardiac death, and stroke are considered MACE.[13]

Results

Out of 127 ACS patients screened, 81 were eligible for enrollment. An overview of the study design is presented in Figure 1. The mean age was 51 years, with males comprising 77% of the study population. The proportion of STEMI, NSTEMI, and unstable angina was 58, 31, and 11%, respectively. Table 1 summarizes the baseline characteristics and compares various clinical and laboratory parameters across various types of ACS.

The mean LDL cholesterol level was 116 ± 36 mg/dL, with similar values among STEMI, NSTEMI, and unstable angina groups. LDL level >130 mg/dL is considered the cutoff for high-risk CAD.[14] Based on this cutoff, 30% of the patients had dyslipidemia. The mean LDL/HDL ratio was 2.7 ± 0.7, which was significantly higher in the STEMI population than the other two types. However, there was no statistically notable difference in ApoB, ApoA1 levels, or the ApoB/ApoA1 ratio across all three groups. Lp(a) levels were not normally distributed and did not show significant changes among STEMI, NSTEMI, and unstable angina. Lp(a) was found to be >50 mg/dL in 74% of the patients, and 12% had Lp(a) levels exceeding 180 mg/dL.

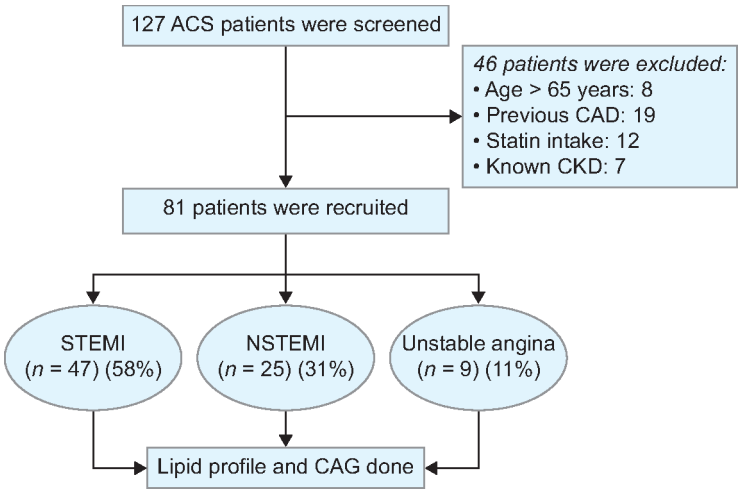

Fig. 1: Study procedure

Table 1: Baseline characteristics of the study population

Baseline characteristics	*All ACS, (n = 81)*	*STEMI, (n = 47)*	*NSTEMI, (n = 25)*	*Unstable angina, (n = 9)*	*p-value*
Number of participants, *n* (%)	81	47 (58)	25 (31)	9 (11)	<0.01
Age in years, mean ± SD	51 ± 8.5	52 ± 8	49 ± 10	50 ± 6	0.48
Male sex, *n* (%)	62 (77)	40 (85)	17 (68)	5 (56)	0.08
Smoking, *n* (%)	43 (53)	30 (64)	10 (40)	3 (33)	0.07
Alcohol consumption, *n* (%)	38 (47)	25 (53)	11 (44)	2 (22)	0.23
Hypertension, *n* (%)	31 (38)	19 (40)	8 (32)	4 (44)	0.73
Diabetes mellitus, *n* (%)	33 (41)	20 (43)	7 (28)	6 (67)	0.12
Family history of CAD, *n* (%)	1 (1.2)	1 (2)	0	0	0.70
Height (cm), mean ± SD	161 ± 8	162 ± 7	160 ± 8	160 ± 10	0.55
Weight (kg), mean ± SD	65 ± 9	66 ± 10	66 ± 8	64 ± 10	0.83
BMI >25 kg/m^2, *n* (%)	37 (46)	20 (43)	12 (48)	4 (44)	0.91
TC (mg/dL), mean ± SD	183 ± 50	188 ± 52	180 ± 51	170 ± 41	0.58
LDL (mg/dL), mean ± SD	116 ± 36	121 ± 38	113 ± 38	102 ± 23	0.28
HDL (mg/dL), mean ± SD					
Males	41 ± 8	42 ± 8	39 ± 7	46 ± 10	0.14
Females	46 ± 12	47 ± 15	44 ± 11	50 ± 10	
TC/HDL, mean ± SD	4.4 ± 0.96	4.48 ± 0.93	4.45 ± 0.97	3.61 ± 0.97	0.04
LDL/HDL, mean ± SD	2.7 ± 0.7	2.9 ± 0.7	2.78 ± 0.64	2.18 ± 0.56	0.02
ApoB (mg/dL), mean ± SD	69.7 ± 23	70.4 ± 23.7	70.5 ± 23.6	63.8 ± 18.8	0.72
ApoA1 (mg/dL), median (IQR)	90.4 (73.8, 109.1)	104.4 ± 66.9	87.8 ± 25.8	90.3 ± 16.3	0.42
Lp(a) mg/dL, median (IQR)	88 (48, 146)	70 (39, 172)	104 (58, 139)	102 (73, 136)	0.99
ApoB/ApoA1 ratio, mean ± SD	0.79 ± 0.3	0.78 ± 0.38	0.83 ± 0.28	0.71 ± 0.18	0.66
Median time to CAG, in days, median (IQR)	7 (2,15)	4 (1,9)	8 (3,20)	24 (23,26)	<0.01
Gensini score, median (IQR)	25 (13.5, 44)	26 (16, 48)	27.5 (15.5, 40)	4.5 (0, 41)	0.23

ACS, acute coronary syndrome; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; CAD, coronary artery disease; CAG, coronary angiogram; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; Lp(a), lipoprotein(a); NSTEMI, non-ST-segment elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol

Table 2: Spearman correlation coefficients between various lipid parameters and the Gensini score

Independent variable	*Spearman coefficient (r)*	*r-squared*	*p-value*
TC/HDL	0.35	0.12	<0.01
LDL/HDL	0.31	0.10	<0.01
Age	0.25	0.06	0.02
ApoB	0.24	0.06	0.03
Lp(a)	0.23	0.05	0.04
LDL	0.17	0.03	0.12
ApoB/ApoA1	0.14	0.02	0.21
ApoA1	0.11	0.01	0.31
HDL	–0.12	0.01	0.27

ApoA1, Apolipoprotein A1; ApoB, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TC, total cholesterol

Moreover, thrombolytic therapy was administered to 39% of STEMI patients (*n* = 32).

Correlation Analysis

Lipid ratios and Gensini scores exhibited a nonnormal distribution. Correlation analysis was done by comparing the Gensini score with each lipid parameter. Spearman correlation coefficients are given in Table 2 in descending order, and corresponding scatter plots are depicted in Figure 2. TC/HDL, LDL/HDL, age, ApoB, and Lp(a) had a statistically significant positive correlation with Gensini score, whereas other markers, like LDL, HDL, ApoA1, and the ApoB/ApoA1 ratio, did not show a significant correlation.

Multiple Linear Regression

Age, the LDL/HDL ratio, and ApoB levels showed statistically significant positive correlations with the Gensini score (r = 0.25, 0.31, and 0.24, respectively). Based on these findings, two multiple linear regression analysis models were proposed. In the first model, age and the LDL/HDL ratio were included as independent variables, with the Gensini score as the dependent variable. The second model included age and ApoB as covariates, with the Gensini score as the outcome variable. The regression coefficients with their confidence intervals are listed in Tables 3 and 4. Both models produced the same adjusted R-squared value of 0.14 (p < 0.01).

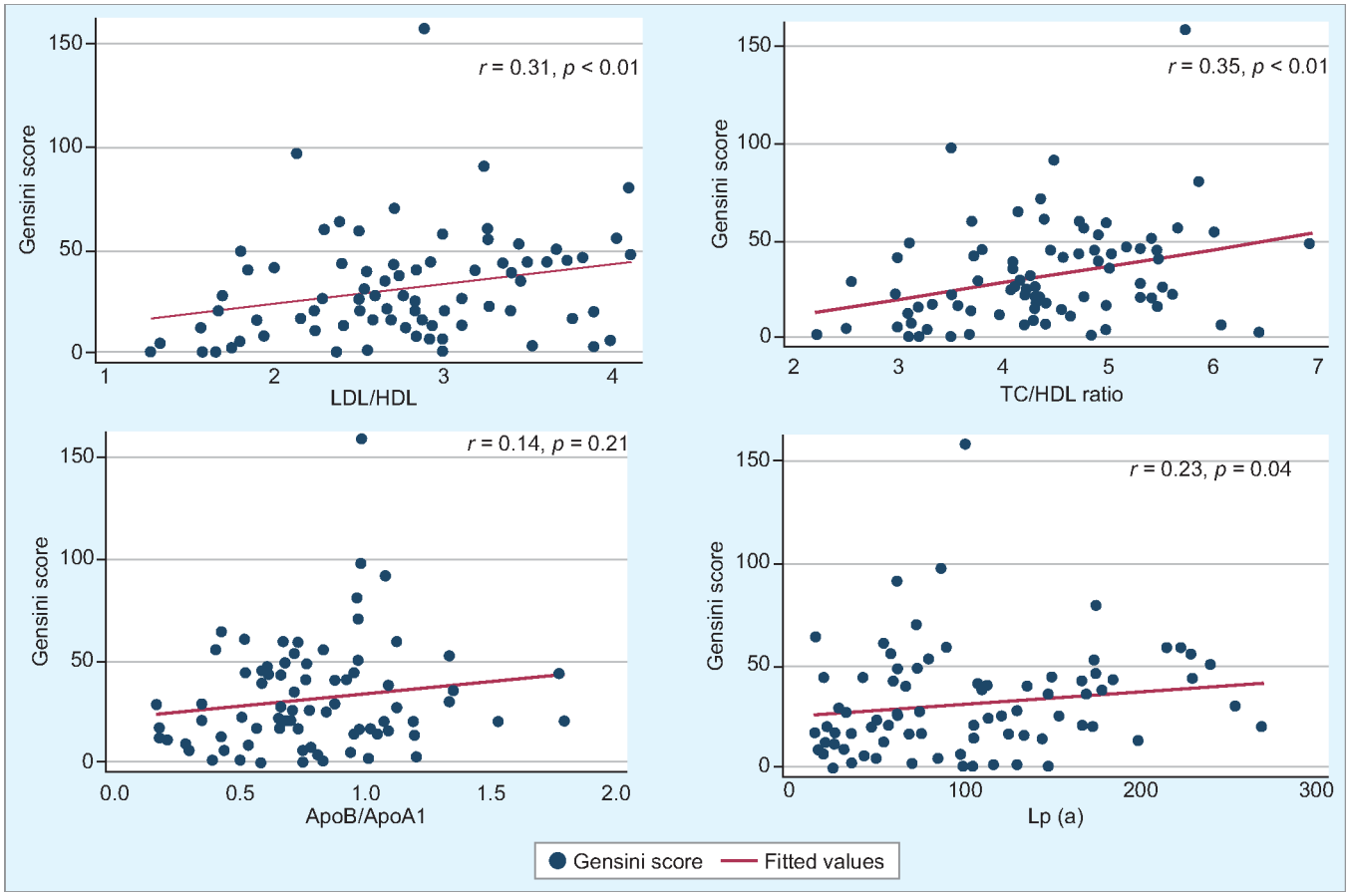

Fig. 2: Correlation of Gensini score with LDL/HDL, TC/HDL, ApoB/ApoA1, and Lp(a); ApoB, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TC, total cholesterol

Table 3: Multiple regression analysis of Gensini score with age and LDL/HDL ratio (adjusted R squared = 0.14, $p < 0.01$)

Variable	*Regression coefficient*	*95% confidence interval*	*p-value*
Age	0.91	0.28, 1.55	<0.01
LDL/HDL ratio	10.43	2.66, 18.21	<0.01

HDL, high-density lipoprotein; LDL, low-density lipoprotein

Table 4: Multiple regression analysis of Gensini score with age and ApoB (adjusted R squared = 0.14, $p < 0.01$)

Variable	*Regression coefficient*	*95% confidence interval*	*p-value*
Age	1.03	0.39, 1.68	<0.01
ApoB	0.32	0.09, 0.56	<0.01

ApoB, apolipoprotein B

Clinical Outcome

Thirteen participants (16%) experienced a MACE either during their hospital stay or within the 28-day follow-up period. The observed MACE included cardiogenic shock (6%), acute decompensated heart failure (4%), recurrent MI (5%), and cardiac death (1.2%).

Discussion

This study found that TC/HDL and LDL/HDL ratios had a better correlation with the Gensini score than ApoB. In contrast, LDL and the ApoB/ApoA1 ratio showed very weak correlations. These results suggest that conventional lipid markers alone can predict the severity of ACS. However, ApoB also predicts the severity of ACS and has the advantage of being a single, reliable lipid parameter for atherogenesis. ApoA1 did not correlate with the Gensini score, and it does not seem to have a role in cardiovascular risk assessment (CRA), consistent with findings from previous studies.[6,15,16]

About 25% of the general Indian population have Lp(a) levels >50 mg/dL, and these levels are genetically determined.[8] Lp(a) level above 180 mg/dL is considered to carry a cardiovascular risk equivalent to that of heterozygous familial hypercholesterolemia.[7] In this study, 74% of the participants had Lp(a) levels >50 mg/dL and 12% had levels >180 mg/dL. A positive correlation was also observed between Lp(a) levels and the Gensini score ($r = 0.23, p < 0.05$). This means that the prevalence of elevated Lp(a) is higher among ACS patients. In a case-control study involving 208 participants at a tertiary care center in South India,

Table 5: Comparison of correlation coefficients of lipid parameters with Gensini score

Variables	*Our study, India, 2024*	*Mashayekhi et al., Iran, 2014*[18]	*Du et al., China, 2016*[19]	*Yaseen et al., Egypt, 2021*[15]	*Siallagan et al., Indonesia, 2023*[20]
Sample size	81	160	380	90	76
LDL/HDL	0.31*	–	0.11	–	–
TC/HDL	0.35*	–	0.10	–	–
LDL	0.17	–	–	–	0.27*
ApoB	0.24*	0.13*	–	0.32*	0.29*
ApoA1	0.11	0.02	–	–0.14	–
ApoB/ApoA1	0.14	–	0.18*	0.73*	–

**p*-value was <0.05; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL, high density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol

Geethanjali et al. reported elevated Lp(a) levels in patients with angiographically confirmed coronary artery disease compared to healthy controls.[17] This could be a reason for the higher prevalence of atherosclerotic heart diseases observed in younger people of South Indian ethnicity.

To the best of our knowledge, this is the first study from India to quantitatively examine the association between lipid profile components and coronary plaque burden using the Gensini scoring system. Correlation coefficients from different studies done in different populations are summarized in Table 5. ApoB consistently showed a positive correlation with the Gensini score. Notably, a single study from Egypt reported a strong correlation for the ApoB/ApoA1 ratio ($r = 0.73$, $p < 0.05$).[15]

The buildup of lipid particles in the arterial wall plays a central role in the development of atherosclerosis. Two mechanisms of lipid deposition have been proposed based on the cholesterol model and the ApoB particle model.[21] According to the cholesterol model, the amount of cholesterol carried within LDL and VLDL determines atherosclerosis. In contrast, the ApoB particle model proposes that the development of atherosclerosis is primarily influenced by the quantity of ApoB-containing lipoprotein particles. As these particles increase in size and cholesterol content, their ability to penetrate the arterial wall diminishes. On the contrary, smaller lipoprotein particles with less cholesterol can easily penetrate the vessel wall. The size of the plaque is determined by the number of ApoB-containing lipoprotein particles rather than the amount of cholesterol. The size of the plaque also increases with age because the greater the age, the longer the duration of dyslipidemia.

In this study, LDL/HDL and TC/HDL ratios among STEMI patients were significantly higher compared to NSTEMI and unstable angina groups. But ApoB, ApoA1, and ApoB/ApoA1 ratio did not have this association. STEMI is an occlusive form of ACS. A Mendelian randomization analysis based on the database obtained from the UK Biobank in 2022 also found that non-HDL cholesterol had a better causal relationship than ApoB concentration.[22] This means that cholesterol content rather than the number of lipoprotein particles is associated with a more vulnerable plaque. This is in favor of the cholesterol model of atherosclerosis.

Two multiple linear regression models were proposed for better comparison and are shown in Tables 3 and 4. The initial regression model explored the association between the Gensini score, age, and LDL/HDL ratio, reflecting the cholesterol-based framework of atherosclerosis. The second model assessed the relationship between the Gensini score, age, and ApoB levels, aligning with the ApoB particle hypothesis. In both these models, the adjusted R-squared was 0.14 ($p < 0.01$), which shows that both these models are equivalent and one is not superior to the other.

Statin therapy requires time to stabilize plaque and to increase lumen size, but it decreases LDL and ApoB levels in a shorter time. As a result, previous lipid-lowering therapy can cause a confounding effect on lipid levels. A key strength of this study was the exclusion of individuals with prior statin use. However, all participants received statin therapy after recruitment as part of the standard treatment of ACS. Statins are very effective and significantly improve cardiovascular outcomes. This could be the reason why lipid parameters did not show a significant association with MACE in this study.

In this study, dyslipidemia was the fourth most common modifiable risk factor, following smoking, obesity, and diabetes. This data is comparable to the data from the ICMR-INDIAB-17 study.[23] However, only 30% of the study participants had dyslipidemia, while the remaining patients presented with other risk factors like smoking, diabetes, and hypertension. These risk factors could have caused confounding effects. Also, severely ill patients were not included as they did not undergo CAG due to logistical reasons. Future study should consider including severely ill patients and excluding patients with risk factors other than dyslipidemia. Such study designs will better assess the predictive value of lipid parameters.

The mean ApoB and ApoA1 levels were lower in this study compared to those reported in previous studies.[6] Most earlier studies used the immunoturbidimetry method to estimate ApoB and ApoA1 levels.[20,24,25] The Quebec cardiovascular study used the rocket immunoelectrophoresis method.[26] In contrast, we used the sandwich ELISA method, which offers greater sensitivity and specificity.[27] Thus, we could speculate that the difference in measurement technique may account for the variation in values. Further research is needed to support these methods to predict consistent results among ACS patients.

This study also had a few limitations, including being a single-center study with a short follow-up period and the absence of a control group.

Conclusion

Conventional lipid indices, particularly the TC/HDL and LDL/HDL ratios, demonstrated predictive ability comparable to that of ApoB in assessing the severity of ACS. These easily accessible parameters remain clinically relevant for CRA and guiding the management of dyslipidemia. However, larger, prospective studies are needed to further validate the utility of extended lipid profiles, including ApoB, in evaluating plaque burden and improving risk stratification in ACS patients.

Author Contributions

Authors	*Mughilan Periasamy*	*Ramu Ramadoss*	*Avinash Anantharaj*	*Balasubramaniyan Vairappan*
Conceptualization	✓	✓	✓	✓
Presentation in Scientific Committee and Ethics Committee meeting	✓	✓	–	–
Data collection	✓	✓	✓	✓
Storage and processing of blood samples	✓	–	–	✓
Data analysis	✓	✓	–	–
Writing-original draft	✓	✓	–	–
Editing	✓	✓	✓	✓
Final approval	✓	✓	✓	✓
Agreement to be accountable for work	✓	✓	✓	✓

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References

1. Anonymous. Cardiovascular Diseases India. n.d. Available from: https://www.who.int/india/health-topics/cardiovascular-diseases. [Last accessed: April 21, 2025].
2. Shin S, Shin DW, Cho IY, et al. Status of dyslipidemia management and statin undertreatment in Korean cancer survivors: a Korean National Health and Nutrition Examination Survey study. Eur J Prev Cardiol 2021;28(8):864–872.
3. Feingold KR. Lipid and lipoprotein metabolism. Endocrinol Metab Clin North Am 2022;51(3):437–458.
4. Marston NA, Giugliano RP, Melloni GEM, et al. Association of apolipoprotein B-containing lipoproteins and risk of myocardial infarction in individuals with and without atherosclerosis: distinguishing between particle concentration, type, and content. JAMA Cardiol 2022;7(3):250–256.
5. Mahley RW, Innerarity TL, Rall SC Jr, et al. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res 1984;25(12):1277–1294.
6. Goswami B, Rajappa M, Mallika V, et al. Apo-B/apo-AI ratio: a better discriminator of coronary artery disease risk than other conventional lipid ratios in Indian patients with acute myocardial infarction. Acta Cardiol 2008;63(6):749–755.
7. Anonymous. ESC Guidelines on Dyslipidaemias (Management of). n.d. Available from: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Dyslipidaemias-Management-of. [Last accessed: April 21, 2025].
8. Enas EA, Varkey B, Dharmarajan TS, et al. Lipoprotein(a): an underrecognized genetic risk factor for malignant coronary artery disease in young Indians. Indian Heart J 2019;71(3):184–198.
9. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51(3):606.
10. Sharma R, Mahajan M, Singh B, et al. Apolipoprotein modifying effects of statins and fibrate in various age groups of coronary artery disease patients. J Indian Med Assoc 2006;104(9):492–498.
11. Rampidis GP, Benetos G, Benz DC, et al. A guide for Gensini score calculation. Atherosclerosis 2019;287:181–183.
12. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138(20):e618–e651.
13. Wang K-Y, Zheng Y-Y, Wu T-T, et al. Predictive value of Gensini score in the long-term outcomes of patients with coronary artery disease who underwent PCI. Front Cardiovasc Med 2022;8:778615.
14. Sawhney JPS, Ramakrishnan S, Madan K, et al. CSI clinical practice guidelines for dyslipidemia management: executive summary. Indian Heart J 2024;76:S6–S19.
15. Yaseen RI, El-Leboudy MH, El-Deeb HM. The relation between ApoB/ApoA-1 ratio and the severity of coronary artery disease in patients with acute coronary syndrome. Egypt Heart J 2021;73(1):24.
16. Hong L-F, Yan X-N, Fan Y, et al. Is the ratio of apoB/apoA-1 the best predictor for the severity of coronary artery lesions in Chinese diabetics with stable angina pectoris? An assessment based on Gensini scores. J Geriatr Cardiol 2015;12(4):402–409.
17. Geethanjali FS, Jose VJ, Kanagasabapathy AS. Lipoprotein (a) phenotypes in south Indian patients with coronary artery disease. Indian Heart J 2002;54(1):50–53.
18. Mashayekhi NR, Sadrnia S, Chehrei A, et al. The correlation between serum ApoA1 and B and coronary artery disease as well as its severity. Int Cardiovasc Res J 2014;8(1):1–5.
19. Du Y, Chen J, Chen M-H, et al. Relationship of lipid and lipoprotein ratios with coronary severity in patients with new on-set coronary artery disease complicated with type 2 diabetics. J Geriatr Cardiol 2016;13(8):685–692.
20. Siallagan D, Siregar J, Hasan R. Correlation between apolipoprotein B levels with coronary lesion area based on the Gensini scores in coronary heart disease patients. J Endocrinol Trop Med Infect Dis 2023;5(3):135–144.
21. Sniderman AD, Thanassoulis G, Glavinovic T, et al. Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA Cardiol 2019;4(12):1287–1295.
22. Helgadottir A, Thorleifsson G, Snaebjarnarson A, et al. Cholesterol not particle concentration mediates the atherogenic risk conferred by apolipoprotein B particles: a Mendelian randomization analysis. Eur J Prev Cardiol 2022;29(18):2374–2385.
23. Anjana RM, Unnikrishnan R, Deepa M, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol 2023;11(7):474–489.
24. Modi R, Kothiwale VA, Patted S, et al. APO B/APO AI ratio with coronary artery disease with normal lipid profile in the Indian population. J Assoc Physicians India 2017;65(12):22–27.
25. Singh K, Thanassoulis G, Dufresne L, et al. A comparison of lipids and apoB in Asian Indians and Americans. Glob Heart 2021;16(1):7.
26. Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec cardiovascular study. Circulation 1996;94(3):273–278.
27. Heydari M, Rezayi M, Ruscica M, et al. The ins and outs of lipoprotein(a) assay methods. Arch Med Sci Atheroscler Dis 2023;8:e128–e139.

ORIGINAL ARTICLE

A Study of the Etiology, Clinical Profile, and Outcome of Nontraumatic Cases of Impaired/Altered Sensorium in Patients Attending the Emergency Department in a South Indian Tertiary Care Hospital

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Abstract

Introduction: Nontraumatic cases of impaired/altered sensorium continue to be one of the most frequent emergencies that casualties encounter. The patient's overall prognosis may depend on early clinical evaluation and etiological diagnosis. In order to make a more accurate and timely diagnosis, it is crucial to understand the etiological profile of comatose patients who arrive at a tertiary care facility, which can successfully predict the outcome.

Materials and methods: This prospective observational study was carried out in a South Indian tertiary care facility. A total of 126 patients with altered mental status of nontraumatic origin who arrived at the emergency room with Glasgow coma scale (GCS) scores below 10 were included in the study.

Results: Of the 126 patients, 48 (38.1%) were female and 78 (61.9%) were male. All patients were 52.65 ± 17.94 years old on average. The comorbidities observed in this study were hypertension (49.2%), diabetes mellitus (36.5%), alcoholism (33.3%), smoking (25.3%), coronary artery disease (CAD) (7%), chronic kidney disease (CKD) (9.5%), epilepsy (4.7%), and previous cerebrovascular accident (CVA) (9.5%). The presenting symptoms other than altered sensorium were fever (4%), vomiting (9.5%), headache (3%), motor weakness (16%), seizures (15.8%), and breathlessness (4.7%). About 36 patients (28.5%) had abnormal neurological examination, with motor weakness being the most common finding in 34 patients (27%). A brain magnetic resonance imaging (MRI) or computed tomography (CT) scan was performed on 104 patients (82.5%), and 50 patients (48%) had abnormal results. The commonest finding was cerebral and cerebellar infarction seen in 35 patients (33.6%). A number of 48 (38%) patients had abnormal electrocardiogram (ECG), 42 (33%) had nonspecific ischemic alterations, and six patients (4.7%) had atrial fibrillation. In our study, 46 patients (36.5%) had neurological causes of impaired/altered sensorium, 32 patients (25.4%) had metabolic causes, 18 patients (14.3%) had multifactorial causes, 14 patients (11.1%) had infections, and 16 patients (12.7%) had other causes [status epilepticus, drug overdose, organophosphate (OP) poisoning]. The commonest neurological cause was ischemic stroke, noted in 32 patients (69.5%), out of which 16 cases were posterior circulation strokes. About 14 cases had anterior circulation stroke. The remaining two cases presented with both anterior and posterior circulation strokes. The mortality rate was 36.5%. A number of 46 patients died out of 126 patients. Out of 46 patients, CVA was the most common cause of death, accounting for 20 cases (43.4%).

Conclusion: In this study, the duration of altered mental status, GCS score, level of altered consciousness, and etiology were found to be significant prognostic markers that correlated with outcome in nontraumatic cases with impaired/altered sensorium. Factors that offer early prognostic information can help with resource allocation decisions because the cost of intensive care has increased significantly. The prognosis can be predicted using a simple clinical evaluation of neurological function, paying particular attention to the degree of consciousness, focal neurological signs, and brainstem reflexes.

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Introduction

Nontraumatic cases with impaired or changed sensorium are among the most prevalent emergencies presenting in the casualty department.[1,2] The prognosis of these individuals has been the subject of numerous international studies, but only a small number of these studies have been conducted in India.[3,4]

A coma is characterized as a state of prolonged unconsciousness in which an individual cannot be awakened by external stimuli and internal need.[5,6] Various etiologies underlie the onset of nontraumatic cases of impaired/altered sensorium.[7–9] Early clinical evaluation and etiological diagnosis may be critical to the patient's overall prognosis.[10,11] Understanding the etiological characteristics of comatose patients who arrive at a tertiary care facility is crucial for making an early and more accurate diagnosis.[12,13] It is essential to recognize the key prognostic clinical indicators which can accurately predict the outcome.[14,15]

Our aim in this study was to determine the etiological profile of nontraumatic cases of impaired/altered sensorium presenting at the emergency department, and additionally, we aimed to evaluate their clinical characteristics and outcome patterns that may be helpful in predicting the overall prognosis.

Materials and Methods

This was a hospital-based prospective observational study conducted from November 2021 to November 2022. Following approval from the Institutional Ethics Committee, the study was carried out. Explicit written consent was taken from all patients. A total of 126 patients over the age of 18, regardless of gender, who arrived at the emergency room with altered mental status of nontraumatic origin and Glasgow coma scale (GCS) scores below 10 were included. Patients with psychiatric disorders and traumatic head injuries were removed from the study. The sociodemographic details, history, clinical examination, laboratory data, radiological data, and neurological investigations were registered.

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Statistical Analysis

The collected data were entered into a Microsoft Office Excel spreadsheet, and SPSS statistics software, database version 16.0, was used for analysis. Analysis was done using percentages and ratios. To ascertain the statistical difference between variables, Excel functions such as mean, standard deviation (SD), and Chi-squared test were utilized. Results were taken as significant if the *p*-value was <0.05.

Results

A total of 126 patients were registered in this study. There were 48 female patients and 78 male patients. The mean age of all patients was 52.65 ± 17.94 years.

The comorbidities observed in this study were hypertension (49.2%), diabetes mellitus (36.5%), alcoholism (33.3%), and smoking (25.3%). Other risk factors were coronary artery disease (CAD) (7%), chronic kidney disease (CKD) (9.5%), epilepsy (4.7%), and previous cerebrovascular accident (CVA) (9.5%). Only 22 patients (17.4%) had no known comorbidities at the time of presentation. About 48 patients (38%) presented to the emergency department within 6 hours. Twenty-six patients (21%) presented to the emergency department within 7–12 hours. Sixteen patients (12.6%) presented within 13–24 hours. Thirty-six patients (28.5%) presented only after 24 hours.

At the time of presentation, eight patients (6%) exhibited delirium, 60 patients (47.6%) were drowsy, 36 patients (28.6%) were stuporous, and 22 patients (17.5%) were in a coma. GCS score at the time of admission was 3–5 in 39 patients (31%), 6–8 in 56 patients (44.4%), and 9–12 in 31 patients (24.6%).

The presenting symptoms other than altered sensorium were fever (4%), vomiting (9.5%), headache (3%), motor weakness (16%), seizures (15.8%), and breathlessness (4.7%). About 36 patients (28.5%) had abnormal neurological examination, with motor weakness being the most common finding in 34 patients (27%). Other findings noted were neck rigidity in eight patients (6.3%), facial palsy in six patients (4.8%), gaze preference in 14 patients (11.1%), absent oculocephalic reflex in 20 patients (15.9%), and anisocoria in six patients (4.8%). Abnormal respiratory findings included crepitations and rhonchi noted in 30 patients (23.8%).

Laboratory parameters noted were anemia in 46 patients (36.5%), hyponatremia (Na^+ <135 mEq/L) in 10 patients (7.9%), hypokalemia (K^+ <3.5 mEq/L) in four patients (3.2%), hypoxia in eight patients (6.3%), hypoglycemia [random blood sugar (RBS) ≤70 mg/dL] in eight patients (6.3%), hyperglycemia (RBS ≥200 mg/dL) in 14 patients (11.1%), hypothyroidism [thyroid-stimulating hormone (TSH) >4 mIU/L] in two patients (1.6%), deranged liver function test (LFT) in six patients (4.8%), and deranged renal function test (RFT) seen in 12 patients (9.5%) (Table 1).

A brain magnetic resonance imaging (MRI) or computed tomography (CT) imaging was performed on 104 patients (82.5%), and 50 patients (48%) had abnormal findings. The commonest finding was cerebral and cerebellar infarction seen in 35 patients (33.6%). Other findings were intracerebral hemorrhage in 12 patients (11.5%), meningeal enhancement in two patients (1.9%), and intraventricular hemorrhage in one patient (0.9%). About 48 patients (38%) had abnormal electrocardiogram (ECG) findings, 42 patients (33%) had nonspecific ischemic changes, and six patients (4.7%) had atrial fibrillation.

In our study, 46 patients (36.5%) had neurological causes of nontraumatic coma, 32 patients (25.4%) had metabolic causes, 18 patients (14.3%) had multifactorial causes, 14 patients (11.1%) had infections, and 16 patients (12.7%) had other causes [status epilepticus, drug overdose, organophosphate (OP) poisoning]. The commonest neurological cause was ischemic stroke, noted in 32 patients (69.5%). Out of these, 16 cases were posterior circulation ischemic strokes. Fourteen cases had anterior circulation ischemic stroke. The remaining two cases presented with both anterior and posterior circulation ischemic strokes.

Other neurological causes were hemorrhagic stroke (26%) and posterior reversible encephalopathy syndrome (PRES) (4%). Metabolic causes in decreasing order of frequency were hyponatremia (37.5%), hypoglycemia (21%), hyperglycemia (18.7%), uremic encephalopathy (15.6%), and hepatic encephalopathy (6.2%). Among infections, tuberculosis (TB) meningitis was diagnosed in two patients, bacterial meningitis in four patients, COVID pneumonia with sepsis in four patients, scrub typhus infection in two patients, and postpartum sepsis in two patients. Other less common causes were status epilepticus in eight patients, drug overdose in six patients, and OP poisoning in two patients (Table 2).

The mortality rate was 36.5%. A number of 46 patients died out of 126 patients. Out of 46 patients, CVA was shown to be the most common cause of death in 20 cases (43.4%) (Table 3).

Discussion

This study observed that neurological causes were the most common causes of mortality in nontraumatic cases of impaired/altered sensorium, with ischemic stroke being the most common etiology.

There were 80 (63.5%) patients who were discharged. The duration of altered mental status, level of consciousness, GCS score, and etiology were found to be significant

Table 1: Abnormal laboratory reports

Lab investigation	*No. of patients*	*Percentage (%)*
Anemia	46	36.5
Hyponatremia	10	7.9
Hypokalemia	04	3.2
Hyperglycemia	14	11.1
Hypoglycemia	08	6.3
Hypothyroidism	02	1.6
Deranged LFT	06	4.8
Deranged RFT	12	9.5

LFT, liver function test; RFT, renal function test

Table 2: Etiology of nontraumatic cases of impaired/altered sensorium

Etiology		*No. of patients*	*Mortality (no. of patients)*
Neurological	CVA—ischemic stroke	32	10
	CVA—hemorrhagic stroke	12	10
	PRES	02	00
Metabolic	Hyponatremia	12	02
	Hypoglycemia	07	00
	Hyperglycemia/DKA	06	00
	Uremic encephalopathy	06	02
	Hepatic encephalopathy	02	02
Infections	Sepsis/MODS/CNS infections	14	04
Multifactorial	Multifactorial	18	12
Others	Drug overdose	06	00
	Status epilepticus	08	04
	OP poisoning	02	00

Table 3: Mortality of patients with different etiologies

Etiology	*No. of patients*	*Mortality (%)*
CVA	46	20 (43.4)
Metabolic encephalopathy	32	06 (18.75)
Infections including CNS infections	14	04 (28.5)
Multifactorial	18	12 (66.7)
Others	16	04 (25)
Total	126	46 (36.5)

Table 4: Prognosis of nontraumatic cases of impaired/altered sensorium

	Death	*Discharged*	*p-value*
Duration of altered mental status			
<6 hours (*N* = 48)	10	38	$p < 0.005$
7–12 hours (*N* = 26)	12	14	
13–24 hours (*N* = 16)	04	12	
>24 hours (*N* = 36)	20	16	
Level of consciousness			
Delirium (*N* = 08)	00	08	$p < 0.001$
Drowsy (*N* = 60)	04	56	
Stuporous (*N* = 36)	26	10	
Coma (*N* = 22)	16	06	
GCS score			
3–5 (*N* = 39)	32	07	$p < 0.001$
6–8 (*N* = 56)	14	42	
9–12 (*N* = 31)	00	31	

prognostic markers that correlated with the prognosis in nontraumatic cases with impaired/altered sensorium. Patients with shorter duration of altered mental status <6 hours ($p < 0.005$), greater conscious levels at admission, that is, delirium ($p = 0.001$), and GCS scores between 9 and 12 at presentation ($p = 0.001$) had better outcomes (Table 4).

Duration of symptoms for >24 hours, GCS score <5, stuporous and coma state of consciousness at admission had poorer prognosis with high mortality rate. Among etiologies, metabolic causes had overall good prognosis. Hypoglycemia patients recovered 100% with management. The mortality rate was highest in multifactorial causes (66.7%).

The results of our study are comparable with that of other studies on nontraumatic impaired/altered sensorium. John et al.,[16] in his study derived that the common etiologies of nontraumatic altered consciousness were neurological (38%), infectious (36%), followed by metabolic causes (33%). In a study by Hiremath and Shashidharan,[17] the commonest cause in patients with nontraumatic altered consciousness was intracranial causes (50%) followed by metabolic causes (44%). Nonetheless, central nervous system (CNS) infections were the most frequent cause of nontraumatic altered consciousness in 55% of patients in an Ethiopian investigation by Melka et al.[18]

Limitations of the Study

- Study sample is small.
- Subarachnoid hemorrhage (SAH) cases were not included in this study.
- Glasgow coma scale score is affected by many factors, which include language impairment, sedated state, coexisting orbital fracture, and hypoxic ischemic encephalopathy after cold exposure.
- Lack of follow-up of patients after discharge.

Conclusion

Timely detection and seeking medical attention within 6 hours of altered sensorium could lower mortality and improve outcomes. The duration of altered mental status, GCS score, level of consciousness, and etiology were the key prognostic markers in this study that correlated with prognosis in nontraumatic cases of impaired/altered sensorium. Factors that offer early prognostic information can help with resource allocation decisions because the cost of intensive care has significantly increased.

The prognosis can be determined by a simple clinical evaluation of neurological function, paying particular attention to the level of consciousness, focal neurological signs, and brainstem reflexes. The management of these patients is improved through comprehension of the most common causes of nontraumatic cases of impaired or altered sensorium.

References

1. Chandra SR, Suresh K, Sanuwatson R, et al. Encephalopathy in critically ill patients. J Assoc Physicians India 2012;60:30–34.
2. Edlow JA, Rabinstein A, Traub SJ, et al. Diagnosis of reversible causes of coma. Lancet 2014;384:2064–2076.
3. Yeolekar ME, Trivedi TH. Febrile encephalopathy: challenges in management. J Assoc Physicians India 2006;54:845–847.
4. Lamar CD, Hurley RA, Taber KH. Sepsis-associated encephalopathy: review of the neuropsychiatric manifestations and cognitive outcome. J Neuropsychiatry Clin Neurosci 2011;23:237–241.
5. Stevens RD, Pustavoitau A, Sharshar T. Acute encephalopathy. In: Bhardwaj A, Mirski MA. Current Clinical Neurology: Handbook of Neurocritical Care, 2nd edition. Totowa, NJ: Springer; 2010. p. 287.
6. Berisavac II, Jovanovic DR, Padjen VV, et al. How to recognise and treat metabolic encephalopathy in neurology intensive care unit. Neurol India 2017;65:123–128.
7. Leong LB, Jian KHW, Vasu A, et al. Prospective study of patients with altered mental status: clinical features and outcome. Int J Emerg Med 2008;1:179–182.
8. Kekec Z, Senol V, Koc F, et al. Analysis of altered mental status in Turkey. Int J Neurosci 2008;118:609–617.
9. Xiao HY, Wang YX, Xu TD, et al. Evaluation and treatment of altered mental status patients in the emergency department: life in the fast lane. World J Emerg Med 2012;3:270–277.
10. Nirhale S, Kanitkar SA, Bhate AS, et al. Study of etiological factors responsible for non-traumatic coma in geriatric population. Indian J Basic Appl Med Res 2015;5:814–817.
11. Sarin SM, Debabrata G, Das M. Study of etiological profile and outcome predictors in nontraumatic coma. Int J Med Res Health Sci 2016;5:122–126.
12. Weiss N, Regard L, Vidal C, et al. Causes of coma and their evolution in the medical intensive care unit. J Neurol 2012;259:1474–1477.
13. Bates D, Caronna JJ, Cartlidge NE, et al. A prospective study of nontraumatic coma: methods and results in 310 patients. Ann Neurol 1977;2:211–220.
14. Forsberg S, Hojer J, Ludwigs U. Prognosis in patients presenting with non-traumatic coma. J Emerg Med 2012;42:249–253.
15. Horsting MWB, Franken MD, Meulenbelt J, et al. The etiology and outcome of non-traumatic coma in critical care: a systematic review. BMC Anesthesiol 2015;15:65.
16. John B, Loomba V, John M. Etiology, clinical profile and outcome of encephalopathy in elderly. J Assoc Physicians India 2020;68:63–66.
17. Hiremath RS, Shashidharan P. A study of nontraumatic coma with respect to etiology and outcome. Int J Contemp Med Res 2016;3:1854–1858.
18. Melka A, Tekie-Haimanot R, Assefa M. Aetiology and outcome of non-traumatic altered states of consciousness in north western Ethiopia. East Afr Med J 1997;74:49–53.

ORIGINAL ARTICLE

Surgical Antimicrobial Prophylaxis Appropriateness and Its Impact on Surgical Site Infection Rate

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Abstract

Objectives: Surgical antimicrobial prophylaxis (SAP) is a critical component of postoperative infection prevention, but its misuse is a widespread global issue. This study aims to assess SAP utilization patterns and appropriateness of SAP in terms of choice, timing of administration, and duration of SAP, and to evaluate possible correlation of SAP compliance with reduction in surgical site infection (SSI) rates.

Methods: A facility-based prospective cross-sectional study was conducted over a period of 6 months to evaluate the prescribing patterns of SAP and the incidence of SSIs. Prophylactic antimicrobial use was considered appropriate when the correct antimicrobial was administered for the appropriate indication, at the correct time, and for the recommended duration, in alignment with institutional protocols.

Results: The findings suggest a general improvement in SAP adherence over the 6-month period, with a peak of 83% in May-24 coinciding with the lowest recorded SSI rate (0.64%). Conversely, the highest SSI rate (5.14%) in Jan-24 corresponded with the lowest adherence (60%), reinforcing the association between proper SAP compliance and reduced infection rates. SAP adherence improvement correlates with reduced SSI rates, but there is still a need to reduce prolonged SAP use.

Conclusion: The relationship between SAP adherence and SSI rates underscores the importance of evidence-based antimicrobial stewardship. Strengthening compliance with established protocols and aligning SAP practices with international guidelines will be critical in sustaining low SSI rates while minimizing antibiotic resistance risks. Further, assessing SAP using days of therapy/100 patient-days (DOT/100 PD) data could provide valuable insights into adherence trends and potential areas for improvement.

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Introduction

Evaluating the appropriateness of surgical antimicrobial prophylaxis (SAP) is crucial, especially in contexts like India, where antibiotic resistance is a growing concern. Ensuring the correct choice, timing, and duration of antibiotics in alignment with current guidelines not only optimizes patient outcomes but also plays a significant role in antimicrobial stewardship. The Indian Council of Medical Research (ICMR) and World Health Organization (WHO) guidelines for SAP[1,2] provide comprehensive recommendations on various aspects of SAP, including selection of appropriate prophylactic antibiotics for different surgical procedures, optimal timing for administering prophylactic antibiotics, recommended routes of administration and dosage guidelines, duration of prophylaxis (emphasizing that it should not exceed 24 hours postoperatively), and guidance on redosing for prolonged surgeries.

The selected antibiotic should cover the most likely pathogens for the specific procedure, following evidence-based guidelines. The first dose should be given within 60 minutes before incision (or 120 minutes for drugs like vancomycin or fluoroquinolones that require longer infusion times). SAP should typically not exceed 24 hours postoperatively, as prolonged use does not provide additional benefit but increases the risk of antibiotic resistance, *Clostridioides difficile* infections, and other complications.[3]

Surgical antimicrobial prophylaxis is a critical component of postoperative infection prevention, but its misuse is a widespread global issue. Irrational use of prophylactic antibiotics is associated with increased medical care costs, prolonged hospitalization, superinfection, the emergence of antimicrobial-resistant strains of hospital pathogens that challenge the patient care process, and adverse drug reactions.[4] From an estimated 30–50% of the antimicrobials used for surgical prophylaxis in hospitals, 30–90% were inappropriate.[5] This highlights a significant gap in adherence to established guidelines, despite strong evidence discouraging prolonged SAP use.

This study aims (1) to assess SAP utilization patterns and appropriateness of SAP in terms of choice, timing of administration, and duration of SAP; and (2) to evaluate possible correlation of SAP compliance with reduction in surgical site infection (SSI) rates.

Methods

A facility-based prospective cross-sectional study was conducted over a 6-month period to evaluate the prescribing patterns of SAP and the rate of SSIs. Data were collected using a structured extraction form, capturing patient demographics, diagnosis, type of surgical procedure, and details of SAP administration including indication, choice of antimicrobial, timing of the first dose, and duration of use. SAP was deemed appropriate when the selected antimicrobial matched the correct indication, was administered at the appropriate time, and maintained for the recommended duration, in accordance with institutional guidelines. Institutional protocols were framed as per recommendations of ICMR Guidelines (India, 2023) and WHO Consensus on SAP (2016).[1,2] SAP adherence rate was calculated using the formula:

$$\text{SAP adherence rate (\%)} = \frac{\text{No. of patients who received appropriate SAP}}{\text{Number of surgeries for which data was captured}} \times 100$$

An internal benchmark rate of 4% for SSI was set based on SSI rates observed in the hospital in the previous years, taking recommendations from standard literature references. SSI rate was calculated using the formula:

$$\text{SSI rate } (\%) = \frac{\text{No. of SSI}}{\text{No. of surgeries done}} \times 100$$

Results

The SAP adherence rate shows a steady increase from 60% in Jan-24 to 83% in May-24, with a slight decline to 82% in Jun-24, as shown in Figure 1. The lowest SSI rate (0.64%)

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in May-24 correlates with the highest SAP adherence (83%) in that month. The highest SSI rate (5.14%) in Jan-24 aligns with low adherence (60%). However, excessive SAP duration remains high (~68–80%) across months, as shown in Table 1.

The SSI rate crossed the internal benchmark (4%) in January (5.14%) and March (4.3%) but remained well below the benchmark in February (1.5%), April (1.91%), May (0.64%), and June (2.4%). Trend analysis (R^2 = 0.337) suggests a weak correlation between time and the downward trend in SSI rates, as shown in Figure 2.

While there is a moderate negative correlation (correlation coefficient −0.54) between SAP adherence rate and SSI rate, the relationship is not statistically significant (p-value = 0.267), as shown in Table 2. Prolonged SAP duration does not show a strong association with SSI reduction, reinforcing guidelines that extended SAP does not prevent SSIs.

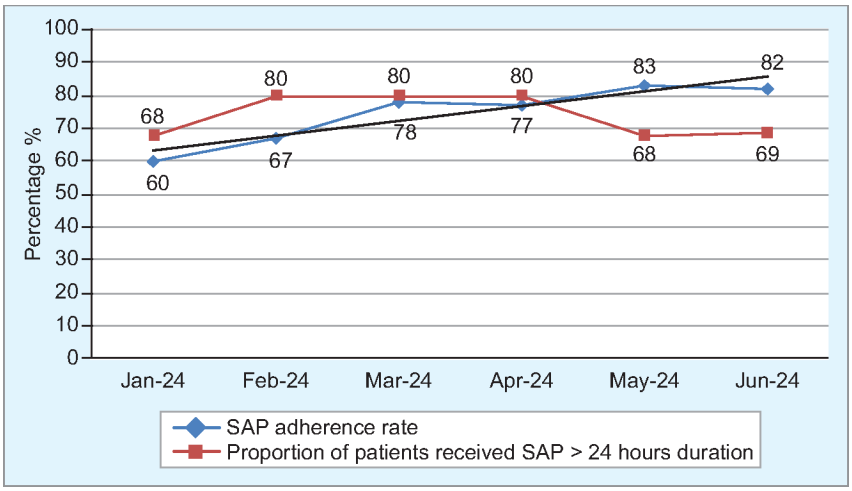

Fig. 1: SAP adherence trends

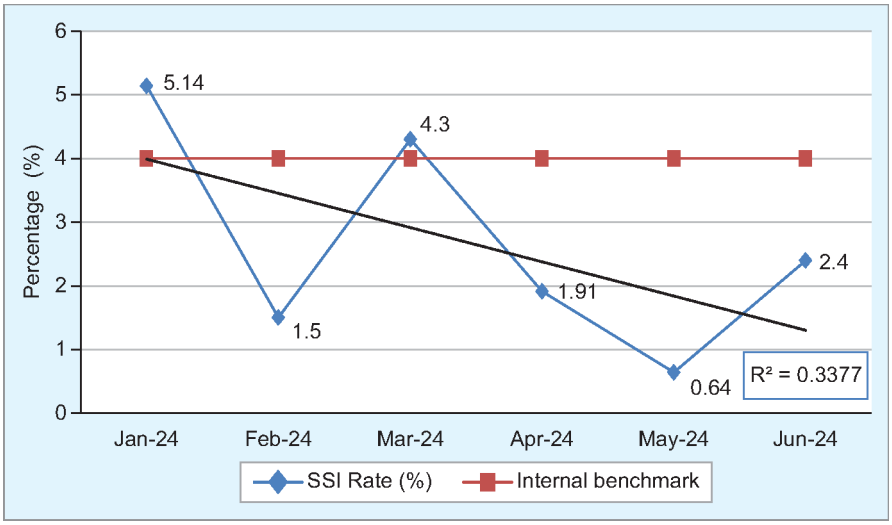

Fig. 2: SSI rate trend analysis

Discussion

The SSI rate shows significant fluctuation over the 6-month period. The overall trend shows a gradual decline over time despite the fluctuations. A comprehensive meta-analysis involving 4,88,594 general surgery patients estimated a global 30-day cumulative SSI incidence of 11%, highlighting a significant worldwide burden.[6] In India, a 2023 study across rural and semi-urban hospitals documented an SSI rate of 7.0%.[7] This rate is comparable to or slightly higher than the internal benchmark set in our institute as well as the findings in our study. The SSI rate exceeded the 4% benchmark in January and March. The R^2 value of 0.337 indicates a moderate correlation between time and SSI rate trends. This suggests that while there is some improvement over time, other factors may also be influencing SSI rates which are not taken into account in this study.

A study in Japanese hospitals found that the overall appropriateness of SAP was only 33.9%.[8] In our study, higher SAP adherence coincided with lower SSI rates in May, and prolongation of SAP did not correlate with better SSI prevention, emphasizing that prolonged SAP use does not reduce SSI rates but increases antimicrobial resistance risks.[3] It was also observed that, as SAP adherence improved, the proportion of patients receiving SAP for >24 hours decreased after April. The decline in May to June suggests a potential shift toward better compliance with recommended SAP duration, while reducing unnecessary prolonged antibiotic exposure. A study in Indian hospitals[7] found that prolonged SAP use (>24 hours) was common (~75%), but hospitals with strict adherence to SAP guidelines had lower SSI rates (~4.2%).

Despite high adherence in our study, a significant proportion of patients (69–80%) received SAP beyond 24 hours. Extending SAP beyond 24 hours does not correlate with lower SSI rates, supporting ICMR and WHO recommendations to limit SAP to ≤24 hours. This study underscores that although SAP plays a vital role in preventing SSIs, its effectiveness depends on the appropriate selection, timing, and duration

Table 1: SAP adherence indicators

SAP adherence indicators	*Jan-24*	*Feb-24*	*Mar-24*	*Apr-24*	*May-24*	*Jun-24*
No. of surgeries performed	214	264	229	261	310	250
No. of patients received SAP	186	196	169	211	198	166
SAP adherence rate	60%	67%	78%	77%	83%	82%
No. of patients received SAP >24 hours duration	127	157	136	169	134	115
Proportion of patients received SAP >24 hours duration	68%	80%	80%	80%	68%	69%
Number of SSI in a month	11	4	10	5	2	6
SSI rate (%)	5.14	1.5	4.3	1.91	0.64	2.4

Table 2: Tabulated summary of the correlation analysis

Comparison	*Correlation coefficient*	*Strength and direction*	*p-value*	*Statistical significance*
SAP adherence rate vs SSI rate	–0.54	Moderate negative	0.267	Not significant
SAP duration >24 hours vs SSI rate	–0.056	Very weak negative	0.917	Not significant

of antibiotic use. Departures from established guidelines such as unnecessarily prolonged administration or the use of broad-spectrum agents without clear indication can disrupt the natural microbial balance and contribute to antimicrobial resistance, posing risks to both patient safety and public health.[9] Adherence to guidelines enables healthcare providers to combat antibiotic resistance while minimizing the risk of antibiotic related adverse events and complications.[10]

Further, assessing SAP using days of therapy/100 patient-days (DOT/100 PD) data could provide valuable insights into adherence trends and potential areas for improvement.

Conclusion

The findings from this study highlight the fluctuating yet gradually declining trend in SSI rates over 6 months. While the observed rates are generally in line with national and global data, the occasional deviations from the internal benchmark suggest the need for continuous monitoring and targeted interventions. The relationship between SAP adherence and SSI rates underscores the importance of evidence-based antimicrobial stewardship. Consistent with global research, our study reaffirms that prolonging SAP beyond 24 hours does not reduce SSI incidence but increases the risk of antimicrobial resistance. Strengthening compliance with established protocols and aligning SAP practices with international guidelines will be critical in sustaining low SSI rates while minimizing antibiotic resistance risks.

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Author Contribution

Conception of the study, analysis of the records, and writing the manuscript are solely done by the first and corresponding author.

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References

1. Indian Centre for Medical Research. Surgical Site Infection (SSI)—Guideline for Antimicrobial Use. India; 2023. Available from: https://amrtg.icmr.org.in/chapter10-ssi.html.
2. World Health Organization (WHO). 2016. Global Guidelines for the Prevention of Surgical Site Infection. Available from: https://www.who.int/publications/i/item/9789241550475.
3. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70(3):195–283.
4. Kefale B, Tegegne GT, Degu A, et al. Surgical site infections and prophylaxis antibiotic use in the surgical ward of public hospital in Western Ethiopia: a hospital-based retrospective cross-sectional study. Infect Drug Resist 2020;13:3627–3635.
5. Moges G, Belete L, Mengesha Y, et al. Evaluation of surgical antimicrobial prophylaxis and incidence of surgical site infection at Borumeda hospital, Northeast Ethiopia: retrospective cross-sectional study. Drug Healthc Patient Saf 2020;12:257–268.
6. Gillespie BM, Harbeck E, Rattray M, et al. Worldwide incidence of surgical site infections in general surgical patients: a systematic review and meta-analysis of 488,594 patients. Int J Surg 2021;95:106136.
7. Nayan A, Sarang B, Khajanchi M, et al. Exploring the perioperative infection control practices & incidence of surgical site infections in rural India. Antimicrob Resist Infect Control 2023;12:65.
8. Morioka H, Ohge H, Nagao M, et al. Appropriateness of surgical antimicrobial prophylaxis in Japanese university hospitals. J Hosp Infect 2022;129:189–197.
9. Dhole S, Mahakalkar C, Kshirsagar S, et al. Antibiotic prophylaxis in surgery: current insights and future directions for surgical site infection prevention. Cureus 2023;15(10):e47858.
10. Menz BD, Charani E, Gordon DL, et al. Surgical antibiotic prophylaxis in an era of antibiotic resistance: common resistant bacteria and wider considerations for practice. Infect Drug Resist 2021;14:5235–5252.

ORIGINAL ARTICLE

Hand Grip Strength as a Functional Marker of Sarcopenia in Liver Cirrhosis: Evidence from an Indian Cohort

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Abstract

Background: Sarcopenia is a frequent and prognostically significant complication of liver cirrhosis. Hand grip strength (HGS) has emerged as a simple, noninvasive tool for assessing muscle function, yet limited data exist on its utility in Indian cirrhotic populations.

Aim: To evaluate the association of HGS with established prognostic scores and biochemical parameters in Indian patients with cirrhosis.

Materials and methods: In this cross-sectional observational study, 100 adult cirrhotic patients were assessed between August 2022 and December 2023. HGS was measured using a validated hand-held dynamometer. Correlations between HGS and clinical scores of severity of cirrhosis [Child–Turcotte–Pugh (CTP), Model for End-Stage Liver Disease (MELD)] and biochemical markers were analyzed using appropriate statistical methods.

Results: Mean patient age was 59.2 ± 8.46 years; 85% were male. The most common etiologies were alcohol (46%) and viral hepatitis (26%). HGS declined significantly with increasing liver disease severity: CTP A (34.0 ± 1.48 kg), B (21.63 ± 1.07 kg), and C (13.5 ± 2.87 kg) ($p < 0.0001$). HGS was inversely correlated with MELD score ($r = -0.820$) and showed strong positive correlations with serum albumin ($r = +0.872$) and hemoglobin ($r = +0.59$). Age, international normalized ratio (INR), and bilirubin were negatively correlated with HGS.

Conclusion: HGS is strongly associated with liver disease severity and key biochemical indicators. As a bedside, radiation-free tool, it offers a practical method for assessing sarcopenia in cirrhosis, especially in resource-limited settings.

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Introduction

Cirrhosis signifies the end stage of chronic liver disease, characterized by progressive hepatocellular dysfunction, portal hypertension, and multisystem complications impacting patient morbidity and mortality.[1] The global burden of cirrhosis continues to escalate, with an estimated 1.16 million deaths annually attributable to cirrhosis and its complications, making it the 11th leading cause of death worldwide.[2] In India, the prevalence of chronic liver disease has increased substantially over the past 2 decades. As per 2021 World Health Organization data, India accounts for the highest number of deaths attributable to cirrhosis globally.[3]

Sarcopenia in Cirrhosis

Sarcopenia, defined as progressive loss of skeletal muscle mass and function, is one of the most clinically significant complications of cirrhosis.[4] Its prevalence in cirrhosis ranges from 20 to 70%, depending on the diagnostic criteria employed and disease severity.[5,6] This wide variation in prevalence estimates underscores the challenges in establishing standardized diagnostic approaches for sarcopenia assessment in clinical practice.

The pathophysiology of sarcopenia involves complex interactions between altered protein metabolism, chronic inflammation, hormonal imbalances, and nutritional deficiencies.[7] Hepatic dysfunction leads to impaired albumin synthesis, altered amino acid metabolism, and increased protein catabolism, resulting in progressive muscle wasting. Additionally, portal-systemic shunting causes hyperammonemia, which impairs muscle protein synthesis and promotes muscle proteolysis *via* the ubiquitin-proteasome pathway.[8] Multiple studies have demonstrated that sarcopenia independently predicts mortality, increases the risk of hepatic encephalopathy, prolongs hospital stay, and adversely affects posttransplant outcomes.[9]

Traditional methods for assessing sarcopenia include bioelectrical impedance analysis, dual-energy X-ray absorptiometry, and cross-sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging.[10] While these modalities provide accurate measurements of muscle mass and composition, their widespread implementation is limited by cost, availability, technical expertise requirements, and radiation exposure concerns, particularly in resource-constrained settings.

Hand Grip Strength: An Emerging Tool

Hand grip strength (HGS) has emerged as a simple, reproducible, and clinically meaningful measure of muscle function that correlates strongly with overall muscle strength and physical performance.[11] The simplicity of HGS measurement using handheld dynamometry, combined with its strong prognostic value, positions it as an attractive option for routine clinical evaluation. Several studies have explored the relationship between HGS and cirrhosis. Tandon et al. demonstrated that reduced HGS independently predicted mortality in cirrhotic patients awaiting liver transplantation, with comparable prognostic accuracy to established scoring systems.[12] Similarly, Sinclair and colleagues showed that HGS provided additional prognostic value beyond the Model for End-Stage Liver Disease (MELD) score in male cirrhotics.[13]

Study Rationale and Objectives

Despite growing evidence supporting HGS as a valuable assessment tool, limited data exist on its application in Indian cirrhotic patients. This study was designed to evaluate the feasibility of HGS testing in routine clinical practice in a cohort of Indian cirrhotic patients of varied etiology. Our primary objective was to determine the correlation between HGS and established prognostic scores of cirrhosis. Secondary objectives included assessment of the relationship between HGS and individual biochemical parameters.

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Materials and Methods

This cross-sectional observational study included patients aged ≥18 years diagnosed with cirrhosis attending the Gastroenterology and Medicine departments (inpatient and outpatient) between August 2022 and December 2023. Cirrhosis was diagnosed using history and clinical examination, biochemical, endoscopic, imaging, and elastography parameters. Decompensation encompassed ascites, variceal bleed, and hepatic encephalopathy. Patients with hepatocellular carcinoma, other organ malignancy, severe extrahepatic disorders, and connective tissue disorders were excluded, as well as patients with inability to perform grip strength testing due to hand or arm pathology.

Demographics, history, and clinical findings were recorded. Body mass index (BMI) was calculated using height and weight adjusted for ascites and pedal edema.[12] Baseline hemogram, liver and renal function tests, and workup for cirrhosis etiology were done. Child–Turcotte–Pugh (CTP) and MELD scores were calculated.

HGS was assessed using a digital hand-grip dynamometer Camry®: Trailite Hand-Dynamometer LSC100 (Zhongshan Camry Electronic Co. Ltd., Zhongshan, China). It has been previously validated in multiple populations, including Indians.[14] Patients were seated with shoulders adducted and in neutral position, elbows flexed at 90°, forearms neutral, and wrists dorsiflexed between 0 and 30°. Three readings were taken on the dominant hand, and the mean value was used for analysis.

Data Analysis

All statistical analyses were done with Statistical Package for the Social Sciences (SPSS) v25 (IBM, Armonk, New York, United States of America). Descriptive statistics were presented as means and standard deviations for continuous variables and frequencies with percentages for categorical variables. Comparisons were made using *t*-tests or Mann–Whitney *U* tests for continuous variables. Chi-squared or Fisher's exact test was used for categorical variables. Multiple regression assessed associations between HGS and various parameters. Significance was set at $p < 0.05$.

Results

Demographic and Clinical Characteristics

A total of 100 patients with liver cirrhosis were recruited during the study period. The mean age was 59.2 ± 8.46 years, with 85% males. The most common etiologies were alcohol (46%) and viral hepatitis (26%). Most patients presented with abdominal distension and had advanced liver disease, with 79% classified as CTP B or C (Table 1). The mean MELD score was 21.81 ± 6.73, which showed strong correlation with CTP score (Table 2 and Fig. 1).

Hand Grip Strength across Disease Severity

There was a significant decline in HGS with increasing severity of cirrhosis, as determined by both CTP class and MELD score.

Table 2: MELD score statistics by CTP class

CTP class (n)	*MELD (mean ± SD)*
CTP A (21)	13.49 ± 2.06
CTP B (19)	17.59 ± 1.98
CTP C (60)	26.06 ± 4.97

Table 1: Baseline characteristics of study participants

Characteristic	*Subgroup*	*Number (n)*	*Percentage (%)*
Gender	Male	85	85
	Female	15	15
Age-group	40–49 years	16	16
	50–59 years	32	32
	60–70 years	52	52
CTP class	CTP-A	21	21
	CTP-B	19	19
	CTP-C	60	60
Etiology	Alcohol	46	46
	Hepatitis B	20	20
	MAFLD	15	15
	Hepatitis C	6	6
	Auto-immune	6	6
	Idiopathic	6	6
	Wilson disease	1	1

Child–Turcotte–Pugh Class Comparison

Mean HGS in CTP A, B, and C were 34.0 ± 1.48 kg, 21.63 ± 1.07 kg, and 13.5 ± 2.87 kg, respectively (Table 3 and Fig. 2). Pairwise comparisons using Mann–Whitney *U* tests with Bonferroni correction showed statistically significant differences between all groups ($p < 0.0001$). Cohen's *d* effect sizes were very large: A vs B = 9.50, A vs C = 7.92, B vs C = 3.17.

Model for End-Stage Liver Disease Score Comparison

Patients with MELD >25 had significantly lower HGS (15.14 ± 7.03 kg) than those with MELD ≤15 (33.35 ± 2.98 kg), with a clear inverse trend (Table 4 and Fig. 3). Patients with low HGS are clustered in the CTP-C, high MELD quadrant (Fig. 4).

Biochemical and Anthropometric Correlations

Pearson correlation analysis demonstrated a strong positive association between HGS and serum albumin and hemoglobin. Moderate positive correlations were observed with serum sodium and platelet count. Significant negative correlations were noted with CTP class, MELD score, and age (Table 5).

Table 3: Hand grip strength across CTP classes

HGS	*Mean ± SD (kg)*	*Range (kg)*
CTP A	34 ± 1.48	30–36
CTP B	21.63 ± 1.07	20–24
CTP C	13.5 ± 2.87	10–20

Table 4: HGS across MELD categories

MELD (n = 100)	*Mean ± SD*
>25 (35)	15.14 ± 7.03
16–25 (48)	17.46 ± 5.18
≤15 (17)	33.35 ± 2.98

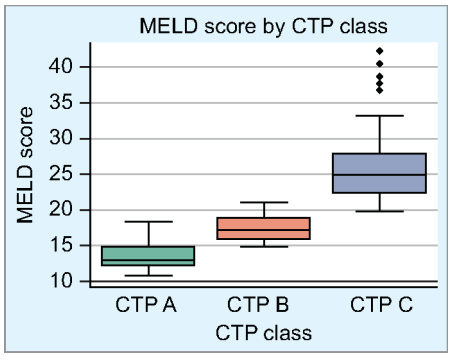

Fig. 1: Boxplot showing distribution of MELD scores across CTP classes

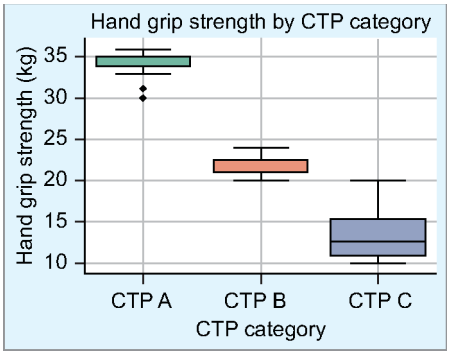

Fig. 2: Boxplot showing decline in HGS across CTP classes

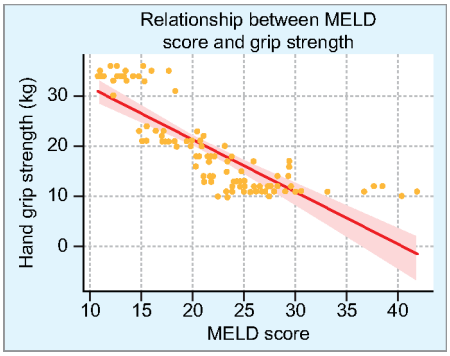

Fig. 3: Scatter plot visualizing inverse relationship between MELD and HGS

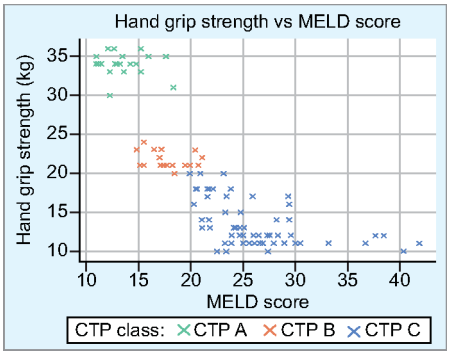

Fig. 4: Clustering of low HGS with CTP-C and high MELD

Discussion

The European Working Group on Sarcopenia in Older People-2 and the recently released South Asian Working Action Group on Sarcopenia (SWAG-SARCO) guidelines emphasize the need for both a functional and quantitative assessment for defining sarcopenia.[15,16] Sarcopenia diagnosis should follow a hierarchical model: probable sarcopenia is identified by reduced muscle strength, confirmed by demonstrating reduced muscle mass, and considered severe when accompanied by impaired physical performance. The SWAG-SARCO consensus reinforces the importance of muscle strength testing as the initial step in sarcopenia assessment, especially in low-resource settings.

Among the various methods to detect sarcopenia, the current gold standard is CT-based skeletal muscle index (SMI). Various society guidelines have advocated using HGS for measurement of muscle strength.[15–18] In a recent study, HGS was shown to be a better predictor of mortality in cirrhotic patients compared to SMI.[13] Since HGS measures muscle function directly, it possibly is a better indicator of physical activity and functional status than markers of muscle mass.

Considering the European and Indian National Association for Study of the Liver suggested cutoffs for HGS (<27 kg for men, <16 kg for women), prevalence of sarcopenia in our cohort would be 79% for males and 40% for females.[17,18] None of the patients in CTP A had HGS <27 kg. Taking the cutoff of ≤31 kg, as suggested by a recent study in Indian male patients, prevalence would be similar (81%).[19] The earlier reported incidence in Indian patients varies from 20 to 80%[19,20] and 50 to 70% in other Asian countries.[21] Most of these studies have used CT-based SMI for assessment of sarcopenia. Moreover, the higher prevalence in our cohort is attributable to more advanced liver disease in the cohort (79% CTP B and C).

The decrease in HGS as we move toward more advanced liver disease was highly significant between the CTP and MELD groups. The mean HGS in patients of CTP C and MELD >25 was less than half of those of CTP A and MELD ≤15, respectively. The substantial effect sizes observed (Cohen's d >0.8) indicate clinically meaningful differences beyond statistical significance. The exceptionally strong correlation between HGS and CTP score suggests that HGS can serve as an accurate predictor of functional liver reserve and disease prognosis. To the best of our knowledge, ours is the first study to demonstrate progressively declining HGS with increasing severity of liver disease.

Analyzing the factors influencing HGS, a particularly strong positive correlation was observed between HGS and serum albumin, indicating that hepatic synthetic capacity directly impacts muscle function. Albumin is not only a marker of liver synthetic function but also reflects systemic protein availability, a crucial component in muscle integrity. Other markers such as hemoglobin, serum sodium, and platelet count also showed significant positive correlations, suggesting that reduced HGS mirrors systemic derangements associated with advanced liver disease. However, unlike these biochemical markers, which may be influenced by acute fluctuations or laboratory variability, HGS provides a direct measure of muscle functional capacity that reflects the cumulative impact of chronic liver disease on patient wellbeing. Notably, etiology of cirrhosis did not influence HGS, suggesting that severity of liver dysfunction, rather than its cause, is the major determinant of muscle dysfunction in cirrhosis.

The age-related decline in HGS observed in our study highlights the compounding effects of chronological aging and cirrhotic

Table 5: Correlation between HGS and other parameters

Parameter	*Pearson correlation*	*95% confidence interval*	*p-value (2-tailed)*
CTP	−0.951	−0.969 to −0.924	<0.0001
MELD	−0.820	−0.877 to −0.747	<0.0001
INR	−0.818	−0.875 to −0.745	<0.0001
Albumin (gm/dL)	+0.872	+0.818 to +0.913	<0.0001
Age (years)	−0.777	−0.845 to −0.693	<0.0001
Bilirubin (mg/dL)	−0.674	−0.764 to −0.562	<0.0001
Hemoglobin (gm/dL)	+0.590	+0.442 to +0.709	<0.001
Sodium (mmol/L)	+0.370	+0.185 to +0.537	0.0100
Platelet count ($\times 10^9$/L)	+0.340	+0.152 to +0.511	0.0200
Weight (kg)	+0.225	+0.029 to +0.409	0.0242
Height (m)	+0.196	−0.001 to +0.384	0.0511
Creatinine (mg/dL)	−0.161	−0.349 to +0.038	0.1090
BMI (kg/m^2)	+0.115	−0.084 to +0.307	0.2544

muscle wasting. This is particularly relevant for elderly cirrhotic patients, who may experience accelerated functional decline and hence require more intensive monitoring and early intervention.

Our study is limited by its cross-sectional design, which precludes assessment of causality or serial changes in muscle function. The majority of patients were male and from a single center, which may limit generalizability. Additionally, incorporating comparative measures of sarcopenia assessment like SMI would have provided a more comprehensive picture of muscle function. While reduced HGS is a key indicator of probable sarcopenia, definitive diagnosis requires confirmation of reduced muscle mass per current consensus guidelines (e.g., EWGSOP2, SWAG-SARCO). This study focused on the functional aspect of sarcopenia through HGS due to feasibility and resource constraints.

In conclusion, the noninvasive nature, ease of use, and strong correlation of HGS with critical clinical parameters position it as a valuable adjunct in the comprehensive assessment of patients with liver cirrhosis. Hand-held dynamometers are readily available, require minimal training for proper use, and provide immediate results. It is especially relevant for resource-limited settings where advanced imaging modalities may not be readily available. As we continue to recognize the importance of sarcopenia in liver disease outcomes, HGS assessment offers a practical approach to identifying and monitoring this critical complication, ultimately supporting improved clinical outcomes.

References

1. Asrani SK, Devarbhavi H, Eaton J, et al. Burden of liver diseases in the world. J Hepatol 2019;70(1):151–171.
2. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5(3):245–266.
3. Sarin SK, Kumar M, Eslam M, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2020;5(2):167–228.
4. Sinclair M, Gow PJ, Grossmann M, et al. Sarcopenia in cirrhosis: aetiology, implications and potential therapeutic interventions. Aliment Pharmacol Ther 2016;43(7):765–777.
5. Hanai T, Shiraki M, Nishimura K, et al. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition 2015;31(1):193–199.
6. Cui Y, Zhang M, Guo J, et al. Correlation between sarcopenia and cirrhosis: a meta-analysis. Front Nutr 2024;10:1342100.
7. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol 2016;65(6):1232–1244.
8. Kumar A, Davuluri G, Silva RNE, et al. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. Hepatology 2017;65(6):2045–2058.
9. Bunchorntavakul C, Reddy KR. Malnutrition/sarcopenia and frailty in patients with cirrhosis. Aliment Pharmacol Ther 2020;51(1):64–77.
10. van Vugt JLA, Levolger S, de Bruin RWF, et al. Impact of CT-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation: a meta-analysis. Am J Transplant 2016;16(8):2277–2292.
11. Roberts HC, Denison HJ, Martin HJ, et al. Measurement of grip strength in clinical and epidemiological studies: towards a standardized approach. Age Ageing 2011;40(4):423–429.
12. Tandon P, Ney M, Irwin I, et al. Severe muscle depletion in patients on the liver transplant wait list: prevalence and prognostic value. Liver Transpl 2012;18(10):1209–1216.
13. Sinclair M, Chapman B, Hoermann R, et al. Handgrip strength adds more prognostic value to the MELD score than imaging-based muscle mass in men with cirrhosis. Liver Transpl 2019;25(10):1480–1487.
14. Mani P, Sethupathy K, Francis AAK. Test–retest reliability of electronic hand dynamometer in healthy adults. Int J Adv Res 2019;7(4):325–331.
15. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48(1):16–31.
16. Dhar M, Kapoor N, Suastika K, et al. South Asian Working Action Group on sarcopenia (SWAG-SARCO) – a consensus document. Osteoporos Sarcopenia 2022;8(2):35–57.
17. European Association for the Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. J Hepatol 2019;70(1):172–193.
18. Puri P, Dhiman RK, Taneja S, et al. Nutrition in chronic liver disease: consensus statement of the Indian National Association for Study of the Liver. J Clin Exp Hepatol 2021;11(1):97–143.
19. De A, Kumari S, Kaur A, et al. Handgrip strength as a screening tool for sarcopenia in males with decompensated cirrhosis. Indian J Gastroenterol 2022;41(3):284–291.
20. Kumar V, Benjamin J, Shasthry V, et al. Sarcopenia in cirrhosis: fallout on liver transplantation. J Clin Exp Hepatol 2020;10(5):467–476.
21. Anand A, Mohta S, Agarwal S, et al. European Working Group on Sarcopenia in Older People (EWGSOP2) criteria with population-based skeletal muscle index best predicts mortality in Asians with cirrhosis. J Clin Exp Hepatol 2022;12(1):52–60.

ORIGINAL ARTICLE

Correlation between Serum Uric Acid Level and Left Ventricular Ejection Fraction in Patients with Heart Failure

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Abstract

Background: Heart failure (HF) is a major public health concern with increasing prevalence worldwide. Serum uric acid (SUA) has been proposed as a potential biomarker in HF, with its levels potentially correlating with the severity of systolic dysfunction. However, the relationship between SUA and left ventricular ejection fraction (LVEF) remains unclear.

Methodology: A cross-sectional study was conducted at DY Patil University School of Medicine, Navi Mumbai, involving 60 patients diagnosed with HF. Patients were categorized based on LVEF into HF with preserved ejection fraction (HFpEF), mid-range ejection fraction (HFmrEF), and reduced ejection fraction (HFrEF). SUA levels were measured, and patients were classified into hyperuricemia or normal uric acid level groups. Demographics, comorbidities, and clinical symptoms were also recorded. Statistical analysis was performed to determine the correlation between SUA and LVEF.

Results: Of the 60 patients enrolled, 65% were female, with a mean age of 61–70 years. The majority had HFrEF (70%), followed by HFmrEF (26.67%) and HFpEF (3.3%). Hyperuricemia was observed in 38.3% of patients. A weak negative correlation was found between LVEF and SUA ($r = -0.070$), which was not statistically significant ($p = 0.599$). Although hyperuricemia was more prevalent in HFrEF, no significant relationship was established between SUA levels and severity of systolic dysfunction.

Conclusion: The study found a weak and statistically insignificant correlation between SUA levels and LVEF in HF patients. This suggests that SUA may not be a reliable biomarker for assessing the severity of systolic dysfunction. Further studies involving larger, more diverse populations are needed to clarify the prognostic role of SUA in HF.

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Introduction

Heart failure (HF) is a complex clinical syndrome characterized by the inability of the heart to pump blood efficiently, leading to inadequate tissue perfusion and fluid congestion. Several mechanisms have been proposed to explain the link between elevated serum uric acid (SUA) levels and cardiovascular dysfunction, such as endothelial dysfunction, oxidative stress, inflammation, and activation of the renin-angiotensin system. Exploring the potential relationship between SUA levels and left ventricular ejection fraction (LVEF) may provide valuable insights into the pathophysiology of HF and contribute to the identification of novel therapeutic targets or risk stratification strategies. This study aims to contribute to the current understanding of this association and potentially suggest clinical decision-making and therapeutic strategies for the management of HF patients.

Aim and Objective

Correlation between SUA level and LVEF in patients with HF.

Methodology

Study Design

An observational study.

Study Population

Patients diagnosed with HF at Dr DY Patil Medical College Hospital, Navi Mumbai.

Study Time

Research study was conducted for 18 months.

Inclusion Criteria

Patients diagnosed with HF age >18 years.

Exclusion Criteria

- Oncological conditions.
- Chronic renal failure.
- Gout.
- Autoimmune disease.
- Congenital heart disease.

To collect the required information from the study subjects, the "direct interview method" of primary source of information technique was used. The patients were interviewed for collection of necessary information using the pretested, semi-structured questionnaire method. The questionnaire was prepared by a thorough review of literature.

All patients with HF >18 years of age were included in the study. Patients were subjected to blood examination for determination of uric acid level and two-dimensional (2D) echocardiography for determination of LVEF. Correlation between uric acid levels and LVEF was studied.

Primary Outcomes

- To validate the increase in SUA levels in congestive HF.
- To correlate SUA levels with ejection fraction.

Secondary Outcome

- To establish the relationship of increased uric acid levels to functional class (NYHA, New York Heart Association) in congestive HF in predicting the severity.

Statistical Analysis

International Business Machines Statistical Package for the Social Sciences (IBM SPSS) (version 25.0) was utilized for statistical analysis, and Microsoft Excel 2016 was employed for data processing. Categorical data were presented as number and percentages, whereas continuous data were presented as mean and standard deviation. Within-group comparison of mean was done by paired *t*-test. For comparison of means between two groups, unpaired *t*-test was used. ANOVA was used for evaluation of difference at different time points. When a *p*-value was <0.05, the parameters were deemed to have significant connections or differences.

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Results

- The majority of patients (33.3%) were in the 61–70 age-group, with a female predominance (65%) (Figs 1 and 2).
- Common comorbidities included diabetes mellitus (56.7%), hypertension (50%), and myocardial infarction (55%) (Fig. 3).
- The most frequent symptom was dyspnea (93.3%), followed by edema (66.7%).
- About 70% of patients had HF with reduced ejection fraction (HFrEF), while 26.67% had HF with mid-range ejection fraction (HFmrEF) (Fig. 4).
- Hyperuricemia was present in 38.3% of patients (Fig. 5).
- There was a distribution of hyperuricemia across all LVEF categories, with the highest prevalence in the HFrEF group.

Discussion

Our study examined 60 patients with HF, analyzing their demographic characteristics, clinical presentation, comorbidities, LVEF, and SUA levels. The findings provide valuable insights into the complex interplay between these factors in HF patients.

Age and Gender Distribution

The study population predominantly consisted of older adults, with the highest proportion (33.3%) in the 61–70 age-group. This age distribution aligns with the known epidemiology of HF, which is more prevalent in older individuals.[1] The gender distribution showed a male predominance (65%), which is consistent with findings from other studies. For instance, a large-scale study by Maggioni et al.[2] reported a similar male predominance in HF patients across Europe.

Comorbidities

Our study revealed a high prevalence of comorbidities, with diabetes mellitus (56.7%), hypertension (50%), and previous myocardial infarction (55%) being the most common. These findings are in line with those reported by van Deursen et al.,[3] who emphasized the significant burden of comorbidities in HF patients and their impact on outcomes.

Clinical Presentation

Dyspnea was the most common presenting symptom (93.3%), followed by edema (66.7%) and chest pain (50%). These findings are consistent with the typical clinical presentation of HF described in major guidelines.[4]

Left Ventricular Ejection Fraction

The majority of patients in our study (70%) had HFrEF, defined as LVEF <40%. This is higher than the proportion reported in some population-based studies. For example, the EPICA study[5] found that approximately 50% of HF patients had reduced ejection fraction. The higher proportion in our study might be due to referral bias or differences in patient selection criteria.

Hyperuricemia and Heart Failure

Our study found that 38.3% of HF patients had hyperuricemia. This prevalence is similar to that reported by Huang et al.[6] who found hyperuricemia in 55.8% of acute HF patients. When analyzing the distribution of hyperuricemia across different LVEF categories, we found that 16 out of 42 patients (38.1%) with HFrEF had hyperuricemia, compared to 6 out of 16 (37.5%) with HFmrEF, and one out of 2 (50%) with HF with preserved ejection fraction (HFpEF).

While our study does not show a clear trend of increasing hyperuricemia prevalence with decreasing LVEF, it is important to note the small sample size, particularly in the HFpEF group. Other studies have reported a more pronounced association. For instance, Cicero et al.[7] found a significant inverse correlation between SUA levels and LVEF in HF patients.

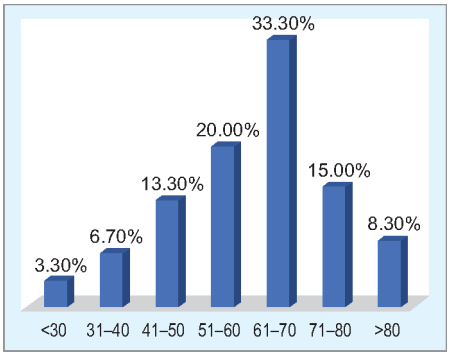

Fig. 1: Distribution of patients according to age

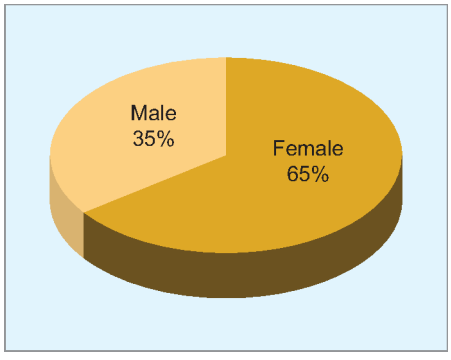

Fig. 2: Distribution of patients according to gender

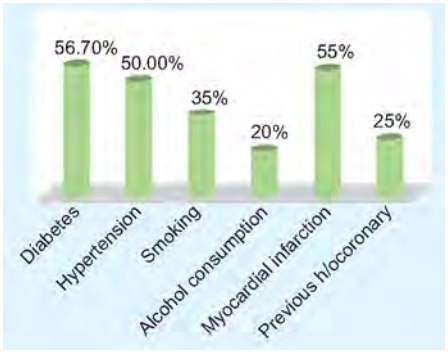

Fig. 3: Distribution of patients according to comorbidities

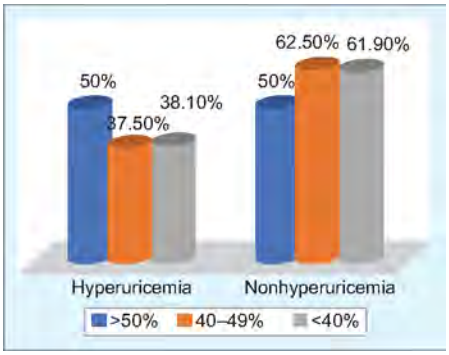

Fig. 5: Distribution of patients according to hyperuricemia and LVEF

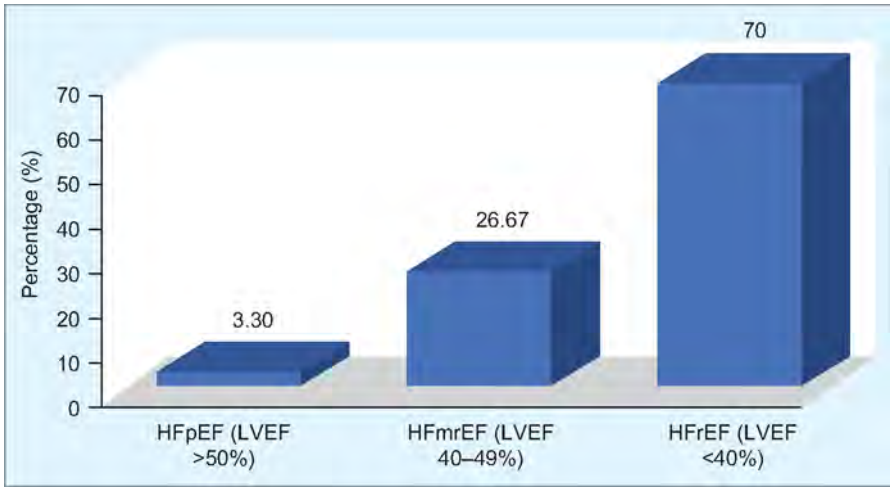

Fig. 4: Distribution of patients according to LVEF

The relationship between hyperuricemia and HF is complex and multifaceted. Elevated uric acid levels may contribute to the pathophysiology of HF through various mechanisms, including increased oxidative stress, endothelial dysfunction, and activation of the renin–angiotensin–aldosterone system.[8] Conversely, HF itself can lead to increased uric acid levels due to reduced renal perfusion and increased xanthine oxidase activity.

Our findings, while not conclusive, add to the growing body of evidence suggesting a potential role for uric acid in HF. The relatively high prevalence of hyperuricemia in our HF cohort, regardless of LVEF category, suggests that uric acid might be a valuable biomarker in HF management.

However, it is important to note the limitations of our study, including its cross-sectional nature and relatively small sample size. Larger, prospective studies are needed to further elucidate the relationship between uric acid levels and LVEF in HF patients and to determine whether uric acid-lowering therapies could have a role in HF management.

Conclusion

The distribution of patients across different LVEF categories, with a majority falling into the HFrEF group, highlights the significance of reduced ejection fraction in the study population. The presence of hyperuricemia in 38.3% of patients, with the highest proportion observed in the HFrEF group, suggests that elevated SUA levels may be associated with more severe cardiac dysfunction.

These results indicate that SUA levels could potentially serve as a biomarker for HF severity and progression. However, it is important to note that while an association has been observed, causality cannot be established based on this study alone. Further research, including longitudinal studies and investigations into the underlying mechanisms, is necessary to fully elucidate the relationship between hyperuricemia and HF.

The findings of this study may have important clinical implications. Monitoring SUA levels in HF patients could provide additional information for risk stratification and disease management. Moreover, therapies targeting uric acid metabolism might represent a potential avenue for future HF treatments, although this would require extensive further investigation.

In conclusion, this study contributes to the growing body of evidence linking hyperuricemia with HF, particularly in patients with reduced ejection fraction. While these results are promising, they also highlight the need for continued research in this area to better understand the complex interplay between uric acid metabolism and cardiac function in HF patients.

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References

1. Dharmarajan K, Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in older adults. Heart Fail Clin 2017;13(3):417–426.
2. Maggioni AP, Dahlström U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013;15(7):808–817.
3. Van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 2014;16(1):103–111.
4. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37(27):2129–2200.
5. Ceia F, Fonseca C, Mota T, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail 2002;4(4):531–539.
6. Huang H, Huang B, Li Y, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail 2014;16(1):15–24.
7. Cicero AFG, Salvi P, D'Addato S, et al. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study. J Hypertens 2014;32(1):57–64.
8. Kanbay M, Segal M, Afsar B, et al. The role of uric acid in the pathogenesis of human cardiovascular disease. Heart 2013;99(11):759–766.

ORIGINAL ARTICLE

Serum Calcium Levels as a Marker of Dengue Severity: A Clinical Observational Study

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Abstract

Background: Dengue fever continues to pose a major global health challenge. Electrolyte disturbances, particularly hypocalcemia, are frequently observed in dengue but are underutilized for prognostication.

Objective: To evaluate the relationship between corrected serum calcium levels and dengue severity.

Materials and methods: A prospective observational study of 210 adult patients with confirmed dengue was conducted at Shiv Ram Hospital. Serum calcium was measured within 24 hours of admission and corrected for albumin. Severity was classified per World Health Organization (WHO) 2009 criteria. Correlation analyses and multivariate logistic regression were used to assess associations with clinical and laboratory parameters.

Results: Mean corrected serum calcium declined with increasing severity (group A: 8.39 ± 0.59 mg/dL, group B: 8.05 ± 0.62 mg/dL, group C: 7.61 ± 0.67 mg/dL; $p < 0.001$). Hypocalcemia (<8.5 mg/dL) was observed in 91.3% of severe cases. Calcium levels negatively correlated with hematocrit, platelet count, and hospitalization duration ($p < 0.01$). Hypocalcemia independently predicted severe dengue (aOR: 3.94; 95% CI: 1.98–7.84; $p < 0.001$).

Conclusion: Hypocalcemia is a frequent and significant predictor of severe dengue. Serum calcium offers a simple, cost-effective tool for early triage and management in dengue-endemic regions.

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Introduction

Dengue fever, a mosquito-borne viral illness caused by the dengue virus (DENV), affects nearly 390 million individuals annually, with approximately 96 million symptomatic cases.[1] India remains hyperendemic, witnessing escalating outbreaks that strain public health systems.[2] Clinical manifestations range from mild febrile illness to life-threatening complications, including plasma leakage, hemorrhage, and multiorgan dysfunction. The 2009 World Health Organization (WHO) classification framework, although helpful, depends on the appearance of warning signs that may not always be timely or specific.[3] Hence, identifying simple, accessible, and early biomarkers of severity remains a pressing priority.

Electrolyte imbalances are common in dengue, with hypocalcemia being frequently reported in both adult and pediatric populations.[4] Calcium is integral to cellular signaling, vascular integrity, platelet aggregation, and cardiac contractility, all of which are crucial in dengue pathophysiology.[5] Infection-induced capillary leakage, proinflammatory cytokines [interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)], and hypoalbuminemia are known to disrupt calcium homeostasis.[6,7] Moreover, reduced total and ionized calcium levels have been implicated in shock, bleeding tendencies, and poor outcomes in various infectious diseases.[8]

This study investigates whether corrected serum calcium levels, obtained early during hospitalization, can serve as a reliable and cost-effective marker of dengue severity. It aims to correlate calcium levels with clinical severity, laboratory abnormalities, and patient outcomes in a representative Indian population.

Materials and Methods

Study Design and Setting

This was a prospective observational study conducted between July 2023 and October 2024 at a tertiary care center catering to both rural and semi-urban populations.

Inclusion and Exclusion Criteria

Adults aged 18 years and older with confirmed dengue infection based on NS1 antigen and/or IgM ELISA were included. Patients with chronic kidney disease, parathyroid disorders, malignancies, or on calcium supplementation were excluded.

Data Collection

Demographic details, comorbidities, clinical symptoms, and laboratory parameters were recorded on predesigned case report forms. Blood samples collected within 24 hours of admission were tested for total serum calcium, albumin, hematocrit, platelet count, liver function, and renal function. Corrected calcium was calculated using Payne's formula. A random subset ($n = 38$) underwent ionized calcium estimation using ion-selective electrode technology.

Clinical severity was categorized based on WHO 2009 classification:

Group A: Dengue without warning signs.

Group B: Dengue with warning signs.

Group C: Severe dengue (plasma leakage, bleeding, or organ failure).

Hypocalcemia was defined as corrected calcium <8.5 mg/dL.

Statistical Analysis

Data were analyzed using SPSS v. 26. Continuous variables were expressed as mean ± SD or median [interquartile range (IQR)] and compared using ANOVA or Kruskal–Wallis tests. Categorical variables were compared using Chi-squared tests. Pearson or Spearman correlations assessed associations between calcium and clinical/laboratory parameters. A multivariate logistic regression model identified predictors of severe dengue. Model calibration was tested with the Hosmer–Lemeshow goodness-of-fit test. A p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics and Severity Distribution

Demographic Characteristics

Out of 210 patients, 120 were male (57.1%), and the mean age was 32.4 ± 11.8 years. Table 1 details demographic data across severity categories. No statistically significant

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differences were observed in age or comorbidities across groups.

Corrected Calcium and Severity Correlation

Mean corrected calcium decreased with increasing severity (group A: 8.39 ± 0.59 mg/dL, group B: 8.05 ± 0.62 mg/dL, group C: 7.61 ± 0.67 mg/dL; F = 14.25; $p < 0.001$). Hypocalcemia prevalence rose from 43.5% in group A to 91.3% in group C ($\chi^2 = 25.4$; $p < 0.001$) (Fig. 1).

Correlations and Outcomes

Calcium levels negatively correlated with hematocrit ($r = -0.42$; $p < 0.001$) and duration of hospitalization ($r = -0.45$; $p < 0.001$), while positively correlating with platelet count ($r = 0.38$; $p < 0.01$) (Fig. 2). Patients with calcium <7.5 mg/dL had significantly longer hospital stays (7.2 vs 4.8 days; $p < 0.01$) and more frequent intensive care unit (ICU) admissions (28.3 vs 9.1%; $\chi^2 = 11.8$; $p < 0.001$) (Table 2).

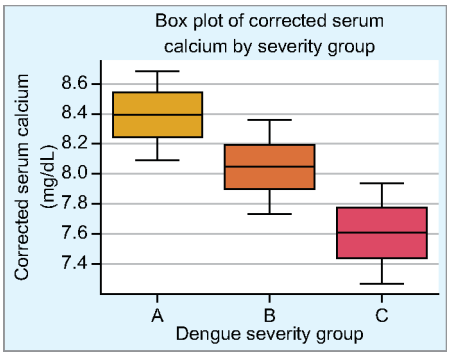


Fig. 1: Box plot of corrected serum calcium by severity group

Logistic Regression Analysis

Hypocalcemia was an independent predictor of severe dengue (aOR: 3.94; 95% CI: 1.98–7.84; $p < 0.001$). Hematocrit was also significant (aOR: 1.12; 95% CI: 1.03–1.20; $p = 0.006$). Age and albumin were not statistically significant predictors (Table 3).

The ANOVA was used for continuous variables, and the Chi-squared test was used for categorical data.

Multivariate logistic regression was performed, with Wald Chi-square values shown.

Discussion

This study underscores the clinical utility of serum calcium as a prognostic marker in dengue fever. Hypocalcemia was highly prevalent among patients with severe dengue and showed a strong inverse relationship with key severity indicators such as hematocrit, platelet count, and hospitalization duration. Importantly, hypocalcemia emerged as an independent predictor of severe dengue on multivariate regression analysis, suggesting its value in clinical triage.

Several pathophysiological mechanisms likely underpin the calcium derangements observed in dengue. Calcium is a tightly regulated ion, essential for membrane stability, vascular tone, intracellular signaling, and homeostasis. The endothelial dysfunction in dengue, driven by proinflammatory cytokines such as IL-6 and TNF-α, can significantly disturb calcium homeostasis by altering membrane calcium channels and transporter expression.[5] This may lead to increased transcellular calcium flux and extravascular loss, particularly during the critical phase marked by plasma leakage.

Hypoalbuminemia, commonly reported in dengue due to capillary leak and hepatic dysfunction, further contributes to decreased total serum calcium levels. Although only ionized calcium reflects biologically active calcium, our study demonstrates that corrected total calcium—calculated using Payne's formula—still provides clinically significant information. This is especially relevant in low-resource settings where ionized calcium measurement is not routinely feasible.[9]

The observed negative correlation between calcium and hematocrit likely reflects the shared pathophysiological pathway of capillary leak. As plasma escapes into interstitial spaces, hemoconcentration occurs (elevated hematocrit), and simultaneously, bound calcium is lost, explaining the parallel reduction in corrected calcium levels. Similarly, the positive correlation between calcium and platelet count aligns with the role of calcium in platelet activation and clot formation. Calcium deficiency impairs platelet aggregation, increasing bleeding risk, which is a hallmark of severe dengue.[4]

Table 1: Demographic characteristics by severity group

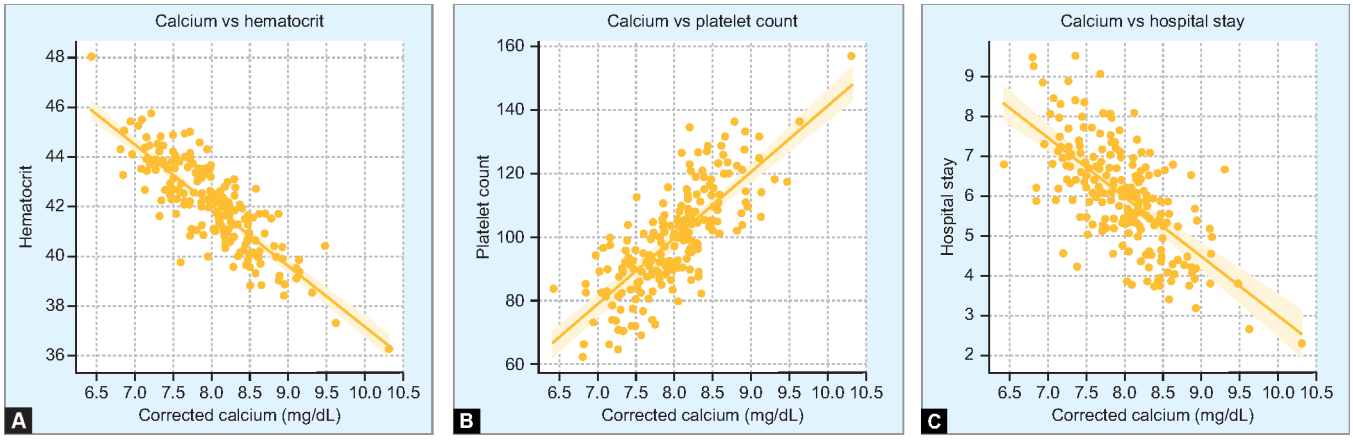
Variable	*Group A (n = 84)*	*Group B (n = 73)*	*Group C (n = 53)*	*Test statistic*	*p-value*
Age (years)	31.8 ± 12.3	33.1 ± 11.5	32.5 ± 11.2	F = 0.38	0.68
Male (%)	56.0	57.5	58.5	$X^2 = 0.12$	0.94
Diabetes (%)	16.7	16.4	17.0	$X^2 = 0.02$	0.98
Hypertension (%)	13.1	12.3	13.2	$X^2 = 0.05$	0.97

Table 2: Clinical and laboratory characteristics by severity group

Parameter	*Group A*	*Group B*	*Group C*	*Test statistic*	*p-value*
Corrected Ca (mg/dL)	8.39 ± 0.59	8.05 ± 0.62	7.61 ± 0.67	F = 14.25	<0.001
Hypocalcemia (%)	43.5	67.1	91.3	$X^2 = 25.4$	<0.001
Hematocrit (%)	38.1 ± 3.5	39.2 ± 4.1	41.7 ± 5.2	F = 5.98	0.002
Platelet count ($\times 10^9$/L)	98 ± 37	74 ± 26	48 ± 21	F = 21.67	<0.001
Hospital stay (days)	4.5 ± 1.6	5.3 ± 2.1	7.2 ± 2.8	F = 10.42	<0.001
ICU admission (%)	9.1	13.7	28.3	$X^2 = 11.8$	<0.001

Table 3: Logistic regression predicting severe dengue

Variable	*aOR*	*95% CI*	*Wald X^2*	*p-value*
Hypocalcemia	3.94	1.98–7.84	14.7	<0.001
Hematocrit	1.12	1.03–1.20	7.5	0.006
Age	1.01	0.98–1.05	1.37	0.24
Albumin	0.86	0.65–1.12	1.12	0.29



Figs 2A to C: Correlation plots of corrected serum calcium

Another critical observation is the association between hypocalcemia and hospitalization metrics. Patients with corrected calcium <7.5 mg/dL had significantly longer hospital stays and were more likely to require ICU admission. This supports the concept that hypocalcemia is not just a surrogate for severity but may also directly contribute to disease complications through its effect on cardiovascular stability, neuromuscular function, and coagulation.

The logistic regression analysis reinforces hypocalcemia as an independent risk factor for severe dengue, with an adjusted odds ratio of 3.94. Even after controlling for albumin, hematocrit, and age, calcium levels remained significantly associated with severity. This suggests that calcium levels offer additive predictive value beyond routine markers. Moreover, while hematocrit and platelet count are already used in clinical practice for dengue monitoring, calcium is rarely considered in prognostication algorithms. Our findings argue for its inclusion as a routine part of dengue evaluation.

This study underscores the clinical utility of serum calcium as a prognostic marker in dengue fever. Hypocalcemia was highly prevalent among patients with severe dengue and showed a strong inverse relationship with key severity indicators such as hematocrit, platelet count, and hospitalization duration. These findings are consistent with prior studies, including an Indian observational study that demonstrated a significant decline in calcium levels with increasing dengue severity.[9] Similar trends have been documented in Sri Lanka by Constantine et al.[10] and by Remya et al.,[11] supporting the broader applicability of calcium monitoring across populations. Our findings regarding predictors of ICU admission are consistent with previous studies on dengue severity.[12] Other tropical infections such as malaria, leptospirosis, and sepsis have also demonstrated hypocalcemia as a marker of poor prognosis, reinforcing its generalizable pathophysiological significance.[13]

Clinically, the ability to use corrected calcium as a triage tool is especially valuable in primary and secondary healthcare settings where rapid decision-making is critical and access to advanced diagnostics is limited. Serum calcium testing is widely available, inexpensive, and already integrated into basic metabolic panels. Its application could therefore be immediate and impactful, helping to prioritize patients for observation, intravenous fluids, and escalation of care.

However, it is also important to contextualize these findings. While hypocalcemia is clearly associated with severe dengue, whether calcium supplementation could modify outcomes remains an open question. Randomized trials are needed to determine whether correcting hypocalcemia therapeutically would reduce complications or shorten hospital stays. Additionally, serial measurements of calcium during the disease course may provide further insights into its dynamic role and prognostic trajectory.

A major limitation of our study is the single-center design, which may restrict generalizability. Ionized calcium was only measured in a subset of patients, limiting comprehensive comparison. Furthermore, our study did not include pediatric patients or track calcium values longitudinally. Despite these limitations, the consistency of our results with existing literature and the strength of statistical associations underscore the robustness of our findings.

Conclusion

This study establishes that corrected serum calcium levels measured at admission are strongly and independently associated with dengue severity. Hypocalcemia was significantly more prevalent in patients with severe dengue, and it correlated with key clinical outcomes such as hospitalization duration, hematocrit levels, and ICU admission rates. The findings suggest that serum calcium, a widely available and inexpensive test, can serve as an early biomarker to identify high-risk patients and guide triage in resource-limited settings. Incorporating calcium assessment into initial clinical evaluation protocols could enhance risk stratification and prompt timely interventions. Given the simplicity and accessibility of this tool, it holds substantial potential for public health impact in dengue-endemic regions, and its clinical application should be further validated through larger multicenter studies.

References

1. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. World Health Organization; 2009.
2. Chakravarti A, Arora R, Luxemburger C. Fifty years of dengue in India. Trans R Soc Trop Med Hyg 2012;106:273–282.
3. Kalayanarooj S, Vaughn DW, Nimmannitya S, et al. Early clinical and laboratory indicators of acute dengue illness. J Infect Dis 1997;176:313–321.
4. Shivanthan MC, Rajapakse S. Dengue and calcium. Int J Crit Illn Inj Sci 2014;4(4):314–316.
5. Bootman MD, Bultynck G. Fundamentals of cellular calcium signaling: a primer. Cold Spring Harb Perspect Biol 2020;12:a038802.
6. Samanta J, Sharma V. Dengue and its effects on liver. World J Clin Cases 2015;3:125–131.
7. Malavige GN, Velathanthiri VGNS, Wijewickrama ES, et al. Patterns of disease among adults hospitalized with dengue infections. QJM 2006;99:299–305.
8. Qi X, Kong H, Ding W, et al. Abnormal coagulation function of patients with COVID-19 is significantly related to hypocalcemia and severe inflammation. Front Med 2021;8:638194.
9. Kumar G, Saini RP, Rani A. Study of correlation of serum calcium level with disease severity in dengue patients. J Assoc Physicians India 2022;70:11–12.
10. Constantine GR, Rajapakse S, Ranasinghe P, et al. Hypocalcemia is associated with disease severity in patients with dengue. J Infect Dev Ctries 2014;8:1205–1209.
11. Remya SR, Kem AK, Sharma R. Role of serum calcium levels as a biomarker for dengue severity and prognosis: insights from a cross-sectional analytic study. Natl J Med Res 2024;14:56–60.
12. Isa ZC, Lim JA, Ain AM, et al. Clinical profiles and predictors of survival in severe dengue cases. Singapore Med J 2023.
13. Sitprija V. Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. Nat Clin Pract Nephrol 2008;4:91–101.

ORIGINAL ARTICLE

Diagnostic Accuracy of Fine Needle Aspirates Using International Academy of Cytology Yokohama System in Categorizing and Diagnosis of Lesions of the Breast: A Clinicopathological Experience

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Abstract

Background: International Academy of Cytology (IAC) introduced a breast category to produce comprehensive standardized guidelines for reporting breast cytopathology. IAC Yokohama System for Reporting Breast Cytopathology highlights the indications for getting breast cytology, procedural techniques, preparation of smear, material yielded, uniform system of reporting, use of ancillary investigations and prognostic tests, and correlation with clinical workup algorithms. The triple approach that includes clinical examination, radiological and pathological workup aims to maximize the preoperative detection of malignancy for early, definitive, appropriate treatment to the patient.

Materials and methods: The present study characterized the cytomorphological features of breast lesions ranging from inflammatory, benign to malignant. The lesions encountered were assigned a specific category on the basis of IAC Yokohama System. Histopathological correlation of cytomorphological findings was done wherever possible.

Results: Out of a total of 450 cases included in our study, 98% (441/450) were females, male to female ratio of 1:49, mean age being 32.6 ± 12.5 years. Majority of cases were in Yokohama category benign comprising 345 breast aspirates (76.66%), followed by 40 cases (8.8%) malignant, 28 cases (6.22%) in Yokohama atypical category. Category suspicious for malignancy consisted of 17 (3.7%) cases. A good inter-kappa agreement was found between cytological impression and histopathology diagnosis (>0.5). A sensitivity and specificity of 100 and 92.96% respectively was seen along with positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) of 98.24%, 100%, and 0.98 respectively. Diagnostic accuracy of 98.57% was seen.

Conclusion: The IAC Yokohama System is a high-quality reporting system used for diagnosing breast fine needle aspirates accurately with greater reproducibility of reports and better communication between the pathologist and clinician.

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Introduction

Breast lesions comprise a major chunk of conditions needing thorough pathological, radiological, and surgical intervention. The spectrum is quite wide, varying from inflammatory (nonneoplastic), benign lesions to invasive carcinoma.[1] Benign breast disease is a heterogeneous group of breast lesions more commonly encountered in routine cytology than the neoplastic lesions. The benign lesions of the breast mostly present in patients in their second decade.[2] As per the Globocon 2020 India, breast carcinoma constituted approximately 13.5% of all cancers and 10.6% of overall cancer deaths.[3] Various risk factors influence the overall incidence of breast carcinoma where genetic, lifestyle, and environmental factors play the most determining role, with the associated risk factors like age, gender, menstrual history, parity, lactation, hormonal factors like hormone replacement therapy or use of birth control pills.[4]

Fine needle aspiration cytology (FNAC) is a simpler and highly specific and sensitive procedure in diagnosing benign vs malignant lesions. Breast FNAC provides many advantages, one of them being minimally invasive, eliminating the need for biopsy in most cases. It has negligible physical and psychological discomfort and is well accepted by the majority of patients. However, multiple factors are known to hinder the overall diagnostic accuracy of breast FNAC depending on procedural skills, experience, smear preparation, and interpreting cytology smears.[5,6] With availability of ultrasound-guided techniques, a useful adjunct helping in detection and aspiration of small and deep-seated lesions, the diagnostic utility of FNA has increased significantly.[7,8] The triple approach aims at the preoperative identification of malignancy so that early, definitive, and appropriate management is offered to the patient.[9] In addition, FNAC allows multidirectional passes aiding in sampling broader areas of the lesion and prompt reporting when essential.[10]

As per NCI guidelines, breast FNAC is divided into five major categories: inadequate (C1), benign (C2), atypical, probably benign (C3), suspicious, favor malignancy (C4), and malignant (C5), and Robinson's grading system for breast carcinoma[11,12] includes six cytomorphological features as parameters (cell size, cell dissociation, cell uniformity, nucleolus, nuclear margin, and nuclear chromatin) to grade the tumors. Scores of 1, 2, 3 are given to cytological features and graded as grade I, II, and III depending on the score. Score 6-11: grade I tumor, score 12-14: grade II tumor, score 15-18: grade III tumor.[11,12]

International Academy of Cytology (IAC) in 2016 formed a breast group to produce set guidelines for reporting breast cytopathology. The concept of structured format reporting system improves not only the quality but by giving quality assurance, clarity, and reproducibility of reports interdepartments, interstates, and

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among countries, improvising overall patient management and hence facilitates the reporting quality.[13,14] Use of cell blocks, immunohistochemistry, *in situ* hybridization, and other molecular tests of prognostic and diagnostic markers will improve patient care. The reporting categories are: category 1: insufficient/inadequate, category 2: benign, category 3: atypical, category 4: suspicious of malignancy, category 5: malignant. The Yokohama System for Reporting Breast Cytopathology aids in reciprocating the implied risk of malignancy (ROM) and recommended clinical management.[15,16] The IAC breast group has established a checklist for fine needle aspiration biopsy (FNAB) cytology using an analytical approach based on pattern identification and crisp cytological criteria which can be used by the reporting cytopathologist.[15]

Materials and Methods

The present study was a cross-sectional study conducted over a period of 4 years and 5 months from January 2018 to May 2022 in the department of pathology and surgery at a tertiary care hospital in South Delhi.

This study characterized the cytomorphological features of the spectrum of breast lesions on FNAC ranging from nonneoplastic to neoplastic. The lesions were also evaluated and assigned a category on the basis of IAC Yokohama System. Histopathological correlation of cytomorphological features was also done wherever available. A total of 450 participants were included presenting with breast masses visiting the outpatient department in the department of surgery. Informed consent was taken from all who participated in the study. All the cases with palpable breast lump who gave consent to get enrolled in the study were included in the study. Detailed clinical history and examination was done prior to FNAC procedure. Hematoxylin and eosin stain, Giemsa, and Papanicolaou stains were used to stain cytology smears. Resected/biopsied specimens were received in 10% buffered formalin for histopathological examination. Specimens were oriented, measured, and sections were submitted for processing. Histopathological diagnosis was correlated with cytological grading.

Statistical analysis was done wherever applicable using SPSS.

Results and Observations

A total of 450 cases were included in our study with 98% (441/450) females and 2% (9/450) male patients with male to female ratio of 1:49. On analyzing the age-wise distribution, majority of cases fell in the age-group 21–30 years, contributing 35.12%, followed by age-group 31–40 years, 26% of the cases.

The patients who presented with painless breast lump (60%) and ones associated with pain were 38% of all cases. Breast lumps presenting with nipple discharge were seen in 2% cases. Most of the lesions were lateralized to the left side (51.11%) with 47.55% cases seen on the right side. Only six (1.33%) cases had a bilateral presentation. Majority of the lesions were localized to the upper outer quadrant (30%) followed by upper inner quadrant (22.6%). Involvement of the central zone (nipple and areola) was seen in 13.1% cases while 4% cases had involvement of multiple quadrants. Lower inner and outer quadrants showed 15.1% cases each.

Majority of the lesions were mobile, 64.88%, with tenderness seen in 44.88% of the lumps on palpation. Overlying skin was found to be normal in appearance in 91.11% of the cases with redness seen in 2.66% cases. Nipple retraction was seen in 2.66% cases and 96% cases showed normal appearance (Table 1). Radiological evaluation was done in 369 (82%) of the cases in the present study. Majority of the cases were BIRADS II (54.74%) followed by BIRADS IV (24.3%), BIRADS I, III, V, VI were seen in 2.71, 7.31, 4.87, 5.96% respectively (Fig. 1).

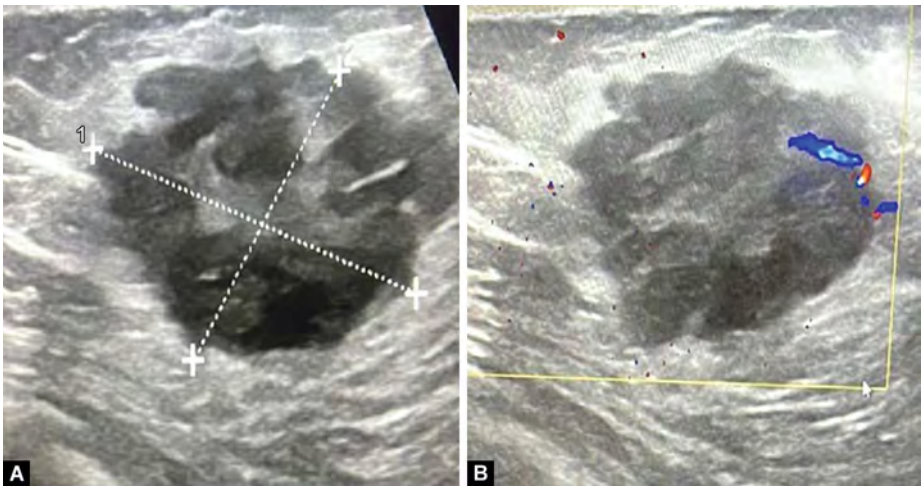
Among the 450 cases, major proportion of cases were seen in Yokohama category benign comprising of 345 breast aspirates (76.66%), this was followed by 40 cases (8.8%) malignant. 28 cases (6.22%) in Yokohama category atypical. Category suspicious for malignancy consisted of 17 (3.7%) cases (Table 2).

Table 1: Distribution of cases according to clinical assessment

Clinical assessment	*Frequency*	*Percentage*
Mobility		
Immobile	158	35.11%
Mobile	292	64.88%
Tenderness		
Nontender	248	55.11%
Tender	202	44.88%
Overlying skin		
Normal	410	91.11%
Atrophied	10	2.22%
Edematous	5	1.11%
Previous surgical scar	5	1.11%
Puckering	8	1.77%
Redness	12	2.66%
Nipple		
Normal	433	96%
Retraction	12	2.66%
Swelling	5	1.11%

Table 2: Distribution of study cases according to "The Yokohama System for Reporting Breast Fine Needle Aspiration"

Yokohama diagnostic category	*Number of cases in each category (n = 450)*	*Percentage (%)*
Insufficient/ inadequate	20	4.44%
Benign	345	76.66%
Atypical	28	6.22%
Suspicious for malignancy	17	3.7%
Malignant	40	8.88%
Total	450	100



Figs 1A and B: (A) Sonogram of breast mass showing a unifocal mass with irregular shape, spiculated margin, echogenic halo with nonparallel orientation, BIRADS 5; (B) Lesion shows internal vascularity on color Doppler

Among the 345 breast FNAC categorized as benign (Fig. 2), 211 cases were categorized as benign breast disease including fibroadenoma. 45 cases were cytologically labeled as cystic lesion. Only 9 cases had fibrocystic change. Inflammatory lesions comprised 37 cases out of which 20 cases were of acute suppurative nature, 15 cases were of granulomatous mastitis, and 2 cases were of chronic mastitis. 23 cases were of gynecomastia, 5 cases were of axillary breast. 15 cases were diagnosed with lactational change/galactocele. A total of 28 cases were categorized as Yokohama category III (atypical, Fig. 3) among 450 aspirates. Of the 28 cases, 57.1% (16 cases) were of proliferative breast disease with atypia while atypical ductal hyperplasia was seen in 8 cases (28.5%) and usual epithelial hyperplasia with focal atypia in 4 cases (14.2%). Out of the 450 breast aspirates, 3.7% (17 cases) were suspicious for malignancy, Yokohama category IV (Fig. 4).

Out of the 450 breast aspirations, 40 were categorized under malignant, category V (Fig. 5). 85% were invasive ductal carcinoma while 5% cases were diagnosed as carcinoma breast with medullary features and 10% were invasive carcinoma of no specific type (NOS).

Association of various parameters with the cytological categories according to the Yokohama System was done and the p value was calculated (Table 3). Significant associations were seen between some of them. On statistically analyzing the association of size of the lesion with cytological categories, a significant association of <0.0001 was seen. Mean size for the malignant cases was 4.63 ± 1.52 cm while the suspicious for malignancy cases had a mean size of 3.8 ± 0.84 cm and the benign lesions had a mean size of 2.25 ± 1.07 cm. The patients presenting to our cytopathology laboratory for FNAC were assessed for clinical presentation such as mobility, tenderness, condition of the overlying skin, and status of the nipple. Statistically significant association was seen in all parameters. *p*-values of 0.0000093 for mobility, 0.0002 for tenderness, and *p*-value was 0 for skin and nipple status. Radiological evaluation and BIRADS scoring are an integral part of breast assessment and the BIRADS score was available in 369 cases presenting with breast lesions. A statistical analysis was done and a significant association (*p*-value 0) was seen between the various cytological categories and BIRADS score.

Histopathological correlation was available in 350 cases (77.7%) (Table 4). In our study, out of 450 cases, 20 cases (9%) were interpreted as inadequate (category I) on cytology, 4 cases underwent further surgical follow-up and were diagnosed as benign (fibroadenoma) on histopathology. A total of 345 cases were diagnosed as Yokohama category II out of which histopathological evaluation was available in 280 cases, 275 out of these cases were diagnosed benign on histopathology while 5 cases were found to be malignant in nature. 28 cases were cytologically categorized as Yokohama category III. Out of 28 cases, histopathological correlation was available in 20 cases. All 20 cases were malignant on histopathological evaluation.

A total of 17 cases were from category IV, with histopathological diagnosis available in 14 cases. All cases were diagnosed as malignant on histopathology. Yokohama category V

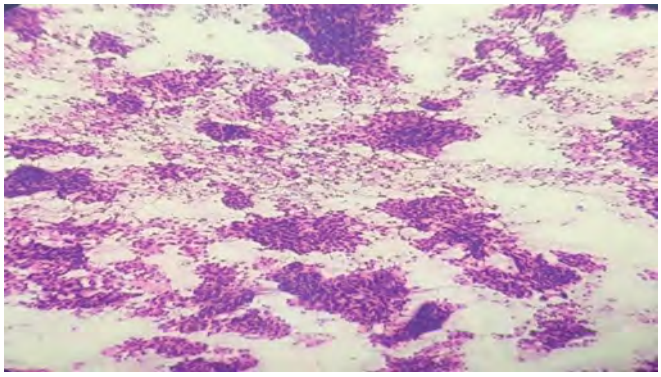
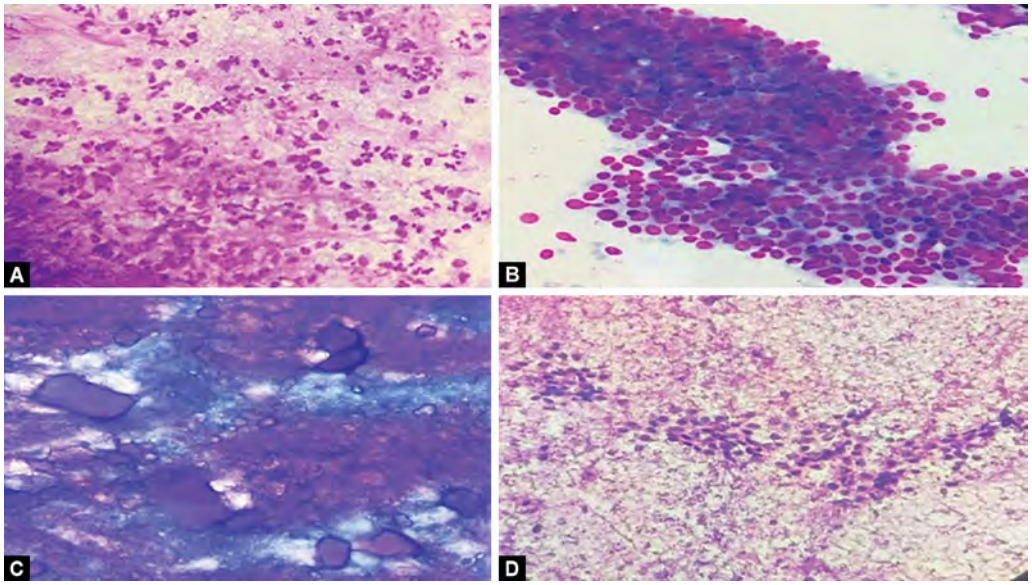


Fig. 3: Category III. FNA smears examined from a case of proliferative breast disease with atypia show A and B—cohesive ductal epithelial cells showing crowding and overlapping of nuclei, mild to moderate nuclear atypia (H&E 10×)



Figs 2A to D: Category II—benign; (A) Tubercular breast abscess shows polymorphs, lymphocytes, eosinophils, cystic macrophages along with ductal epithelial cells (H&E 40×); (B) Fibroadenoma, high-power view (H&E 100×); (C) Crystallizing galactocele shows many crystals of variable shapes and sizes and thin granular amorphous debris, high-power view (H&E); (D) Lactational change, high power (H&E 40×)

(malignant) was assigned to 40 cases on cytology with histopathology available in 32 cases, all were proven to be malignant. Smears obtained on FNAC were evaluated and categorized according to Yokohama System, association of these cytological grades with the histopathologically confirmed categories was assessed. Out of the 450 cases, 350 cases had histopathological follow-up. A significant association was seen between the cytological grade and histopathological diagnosis ($p = 0$) (Table 5).

From the histopathological data, ROM of each Yokohama category was calculated. Out of 450 cases, histopathological evaluation was available in only 280 cases, among which 5 cases were found to be malignant (Table 6).

The risk of malignancy estimated in the benign (Yokohama category II) was 1.8%. Out of 28 cases in the atypical category (Yokohama category III), 20 cases could be followed up on histopathology, all of which were malignant with a risk of malignancy of 100%. Similarly, the risk of malignancy in Yokohama category IV was 100%, where 14 out of 20 cases had follow-up surgery and their histopathology showed malignancy. In category V, 32 out of 40 cases had surgery and all cases turned out to be 100%, ROM 100%.

Table 3: Association of various parameters with cytological categories

Parameter	*p-value*	*Relationship*
Age	<0.5	Significant
Gender	>0.5	Not significant
Breast lump (painful/painless, nipple discharge)	>0.5	Not significant
Lateralization of the lesion (left or right breast)	>0.5	Not significant
Quadrant of involvement	<0.5	Significant
Size of the lesion	<0.5	Significant
Mobility	<0.5	Significant
Tenderness	<0.5	Significant
Overlying skin and nipple	<0.5	Significant
BIRADS score	<0.5	Significant

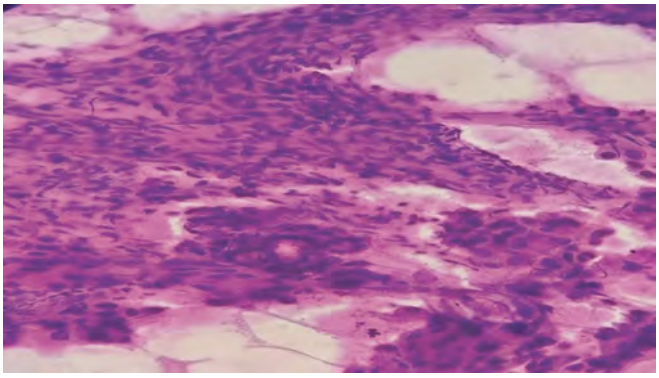


Fig. 4: Category IV. Suspicious for malignancy, probably ductal carcinoma, shows overlapping of nuclei with nuclear atypia (H&E 100×)

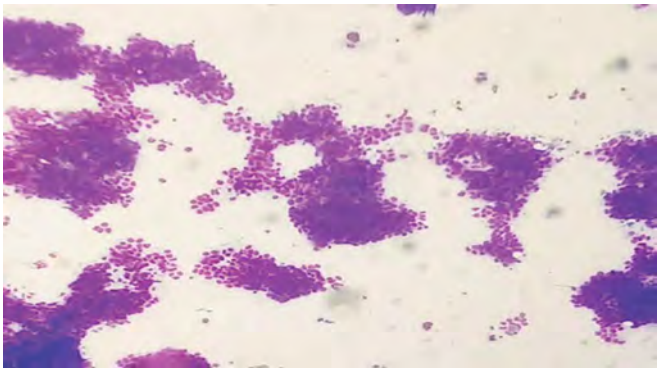


Fig. 5: Category V. FNA smears examined from a case of invasive ductal carcinoma show atypical ductal epithelial cells with high N:C ratio and prominent nucleoli (H&E 40×)

Table 4: Distribution of cases according to histopathological diagnosis of lesions in each cytological category

Yokohama category	*No. of cases*	*Cytological category*	*Histopathology follow-up (n = 350)*	*Histopathological diagnosis*	
				Benign	*Malignant*
1	20	Inadequate	4	4	–
2	345	Benign breast disease/fibroadenoma (211)	280	187	5
		Cyst (45)		30	
		Fibrocystic change (9)		6	
		Granulomatous mastitis (15)		11	
		Acute suppurative lesion/breast abscess (20)		12	
		Lactational change/galactocele (15)		9	
		Gynaecomastia (23)		15	
		Normal/axillary breast (5)		4	
		Chronic mastitis (1)		1	
3	28	Proliferative breast disease with atypia	20		20
		Atypical ductal hyperplasia			
		Usual epithelial hyperplasia with focal atypia			
4	17	Suspicious for malignancy favoring ductal carcinoma	14		14
5	40	Invasive carcinoma, NST	32		32
		Invasive ductal carcinoma			
		Carcinoma with medullary features			
Total	450		350		

On evaluating further, a good inter-kappa agreement was found between cytological impression and histopathology diagnosis (>0.5). In our study, interrater kappa was 0.954, considered to be a very good agreement between the two categories (Table 7).

The sensitivity of cytology was 100%, meaning it correctly identified all true positive cases of cancer. The specificity was 92.96%, indicating that it accurately ruled out cancer in most noncancer cases. The positive predictive value was 98.24%, showing that when cytology indicated malignancy, it was correct nearly most of the time. The negative predictive value was 100%, that is, all cases labeled as nonmalignant by cytology were truly negative. The AUC was 0.98, reflecting good overall test performance. The diagnostic accuracy was 98.57%, confirming that fine needle cytology is a highly reliable tool for predicting malignancy. Table 8 shows that cytology is highly effective in detecting malignancy when compared to histopathology, which is considered the gold standard.

Discussion

Fine needle aspiration cytology of breast lumps is a simple, fast, cost-effective, and safe diagnostic procedure performed to determine the nature of breast masses with a high degree of accuracy and precision. The need for a newer widely accepted reporting system for breast cytology was recognized by IAC, which emphasized that appropriate resources and protocols for breast imaging, biopsy, and treatment would greatly add to the diagnostic workup and management of breast diseases.[16] Breast lesions account for one of the largest chunks of pathological conditions needing thorough diagnostic and surgical intervention.[17]

Breast lumps commonly present with pain, nipple discharge, cysts, and more commonly as a mass. All the patients enrolled in the current study presented with a complaint of lump similar to Bukhari et al. and Farhath et al.[18,19] Jan et al. as well as Chaudhary et al. reported breast lump as the most common clinical presentation in their study, 96.5 and 98%.[20,21] Right-sided lump (46.6%) was reported by Chauhan et al. (52%)[22] and 56% were also observed by Umat et al. and Farhath et al. respectively[23,19] while in the present study left-sided lateralization was seen contributing to 51.11% of cases. The upper outer quadrant was the most common site involved in 30% of cases followed by upper inner quadrant in 22.6% and lower outer quadrant and lower inner quadrant contributing 15.1% each. Our findings were similar to Farhath et al.[19] where upper outer quadrant was the most common quadrant with 46% masses and upper inner quadrant in 20% of lumps. Evaluation of breast masses clinically is a crucial part of the triple assessment.

Lesions were also evaluated on the basis of size that ranged from 1 to 7 cm with a mean

Table 5: Association of cytological Yokohama category with histological subtype

Yokohama category		*Total FNAC (n = 450)*		*FNAC with histopathological follow-up (n = 350)*		*Histopathological categories*		*p-value*
		No.	*%*	*No.*	*%*	*Benign (n = 279)*	*Malignant (n = 71)*	
Category I	Inadequate	0	0%	4	1.1%	4	0	0.0
Category II	Benign	345	76.6%	280	80%	275	5	
Category III	Atypia	28	6.2%	20	71.4%	0	20	
Category IV	Suspicious for malignancy	17	3.7%	14	82.3%	0	14	
Category V	Malignant	40	8.8%	32	80%	0	32	
Total		450	100%	350	56%	279	71	

Table 6: Cytohistological correlation with assessment of risk of malignancy (ROM)

Yokohama category		*Total FNAC (n = 450)*		*FNAC with histopathological follow-up (n = 350)*		*Histopathological categories*		*Risk of malignancy (%)*
		No.	*%*	*No.*	*%*	*Benign (n = 279)*	*Malignant (n = 71)*	
Category I	Inadequate	20	4.4%	4	1.1%	4	0	0
Category II	Benign	345	76.6%	280	80%	275	5	1.8
Category III	Atypia	28	6.2%	20	5.7%	0	20	100
Category IV	Suspicious for malignancy	17	3.7%	14	4%	0	14	100
Category V	Malignant	40	8.8%	32	9.1%	0	32	100
Total		100	100%	350	100%	279	71	

Table 7: Interrater kappa agreement between cytological impression and histopathological diagnosis

Cytological impression	*Histopathological diagnosis*		*Total*	*Kappa*
	Benign (n = 279)	*Malignant (n = 71)*		
Benign	279 (79.7%)	5 (1.4%)	284 (81.1%)	0.954
Malignant	0 (0.00%)	66 (18.8%)	66 (18.8%)	
Total	279 (79.7%)	71 (20.2%)	350 (100.00%)	

size of 2.73 ± 1.43 cm. Marabi et al. in their study concluded the mean size of lesions to be 1.7 cm in maximum dimension ranging from 0.17 to 10.0 cm.[24] A study reported a size range of 2–5 cm.[20] In a study by Chauhan et al., the size of the lumps ranged from 1 to 12 cm in diameter with a mean of 2.4 ± 1.49.[22]

The results of our study of 450 breast FNAC in accordance with IAC Yokohama system were comparable to studies as depicted in Table 9.

In our study, the lesser percentage of cases in category I may be due to the reason that FNAC of breast lesions was performed from multiple sites and often guided FNAC was used; hence aspirate could be procured from the exact pathological site. Relatively limited sample size may also contribute to the lower percentage. The most common diagnosis rendered in category II was fibroadenoma accounting for 61.1% of the benign cases, which is in concordance with various other studies: Chauhan et al. (50%), Sarangi et al. (42.9%), Agrawal et al. (41.3%), and Sundar et al. (30.7%).[22,25–27] Inflammatory lesions accounted for 36 cases (8%) that included lesions such as acute suppurative lesions (4.4%), chronic mastitis (0.2%), and granulomatous mastitis (3.3%). Our numbers were higher than those reported by Agrawal et al., which included inflammatory lesions (47, 6.3%). Fibrocystic disease diagnosed in 2% of cases was lesser as compared to 12.28% (22), 8.2% (33), and 6.5% (31). Galactocele (3.3%), gynecomastia (5.1%), and axillary breast (1.1%) were the other cytological diagnoses in the present study and were comparable to those seen in the above studies.[22,25–27]

Table 8: Sensitivity, specificity, PPV, and NPV of cytology for predicting malignancy taking histopathology as gold standard

Variables (for predicting malignancy)	*Cytology (histopathology, gold standard)*
Sensitivity (95% CI)	100% (98.69–100%)
Specificity (95% CI)	92.96% (84.33–97.67%)
Positive predictive value (95% CI)	98.24% (95.99–99.24%)
Negative predictive value (95% CI)	100% (94.56–100%)
AUC (95% CI)	0.98 (0.96–1.00)
Diagnostic accuracy	98.57% (96.70–99.53%)

Out of a total of 28 cases, 6.2% fell under atypical category III in the present study similar to previous studies being 7, 7.2, and 6.2%.[22,27,28] The majority of the cases (42.8%) in the present study were in the 41 to 50 years age range. Sarangi et al. also reported 29% of cases in this category with 35.4% in the age range of 41–50 years.[25] Histopathological follow-up was available in 20 (4.4%) cases and all were malignant. Chauhan et al. reported 8 out of 10 cases to be malignant on histopathology with 2 cases having atypical features.[22] Montezuma et al. reported 35 cases in this category with histopathology follow-up of which 1 was benign and the rest 34 were malignant.[29]

Category V in the present study made up 40 of the cases; the majority of the diagnoses (28 cases) comprised invasive ductal carcinoma, and 2 cases were reported as carcinoma breast with medullary features. Previous literature revealed cases in category V similar to the present study 8.2% and 11.5%.[25,30] Histopathological correlation was available in 80% of cases and all cases were malignant: invasive ductal carcinoma, invasive carcinoma NOS, and carcinoma with medullary changes. The concordance between malignant cytology and histology was 100%; however, it was reported as 97.5% by Sundar et al.[27] Radiological evaluation was done in 35 out of the 40 cases BIRADS IV, V, and VI with 11.4% of the cases in the BIRADS IV category. BIRADS 4 lesions are not frankly malignant but suspicious enough for a call for biopsy. BIRADS 5 lesions have a higher ROM and always need to undergo biopsy. Spiculated masses and clusters of pleomorphic and microcalcifications are classified in this category.[31]

The false-negative cases are usually acellular, paucicellular, or show few benign ductal epithelial cells. The skill of the procedure and size of the masses were the major reasons for inadequacy reported in breast FNAC. This emphasizes the role of triple tests in patients with breast lump.[24] ROM for category III (atypical) was higher in the present study as compared to the limits proposed by IAC Yokohama system and previously published studies.[7,25] This difference may be attributed to interobserver variability and procedural skills in placing the findings in the atypical category.[27] Kamatar et al. in their study reported a ROM of 66%, higher as compared to other authors, shown in Table 10.[32] The high ROM of the atypical category compared to previous studies can be attributed to possible sampling error which can be overcome by ultrasound-guided FNAC and the fact that not all the cases of this category undergo confirmation with core biopsy.[33]

Category IV (suspicious for malignancy) reported by us as 100% was similar to other studies in literature.[25,26] There were no benign lesions typed as suspicious for malignancy in our study when compared with other studies.[34,35] This could be explained by our routine practice of obtaining a second opinion from intradepartmental colleagues before assigning a category to the cases. ROM for category V malignant cases was concordant with other published reports.[22,30,36]

Specificity and positive predictive value were 100%, similar to studies as seen in Table 11. Diagnostic precision is the ability of a test to discriminate between the target condition and health; it has been variably reported in literature ranging from 95 to 99.5%.[22,30] Diagnostic accuracy of the present study was within this range. The area under the curve (AUC) was 0.98 (0.96 to 1.00), indicating a high level of overall accuracy.

Interrater kappa is defined as a statistical measure of agreement beyond chance. In our study, a kappa value of 0.954 indicated excellent concordance between cytological and histopathological categories.

One of the limitations of our study can be its retrospective nature and hence more prospective studies need to be conducted to enhance the existing database.

Table 9: Comparison of breast cases according to "Yokohama System for Reporting Breast Fine Needle Aspiration" in various studies

Study	*Period of study*	*No. of cytology cases*	*Yokohama category (%)*				
			I Inadequate	*II Benign*	*III Atypical*	*IV Suspicious*	*V Malignant*
Niaz et al.[28]	2008–2019	2133	147 (6.9)	1403 (65.8%)	153 (7.2%)	160 (7.5%)	270 (12.6%)
Dixit et al.[30]	2016–2018	512	38 (7.4%)	379 (74%)	29 (5.7%)	7 (1.4%)	59 (11.5%)
Agnani et al.[35]	2017	603	77 (12.7%)	448 (74.2%)	21 (3.4%)	16 (2.6%)	41 (6.7%)
Makker et al.[37]	Not specified	200	18 (8.9%)	110 (54.4%)	1 (0.9%)	2 (1.48%)	69 (34.1%)
Ahuja et al.[38]	2018	554	20 (3.6%)	385 (69.5%)	35 (6.3%)	13 (2.3%)	101 (18.2%)
Present study	2018–2022	450	20 (4.4%)	345 (76.6%)	28 (6.2%)	17 (3.7%)	40 (8.8%)

Table 10: Comparison of risk of malignancy in each Yokohama category in various studies

Study	*Cases with histopathology follow-up*	*Risk of malignancy in Yokohama category (%)*				
		Inadequate	*Benign*	*Atypical*	*Suspicious*	*Malignant*
Apuroopa et al.[39]	609	5.0	1.2	12.5	93.6	100
Sundar et al.[27]	288	38	0.6	21.9	100	97
Sarangi et al.[25]	400	33.3	0.8	38	98.7	100
De Rosa et al.[7]	1745	49.6	4.9	21	78.7	98.8
Wong et al.[38]	579	2.6	1.7	16	84.6	99.5
Present study	350	0	1.8	100	100	100

Table 11: Comparison of various statistical parameters of FNAC with other studies

Study	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*	*Diagnostic accuracy (%)*
Chauhan et al.[22]	98.9	99.1	99.0	97.8	99.5
Montezuma et al.[29]	97.5	100	100	98.2	99.1
Dixit et al.[30]	95	99.5	98.2	98.6	98.5
Sunitha et al.[40]	100	96.6	94.5	100	97.8
Moschetta et al.[36]	97	94	91	98	95
Present study	100	92.9	98.2	100	98.5

Conclusion

The IAC Yokohama system of reporting breast cytology is an excellent system for accurately diagnosing fine needle aspirates, with an improved system for reporting helping clearer communication between pathologist and clinician. Our study, though limited in terms of being a single institution-based study with a relatively smaller sample size, validates FNAC as a safer and cost-effective test for differentiating benign vs malignant lesions. Hence, FNAC and histopathological along with radiological findings (triple approach) aid together to provide a definitive diagnosis for subsequent management. These newer diagnostic categories by IAC Yokohama system carry an implied ROM increasing from benign to malignant categories. Categorization of the breast FNAB cytology according to IAC Yokohama system of reporting breast lesions helps pathologist in diagnostic clarity and guides clinician in appropriate patient management.

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References

1. Moolamalla RM, Raghu K. Histopathological spectrum of neoplastic and non-neoplastic breast lesions—a two-year study. Int J Sci Stud 2017;4:158–162.
2. Padmon L, Sapru K, Beena D. Histopathological spectrum of breast lesions-a study done in a tertiary care hospital. J Evolution Med Dent Sci 2020;9:1412–1415.
3. Mehrotra R, Yadav K. Breast cancer in India: present scenario and the challenges ahead. World J Clin Oncol 2022;13:209–218.
4. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer (Dove Med Press) 2019;11:151–164.
5. Khattak MS, Ahmad F, Rehman KU. Role of fine needle aspiration cytology in diagnosis of palpable breast lesions and their comparison with histopathology. J Ayub Med Coll Abbottabad 2020;32:83–86.
6. Veerendrasagar RS, Nandish VS. Cytomorphological spectrum of breast lesions and diagnostic utility of fine needle aspiration cytology. IP Arch Cytol Histopathology Res 2020;5:22–25.
7. De Rosa F, Migliatico I, Vigliar E, et al. The continuing role of breast fine-needle aspiration biopsy after the introduction of the IAC Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy Cytopathology. Diagn Cytopathol 2020;48:1244–1253.
8. Takhellambam YS, Lourembam SS, Sapam OS, et al. Comparison of ultrasonography and fine needle aspiration cytology in the diagnosis of malignant breast lesions. J Clin Diagn Res 2013;7:2847–2850.
9. Field AS, Vielh P, Schmitt F. IAC standardized reporting of breast FNA biopsy cytology. Acta Cytol 2017;61:3–6.
10. Arul P, Masilamani S. Application of National Cancer Institute recommended terminology in breast cytology. J Can Res Ther 2017;13:91–96.
11. Robinson IA, McKee G, Nicholson A, et al. Prognostic value of cytological grading of fine-needle aspirates from breast carcinomas. Lancet 1994;343:947–949.
12. Sinha S, Sinha N, Bandyopadhyay R, et al. Robinson's cytological grading on aspirates of breast carcinoma: correlation with Bloom Richardson's histological grading. J Cytol 2009;26:140–143.
13. Saha K, Raychaudhuri G, Chattopadhyay BK, et al. Comparative evaluation of six cytological grading systems in breast carcinoma. J Cytol 2013;30:87–93.
14. Ellis DW, Srigley J. Does standardised structured reporting contribute to quality in diagnostic pathology? The importance of evidence-based datasets. Virchows Arch 2016;468:51–59.
15. Field AS, Raymond WA, Schmitt F. The International Academy of Cytology Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy Cytopathology. Switzerland: Springer; 2020.
16. Hoda RS, Brachtel EF. International Academy of Cytology Yokohama System for reporting breast fine-needle aspiration biopsy cytology: a review of predictive values and risks of malignancy. Acta Cytologica 2019;63:292–301.
17. Field AS. Fine needle aspiration biopsy cytology of breast: a diagnostic approach based on pattern recognition. In: Field AS, Zarka MR (Eds). Practical cytopathology: a diagnostic approach to fine needle aspiration biopsy. Amsterdam: Elsevier; 2017. Chapter 5.
18. Bukhari MH, Arshad M, Jamal S, et al. Use of fine-needle aspiration in the evaluation of breast lumps. Pathol Res Int 2011;2011:689521.
19. Farhath S, Sravan Kumar K. Diagnostic accuracy of FNAC in evaluation of breast lumps. J Med Sci Clin Res 2016;4:9275–9279.
20. Jan M, Mattoo JA, Salroo NA, et al. Triple assessment in the diagnosis of breast cancer in Kashmir. Indian J Surg 2010;72:97–103.
21. Chaudhary M, Bhat P, Wankhede V, et al. Clinicopathological study of benign breast diseases a study of 50 cases. Int Surg J 2021;8:1462–1465.
22. Chauhan V, Pujani M, Agarwal C, et al. IAC standardized reporting of breast fine-needle aspiration cytology, Yokohama 2016: a critical appraisal over a 2-year period. Breast Dis 2019;38:109–115.
23. Umat PD, Desai H, Goswami H. Correlation between BI-RADS categories and cytological findings of breast lesions. Int J Clin Diagn Pathol 2020;3:43–48.
24. Marabi M, Aphivatanasiri C, Jamidi SK, et al. The International Academy of Cytology Yokohama System for Reporting Breast Cytopathology showed improved diagnostic accuracy. Cancer Cytopathol 2021;129(11):852–864.
25. Sarangi S, Rao M, Elhence PA, et al. Risk stratification of breast fine-needle aspiration biopsy specimens performed without radiologic guidance by application of the International Academy of Cytology Yokohama System for Reporting Breast Fine-Needle Aspiration Cytopathology. Acta Cytologica 2021;65:483–493.
26. Agrawal N, Kothari K, Tummidi S, et al. Fine-needle aspiration biopsy cytopathology of breast lesions using the International Academy of Cytology Yokohama System and Rapid On-Site Evaluation: a single-institute experience. Acta Cytologica 2021;65:463–477.
27. Sundar PM, Shanmugasundaram S, Nagappan E. The role of the IAC Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy and the ACR Breast

Imaging-Reporting and Data System in the evaluation of breast lesions. Cytopathology 2022;33:185–195.
28. Niaz M, Khan AA, Ahmed S, et al. Risk of malignancy in breast FNAB categories, classified according to the newly proposed International Academy of Cytology (IAC) Yokohama System. Cancer Manag Res 2022;14:1693–1701.
29. Montezuma D, Malheiros D, Schmitt F. Breast fine needle aspiration biopsy cytology using the newly proposed IAC Yokohama System for reporting breast cytopathology: the experience of a single institution. Acta Cytol 2019;63:274–279.
30. Dixit N, Trivedi S, Bansal VK. A retrospective analysis of 512 cases of breast fine needle aspiration cytology utilizing the recently the recently proposed IAC Yokohama System for Reporting Breast Cytopathology. Diagn Cytopathol 2021;49:1022–1031.
31. Ghaemian N, Haji Ghazi Tehrani N, Nabahati M. Accuracy of mammography and ultrasonography and their BI-RADS in detection of breast malignancy. Caspian J Intern Med 2021;12:573–579.
32. Kamatar PV, Athanikar VS, Dinesh US. Breast fine needle aspiration biopsy cytology reporting International Academy of Cytology Yokohama System—two-year retrospective study in tertiary care centre in Southern India. Natl J Lab Med 2019;8:1–3.
33. Goyal P, Sehgal S, Ghosh S, et al. Histopathological correlation of atypical (c3) and suspicious (c4) categories in fine needle aspiration cytology of the breast. Int J Breast Cancer 2013;2013:965498.
34. Chaiwun B, Sukhamwang N, Lekawanvijit S, et al. Atypical and suspicious categories in fine needle aspiration cytology of the breast: histological and mammographically correlation and clinical significance. Singapore Med J 2005;46:706–709.
35. Agnani B, Hemrajnani D, Mathur K, et al. Breast cytopathology reporting using the newly proposed IAV Yokohama system: a single institutional retrospective study of the application of the system and utility of breast FNAC. Int J Sci Res 2020;9:27–29.
36. Moschetta M. Comparison between fine needle aspiration cytology (FNAC) and core needle biopsy (CNB) in the diagnosis of breast lesions. G Chir 2014.
37. Makker I, Agarwal P, Raghuvanshi S, et al. Strength and weaknesses of application of International Academy of Cytology Yokohama system for reporting breast fine-needle aspiration cytopathology. J Cytol 2022;39:89–90.
38. Ahuja S, Malviya A. Categorization of breast fine needle aspirates using the International Academy of Cytology Yokohama system along with assessment of risk of malignancy and diagnostic accuracy in a tertiary care centre. J Cytol 2021;38:158–163.
39. Apuroopa M, Chakaravarthy VK, Ranga RD. Application of Yokohama system for reporting breast fine needle aspiration cytology in correlation with histopathological and radiological findings. Ann Pathol Lab Med 2020;7:211–215.
40. Sunitha A, Chandra S, Rambabu, et al. Application of IAC Yokohama system for breast cytology: the experience at a tertiary care hospital. IP Arch Cytol Histopathol Res 2021;6:237–242.

ORIGINAL ARTICLE

Quantification of Liver Stiffness Using Magnetic Resonance Elastography in Comparison with Transient Elastography and Noninvasive Fibrosis Score in Fatty Liver

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Abstract

Background: The global incidence of fatty liver (FL) [alcoholic and nonalcoholic FL disease (NAFLD)] is increasing. Imaging-based elastography techniques, being noninvasive, may eliminate the need for more invasive techniques for the diagnosis and staging of liver fibrosis in FL disease.

Objective: Our study aims to address the gap in the current research by exploring the correlation between mean liver stiffness measurement (LSM) as obtained through magnetic resonance elastography (MRE) and transient elastography (TE), and two commonly used clinical scores, fibrosis-4 index (FIB-4) score and aspartate aminotransferase to platelet ratio index (APRI) score.

Materials and methods: In this hospital-based cross-sectional study, 62 patients diagnosed with FL on ultrasound were recruited. The patients were further subjected to MR liver elastography and TE, and LSM using both modalities was recorded. A history of diabetes mellitus and alcohol intake was taken. Moreover, noninvasive fibrosis scores such as FIB-4 and APRI were calculated using standard formulas.

Results: The correlation analysis revealed a strong positive correlation between LSM values obtained from MRE and TE ($r = 0.88$) (Cohen's $\kappa = 0.87$), a moderate correlation between MRE and FIB-4 score ($r = 0.44$), and weak positive correlations involving MRE and APRI ($r = 0.34$), TE and FIB-4 score ($r = 0.36$), and TE and APRI ($r = 0.29$). Additionally, significantly higher fat fractions were quantified [median (IQR)] in grade III FL [23.6 (15.9–29.5)] as compared to grades I [8.45 (2.25–13.9)] and grade II [13.1 (8.4–19.7)].

Conclusion: MRE shows a strong positive correlation with TE for LSM and stage of fibrosis. Our findings suggest that MRE could be a valuable tool in the diagnostic armamentarium of FLD.

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Introduction

Fatty liver (FL) represents the common underlying factor in the two most prevalent and emerging determinants of chronic liver disease (CLD), that is, alcoholic liver disease (ALD) and nonalcoholic FL disease (NAFLD). The adoption of a westernized lifestyle and consumption of a high-calorie diet contribute to the development of NAFLD. The accumulation of an excessive amount of fat within hepatocytes leads to fatty change, often asymptomatic, and can be reversed. However, when conditions are conducive to inflammation and, more importantly, the development of fibrosis, it becomes an irreversible process.[1,2] Biopsy is considered the gold standard for examining liver fibrosis, but it is an invasive examination that may cause sampling error and other complications.[3] Hence, there is a need for the development of noninvasive tests (NITs). NITs are increasingly replacing biopsies, effectively addressing the limitations of the invasive procedure and gaining popularity in clinical practices. The two primary categories of NITs for liver fibrosis staging are imaging-based elastography and serum biomarkers. Biomarkers such as the aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) scores have undergone extensive validation and are widely used due to their ease of accessibility. Furthermore, methods like transient elastography (TE), shear wave elastography (SWE), and magnetic resonance elastography (MRE) have demonstrated exceptional accuracy in detecting liver fibrosis.[4] Out of these techniques, MRE is considered the most accurate diagnostic tool.[5]

Magnetic resonance elastography utilizes magnetic resonance imaging (MRI) to calculate the mechanical properties of tissues quantitatively and is carried out using a source of vibration to generate mechanical low-frequency waves in tissues and analyze wave information to create images. Liver MRE is used to measure liver stiffness in assessing fibrosis or cirrhosis. Moreover, MRE offers the advantage of scanning a wide area of liver parenchyma while allowing the flexibility to select specific region of interest (ROI).[6–8] It allows for the detection of fibrosis and accurately stages the same.[9] MRE proves valuable in the early changes in liver stiffness, making it easier to identify individuals with FL who could potentially develop cirrhosis.[10]

Materials and Methods

In this hospital-based cross-sectional study, we recruited 62 patients diagnosed with FL who met the specified inclusion and exclusion criteria. Patients referred for abdominal ultrasound on clinical suspicion (age-group 18–65 years) were included. Pregnant women, individuals with a history of hemochromatosis, iron overload disease or storage disorders, ascites, claustrophobic patients, and those who have ferromagnetic substances, implants, or any established contraindication for MRI were excluded [details described in supplementary data (Table 1)]. The other variables considered, and their criteria are discussed in supplementary data.[11–15] Anthropometric measures such as height and weight were recorded, and body mass index (BMI) was calculated. A history of diabetes mellitus and alcohol intake was taken, considering known diabetics on medication, and according to standard measures of alcohol consumption, patients were classified as alcoholic or nonalcoholic. Furthermore, noninvasive fibrosis scores such as FIB-4 and APRI were calculated using standard formulae.

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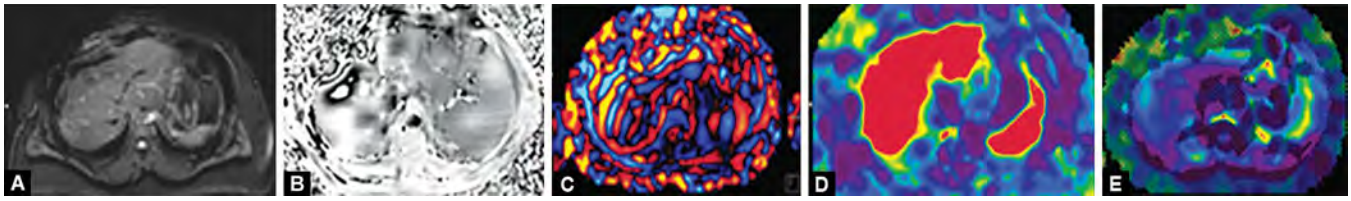

Figs 1A to E: Development of color elastogram from magnitude and phase sequences: (A) Magnitude image; (B) Phase image; (C) Wave image; (D) Color elastogram; and (E) Color elastogram with 95% confidence map

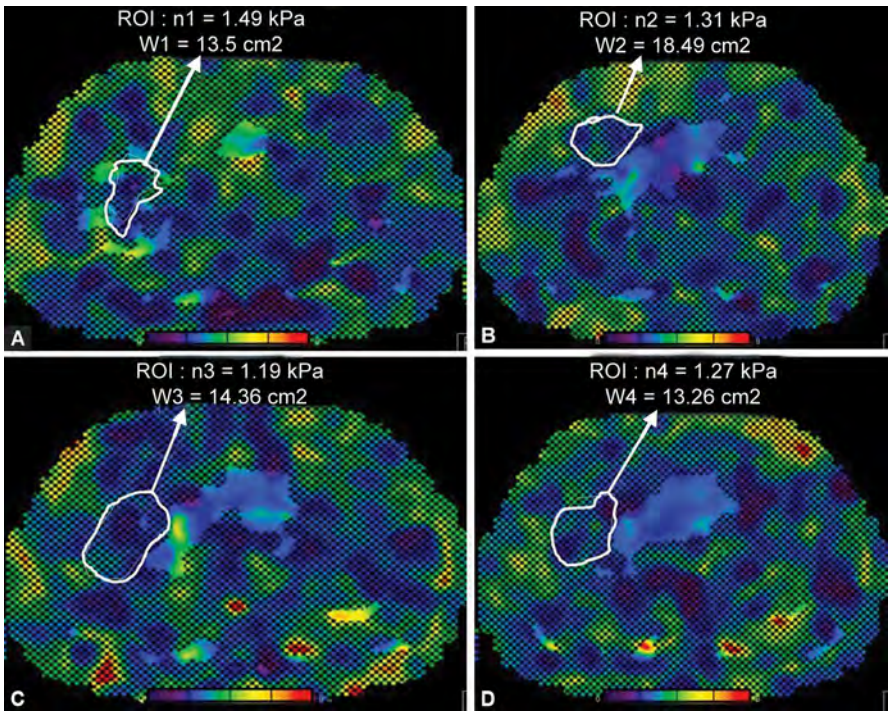

Fig. 2: Freehand ROIs drawn at various sections of the liver elastograms obtained, for calculating the mean liver stiffness

The data obtained from MRE, TE, and other NITs were compared, correlated, and subjected to further analysis.

Equipment used:

- Ultrasound machine: Alpinion E-Cube i7.
- Transducer: convex–C1-6T.

The liver was scanned in the supine position using a convex transducer. The grade of FL if seen was assigned according to the standard ultrasound grading described in supplementary data Table 2.[16]

- Siemens 3 Tesla Magnetom Skyra.
- Body coil.
- Resonant passive driver (rigid type) with elastic band to fasten the driver.
- Resonant active driver (placed outside the MRI room).

Patient Positioning

Patients were positioned in a supine posture. The passive driver was installed along the midclavicular line, placed above the lower right chest wall at the xiphisternum level. It was placed in direct contact with the body wall and fastened with an elastic band. The passive driver was then linked through a plastic tube to the active driver located outside the scanning room.

Sequences used: two-dimensional (2D) gradient-echo sequences with cyclic motion-encoding gradients (MEG) for MRE.

The generation of a color elastogram from the magnitude and phase sequences is represented in Figure 1.

Generic formula for calculating the weighted arithmetic mean (AMw) of the mean liver stiffness (*n*) for ROIs drawn on four images (Fig. 2), with an ROI size of w pixels:

$$AMw = (n1w1 + n2w2 + n3w3 + n4w4) \div (w1 + w2 + w3 + w4)$$

Where:

- n1, n2, n3, and n4 were the mean liver stiffness values measured on four elastograms.
- w1, w2, w3, and w4 are the sizes of the ROIs drawn on each of the four elastograms.

Siemens liver lab sequences for quantification of fat in the liver.

- T1 VIBE—enhanced Dixon technique (eDIXON).
- T1 VIBE—quantitative Dixon technique (qDIXON).

Guidelines for interpreting liver stiffness through the application of MRE are provided in supplementary data (Table 3).[17]

- Transient elastography: Echosens FibroScan 502 Touch.

The grading of liver fibrosis in both alcoholic and nonalcoholic patients is determined by liver stiffness measurements (LSMs) obtained from TE, as detailed in supplementary data Table 4.[18]

The workflow employed in the study is depicted in Figure 1 of the supplementary data.

Statistical Analysis

Statistical analysis was conducted using SPSS version 23.0. Continuous variables were expressed as the mean and standard deviation (SD), reported as mean ± SD, and compared using the independent *t*-test. For variables not following a normal distribution, the median and interquartile range were used, with comparisons made *via* the Mann–Whitney *U* test. Categorical variables were presented as percentages and analyzed using the Chi-squared test. When comparing continuous variables across more than two groups, the Kruskal–Wallis test was applied (if they were not following a normal distribution), and further pairwise analysis was done using Tukey's test. Interrater reliability between MRE LSM and FibroScan LE was done using Cohen's kappa. Correlation analysis was done between MRE vs TE, MRE vs scores, TE vs scores, and *r*-values calculated. Variables with p-value < 0.05 were considered statistically significant.

Results

This study included 62 patients (40 males and 22 females) with a diagnosis of FL on ultrasound and further subjected to MR liver

elastography and TE, and measurement of LSM using both modalities was recorded. The mean age of the patients was 47.5 ± 10.52 years. Additionally, about 40% of the population was alcoholic and 17.74% was diabetic.

Mean Liver Stiffness Measurement from Magnetic Resonance Elastography

The mean LSM obtained through MRE was 3.39 ± 1.53 in males and 3.08 ± 1.15 in females. Based on grading of liver stiffness measurement obtained through MR elastography, 25.8% had stage 1–2 fibrosis, 14.5% had stage 2–3 fibrosis, 8.1% had stage 4 fibrosis/cirrhosis, and 4.8% had stage 3–4 fibrosis.

Mean Liver Stiffness Measurement in Alcoholic vs Nonalcoholic and Diabetic vs Nondiabetic

The mean LSM obtained through MRE for alcoholic and nonalcoholic, and diabetic and nondiabetic patients is shown in Table 1. Based on adjusted standardized residuals, stage 2–3 fibrosis was seen as significantly higher in diabetic patients, and normal and normal/inflammation were seen as significantly higher in nondiabetic patients (Table 2 and 3).

Correlation Analysis

A strong correlation was noted between LSM obtained with MRE and TE (R = 0.883). Good correlation was noted between LSM values obtained with MRE and Fib-4 (R = 0.446) (Fig. 3). Weak correlation was noted between LSM measurements obtained with MRE and APRI score (R = 0.34), and also LSM obtained with TE and Fib-4 score (R = 0.36) (Fig. 4). Also, a weak correlation was noted between LSM measurement obtained with TE and APRI score (R = 0.298) (Fig. 5).

Subgroup Analysis

Median FIB-4 and APRI Scores across Different Grades of Liver Stiffness

Table 1: Mean LSM (MRE) in alcoholics vs nonalcoholics and diabetics vs nondiabetics

LSM MRE	*Alcoholic (N = 16)*	*Nonalcoholic (N = 46)*	*p-value*	*Diabetic (N = 11)*	*Nondiabetic (N = 51)*	*p-value*
Mean ± SD	4.04 ± 1.82	3.02 ± 1.15	0.012	3.69 ± 1.43	3.19 ± 1.4	0.314

Table 2: Distribution of stage of LSM (MRE) in alcoholic/nonalcoholic and diabetic/nondiabetic

LSM stage		*Alcoholic (N = 16)*	*Nonalcoholic (N = 46)*	*p-value*	*Diabetic (N = 11)*	*Nondiabetic (N = 51)*	*p-value*
Normal	Number (percentage)	1 (6.3)	15 (32.6)	0.111	1 (9.1)	15 (29.4)	0.046
Normal/inflammation		2 (12.5)	11 (23.9)		0 (0)	13 (25.5)	
Stage 1–2 fibrosis		5 (31.5)	11 (23.9)		5 (45.5)	11 (21.6)	
Stage 2–3 fibrosis		4 (25)	5 (10.9)		4 (36.4)	5 (9.8)	
Stage 3–4 fibrosis		1 (6.3)	2 (4.3)		0 (0)	3 (5.9)	
Stage 4/cirrhosis		3 (18.8)	2 (4.3)		1 (9.1)	4 (7.8)	

Table 3: Distribution of LSM measured using TE vs alcoholic/nonalcoholic and diabetic/nondiabetic

TE stage		*Alcoholic (N = 16)*	*Nonalcoholic (N = 46)*	*p-value*	*Diabetic (N = 11)*	*Nondiabetic (N = 51)*	*p-value*
F0–F1	Number (percentage)	4 (25)	27 (58.7)	0.076	1 (9.1)	30 (58.8)	0.025
F2		8 (50)	9 (19.6)		6 (54.5)	11 (21.6)	
F3		2 (12.5)	4 (8.7)		2 (18.2)	4 (7.8)	
F4		2 (12.5)	6 (13)		2 (18.2)	6 (11.8)	

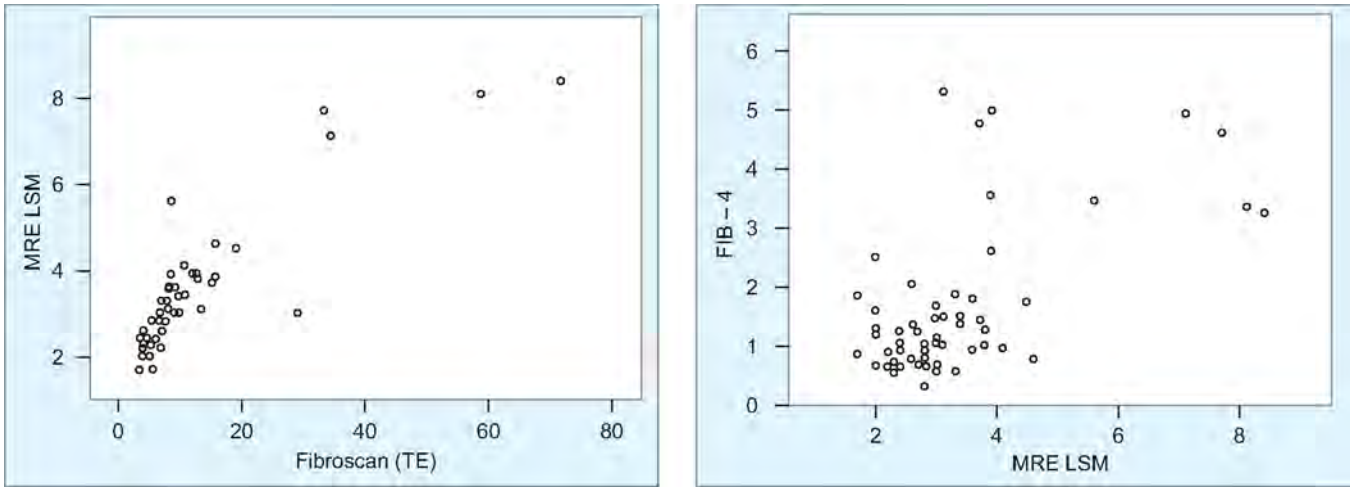

Fig. 3: Correlation between MRE vs TE [scatter plot showing very strong correlation (R = 0.883) between LSM values obtained through MRE and TE] and correlation between MRE vs FIB-4 [scatter plot showing moderate correlation (R = 0.446) between MRE LSM and FIB-4 score]

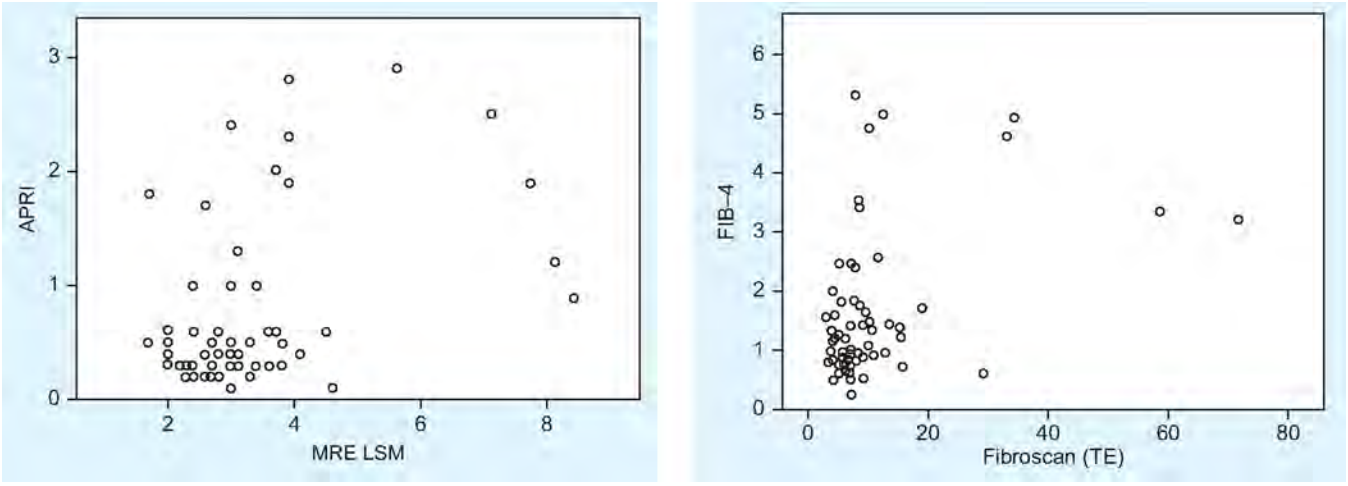

Fig. 4: MRE vs APRI [scatter plot showing weak correlation (R = 0.34) between MRE LSM and APRI score] and correlation between TE vs FIB-4 [scatter plot showing weak correlation (R = 0.36) between TE LSM and FIB-4 score]

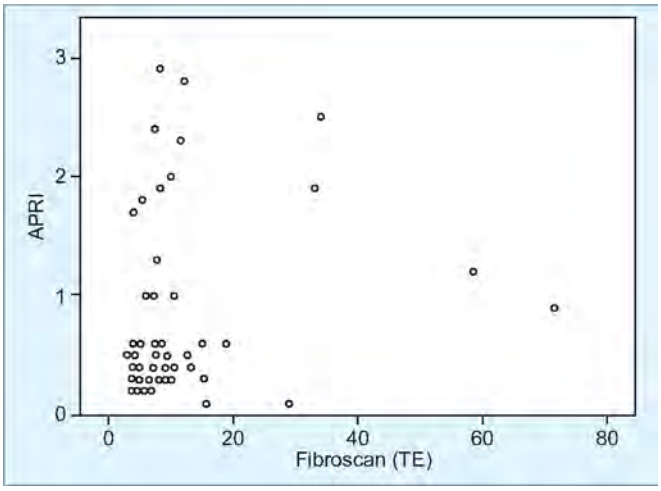

Fig. 5: Correlation between TE vs APRI [scatter plot showing weak correlation (R = 0.298) between TE LSM and APRI score]

Table 4: FIB-4 vs MRE scores pairwise

Pairs	*p-value*
Normal vs normal/inflammation	1
Normal vs stage 1–2 fibrosis	1
Normal vs stage 2–3 fibrosis	0.177
Normal vs stage 3–4 fibrosis	1
Normal vs stage 4/cirrhosis	0.007
Normal/inflammation vs stage 1–2 fibrosis	0.717
Normal/inflammation vs stage 2–3 fibrosis	0.054
Normal/inflammation vs stage 3–4 fibrosis	1
Normal/inflammation vs stage 4/cirrhosis	0.002
Stage 1–2 fibrosis vs stage 2–3 fibrosis	1
Stage 1–2 fibrosis vs stage 3–4 fibrosis	1
Stage 1–2 fibrosis vs stage 4/cirrhosis	0.211
Stage 2–3 fibrosis vs stage 3–4 fibrosis	1
Stage 2–3 fibrosis vs stage 4/cirrhosis	1
Stage 3–4 fibrosis vs stage 4/cirrhosis	0.335

Measurement Obtained through Magnetic Resonance Elastography

In addition, on subgroup analysis, a significant difference in FIB-4 score was seen between normal vs stage 4 fibrosis/cirrhosis, and normal/inflammation vs stage 4 fibrosis/cirrhosis of MRE LSM grading (Table 4), and a significant difference in APRI score was seen between normal vs stage 4 fibrosis/cirrhosis, and normal/inflammation vs stage 4 fibrosis/cirrhosis of MRE LSM grading (Table 5). Furthermore, the median FIB-4 score and APRI score across different grades of fibrosis were obtained through MRE summarized in Table 6.

Median FIB-4 and APRI across Different Grades of Liver Stiffness Measurement Obtained through Transient Elastography

In the subgroup analysis, a significant difference in FIB-4 score was seen between F0 and F1 vs F2 stages of TE LSM grading (Table 7). On the contrary, a significant difference in APRI score was seen between F0–F1 vs F2 and F0–F1 vs F3 stages of TE LSM grading in the case of APRI and TE subgroup analysis (Table 8).

Median FIB-4 score and APRI score across different grades of fibrosis were obtained through TE (Table 9).

The proton density fat fraction (PDFF) values obtained through quantitative MRI sequences were significantly different in grade I FL and grade III FL determined on ultrasonography (USG) (Table 10).

Correlation analysis revealed a very strong correlation between LSM values obtained through MRE and TE, a moderate correlation between MRE LSM and FIB-4 score, and a weak correlation between MRE LSM and APRI score,

Table 5: APRI vs MRE scores pairwise

Pairs	*p-value*
Normal vs normal/inflammation	1
Normal vs stage 1–2 fibrosis	1
Normal vs stage 2–3 fibrosis	0.472
Normal vs stage 3–4 fibrosis	1
Normal vs stage 4/cirrhosis	0.044
Normal/inflammation vs stage 1–2 fibrosis	1
Normal/inflammation vs stage 2–3 fibrosis	0.08
Normal/inflammation vs stage 3–4 fibrosis	1
Normal/inflammation vs stage 4/cirrhosis	0.007
Stage 1–2 fibrosis vs stage 2–3 fibrosis	0.783
Stage 1–2 fibrosis vs stage 3–4 fibrosis	1
Stage 1–2 fibrosis vs stage 4/cirrhosis	0.076
Stage 2–3 fibrosis vs stage 3–4 fibrosis	1
Stage 2–3 fibrosis vs stage 4/cirrhosis	1
Stage 3–4 fibrosis vs stage 4/cirrhosis	0.326

Table 7: FIB-4 vs TE scores subgroups

Pairs	*p-value*
F0–F1 vs F2	0.015
F0–F1 vs F3	0.114
F0–F1 vs F4	0.077
F2 vs F3	1
F2 vs F4	1
F3 vs F4	1

Table 8: APRI vs TE scores subgroups

Pairs	*p-value*
F0–F1 vs F2	0.039
F0–F1 vs F3	0.026
F0–F1 vs F4	0.703
F2 vs F3	1
F2 vs F4	1
F3 vs F4	1

Table 6: MRE vs FIB-4 and APRI scores

Scores		*Normal*	*Normal/inflammation*	*Stage 1–2 fibrosis*	*Stage 2–3 fibrosis*	*Stage 3–4 fibrosis*	*Stage 4/cirrhosis*	*p-value*
FIB–4	Median (IQR)	0.96 (0.64–1.49)	0.83 (0.69–1.22)	1.44 (0.99–1.79)	1.77 (1.11–4.14)	0.93 (0.75)	3.44 (3.28–4.77)	0.001
APRI		0.35 (0.3–0.57)	0.3 (0.2–0.45)	0.35 (0.3–0.87)	0.6 (0.4–2.15)	0.4 (0.1)	1.9 (1.05–2.7)	0.003

Table 9: TE vs scores

Scores		*F0–F1*	*F2*	*F3*	*F4*	*p-value*
FIB-4	Median (IQR)	0.91 (0.64–1.25)	1.65 (0.95–1.95)	1.43 (1.25–3.18)	2.47 (0.87–4.29)	0.003
APRI		0.3 (0.2–0.5)	0.5 (0.3–1.6)	0.8 (0.475–2.42)	0.75 (0.15–1.72)	0.005

Table 10: PDFF vs grades of FL

PDFF	*Grade I*	*Grade II*	*Grade III*	*p-value*
Median (IQR)	8.45 (2.25–13.9)	13.1 (8.4–19.7)	23.6 (15.9–29.5)	0.001

Table 11: Correlation analysis

Correlation	*p-value*	*r-value*
MRE vs TE	<0.001	0.883
MRE vs FIB-4	<0.001	0.446
MRE vs APRI	0.007	0.34
TE vs FIB-4	0.004	0.364
TE vs APRI	0.019	0.298

Table 12: Interrater reliability between MRE and TE

	Cohen's kappa	*p-value*
MRE LSM vs TE LSM	0.363	<0.001

TE and FIB-4 score, as well as TE and APRI score (Table 11).

The interrater reliability between MRE LSM and TE LSM across different grades of fibrosis showed a Cohen's kappa value of 0.363, indicating fair agreement (Table 12).

Table 13: Level of agreement between MRE and TE for fibrosis detection

Fibrosis detected by MRE and TE	*Fibrosis not detected by both MRE and TE*	*Fibrosis detected by MRE only*	*Fibrosis detected by TE only*
30	28	3	1

Percentage of agreement = 93.54%; Cohen's κ = 0.871; almost perfect agreement

Our data shows an almost perfect agreement (93.54%) between MRE and TE for the measurement of LSM (Cohen's κ of 0.871) with a strong positive correlation. The interrater reliability between MRE and TE across various stages of fibrosis showed a fair agreement (Table 13).

Discussion

Fibrosis is the result of injury to hepatocytes, which may be incited by various etiologies. Hepatocyte injury leads to a cascade of events, mediated by various intermediate compounds such as free radicals and inflammatory cytokines, which culminate in cell death and subsequent fibrosis.[19] The stiffness of the liver undergoes a change during this process of hepatocyte injury and ultimately fibrosis. An inflamed liver parenchyma is stiffer than a normal parenchyma. With the progression of inflammation into fibrosis, liver stiffness progressively increases. While cirrhosis represents an irreversible end-stage liver parenchymal damage because of fibrosis, the earlier stages of liver inflammation could be potentially reversible. This is especially important in the setting of FL disease, whereby an intervention (such as alcohol cessation, modification of lifestyle, etc.) may halt the progression of steatosis into steatohepatitis and ultimately cirrhosis.[20] This underscores the

need for early diagnosis of FL disease. While biopsy may be considered the "gold standard" for establishing a diagnosis of FL disease, steatohepatitis, and cirrhosis, it is an invasive procedure and exposes patients to risks such as postprocedure hemorrhage and pain. Also, sampling error, as well as the subjective nature of the interpretation of biopsy specimens, may lead to false negative results and may not be particularly useful in the early stages of the disease. Due to these potential limitations, there has been growing interest in developing NITs for early detection of the stage of liver fibrosis.[21]

This study was intended to answer a specific research question as to how well the LSM measured with MRE correlates with that obtained by TE, FIB-4 score, and APRI score. Our data suggests a very strong correlation between LSM obtained by MRE and TE, with an *r*-value of 0.88. TE uses a probe to measure the velocity of shear waves to determine the LSM, while MRE uses an acoustic driver vibrating at a particular frequency to transmit shear waves into the liver parenchyma synchronized with a phase-contrast pulse sequence to determine the displacement of tissue at the microlevel and create an elastogram map.[7] While TE uses about 10 measurements to improve the precision of measurements of liver stiffness, it suffers from a few limitations, such as not being able to map the measurement to the exact site from which the signal is measured, and limitations of measurement in obese patients.[22] While MRE and TE measure the same fundamental tissue property (i.e., stiffness), they differ in the basic methods by which the measurements are acquired. This may explain, in part at least, the variation in absolute measurements of LSM obtained from TE and MRE, as suggested by our data as well as previous studies. Our study shows a mean LSM of 3.28 ± 1.4 kPa using MRE, indicating stage one to two fibrosis, while the mean stiffness value of 10.72 ± 11.8 kPa using TE indicates severe scarring. However, since the tissue property being measured by both these modalities is the same (i.e., LSM), it is prudent to expect a good positive correlation between MRE and TE regarding the measurement of LSM. Indeed, our data shows an almost perfect agreement (93.54%) between MRE and TE for the measurement of LSM (Cohen's κ of 0.871) with a strong positive correlation. The interrater reliability between MRE and TE across various stages of fibrosis showed a fair agreement. It has been shown in previous studies[7] that MRE has a higher sensitivity and specificity for the determination of the stage of hepatic fibrosis as compared with TE. Thus, MRE may become an accurate screening tool for early diagnosis of fibrotic changes in the liver parenchyma. MRE, in addition, offers an advantage of coverage of the whole of the liver parenchyma as well as exact mapping of LSM of various regions of the parenchyma. This may be useful in the planning of biopsies from the regions showing higher LSM and thus improving the diagnostic yield of biopsies.

As far as the correlation between MRE, TE, and other noninvasive scores, that is, FIB-4 and APRI, is considered, only a moderate correlation was found between MRE and FIB-4, while a weak correlation was noted between MRE and APRI, TE and FIB-4, and TE and APRI scores. On comparing these scores across different grades of LSM measured using MRE, a statistically significant difference was found between normal and normal/inflammation vs stage 4 fibrosis/cirrhosis. Similarly, on comparing these scores across different grades of LSM measured using TE, a significant difference was found between F0–F1 vs F2 and F3. The noninvasive fibrosis scores have been specifically designed for hepatitis C-related liver parenchymal disease[23]; however, these have been used in NAFLD also. These scores have been shown to have a good negative predictive value for very low scores and a good positive predictive value for very high scores. However, these scores may not be indicative of the stage of hepatic fibrosis in the intermediate score range. Since these scores are dependent on AST and ALT levels in the mathematical formula, the scores may be normal in settings where there may not be transaminitis in the face of established fibrosis. This underscores the limitations of these noninvasive fibrosis scores and may thus explain the finding of our study, which suggests a rather moderate to weak correlation between these scores, TE, and MRE.

As a secondary objective of our study, we quantified the fat fraction of the liver using MRI-based sequences. We found a significantly higher mean fat fraction in patients with grade III FL (23.6) as compared with grade I and grade II FL (as stratified using ultrasound). PDFF values were significantly different between grade I and grade III of FL determined through ultrasound. This indicates the feasibility of the use of MRI as a tool for early detection and quantification of liver fat, a distinct advantage over ultrasound-based qualitative stratification.

Another interesting finding of our study is that the mean LSM measured using MRE is significantly higher in alcoholics (4.04 ± 1.82) compared to nonalcoholics (3.02 ± 1.15). The same was found to be true for LSM measured using TE, with median LSM values significantly higher in alcoholics (8.45) compared to nonalcoholics (6.8). This shows a higher prevalence of fibrosis in alcoholics compared to nonalcoholics in our study. This may indicate an accelerated progression of steatohepatitis and fibrosis in alcoholics as compared to nonalcoholics.

In LSM measured through MRE, stage 2–3 fibrosis was seen to be significantly higher in the diabetic population, while initial grades of stiffness such as normal and normal/inflammation were seen higher in the nondiabetic population. Similarly, in LSM measured through TE, the F0–F1 stage of fibrosis was significantly higher in nondiabetics while median LSM values were significantly raised in the diabetic population. This also highlights diabetes as an important risk factor for the progression of fibrosis in FL patients.

Limitations

We did not have any histopathological confirmation of the stage of hepatic fibrosis and predictive analysis could not be performed for each of the noninvasive methods of quantification of LSM.

Conclusion

Magnetic resonance elastography shows a strong positive correlation with TE for LSM and the stage of fibrosis. A moderate to weak correlation was noted between MRE, TE, and NIF scores. MRI-derived FF values increase with increasing grade of FL. MRE could be a useful screening tool for the detection of liver fibrosis in FLD, comparable to the established noninvasive method of TE.

Ethical Approval

Approval was obtained from the Institute Ethics Committee under IEC letter no. 283.

Consent for Publication

As the corresponding author, I confirm that I have read and understood the publication policies of the Journal of the Association of Physicians of India and that the manuscript titled "Role of Magnetic Resonance Elastography as a Quantitative Tool for the Assessment of Liver Stiffness in Fatty Liver Disease in Comparison with Transient Elastography and Noninvasive Fibrosis Scores" complies with these policies. On behalf of all authors, I provide my consent for the publication of this manuscript in the Journal of the Association of Physicians of India.

Author Contributions

The authors confirm their contributions to the paper as follows:

Dr Preethi Sharon M: Conceptualization, methodology, data collection, writing original draft, and data analysis.

Dr Paramdeep Singh: Conceptualization, methodology, data collection, writing original draft, and data analysis.

Dr Sameer Peer: Conceptualization, validation, interpretation, supervision, and editing.

Ms Anjali Raj: Visualization, writing and editing, and interpretation.

Dr Gourav Kaushal: Data curation, conceptualization, and validation.

Dr Arvinder Wander: Data curation, conceptualization, and validation.

Dr Harmeet Kaur: Writing, reviewing, methodology, and data analysis.

Mr Sandeep Singh: Validation and editing of the manuscript.

All authors reviewed the results and approved the final version of the manuscript.

Data Availability

We confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials. Additional data, if required, can be obtained from the corresponding author upon reasonable request.

Supplementary Material

Supplementary files are available with author. Please connect with author for the supplementary content.

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References

1. Mitra S, De A, Chowdhury A. Epidemiology of non-alcoholic and alcoholic fatty liver diseases. Transl Gastroenterol Hepatol 2020;5:16.
2. Bedogni G, Nobili V, Tiribelli C. Epidemiology of fatty liver: an update. World J Gastroenterol 2014;20(27):9050–9054.
3. Venkatesh SK, Yin M, Takahashi N, et al. Non-invasive detection of liver fibrosis: MR imaging features vs. MR elastography. Abdom Imaging 2015;40(4):766–775.
4. Thanapirom K, Suksawatamnuay S, Tanpowpong N, et al. Non-invasive tests for liver fibrosis assessment in patients with chronic liver diseases: a prospective study. Sci Rep 2022;12(1):4913.
5. Guglielmo FF, Venkatesh SK, Mitchell DG. Liver MR elastography technique and image interpretation: pearls and pitfalls. Radiographics 2019;39(7):1983–2002.
6. Mariappan YK, Glaser KJ, Ehman RL. Magnetic resonance elastography: a review. Clin Anat 2010;23(5):497–511.
7. Liang Y, Li D. Magnetic resonance elastography in staging liver fibrosis in non-alcoholic fatty liver disease: a pooled analysis of the diagnostic accuracy. BMC Gastroenterol 2020;20(1):89.
8. Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. J Magn Reson Imaging 2013;37(3):544–555.
9. Serai SD, Obuchowski NA, Venkatesh SK, et al. Repeatability of MR elastography of liver: a meta-analysis. Radiology 2017;285(1):92–100.
10. Reddy JK, Rao MS. Lipid metabolism and liver inflammation. II. Fatty liver disease and fatty acid oxidation. Am J Physiol Gastrointest Liver Physiol 2006;290(5):G852–G858.
11. Riestra-Candelaria BL, Rodriguez-Mojica W, Jorge JC. Anatomical criteria to measure the adult right liver lobe by ultrasound. Sonography 2018;5(4):181–186.
12. Weir CB, Jan A. BMI Classification Percentile and Cut Off Points. 2023 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
13. Petroni ML, Brodosi L, Marchignoli F, et al. Moderate alcohol intake in non-alcoholic fatty liver disease: to drink or not to drink? Nutrients 2019;11(12):3048.
14. Li Y, Chen Y, Zhao Y. The diagnostic value of the FIB-4 index for staging hepatitis B-related fibrosis: a meta-analysis. PLoS One 2014;9(8):e105728.
15. De Matteis C, Cariello M, Graziano G, et al. AST to platelet ratio index (APRI) is an easy-to-use predictor score for cardiovascular risk in metabolic subjects. Sci Rep 2021;11(1):14834.
16. Goel A. Diffuse hepatic steatosis (grading). Radiology Reference Article. Radiopaedia.org [Internet]. Radiopaedia. Available from: https://radiopaedia.org/articles/diffuse-hepatic-steatosis-grading.
17. Venkatesh SK, Ehman RL. Magnetic resonance elastography of liver. Magn Reson Imaging Clin N Am 2014;22(3):433–446.
18. de Lédinghen V, Vergniol J. Transient elastography for the diagnosis of liver fibrosis. Expert Rev Med Devices 2010;7(6):811–823.
19. Shao M, Wang Y, Dong H, et al. From liver fibrosis to hepatocarcinogenesis: role of excessive liver H_2O_2 and targeting nanotherapeutics. Bioact Mater 2022;23:187–205.
20. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115(2):209–218.
21. Afdhal NH. Fibroscan (transient elastography) for the measurement of liver fibrosis. Gastroenterol Hepatol (N Y) 2012;8(9):605–607.
22. Venkatesh SK, Wang G, Lim SG, et al. Magnetic resonance elastography for the detection and staging of liver fibrosis in chronic hepatitis B. Eur Radiol 2014;24(1):70–78.
23. Lee YS, Lee JE, Yi HS, et al. MRE-based NASH score for diagnosis of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease. Hepatol Int 2022;16(2):316–324.

REVIEW ARTICLE

Reimagining Type 1 Diabetes Care in India: A Three-decade Reflection on Challenges, Innovations, and Opportunities since the Diabetes Control and Complications Trial

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Abstract

Three decades after the landmark Diabetes Control and Complications Trial (DCCT), type 1 diabetes (T1D) care in India continues to face systemic, socioeconomic, and technological challenges. Despite a relatively lower incidence compared to high-income countries, India bears a disproportionate burden of T1D-related morbidity and premature mortality due to late diagnoses, fragmented care, limited access to insulin, and underutilization of glucose-monitoring technologies. This editorial explores the current landscape of T1D management in India through the lens of the T1D Index, highlighting critical disparities in care quality, life expectancy, and health-adjusted life years lost. We reflect on the need for a national T1D registry, improved access to advanced therapies such as continuous glucose monitoring (CGM) and automated insulin delivery (AID) systems, and the establishment of multidisciplinary pediatric diabetes centers. The manuscript emphasizes systemic reforms, including public–private partnerships, indigenous manufacturing of diabetes technologies, and expanded education and psychosocial support frameworks. By integrating global best practices with localized solutions, India can bridge the care gap and redefine T1D outcomes for future generations.

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Introduction

Type 1 diabetes (T1D) is a growing global health concern, affecting approximately 1.48 million individuals under the age of 20 worldwide, according to the International Diabetes Federation (IDF). India alone accounts for nearly 0.28 million cases within this age group, making it home to one of the largest populations of children and adolescents with T1D.[1,2] The prevalence of youth onset diabetes, both T1D and type 2 diabetes (T2D), is rising globally, with low- and middle-income countries (LMICs) projected to experience a 60–107% increase in T1D prevalence by 2040.[2] However, the healthcare system in India faces significant challenges in meeting the growing demands of T1D management.

The incidence of T1D in India remains considerably lower than in high-income countries, such as the United States, where the SEARCH registry reports an incidence rate of 21.2 cases per 100,000 per year compared to 4.9 cases per 100,000/year in India, as per the Indian Council of Medical Research–Youth Onset Diabetes Registry (ICMR–YDR) registry.[3] Despite this lower incidence, the burden of T1D in India is exacerbated by systemic barriers, including delayed diagnoses, limited access to essential treatments such as insulin and glucose monitoring devices, and a lack of structured diabetes education.

Early diagnosis and effective management are essential for preventing both acute and chronic complications of T1D. In India, data from the YDR reveal that a significant proportion of youth with T1D present with complications at the time of registration. Notably, diabetic ketoacidosis (DKA) and severe hyperglycemia are among the most common acute complications leading to hospitalizations, with 59.3% of T1D patients reporting at least one hospitalization prior to registration. Chronic complications, such as diabetic kidney disease, are also prevalent. Studies indicate that approximately 25% of individuals with T1D of more than 10 years' duration and 32% of those with over 25 years' duration develop this condition. Furthermore, premature mortality due to complications such as chronic kidney disease, DKA, infections, and coronary artery disease remains a substantial concern in Indian cohorts. The life expectancy of individuals with T1D in India is estimated to be reduced by over 30 years compared to their nondiabetic counterparts, underscoring the urgent need for systemic reforms and targeted interventions to improve outcomes.[4]

This editorial examines the current landscape of T1D care in India, focusing on the unique barriers to effective management and opportunities for improvement. By addressing gaps in healthcare infrastructure, access to technology, and education, India can transform its approach to T1D care and align outcomes with global benchmarks. The time for action is now, to ensure a better quality of life for the growing population of individuals living with T1D in India.

Type 1 Diabetes Landscape: Burden and Barriers

Type 1 Diabetes Index: A Global Perspective

Type 1 diabetes index sheds light on the global disparities in life expectancy and the quality of care for individuals living with T1D. This tool, developed by JDRF, Life for a Child, International Society for Pediatric and Adolescent Diabetes (ISPAD), and IDF, leverages advanced modeling techniques to estimate prevalence, mortality, and health-adjusted life years (HALYs) lost due to T1D. For India, the T1D index paints a concerning picture, with substantial gaps in care compared to global benchmarks.[2,5]

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Life Expectancy and Healthy Life Years Lost

India's T1D population suffers from reduced life expectancy and significant morbidity. On average, individuals with T1D in India lose 45 healthy years compared to their nondiabetic counterparts, a statistic driven by both early mortality and diabetes-related complications. These figures contrast starkly with outcomes in high-income countries, where advancements in early diagnosis, treatment, and technology have drastically improved outcomes. Comparisons to countries such as Sudan—where delayed diagnoses and inadequate insulin access are common—underscore the urgent need for systemic reforms in India.[6,7]

Delayed Diagnoses and Mortality

The T1D index reveals that delayed diagnoses are a critical issue in resource-limited settings, including India. Globally, 67% of T1D deaths in individuals under 25 years occur due to nondiagnosis, with South Asia contributing significantly to these numbers.[7,8] For example, in India, the absence of routine antibody testing and insufficient awareness among healthcare providers result in late presentations, often during life-threatening emergencies such as DKA.[4,9] Such delays reduce survival rates and compromise long-term outcomes.

Rationed Insulin and Inadequate Monitoring

Access to insulin and glucose-monitoring technologies is another area where India faces challenges. Approximately 50% of T1D patients in South Asia, including India, receive only minimal care, defined as basic insulin therapy with limited or no self-monitoring of blood glucose (SMBG). This contrasts with high-income countries, where 99% of patients receive advanced care, including continuous glucose monitoring (CGM) and insulin pump technologies.[6] Minimal care in India contributes to poor glycemic control, increasing the risk of complications such as retinopathy, nephropathy, and neuropathy.

Geographic and Socioeconomic Disparities

In India, T1D care outcomes vary widely based on geographic and socioeconomic factors. Urban centers offer better diagnostic and treatment facilities, whereas rural areas lack even basic diabetes care infrastructure. Middle-income families bear a disproportionate financial burden, often spending over 50% of their income on diabetes care.[10] Such disparities perpetuate inequitable outcomes and reduce the effectiveness of public health interventions.

Recommendations for India

To align with global standards and reduce the burden of T1D, India must prioritize systemic reforms:

- Establish a national T1D registry: Accurate data is essential for planning and resource allocation. A centralized registry will enable tracking of prevalence, incidence, and outcomes across diverse demographics.
- Expand access to advanced therapies: Subsidies for insulin analogs, CGM devices, and insulin pumps can bridge the gap between affordability and accessibility.
- Promote early diagnosis: Introducing routine antibody testing in primary healthcare settings will facilitate early identification and timely interventions.
- Scale public health initiatives: Expanding programs such as the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS) to include pediatric diabetes care can improve access to essential services in underserved areas.
- Integrate education and psychosocial support: Structured education programs for patients, caregivers, and healthcare providers will enhance adherence and outcomes.
- Invest in indigenous innovation: Local production of CGM devices and insulin pumps can lower costs and increase availability, particularly in rural regions.

The T1D index highlights the urgent need for action to improve T1D outcomes in India.[6] By adopting evidence-based policies, fostering public–private partnerships, and prioritizing technological integration, India can significantly enhance the quality of life for its T1D population. Bridging these gaps is not only a matter of public health but also an ethical imperative to ensure equitable care for all.

Key Challenges in Type 1 Diabetes Care in India

Fragmented Care Delivery

In India, the management of T1D is often handled by general practitioners or nonspecialist diabetologists rather than dedicated multidisciplinary teams (MDTs). This fragmented care delivery compromises both clinical outcomes and psychosocial support for patients. MDTs that include endocrinologists, dietitians, diabetes educators, and psychologists are essential to provide holistic care, but their presence is sparse, particularly in rural and underserved areas.

Underutilization of Diagnostic Tools

Autoantibody testing, a critical component for diagnosing atypical diabetes presentations and confirming T1D, remains underutilized in India due to limited availability, lack of awareness, and high costs. This underutilization results in frequent misdiagnoses, delayed initiation of appropriate therapy, and an increased risk of acute and long-term complications.[11]

Socioeconomic Inequities

The socioeconomic divide significantly impacts diabetes care in India. Middle-income families, who comprise a majority of the population, often bear the brunt of out-of-pocket expenditures. These families may spend up to 50% of their annual income on T1D management, including insulin, glucose monitoring supplies, and medical consultations.[10,11] Government initiatives, such as subsidized insulin programs, primarily target families below the poverty line, leaving middle-income households struggling with unaffordable healthcare.

Awareness and Education

Structured education programs addressing SMBG, insulin administration techniques, carbohydrate counting, and emergency preparedness are critically lacking. This gap in education is most prominent in rural areas, where healthcare professionals themselves often lack the training necessary to educate patients effectively. The absence of such programs leads to poor glycemic control and long-term nonadherence to treatment plans.

Barriers to Advanced Technologies

Technological solutions, such as CGM and insulin pumps, which have shown remarkable benefits in glycemic control and quality of life globally, remain largely inaccessible in India due to high costs and a lack of insurance coverage. Even in urban centers where these technologies are available, issues such as maintenance, training, and awareness limit their widespread adoption.[12–14]

Limited Focus on Pediatric Care

Pediatric diabetes care in India is often neglected, with many children being managed in adult-focused clinics. This results in inadequate consideration of developmental and psychosocial aspects unique to children and adolescents, such as insulin sensitivity changes during puberty and the need for family-centered education and support.[14]

Psychosocial Barriers

Diabetes distress, stigma, and emotional strain often accompany a T1D diagnosis, especially for young patients and their caregivers. In India, where psychosocial support systems are underdeveloped, addressing these issues is rarely prioritized, contributing to poor adherence to treatment and increased diabetes-related complications.[14,15]

In addition to emotional distress, cultural beliefs and stigma also influence acceptance of advanced diabetes technologies. In many Indian communities, visible devices such as insulin pumps or CGM sensors are perceived as a sign of serious illness or dependency, leading to embarrassment or social withdrawal—especially among adolescents. Families may avoid adopting these tools due to fear of social judgment, marriage prospects, or misinformation about side effects. These sociocultural dynamics significantly hinder technology uptake, even when devices are clinically indicated and financially supported.

techniques, and advanced technologies can improve adherence and outcomes.
- Promoting local manufacturing of diabetes technologies: Encouraging the production of CGMs, insulin pumps, and other tools within India can reduce costs and increase accessibility.
- Incorporating pediatric-specific care: Training programs for healthcare providers should emphasize pediatric-specific approaches, ensuring age-appropriate care for children with T1D.
- Strengthening psychosocial support systems: Integrating psychological services into diabetes care frameworks can help address the emotional and social challenges of managing T1D.

By addressing these barriers through targeted reforms and innovations, India can improve the quality of life for individuals with T1D and set an example for diabetes care in resource-limited settings.

Voices from the Field: Living with Type 1 Diabetes in Rural Ahmedabad

"We first thought it was just a fever and weight loss. My daughter, Asha, was 11 when she collapsed in school. We rushed her to the district hospital, where they said she had 'sugar in urine' and transferred her to Ahmedabad city. That's when we heard the word 'Type 1 Diabetes' for the first time."
—Meena Patel, mother of a young girl with T1D, Dholka Taluka, Rural Ahmedabad

Asha was diagnosed with T1D after presenting in DKA at a tertiary care center in Ahmedabad. The family had no prior knowledge of the disease and was unaware of the condition. The family found that insulin was not even available at their local primary health center. For the first year postdiagnosis, Asha's parents traveled 70 km each month to procure insulin and test strips.

Despite free insulin under the state program, the cost of regular glucose monitoring strips, emergency visits, and travel amounted to ₹1,200–1,500 monthly—over 25% of the family's income. The local school lacked awareness and initially discouraged Asha's return due to concerns about managing her condition on-site.

Meena recalls, "Nobody in our village had heard of children getting diabetes. Even now, we hide the injections when visitors come. People say it is a curse or bad parenting."

Asha's condition began to stabilize after the family was connected to a charitable pediatric diabetes center in the city, where she received structured education, regular follow-up, and psychosocial support. Access to consistent care, combined with her family's unwavering determination, enabled her to overcome many of the early challenges she faced. Through their persistence and the responsive care framework of the diabetes center, Asha is now thriving in school and beginning to live a fuller life again—an inspiring testament to what resilient families can achieve when backed by a supportive healthcare system.

Note: Names and identifying details have been changed to protect patient confidentiality.

Addressing the Challenges: The Way Forward

- Establishing multidisciplinary diabetes centers: Implementing centers dedicated to T1D management can ensure comprehensive care, combining clinical, educational, and psychological support.
- Expanding subsidies for middle-income groups: Tailored government programs targeting middle-income households can alleviate financial burdens and improve access to essential care.
- Enhancing educational programs: National initiatives to educate healthcare providers and patients on SMBG, insulin

Advances in Type 1 Diabetes Management in India

Role of Continuous Glucose Monitoring

Continuous glucose monitoring has become a cornerstone in modern T1D management globally, providing real-time glucose trend data that significantly enhances glycemic control. CGM's ability to assess time-in-range (TIR)—a metric measuring the percentage of time glucose levels stay within the target range of 70–180 mg/dL—offers a critical complement to traditional HbA1c measurements. This technology is transformative in reducing hypoglycemia, hyperglycemia, and glycemic variability, leading to improved clinical outcomes.[12,13]

In India, however, CGM adoption remains limited. High costs, lack of government subsidies, and restricted availability in rural and semiurban areas are significant barriers.[12] Studies indicate that CGM use in India is predominantly confined to urban centers and higher-income groups.[12,16] Reports from ISPAD clinical practice guidelines and localized studies emphasize the need for subsidized CGM devices and the promotion of indigenous manufacturing to reduce costs and increase accessibility.[14]

Automated Insulin Delivery Systems

Automated insulin delivery (AID) systems integrate CGM, insulin pumps, and sophisticated algorithms to provide real-time, automated insulin adjustments. This closed-loop technology reduces glycemic variability, improves TIR, and lowers the burden of disease management. The Omnipod 5 AID system, for instance, has demonstrated long-term effectiveness in improving HbA1c levels and TIR, with sustained benefits over 2 years of use.[17]

In India, the adoption of AID systems is minimal due to:

- Economic barriers: High upfront costs and ongoing maintenance expenses limit access.
- Healthcare infrastructure Gaps: Limited availability of trained healthcare professionals to manage and optimize AID systems.
- Cultural perceptions: Resistance to adopting new medical technologies due to a lack of education and awareness.

Addressing these challenges requires public–private partnerships to subsidize AID technologies and foster indigenous innovation. Government and private sector collaboration can help create cost-effective solutions tailored to India's socioeconomic landscape.

SWEET Centers and the ISPAD Initiative

India's involvement in the ISPAD and the establishment of SWEET centers represent pivotal steps toward harmonizing T1D care. SWEET centers are designed as regional hubs to address disparities in pediatric diabetes management.[14,18] The initiative emphasizes:

- Structured diabetes education for patients and caregivers.
- Regular follow-ups to monitor glycemic trends and adjust treatment regimens.
- Access to advanced technologies, including CGM and insulin pumps.

These centers aim to create equitable access to high-quality care, particularly in regions with limited resources. For example, SWEET centers in Southeast Asia have demonstrated success in improving clinical outcomes through standardized protocols and collaborative training.[19]

Key Challenges and Future Directions

While these advancements signal progress, significant barriers remain. The cost of CGM and AID systems, coupled with inadequate healthcare infrastructure, continues to hinder widespread adoption. Integrating these technologies into public health programs and training healthcare professionals on their usage are critical steps. Additionally, expanding subsidies and fostering local manufacturing will enhance affordability and accessibility, ensuring that T1D management aligns with global standards.

Advances in CGM and AID systems hold immense potential to revolutionize T1D care in India. However, achieving equitable access to these innovations requires systemic reforms, robust public-private partnerships, and a focus on affordability.[20,21] Initiatives like SWEET centers and ISPAD collaborations provide a promising framework for scaling these technologies while addressing disparities in care.[19,20] By prioritizing these efforts, India can significantly improve clinical outcomes for individuals living with T1D.

Technology and Glycemic Control

Impact of Technology

The integration of technology into type 1 diabetes (T1D) management has revolutionized glycemic control, enhancing the quality of life and clinical outcomes for patients globally. Key technological advancements include:

- Continuous glucose monitoring devices
  - CGM devices provide real-time glucose monitoring and trends, empowering patients to make informed decisions about insulin dosing and dietary adjustments.
  - Studies show that CGM use reduces HbA1c levels by 0.5% to 1%, significantly lowering the risk of both acute and long-term complications like hypoglycemia and microvascular damage.[19,21]
  - CGM also improves patient adherence by offering alerts for high or low glucose levels, preventing extreme glycemic excursions, and enabling better TIR control.
- Hybrid closed-loop systems
  - Advanced systems such as the Medtronic 780G have set new benchmarks in glycemic management by integrating insulin pumps with CGM devices and advanced algorithms to provide semi-automated insulin delivery.
  - These systems have achieved TIR levels exceeding 75%, translating to more than 18 hours per day of glucose levels within the target range (70–180 mg/dL). Such advancements reduce the burden of continuous self-monitoring and improve patient outcomes.[22]
- Sensor-augmented pump therapy[23]
  - Combining CGM devices with insulin pumps—known as sensor-augmented pump therapy—has demonstrated significant improvements in glycemic control compared to multiple daily injections (MDI).
  - Studies highlight reductions in severe hypoglycemia rates and HbA1c improvements of 0.7–1.0%, alongside better management of postprandial hyperglycemia.
  - These systems offer tailored insulin delivery based on real-time glucose data, effectively reducing glycemic variability.

Challenges in Technology Integration

Despite the transformative potential of these technologies,[24] their adoption in India remains limited due to several challenges:[25,26]

- Affordability
  - CGM devices, insulin pumps, and hybrid closed-loop systems are prohibitively expensive for most Indian families, with costs often exceeding ₹200,000 annually for comprehensive management.
  - The absence of widespread insurance coverage for diabetes technologies exacerbates financial barriers, restricting access to only high-income groups.
- Sensor maintenance and availability
  - Maintenance of CGM sensors and insulin pump components is a recurring challenge, with supply chain issues frequently causing disruptions in patient care.
  - Limited local manufacturing leads to reliance on imports, driving up costs and reducing accessibility in rural and semi-urban areas.
- Lack of awareness and training
  - Many healthcare providers and patients are unfamiliar with the usage and benefits of advanced diabetes technologies, resulting in low adoption rates.
  - Training programs for healthcare professionals on managing sensor-augmented and hybrid closed-loop systems are sparse, leaving gaps in effective implementation.
- Sociocultural resistance
  - Cultural stigma surrounding medical devices and the invasive nature of technologies like insulin pumps can discourage their use, particularly among children and adolescents.

Overcoming Challenges: Strategies for Success

Addressing these challenges requires systemic reforms and targeted interventions to promote the adoption of diabetes technologies:

- Subsidies and public health integration
  - Government-led initiatives to subsidize CGM devices and insulin pumps can make these technologies accessible to a broader population.
  - Integrating diabetes technologies into public health programs, such as the NPCDCS, can enhance reach and impact, particularly in underserved regions.
- Local manufacturing and innovation
  - Encouraging indigenous production of CGM sensors, insulin pumps, and related components can reduce costs and ensure an uninterrupted supply.
  - Collaborations between government agencies, private companies, and research institutions can foster innovation tailored to India's socioeconomic landscape.
- Education and awareness campaigns
  - Nationwide campaigns targeting healthcare professionals and patients can promote the benefits of advanced technologies, dispel misconceptions, and improve adoption rates.
  - Structured training programs for clinicians on the management of CGM and hybrid closed-loop systems can enhance implementation and patient outcomes.
- Focus on rural and semiurban areas
  - Deploying mobile diabetes units equipped with advanced technologies can improve access to care in remote areas.
  - Partnerships with local NGOs and community health workers can drive adoption of diabetes technologies in low-resource settings.

Technological advancements such as CGM, hybrid closed-loop systems, and sensor-augmented pumps have significantly improved glycemic control, reducing HbA1c levels, hypoglycemia, and glycemic variability globally. However, in India, affordability, accessibility, and awareness remain critical barriers to widespread adoption. Systemic reforms, including subsidies, local manufacturing, and targeted education initiatives, are essential to bridge these gaps. By leveraging these strategies, India can ensure equitable access to transformative diabetes technologies, improving the quality of life for individuals living with T1D.

Implementation Challenges

Despite well-meaning recommendations and emerging innovations, implementing reforms in type 1 diabetes (T1D) care across India is fraught with practical challenges. One of the most pressing barriers is insufficient funding and fragmented financing mechanisms, particularly for outpatient services, diabetes education, and advanced technologies such as CGM and insulin pumps. Current public programs prioritize type 2 diabetes and acute care, leaving chronic pediatric conditions under-resourced.

A second barrier is the shortage of trained pediatric endocrinologists, diabetes educators, and psychologists. Most district hospitals lack multidisciplinary teams, and existing personnel often have minimal training in T1D-specific protocols, contributing to poor care continuity. In rural and semiurban areas, infrastructure gaps—including erratic supply chains for insulin, lack of laboratory facilities, and limited cold storage—disrupt access to even basic services.

Moreover, the absence of dedicated leadership or accountability frameworks at the state level often results in uneven implementation of national guidelines. Health programs piggybacking on NPCDCS often face logistical constraints due to adult-focused workflows, resulting in poor uptake of juvenile diabetes initiatives.

Lastly, low political prioritization of pediatric diabetes and a general lack of awareness among policymakers about the long-term health and economic burden of unmanaged T1D delay the scaling of proven models such as the West Bengal pilot. Without proactive stakeholder engagement, such pilots risk remaining isolated successes rather than national frameworks.

To overcome these challenges, there is a need for sustained policy commitment, strategic resource allocation, and institutional capacity-building across all levels of care—from subcenters to tertiary hospitals.

Opportunities and Future Directions in T1D Care in India

Rapid Progress with Technology

Global advancements in diabetes technology present a transformative opportunity for India to improve glycemic outcomes and quality of life for individuals with type 1 diabetes (T1D). CGM devices, insulin pumps, and AID systems have significantly advanced T1D management in high-income countries, demonstrating improvements in glycemic metrics such as time-in-range (TIR) and reductions in HbA1c levels. By adopting a strategic approach, India can bridge the technological divide and scale up access to these life-changing tools.[26,27]

Local Production of Diabetes Technologies

Encouraging indigenous manufacturing of CGM devices, insulin pumps, and sensor components can drastically reduce costs, making these technologies affordable for middle- and low-income families. Local production not only reduces reliance on imports but also addresses supply chain challenges, ensuring uninterrupted access in rural and semiurban areas.

Government-led Subsidies

Subsidies for diabetes technologies can enhance affordability and access. Incorporating these devices into public health insurance schemes will allow greater adoption among vulnerable populations, reducing the financial burden on families and promoting equitable healthcare delivery.

Leveraging Global Innovation

India can draw insights from countries with advanced T1D care frameworks, such as the integration of CGM and AID systems into routine care in developed nations. Collaborative efforts with international organizations such as ISPAD and JDRF can help India adopt best practices and adapt them to local healthcare needs.[19,26]

Key Recommendations

Establish a National T1D Registry

Rationale: A centralized T1D registry is essential for capturing comprehensive data on disease incidence, prevalence, outcomes, and access to care. This information is crucial for informed policymaking, effective resource allocation, and targeted interventions.

Implementation: Partnering with healthcare institutions, research bodies, and government agencies to develop a robust database infrastructure. Using digital tools to enable real-time data collection and analysis will enhance the utility of the registry.

Expand Public Health Programs

Rationale: Current public health initiatives under NPCDCS predominantly focus on T2D, leaving a gap in T1D care. Expanding these programs to include juvenile diabetes will ensure more comprehensive coverage.

Implementation: Develop state-level pilot programs under NPCDCS to provide free or subsidized insulin, glucose-monitoring supplies, and structured education for children with T1D. Leveraging existing healthcare infrastructure can accelerate scale-up and reduce implementation costs.

Promote Public–Private Partnerships

Rationale: Collaborations between government agencies, private companies, and nonprofit organizations can drive innovation, reduce production costs, and expand access to advanced diabetes technologies.

Implementation: Encourage PPPs to manufacture affordable CGM devices and insulin pumps locally. Partnerships with global diabetes technology leaders can facilitate knowledge transfer and training for healthcare professionals. Companies can also subsidize pilot projects to demonstrate the impact of advanced technologies.

Enhance Healthcare Delivery

Rationale: The absence of specialized T1D care centers limits the quality of clinical management and psychosocial support available to patients. Establishing multidisciplinary centers dedicated to T1D can address this gap.

Implementation: Develop T1D centers across major cities and rural hubs to provide holistic care. These centers should integrate endocrinology, dietetics, diabetes education, and psychological counseling. Government support and collaboration with academic institutions can ensure sustainability.

Scale-up Education Campaigns

Rationale: Misconceptions, stigma, and lack of awareness about T1D impede timely diagnosis and effective management. Comprehensive education campaigns targeting patients, caregivers, schools, and healthcare providers can combat these barriers.

Implementation: Deploy nationwide awareness initiatives leveraging social media, print, and electronic media. Engage community health workers and nonprofits to conduct on-ground education programs in rural and underserved areas. Develop age-appropriate educational content for schools to

create a supportive environment for children with T1D.

India stands at a pivotal moment in its journey toward transforming T1D care. The path forward must be built upon the foundation of the two "Es" in T1D management—Education and Empathy. Dedicated T1D centers should prioritize comprehensive education for patients and caregivers, empowering them with the knowledge and skills required to manage the complexities of this lifelong condition. This involves not only structured training on insulin administration, SMBG, and dietary adjustments but also fostering an environment where caregivers feel confident and supported in their roles.

Equally important is the need to approach T1D management with empathy, recognizing that it requires specialized attention far beyond the scope of general outpatient clinics. Unlike T2D, which can often be managed in routine OPD settings, T1D demands specialized care that includes longer consultation times, tailored treatment plans, and psychosocial support. The emotional and physical toll of managing T1D necessitates a compassionate approach to build trust and adherence among patients and their families.

By integrating education and empathy into every level of T1D care delivery, alongside leveraging global technological advancements, public health reforms, and public–private partnerships, India can bridge existing gaps in care. These efforts will not only enhance glycemic outcomes but also improve the quality of life for millions living with T1D. Coordinated actions across stakeholders—including the government, private sector, healthcare professionals, and patient communities—can help India set a global benchmark for equitable, high-quality diabetes care, especially in resource-constrained settings (Table 1).

Health Policy Landscape and Gaps

India, despite having one of the world's largest populations of children and adolescents with T1D, lacks a comprehensive, structured health policy to support their clinical, educational, and psychosocial needs. Although the NPCDCS, launched in 2008, provides a foundational framework for noncommunicable disease (NCD) control, it is fundamentally adult-centric and fails to address the distinct demands of juvenile NCDs, including T1D.

The absence of pediatric-focused diabetes policies within NPCDCS has resulted in widespread service delivery gaps, such as the non-availability of free insulin, lack of diagnostic and monitoring tools, poor training of health professionals, and an absence of structured diabetes education or counseling for young patients and their families. According to the International Diabetes Federation (2021), India has the highest global burden of children and adolescents with T1D.[1] Yet, no national registry exists to estimate prevalence or track clinical outcomes, severely limiting data-driven policymaking.

A promising innovation is the West Bengal pilot project detailed by Yasmin et al., which represents a scalable model of care by integrating T1D management into the existing NPCDCS framework. The initiative transformed district hospital NCD clinics into weekly T1D care clinics, offering insulin, test strips, routine lab investigations, counseling, and emergency support—demonstrating that T1D care can be woven into the current infrastructure. The program also included structured education camps, caregiver training, and a digital health record system, laying the groundwork for a future juvenile NCD strategy at the national level.[26]

In parallel, India's flagship public insurance program—Ayushman Bharat-Pradhan Mantri Jan Arogya Yojana (AB-PMJAY)—does not yet provide adequate coverage for critical T1D technologies such as CGM, insulin pumps, or even essential outpatient glycemic monitoring. This insurance exclusion significantly impacts middle-income families, who often fall outside the safety net of subsidy programs but cannot afford advanced care.

To bridge these policy gaps, the following reforms are recommended:

- Explicit inclusion of pediatric T1D in NPCDCS guidelines, with defined service delivery protocols.
- National T1D registry creation to capture epidemiological and clinical data for better program design.
- Expansion of AB-PMJAY coverage to subsidize diabetes technologies and outpatient care.
- Launch of a juvenile NCD program, modeled on successful state-led pilots such as West Bengal's, ensuring scalability, sustainability, and equity.

Table 1: Global innovations in T1D care—lessons for India

Country	*Key innovations in T1D care*	*Relevance to India*
Israel	National multidisciplinary centers (e.g., Schneider Children's Medical Center) offer comprehensive pediatric diabetes care including CGM and insulin pump use, with structured education and public reimbursement for devices. CGM devices are covered for all children, and teacher education is standard.[28]	Demonstrates the power of national insurance and centralized, multidisciplinary models for early access to diabetes technologies, school integration, and family education.
United Kingdom	The National Pediatric Diabetes Audit (NPDA) monitors over 27,000 children, ensuring quality benchmarking via HbA1c reports, complication screening, and PROMs. School-based diabetes care plans are mandated by law. NICE-recommended structured education programs (DAFNE, KICk-OFF) focus on intensive insulin management and therapeutic learning. Importantly, the NHS now funds CGM for all children with T1D (since 2022) and promotes insulin pump use under defined clinical criteria. The T1Early initiative incorporates genetic/autoantibody screening during routine vaccinations to reduce DKA at diagnosis.[29,30]	A gold-standard model for India combining national registries, universal CGM access, structured education, school-based care protocols, and early risk screening. Demonstrates how government funding and audits can drive equity, technology adoption, and better glycemic outcomes.
Australia	Australia implements a centralized, tech-enabled care system via the National Diabetes Services Scheme (NDSS), which offers subsidized insulin, continuous glucose monitors (CGMs), insulin pumps, education, and peer support. It is connected to national registries such as the Australasian Diabetes Data Network (ADDN), supports early screening pilots for T1D, and encourages multi-disciplinary care models. The system also supports national studies mapping pediatric and transitional diabetes care to address equity and outcomes.[31]	Demonstrates a nationally coordinated, cost-shared model enabling equitable access to modern diabetes technologies and education, particularly through subsidization and registry-linked care, which can be adapted to India's public-private health infrastructure.

- Cross-sectoral collaboration among health, education, and digital technology ministries to support integrated school-based diabetes management and caregiver education.

Unless national policy frameworks evolve to reflect the realities of pediatric T1D, India risks widening disparities in diabetes outcomes. Strategic integration, backed by public funding, trained personnel, and data infrastructure, is vital to meet the goals of equitable and effective care for all children with T1D.

Conclusion

Three decades after the Diabetes Control and Complications Trial (DCCT), its principles remain critical in shaping T1D care globally. For India, addressing gaps in affordability, accessibility, and awareness is essential to achieving equitable outcomes. Expanding public health programs, leveraging innovative technologies, and fostering collaborations among stakeholders are vital steps forward.

India has the potential to become a global model for managing T1D in resource-constrained settings. By addressing these challenges comprehensively and adopting evidence-based strategies, India can improve the quality of life for individuals living with T1D and set new benchmarks for diabetes care worldwide.

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References

1. Ogle GD, James S, Dabelea D, et al. Global estimates of incidence of type 1 diabetes in children and adolescents: results from the International Diabetes Federation Atlas. Diabetes Res Clin Pract 2022;183:109083.
2. Gregory GA, Robinson TIG, Linklater SE, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 2022;10:741–760.
3. Jensen ET, Dabelea DA, Praveen PA, et al. Comparison of the incidence of diabetes in United States and Indian youth: an international harmonization of youth diabetes registries. Pediatr Diabetes 2021;22(1):8–14.
4. Praveen PA, Madhu SV, Viswanathan M, et al. Demographic and clinical profile of youth onset diabetes patients in India-results from the baseline data of a clinic based registry of people with diabetes in India with young age at onset-[YDR-02]. Pediatr Diabetes 2021;22(1):15–21.
5. Chan JCN, Lim L-L, Wareham NJ, et al. The Lancet Commission on diabetes: using data to transform diabetes care and patient lives. Lancet 2021;396:2019–2082.
6. JDRF, Life for a Child, ISPAD, IDF. (2025). Type 1 Diabetes Index. [online] Available from: https://www.t1dindex.org/ [Last accessed November, 2025].
7. Ogle GD, Gregory GA, Wang F, et al. The T1D Index: implications of initial results, data limitations, and future development. Curr Diab Rep 2023;23(10):277–291.
8. Ong KL, Rimm EB, Leong DP, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2023;402(10397):203–234.
9. Madhu SV, Shukla P, Kaur T, et al. Mortality in type 1 diabetes mellitus: a single centre experience from the ICMR—Youth onset diabetes registry in India. Diabetes Res Clin Pract 2024;217:111868.
10. Rohilla L, Gujjar N, Kaur G, et al. Financial burden for families of children with type 1 diabetes: a cross-sectional survey from North India. Diabetol Int 2022;13(4):665–671.
11. Das AK, Saboo B, Maheshwari A, et al. Health care delivery model in India with relevance to diabetes care. Heliyon 2022;8(10):e10904.
12. Singh K, Chakma T, Nagwanshi A, et al. Is continuous glucose monitoring feasible in tribal India? Navigating the benefits and overcoming the challenges. J Diabetes Sci Technol 2024;19(2):600–601.
13. Mohan V, Joshi S, Mithal A, et al. Expert consensus recommendations on time in range for monitoring glucose levels in people with diabetes: an Indian perspective. Diabetes Ther 2023;14(2):237–249.
14. Gregory JW, Cameron FJ, Joshi K, et al. ISPAD Clinical Practice Consensus Guidelines 2022: diabetes in adolescence. Pediatr Diabetes 2022;23(7):857–871.
15. Monaghan M, Bryant BL, Inverso H, et al. Young children with type 1 diabetes: recent advances in behavioral research. Curr Diab Rep 2022;22(6):247–256.
16. Kesavadev J, Krishnan G, Mohan V. Digital health and diabetes: experience from India. Ther Adv Endocrinol Metab 2021;12:20420188211054676.
17. DeSalvo DJ, Bode BW, Forlenza GP, et al. Glycemic outcomes persist for up to 2 years in very young children with the Omnipod® 5 automated insulin delivery system. Diabetes Technol Ther 2024;26(6):383–393.
18. Prahalad P, Zaharieva DP, Addala A, et al. Improving clinical outcomes in newly diagnosed pediatric type 1 diabetes: teamwork, targets, technology, and tight control-the 4T study. Front Endocrinol (Lausanne) 2020;11:360.
19. Gerhardsson P, Schwandt A, Witsch M, et al. The SWEET Project 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. Diabetes Technol Ther 2021;23(7):503–510.
20. Reddy N, Verma N, Dungan K. Monitoring technologies—continuous glucose monitoring, mobile technology, biomarkers of glycemic control. In:Feingold KR, Anawalt B, Blackman MR, et al. (Eds). Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000.
21. Di Molfetta S, Caruso I, Cignarelli A, et al. Professional continuous glucose monitoring in patients with diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2023;25(5):1301–1310.
22. Quirós C, Alonso-Carril N, Rodríguez-Rodríguez S, et al. The Medtronic 780G advanced hybrid closed-loop system achieves and maintains good glycaemic control in type 1 diabetes adults despite previous treatment. Endocrinol Diabetes Nutr (Engl Ed) 2023;70(2):130–135.
23. Pedone E, Laurenzi A, Allora A, et al. Insulin pump therapy and continuous glucose monitoring in adults with type 2 diabetes: where are we now? Explor Med 2020;1:314–330.
24. Agarwal S, Simmonds I, Myers AK. The use of diabetes technology to address inequity in health outcomes: limitations and opportunities. Curr Diab Rep 2022;22(7):275–281.
25. Bhagwat Y, Kumar S. A review on case burden of diabetes mellitus before and after the implementation of National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke. Cureus 2023;15(11):e49446.
26. Yasmin M, Mukhopadhyay P, Ghosh S. Model of care for type 1 diabetes in India: integrated approach for its incorporation in future national health care policy. Lancet Reg Health Southeast Asia 2022;3:100014.
27. Sherwood JS, Russell SJ, Putman MS. New and emerging technologies in type 1 diabetes. Endocrinol Metab Clin North Am 2020;49(4):667–678.
28. Bratina N, Shalitin S, Phillip M, et al. Type 1 diabetes in the young: organization of two national centers in Israel and Slovenia. Zdr Varst 2015;54(2):139–145.
29. Ng SM, Soni A. Ten-year review of trends in children with type 1 diabetes in England and Wales. World J Diabetes 2023;14(8):1194–1201.
30. Association of British Clinical Diabetologists (ABCD). (2023). Standards of care for children and young people with type 1 diabetes mellitus. [online] Available from: https://abcd.care/sites/default/files/resources/Standards_of_Care_T1DM_ABCD_FINAL.pdf [Last accessed November, 2025].
31. Carrigan A, Lake R, Zoungas S, et al. Mapping care provision for type 1 diabetes throughout Australia: a protocol for a mixed-method study. BMJ Open 2022;12(12):e067209.

REVIEW ARTICLE

A Narrative Review of Strengthening Cardiac Rehabilitation in India: Challenges and Opportunities

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Abstract

Cardiac rehabilitation (CR) is a critical component of secondary prevention in cardiovascular disease (CVD) management. In India, where CVD prevalence is rising rapidly, CR remains severely underutilized due to multiple systemic barriers. These include limited infrastructure, insufficient funding, low awareness, and inequitable access across urban and rural regions. This review assesses the current CR landscape in India, contrasts it with global benchmarks, and highlights key implementation gaps. It further explores scalable solutions such as telerehabilitation, community-based programs, and integrated multidisciplinary models. The paper emphasizes the need for robust policy frameworks, sustainable funding, infrastructure strengthening, and comprehensive workforce development. Achieving universal access to CR in India demands a multisectoral, collaborative approach involving government agencies, healthcare providers, academic institutions, nongovernmental organizations (NGOs), and private stakeholders. Enhancing CR services is not only a clinical necessity but also a national public health priority.

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Introduction

India is experiencing a sharp rise in cardiovascular disease (CVD), a major contributor to morbidity and mortality from noncommunicable diseases. Cardiac rehabilitation (CR), a multidisciplinary, evidence-based intervention, significantly improves survival, functional capacity, and quality of life following cardiac events. Despite its proven benefits and endorsement by international guidelines, CR remains inadequately implemented in India.[1] Several factors contribute to this gap—lack of awareness among patients and providers, inadequate funding, infrastructural deficits, and disparities in urban vs rural healthcare access. Out-of-pocket expenses further hinder CR utilization.[2] This paper examines the present challenges in CR adoption, compares India's performance with global trends, and presents pathways for expanding and institutionalizing CR nationwide.

The Unmet Need

Cardiovascular disease is the leading cause of death in low- and middle-income countries (LMICs), including India. India's public healthcare system operates through a three-tier structure comprising primary, secondary, and tertiary levels, as outlined by the Indian Public Health Standards (IPHS). National health programs are designed to be implemented across all these levels to ensure comprehensive and equitable healthcare delivery. Although CR is recommended as a class IA intervention, its availability remains limited. According to a global audit, India has a CR patient-to-spot ratio of 1:360, significantly lower than the Eastern Mediterranean (1:104), Southeast Asia (1:283), and Canada (1:24). India ranks second only to China in the scale of unmet CR needs, requiring over 3.3 million additional CR spots annually.[3] Financial barriers, particularly the lack of insurance coverage, further limit access and affordability. At the primary level, subcenters (SCs) serve as the initial point of contact, providing basic preventive and promotive services. These are supported by primary health centers (PHCs), which offer outpatient care, minor emergency treatment, and serve as referral units for SCs. Secondary care is delivered through community health centers (CHCs), subdistrict hospitals (SDHs), and district hospitals (DHs), offering more advanced diagnostic and inpatient services. Tertiary care is provided at medical colleges and super-specialty institutes, including national centers for rehabilitation. Rehabilitation services are integrated into several national programs. The National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS) includes physiotherapy and counseling for risk factor management. Similarly, speech and audiology rehabilitation are provided under the National Program for Prevention and Control of Deafness (NPPCD), while medical rehabilitation is covered under the National Leprosy Eradication Programme.[4] Despite these provisions, specific and structured CR services are not prominently featured in the policies or implementation strategies, particularly at the primary and secondary levels.

Infrastructure data from Maharashtra shows a vast network of health facilities, including over 10,000 SCs and nearly 2,000 PHCs, supported by a physiotherapy workforce of around 3,190 professionals. However, even with this infrastructure, there is no clear policy framework or service protocol dedicated to CR across the levels of care.[5] A review of various ministry websites, national health portals, and geographically based data sources did not yield substantial evidence of dedicated CR programs. This reveals a critical gap in rehabilitative care for cardiac conditions, despite their inclusion under broader noncommunicable disease programs.[6] To bridge this gap, there is a need to institutionalize CR through clear guidelines, trained human resources, and integration into existing public health infrastructure at all levels.

Challenges in Implementing Cardiac Rehabilitation in India

Cardiac rehabilitation's widespread adoption in India remains limited due to several interrelated challenges. These include low awareness, inefficient referral systems, inadequate infrastructure, financial constraints, and disparities across healthcare levels and geographic regions.

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Awareness and Education Gaps

Awareness about CR is limited among both patients and healthcare professionals. Postevent cultural norms that discourage physical activity also reduce participation. CR is largely absent from medical and allied health curricula, leading to low referral rates. CR's role in long-term cardiovascular health is often overlooked. Misconceptions of viewing rest as the preferred mode of healing, and cultural stigma around illness, can discourage participation in CR.[7]

Unstructured Referral Systems

Referral systems play a critical role in ensuring patient access to CR. Cardiologists, often the first point of contact postcardiac events, may hesitate to refer patients due to limited CR training, lack of standardized referral protocols, and insufficient availability of dedicated CR centers.[8] Many physicians lack formal CR training or hesitate to refer due to the absence of standardized referral protocols and limited availability of CR centers.

Infrastructural Limitations

Rural and semi-urban areas often lack CR facilities, trained staff, and necessary equipment. Rehabilitative care is deprioritized compared to acute interventions. Acute-care services tend to be prioritized over preventive CR, resulting in underfunding and under-prioritization of long-term CR, contributing to poor outcomes.[9]

Financial Constraints

Cardiac rehabilitation in India is funded through a mix of government programs, private institutions, insurance, and out-of-pocket payments. The high cost of CR, combined with limited insurance coverage, deters patients, especially from lower socioeconomic strata.[10] With minimal insurance coverage, most patients bear the full cost of CR. Expansion of government schemes like Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PM-JAY) to include CR is essential.

Inequitable Access

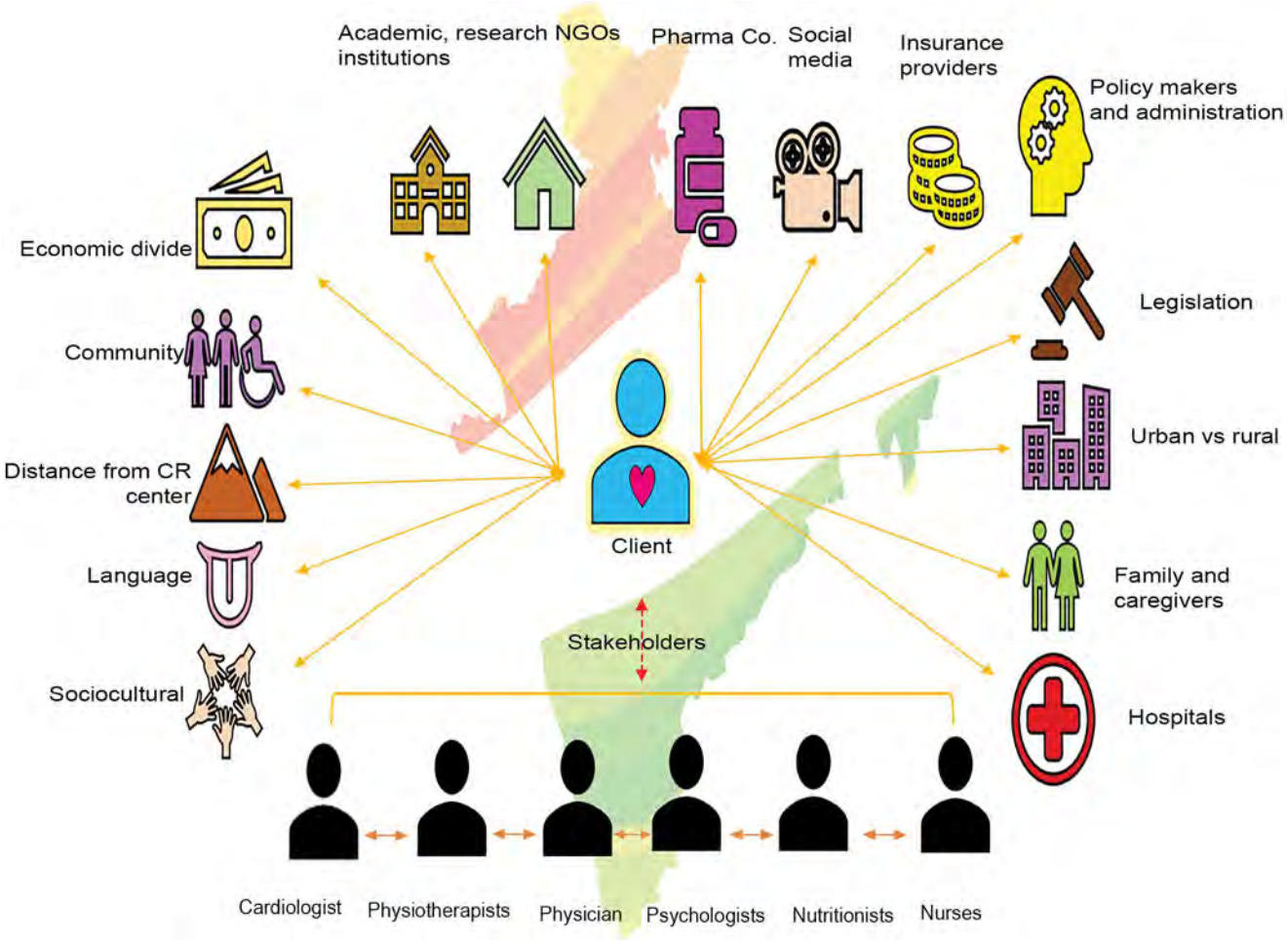
Cardiac rehabilitation services are concentrated in urban tertiary centers, leaving rural communities underserved. Fragmented care and lack of integration across health tiers affect continuity and outcomes.[11]

Opportunities and Innovative Approaches in Advancing Cardiac Rehabilitation in India

India has the potential to significantly improve its CR by adopting context-specific, innovative strategies and engaging a broad coalition of stakeholders (Fig. 1A). Digital technologies, telemedicine, community-based programs, and multidisciplinary approaches offer scalable and sustainable solutions to bridge gaps in access and quality of CR (Fig. 1B).

Digital Health and Telecardiac Rehabilitation

Emerging technologies such as mobile apps, wearable devices, and digital platforms offer patients personalized exercise plans, educational content, and real-time monitoring, empowering them to take an active role in recovery. Programs like Narayana Health's telecardiology and government initiatives such as "eSanjeevani" and "mHealth" exemplify use of telemedicine to overcome geographic barriers and improve adherence.[12] Integrating CR into



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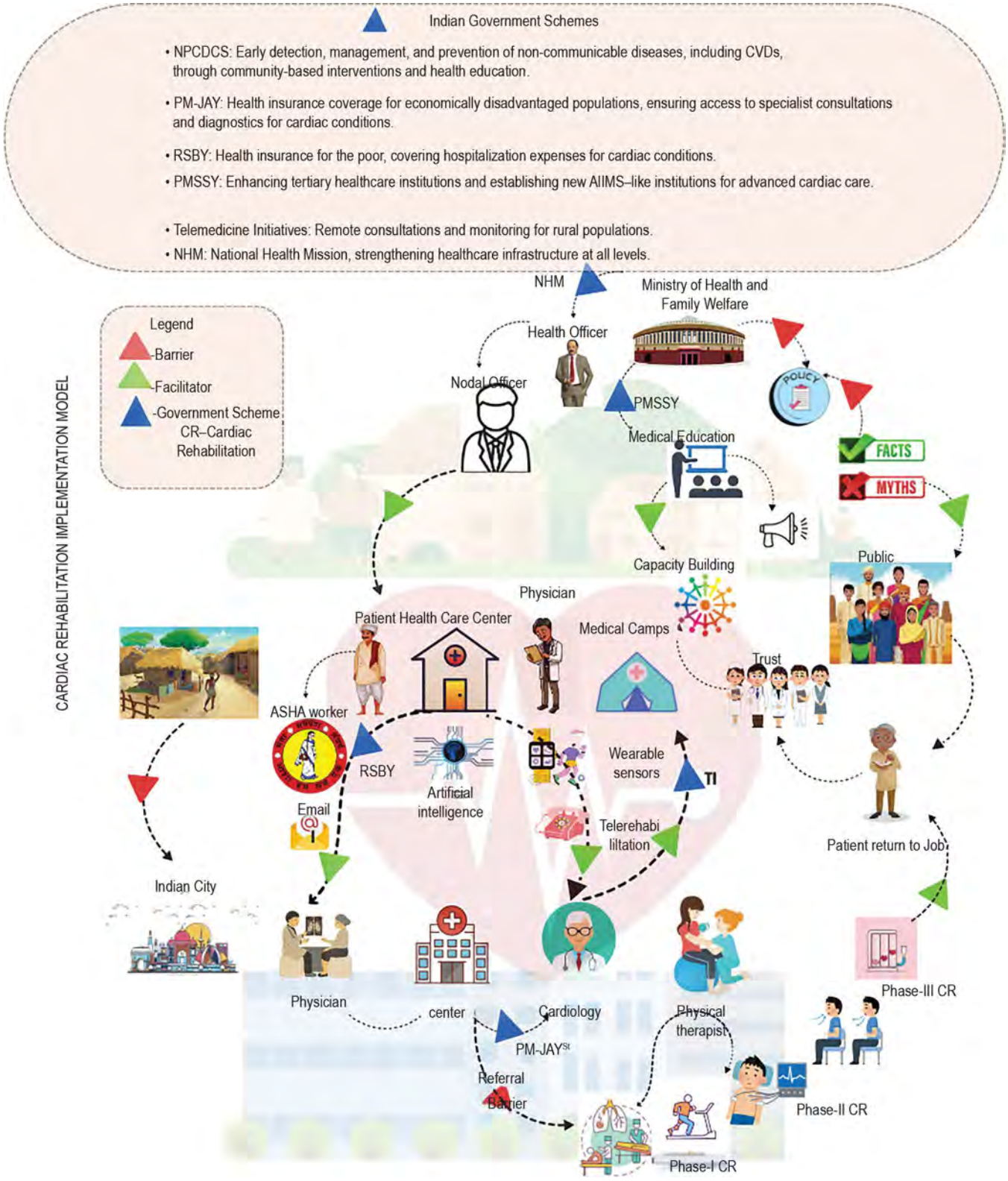

Figs 1A and B: (A) An illustration of stakeholders for the implementation of CR in India; and (B) CR implementation model

electronic health record (EHR) systems and adapting successful international models, such as Kaiser Permanente's referral protocol, can streamline care coordination. Continuing medical education sessions and workshops are essential to train healthcare providers in digital CR delivery for capacity-building. Stakeholders have distinct yet interdependent roles.[13]

Technology developers must create user-friendly, secure, and culturally sensitive platforms. Healthcare professionals should integrate digital tools into routine CR care and provide remote monitoring and support. Patients are encouraged to use these tools to manage their recovery and maintain communication with providers. Investments in digital infrastructure,

standardized guidelines, and pilot programs are needed to ensure safe and effective telerehabilitation. Wearable devices, remote monitoring systems, and data analytics should be leveraged to track progress and outcomes. Evidence from local studies is essential to validate these models and inform scale-up strategies.[14] Telerehabilitation using mobile apps, wearable technologies, and video consultations provides a scalable and cost-effective CR model. Initiatives like eSanjeevani and Narayana Health's telecardiology services show promise. Incorporating CR into EHRs and clinical pathways can streamline delivery and tracking.

Community- and Home-based Cardiac Rehabilitation

Community-based CR initiatives such as the yoga-based models and the Karnataka pilot led by Salim Yusuf highlight scalable, culturally relevant approaches to rehabilitation. Home-based CR has shown efficacy in improving exercise capacity and reducing hospital readmissions. Community health workers can play a pivotal role by raising awareness, providing support, and facilitating implementation. Training Accredited Social Health Activist (ASHA) workers in CR can extend outreach through screenings, education, and referrals. Providing culturally sensitive education, conducting home visits, and continuous patient monitoring enhances long-term adherence.[15] Localized models, including yoga-based and home-based CR, have shown efficacy. Training community health workers, such as ASHAs, to support basic CR can expand reach and improve adherence.

Multidisciplinary, Person-centered Models

Effective CR requires collaboration among cardiologists, physiotherapists, nurses, dietitians, and mental health professionals. Embedding CR training in medical and allied health education and developing national clinical guidelines can help standardize and elevate care quality.

Strengthening the Cardiac Rehabilitation Ecosystem: Policies, Financing, and Capacity Building

Sustainable Financing Models

Cardiac rehabilitation funding in India is fragmented, involving government support, private healthcare, insurance, and out-of-pocket payments. Private centers (e.g., Apollo Hospitals) fund CR through hospital revenue and corporate social responsibility (CSR) initiatives. CR inclusion under national health insurance schemes such as Ayushman Bharat PM-JAY is essential to lower costs and improve access. Innovative financing models like social impact bonds (SIB) and health savings accounts can diversify funding and promote sustainability. Kerala's health savings scheme and Rajasthan's SIB model offer replicable frameworks.[16] Institutionalizing CR within public and private insurance systems is critical. Innovative funding mechanisms, such as health savings accounts and SIB (piloted in Kerala and Rajasthan), can support scale-up.

Infrastructure and Workforce Development

Strengthening CR infrastructure and expanding training programs for CR professionals is essential. Regional centers of excellence can serve as hubs for training, service delivery, and research.[17]

Referral System Optimization and Public Engagement

Timely and systematic referral pathways are critical to CR utilization. Implementing clear referral protocols in cardiology and primary care settings, combined with EHR integration, will streamline patient transitions into CR. Community-based CR models, tailored to linguistic and cultural needs, are key to expanding access. Public awareness campaigns should highlight the benefits of CR, reduce stigma, and encourage participation. Integrating CR education into undergraduate and continuing medical education will improve healthcare providers' understanding and advocacy. India's CR services remain concentrated in metropolitan areas, leaving rural populations underserved. Geographic and socioeconomic disparity contributes to poor outcomes and necessitates targeted interventions.[18] Automating referrals through EHRs and increasing provider and public awareness *via* CME and health campaigns can boost participation.

National Integration

Cardiac rehabilitation is partially supported under programs like the NPCDCS, PM-JAY, and Pradhan Mantri Swasthya Suraksha Yojana (PMSSY). CR remains underutilized due to fragmented delivery and inconsistent integration. Policy advocacy plays a critical role in India. It is essential to allocate dedicated funding for CR under the National Health Mission (NHM) to ensure sustained program implementation. Inclusion of CR in the benefit packages of Ayushman Bharat PM-JAY can significantly improve affordability and access. Training ASHA workers in basic CR principles and referral pathways will enhance early identification and community-level support.[19] Furthermore, promoting CR through public–private partnerships and CSR initiatives, by actively involving nongovernmental organizations (NGOs) and community leaders, can help expand reach, reduce stigma, and ensure community engagement.

Cardiac rehabilitation programs are relatively cost-effective, but they are generally not covered under standard insurance schemes in India. Some private insurance policies may offer partial coverage for CR services, but such policies are limited and not widely adopted. Policy reforms to include CR under health insurance like PM-JAY can lower costs. Incorporating CR into PM-JAY ensures patients access essential services without high costs.

The NPCDCS emphasizes early detection through community-based interventions. Rashtriya Swasthya Bima Yojana (RSBY) offers insurance to the underprivileged. DHs, specialist consultations, and diagnostics are backed by PM-JAY, providing insurance coverage to the underprivileged with tertiary setups. PMSSY upgrades institutions like the All India Institute of Medical Sciences (AIIMS) and establishes state-of-the-art institutions. NHM initiatives focus on strengthening tertiary care CR. India has 1,55,000 SCs, 25,000 primary centers, 5,000 community centers, and 700 DHs. CR availability is limited but growing, with 3,000 physiotherapists (primary), 10,000 (secondary), and 5,000 (tertiary) healthcare setups across India.[20] Training ASHA workers in CR can enhance outreach by steering screenings, preliminary CR guidance, and referral.

Policy Advocacy for Cardiac Rehabilitation in India

Innovative financing models like SIB or health savings schemes could provide funding avenues for CR. NPCDCS establishes funding for CVD prevention and rehabilitation in PM-JAY. Health savings schemes in Kerala are an example where individuals are encouraged to save in savings accounts for health expenses, including CR, which allow patients to allocate pretax income for the middle-income bracket. SIBs were introduced in Rajasthan to fund private health investment in public health programs, with returns based on achieving specific health outcomes.[21] Advocacy can result in increased government and private sector funding for enhancing CR infrastructure, training professionals, and developing models to ensure quality.

Conclusion and Call to Action

Expanding CR access in India requires an integrated, multisectoral approach encompassing legislation, sustainable financing, infrastructure investment, digital innovation, and workforce development. Collaboration among government bodies, healthcare providers, NGOs, academic institutions, and private players is essential to achieve equitable access and quality care. Aligning national efforts with global frameworks like the WHO Rehabilitation 2030 initiative can offer a structured and effective pathway.[22] Strengthening CR is vital not only for improved individual health outcomes but also for addressing the broader CVD burden in India.

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References

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol 2020;76:2982–3021.
2. Munshi H, Gajbhiye RK. Addressing disparities and challenges in global health from an LMIC perspective. Lancet 2023;402(10396):102–103.
3. Babu AS, Turk-Adawi K, Supervia M, et al. Cardiac rehabilitation in India: results from the International Council of Cardiovascular Prevention and Rehabilitation's global audit of cardiac rehabilitation. Glob Heart 2020;15:28.
4. Venugopal V, Richa R, Singh D, et al. National programme for prevention and control of cancer, diabetes, cardiovascular diseases, and stroke: a scoping review in the context of hypertension prevention and control in India. Indian J Public Health 2023;67(Suppl 1):S50–S57.
5. Das T, Guha P. The puzzle of public health expenditure and healthcare infrastructure in India: an empirical investigation. Reg Sci Policy Pract 2024;16(2):12710.
6. Chandran A, Roy P. Applications of geographical information system and spatial analysis in Indian health research: a systematic review. BMC Health Serv Res 2024;24:1448.
7. Rodrigo SF, Van Exel HJ, Van Keulen N, et al. Referral and participation in cardiac rehabilitation of patients following acute coronary syndrome; lessons learned. Int J Cardiol Heart Vasc 2021;36:100858.
8. Seyed-Nezhad M, Ahmadi B, Akbari-Sari A. Factors affecting the successful implementation of the referral system: a scoping review. J Family Med Prim Care 2021;10:4364–4375.
9. Field PE, Franklin RC, Barker RN, et al. Cardiac rehabilitation services for people in rural and remote areas: an integrative literature review. Rural Remote Health 2018;18:4738.
10. Chaudhary RS, Venkateshmurthy NS, Dubey M, et al. Regional and socio-demographic variation in laboratory-based predictions of 10-year cardiovascular disease risk among adults in north and south India. Indian Heart J 2024;76:271–279.
11. Ghisi GLM, Contractor A, Abhyankar M, et al. Cardiac rehabilitation knowledge, awareness, and practice among cardiologists in India. Indian Heart J 2018;70:753–755.
12. Adithyan GS, Ranjan A, Muraleedharan VR, et al. Kerala's progress towards universal health coverage: the road travelled and beyond. Int J Equity Health 2024;23:152.
13. Meena S, Rathore M, Gupta A, et al. Assessment of National Program for Prevention and Control of Cancer, Diabetes, CVD and Stroke (NPCDCS): an observational study in rural Jaipur, Rajasthan. J Family Med Prim Care 2022;11:3667–3672.
14. Stoumpos AI, Kitsios F, Talias MA. Digital transformation in healthcare: technology acceptance and its applications. Int J Environ Res Public Health 2023;20:3407.
15. Chattopadhyay K, Chandrasekaran AM, Praveen PA, et al. Development of a yoga-based cardiac rehabilitation (Yoga-CaRe) programme for secondary prevention of myocardial infarction. Evid Based Complement Alternat Med 2019;2019:7470184.
16. Kumar A. The transformation of the Indian healthcare system. Cureus 2023;15:e39079.
17. Rathi A, Jiandani MP. Patient perceived barriers to phase II cardiac rehabilitation in patients with and without percutaneous coronary angioplasty. World J Adv Res Rev 2023;17:883–889.
18. Grace SL, Leung YW, Reid R, et al. The role of systematic inpatient cardiac rehabilitation referral in increasing equitable access and utilization. J Cardiopulm Rehabil Prev 2012;32:41–47.
19. Day A, McLeod B, Hawkins RL, et al. The importance of policy advocacy in social work. Fam Soc 2023;104:243–244.
20. Parisi D, Srivastava S, Parmar D, et al. Awareness of India's national health insurance scheme (PM-JAY): a cross-sectional study across six states. Health Policy Plan 2023;38:289–300.
21. Hulse ESG, Atun R, McPake B, et al. Use of social impact bonds in financing health systems responses to non-communicable diseases: scoping review. BMJ Global Health 2021;6:e004127.
22. Macias-Konstantopoulos WL, Collins KA, Diaz R, et al. Race, healthcare, and health disparities: a critical review and recommendations for advancing health equity. West J Emerg Med 2023;24:906–918.

REVIEW ARTICLE

Beyond Traditional Models—The Impact of Machine Learning on Intensive Care Unit Outcome Predictions: A Narrative Review

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Abstract

Accurate prediction of patient outcomes in intensive care units (ICUs) is crucial for enhancing clinical decision-making, patient care, and resource allocation. Traditional scoring systems like Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), and Sequential Organ Failure Assessment (SOFA), while valuable, fall short of fully capturing the complexities of critically ill patients. Advances in machine learning (ML) enable the analysis of high-dimensional data, including electronic health records (EHRs), physiological parameters, and genomic information, providing a more comprehensive approach to outcome prediction.

This review aims to assess the impact of ML techniques, including deep learning (DL), ensemble machine learning (EML), and reinforcement learning (RL), in improving ICU outcome predictions, particularly in identifying high-risk patients and enabling proactive interventions.

Machine learning models have shown superiority over traditional systems, enabling more accurate identification of critical patients. However, implementing ML in ICU settings comes with challenges, including data quality, model interpretability, ethical concerns, and workflow integration. Collaborative efforts between clinicians, data scientists, and multidisciplinary teams, supported by shared databases like Medical Information Mart for Intensive Care (MIMIC), are essential for developing generalizable ML models that work across diverse healthcare environments.

Future research should focus on improving real-time prediction using wearable technology and personalized risk assessments to further individualize ICU care. Ethical considerations, particularly data privacy and model transparency, must be addressed as ML becomes more integrated into critical care.

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Introduction

Optimizing intensive care unit (ICU) resource allocation is essential for improving patient outcomes and efficiency. Traditional models like APACHE, SAPS, and SOFA estimate mortality but offer static snapshots, often limited by data inconsistencies and hospital-specific variations.[1] These models, while valuable, may not fully capture the rapidly changing nature of critical illness, leading to delayed or suboptimal decision-making.

Machine learning (ML) provides a more dynamic alternative by analyzing complex time-series data to identify nonlinear patterns, enabling real-time proactive predictions. This is crucial in ICU settings where patient conditions change quickly. Studies demonstrate ML's potential, such as Komorowski et al.'s reinforcement learning algorithms, which optimized sepsis treatment and reduced mortality by 20%. Additionally, ML models can predict respiratory failure early, prompting timely interventions and improving patient outcomes.[2,3]

This review explores how ML addresses the limitations of traditional models by identifying high-risk patients, preventing unnecessary ICU admissions, optimizing resource use, and enhancing intervention precision. However, challenges like data quality, model interpretability, and integration into clinical workflows remain significant, with generalizability across diverse populations also critical. The literature search used keywords like "AI in ICU" and "ICU mortality prediction models" across platforms like Google and PubMed Central.

Objectives

The primary objective of this narrative review is to explore the role of artificial intelligence (AI) and ML in predicting ICU mortality and improving resource management. Specifically, it will address the following key questions:

1. How do AI models compare to traditional scoring systems in predicting ICU outcomes?
2. What impact do predictive models have on ICU resource optimization?
3. What challenges exist in implementing AI-driven prediction models in ICU settings?

This review highlights advancements, limitations, and practical considerations in adopting AI for ICU outcome prediction.

Methods

This narrative review was conducted to synthesize existing literature on the role of ML and AI in predicting ICU outcomes and optimizing resource management. A comprehensive literature search and analysis were performed, focusing on studies that assessed the application of ML/AI models in ICU settings. The methodology aimed to provide a structured and detailed review of advancements in AI-driven ICU outcome prediction.

A narrative synthesis was conducted to compare AI/ML models with traditional systems, emphasizing improvements, challenges, and ethical considerations. Recommendations for future research were drawn based on these comparisons. The search covered the period from 2016 to 2024, focusing on publications in English across databases such as PubMed, Embase,

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Cochrane Library, and Google Scholar. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text terms, including "ICU mortality prediction," "ML in outcome prediction," "artificial intelligence in ICU," "predictive models," "ICU resource optimization," and "healthcare analytics." Inclusion criteria encompassed all relevant study designs, including randomized controlled trials, cohort studies (retrospective and prospective), case-control studies, and narrative reviews.

Discussion

The Role of Accurate Outcome Prediction in Intensive Care Unit Patient Care

Accurate outcome prediction in the ICU is crucial for improving patient care and resource management. Mortality rates in ICUs range from 10 to 50% in high-risk groups, making timely predictions essential for enhancing clinical decision-making and optimizing treatments.[4,5] Early identification of patients at risk of deterioration helps prioritize interventions and improves communication with families regarding prognosis and end-of-life decisions. Traditional scoring systems like APACHE, SAPS, and SOFA have been widely used for mortality prediction based on clinical and physiological parameters.[1,6] However, these models are static and rely on a limited set of variables, often missing the complex, dynamic changes occurring in critically ill patients.[6] Studies show that the predictive accuracy of models like APACHE IV declines over time, achieving about 75% accuracy in some cohorts.[7] Furthermore, these models may not account for changing conditions during an ICU stay, potentially leading to delayed interventions or misjudging patient trajectories.[8]

Artificial intelligence-based ML models offer a more dynamic and personalized approach by processing large amounts of real-time patient data from electronic health records (EHRs), lab results, and vital signs, leading to higher predictive accuracy of 85 to 90%.[9] Additionally, AI can integrate nontraditional data, such as medical imaging and genomics, to further enhance prediction capabilities.[10] During the COVID-19 pandemic, AI models were effectively used to predict patient deterioration based on respiratory metrics and biomarkers, achieving pooled sensitivity of 93% and specificity of 94%, with an AUC of 0.98.[11] These results highlight the potential of AI in improving ICU outcome prediction.

Impact of Outcome Prediction on Resource Allocation and Management

Optimizing the allocation of resources within the ICU presents a pivotal challenge due to constraints such as limited bed availability, specialized personnel, and equipment.

In modern healthcare, predictive analytics significantly impact resource allocation and management in the ICU, enhancing both patient outcomes and operational efficiency.

Prioritizing Intensive Care Unit Beds

Predictive models enable healthcare providers in proactive bed allocation by forecasting patient needs based on the severity of conditions and anticipated monitoring requirements. This helps prioritize ICU admissions, minimize treatment delays, reduce adverse events, and ensure timely interventions for high-risk patients.[12,13]

Optimizing Staffing Levels

Predictive analytics enable hospitals to adjust staffing schedules based on anticipated admissions and patient acuity levels. By matching staffing to demand, hospitals can ensure that adequate and skilled staff are available during peak periods, preventing burnout and ensuring optimal patient care.[14,15] It also ensures that experienced specialists are available when necessary, further enhancing patient outcomes.

Managing Equipment Usage

By forecasting equipment needs, predictive models optimize the use of critical ICU resources like ventilators and monitors, reducing idle time and maintenance costs. This ensures the right equipment is available for patients in need, preventing shortages and reducing overuse, which enhances operational efficiency and care quality.[12,9,16]

Reducing Healthcare Costs

Predictive models help lower costs by preventing unnecessary ICU admissions and reducing the overuse of expensive equipment. Early intervention for conditions like sepsis reduces ICU stays and avoids costly treatments. Moreover, identifying patients unlikely to benefit from aggressive treatment prevents futile interventions, leading to cost savings. Accurate prediction of high-risk readmission patients enables targeted postdischarge plans, preventing expensive readmissions and leading to substantial cost savings.[17–19]

Enhancing Patient Outcomes

Accurate outcome prediction ensures that patients receive timely, appropriate care, reducing complications and improving recovery rates. By identifying high-risk patients early, predictive models support intensive monitoring and timely interventions, improving overall patient outcomes.[20,21]

Artificial intelligence and ML technologies have emerged as powerful tools in healthcare, with significant potential for improving patient care, risk stratification, and resource allocation in ICU admissions.

Machine Learning Innovations in Intensive Care Unit Outcome Prediction

Machine learning is revolutionizing ICUs by offering advanced tools for predicting patient outcomes. In healthcare, ML involves training algorithms to recognize patterns from large datasets, allowing computers to make accurate predictions based on historical data. This transformative technology is particularly beneficial in ICU settings, where timely decisions are critical.

In an ICU, a vast amount of data is collected, such as patient demographics, physiological measurements, lab results, and treatment history. ML models process this complex data to identify patterns that may be missed by traditional statistical methods. These models are trained on historical data to learn from past cases, and as more data becomes available, the predictions become increasingly precise.

Conventional scoring systems like APACHE, SAPS, and SOFA are used to evaluate patient severity, but they rely on static data inputs and predefined variables. ML models, on the other hand, can process larger and more complex datasets, enabling dynamic predictions that adapt to real-time changes in patient conditions. This ability to integrate multiple variables and detect subtle patterns makes ML particularly valuable in ICU outcome prediction.

Several studies have demonstrated the effectiveness of ML in ICU mortality prediction. Marafino et al.,[22] Pirracchio et al.,[23] and Weissman et al.[2] used ML models to predict inhospital mortality based on clinical data. Marafino et al.[22] focused on nursing notes from the first 24 hours of ICU admission, while Weissman et al.[2] combined structured and unstructured data from the first 48 hours. Awad et al.[24] took a different approach, predicting mortality within the first 6 hours of ICU admission. Rajkomar et al.[25] developed a deep learning (DL) model that achieved an AUC-ROC score of 0.95 for inhospital mortality,

significantly outperforming traditional models.

In addition to general mortality prediction, ML has been applied to disease-specific outcomes. Celi et al.[26] developed an ML model for predicting outcomes in acute kidney injury (AKI) patients, while Garcia-Gallo et al.[27] focused on sepsis patients. These models highlight the ability of ML to tailor predictions to individual patient profiles, improving the precision of clinical interventions.[28]

Machine learning also plays a crucial role in real-time monitoring and clinical decision support. Advanced techniques like DL, EML, and RL have been successful in predicting complex medical outcomes. Liu et al.[29] developed a logistic regression model to predict mortality risk in ICU patients with pulmonary tuberculosis. Their model, which identified key factors like APACHE II scores and C-reactive protein levels, achieved sensitivities and specificities of 83.3 and 73.1%, respectively.

On the other hand, studies by Hou et al.[30] and Nemati et al.,[31] which relied on MIMIC-III (a public ICU database), faced challenges related to data size and diversity. Nonetheless, these models demonstrated the early identification of case severity, allowing for better clinical decision-making and improved patient outcomes.

The COVID-19 pandemic highlighted ML's potential in critical care. ML models predicted ICU transfer needs, severe outcomes, and inhospital mortality for COVID-19 patients. Key factors like lymphocyte percentage, lactate dehydrogenase, and creatinine levels significantly influenced predictions, demonstrating ML's utility in complex ICU care. Despite constraints with small databases, the promising results emphasize ML's crucial role in tackling pandemics and enhancing ICU care.[32]

A variety of ML models have been applied in ICU settings. Neural networks (NN), for instance, excel at recognizing patterns in complex data, while decision trees (DT) are favored for their interpretability. Support vector machines (SVM) and gradient-boosting (GB) algorithms have also been used for ICU outcome prediction.[33] Ensemble machine learning (EML), which combines multiple models, often performs better than single models.[34] Johnson et al. demonstrated that a combination of random forests (RF) and logistic regression (LR) outperformed individual models for ICU mortality prediction.[35]

Recent studies have increasingly employed deep learning techniques to improve prediction accuracy. Hao et al.,[36] Zahid et al.,[37] and Caicedo-Torres et al.[38] used deep learning models with accuracy ranges between 0.86 and 0.87. Zahid et al.'s self-normalizing neural network (SNN) slightly outperformed Pirracchio et al.'s[23] super learner model (AUC-ROC 0.86 vs 0.85). However, DL models, though highly accurate, are often criticized for their lack of interpretability. This has prompted efforts to improve transparency, as demonstrated by Caicedo-Torres et al.[38] and Sha et al.,[39] who employed visualization techniques to make the predictions more understandable for clinicians.

In addition to model development, ML innovations have extended to real-time monitoring and EHRs.[40] This allows predictive models to be continuously updated as patient conditions change. Another exciting development is the use of natural language processing (NLP) to analyze unstructured clinical notes. By incorporating NLP, Shickel et al. significantly enhanced the accuracy of ICU outcome predictions.[41] Challenges with data availability and the absence of AKI prognostic markers in MIMIC datasets were pointed out by He et al.[42]

Despite these limitations, the increasing availability of high-quality data and advancements in model interpretability are paving the way for ML to have a profound impact on ICU care.

Challenges in Implementing Machine Learning-based Outcome Prediction

Using ML for predicting patient outcomes in ICUs holds great promise but faces several challenges. These challenges cover technical, ethical, and logistical aspects and need to be addressed for the successful integration of ML into healthcare.[43,44]

Data Quality and Availability

Intensive care unit data is complex and comes from various sources, leading to inconsistencies and errors. Some facilities still rely on paper records, making digitization difficult. Missing data, especially in mortality cases, further hampers ML model performance.[45–48] Additionally, organizations are often reluctant to share data, which limits the development of effective models. Standardizing data formats, such as Fast Healthcare Interoperability Resources (FHIR) and Critical Care Data Exchange Format (CCDEF), could improve data exchange.[49]

Model Interpretability

Complex ML models, like DL, often lack transparency, hindering clinical acceptance. Clinicians need interpretable outputs for effective integration into practice. Early clinician involvement in model design ensures better workflow integration and trust.[49–51] Inclusive datasets capturing diverse patient characteristics and techniques like multivariate imputation enhance model accuracy and timely interventions.[47,48,50,51] Clinicians must understand how algorithms improve patient care within workflows. An accessible AI curriculum for medical students and clinicians can foster critical appraisal and safe use of AI tools.

Generalization and Validation

Machine learning models often struggle to generalize across different patient populations. Overfitting, where models perform well on training data but fail with new data, is a key issue. External validation is necessary but rare, and the use of multi-center databases raises privacy concerns. Class imbalance, particularly in mortality cases, skews performance, affecting critical care predictions. Underrepresentation of ethnic minorities impacts model accuracy.[20,43] Addressing imbalances in mortality data and including underrepresented groups are essential for reliable, equitable ML applications across diverse healthcare settings.[20,52]

Ethical and Legal Considerations

Data privacy and consent are major ethical issues in AI-based healthcare. High-profile cases like NHS's data sharing with DeepMind and Google's Project Nightingale show the risks of using patient data without consent.[53–55] Biases in training data can lead to unequal treatments, and frameworks like the Personal Data Protection Bill, 2019, aim to protect patient privacy.[53–56]

Integration with Clinical Workflow

To be effective in ICUs, ML models must fit seamlessly into existing workflows. ICU settings require real-time data processing, and the model's output should be actionable. Ensuring these models work across both advanced hospitals and resource-limited settings is key to their widespread adoption.[43,52]

Feature Engineering and Selection

Intensive care unit data is dynamic, making feature engineering challenging. Identifying relevant variables and capturing time-sensitive data requires advanced techniques. Measurement errors and self-reporting inaccuracies also introduce biases, which must be corrected to ensure fairness, which requires deep domain knowledge and advanced analytical techniques.[43,52,57]

Regulatory Approval

Gaining regulatory approval is essential for deploying ML models in healthcare. Bodies like the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Central Drugs Standard Control Organization (CDSCO)[58] require rigorous testing to confirm a model's safety and reliability. While this process is time-consuming, it is necessary for ensuring the safe use of ML in clinical settings.[43,44,52]

Maintenance and Updating

Machine learning models need to be updated regularly to maintain their accuracy as healthcare practices evolve. Continuous monitoring is required to avoid model drift, ensuring reliable predictions over time.[59]

Accountability

Determining who is responsible when ML-based predictions fail is a challenge. Clinicians may be hesitant to rely on models if they are held liable, while developers are often detached from clinical practice. Ensuring accountability and building trust through transparent models is critical.[60,61]

Shortage of Machine Learning Experts

The lack of professionals skilled in both healthcare and ML is slowing the adoption of these technologies. Investing in training programs is crucial to developing a workforce capable of deploying ML tools effectively.[44]

Addressing these challenges will be key to unlocking the full potential of ML in critical care settings.

Future Directions in Machine Learning-based Outcome Prediction

The future of ML-based outcome prediction in healthcare is set to evolve along multiple dimensions, driven by advancements in AI, big data, and emerging technologies. A key trend is integrating explainable AI (XAI) to improve transparency and clinician trust. Techniques like local interpretable model-agnostic explanations (LIME), SHapley additive exPlanations (SHAP), and gradient-weighted class activation mapping (Grad-CAM) will help healthcare professionals understand how specific factors influence predictions.[62] Lundberg et al. showed SHAP's effectiveness in improving ICU prediction model interpretability.[63]

With growing high-dimensional data availability—genomics, proteomics, lifestyle—ML will support personalized medicine by tailoring predictions to individual patients.[64] Continuous monitoring *via* wearables and EHR updates will enable dynamic adjustments to patient care, improving both short- and long-term outcomes.[65]

Federated learning (FL) addresses data privacy while enhancing ML model accuracy and generalizability by allowing hospitals to collaborate without sharing sensitive data, crucial for ICUs.[66] XAI will help detect and mitigate biases, promoting equitable interventions.[62] RL also shows promise in ICU care, optimizing treatment decisions using real-time feedback.[62,66]

Artificial intelligence integration into clinical workflows will require collaboration among data scientists, healthcare professionals, ethicists, and regulatory bodies. Shared databases like the MIMIC database can accelerate model development and validation across diverse patient populations.[67]

Limitations of Artificial Intelligence in Outcome Prediction

The applicability of AI remains theoretical, with models having shown promise in controlled environment settings; validation in real-world clinical scenarios is yet to be explored in operational hospital environments. There has been insufficient focus on model interpretability, which limits adoption by healthcare professionals. Many studies referenced in the literature have relied heavily on retrospective datasets for training and testing models, which fail to account for dynamic changes in patient conditions or real-time decision-making in ICUs.

Scalability and resource constraints in low-resource settings are questionable, with most references focusing on the development of models in well-resourced, high-income country settings where data collection infrastructure and computational power are readily available. Ethical concerns are also not adequately addressed, particularly in terms of algorithmic bias, data privacy, and fairness, which are essential for equitable healthcare solutions. A key limitation is the lack of focus on patient-centered outcomes. While clinical metrics are often the focus, patient-centered outcomes and long-term impacts remain underexplored.

These gaps highlight the need for more comprehensive, interdisciplinary, and ethically aware research that moves beyond technical innovation to address real-world challenges in deploying AI for ICU mortality prediction.

Conclusion

In conclusion, this narrative review highlights the transformative potential of ML in healthcare, potentially significantly enhancing patient outcomes and resource management. ML's ability to analyze complex, real-time data offers significant advantages over traditional scoring systems like APACHE, SAPS, and SOFA, facilitating more accurate and personalized patient predictions that enhance clinical outcomes and resource allocation.

Despite these advancements, challenges such as data quality, model interpretability, and integration into clinical workflows remain barriers to widespread adoption. Future research must focus on improving data accuracy, ensuring transparency in ML models, and establishing robust validation methods.

Integrating ML into clinical practice could revolutionize ICU care through timely, data-driven decision-making, leading to reduced unnecessary admissions and improved intervention precision. Ultimately, by addressing current challenges and embracing ongoing advancements, ML has the potential to become an indispensable tool in critical care, significantly enhancing patient outcomes and healthcare delivery.

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References

1. Hosseini M, Ramazani J. Evaluation of acute physiology and chronic health evaluation II and sequential organ failure assessment scoring systems for prognostication of outcomes among intensive care unit's patients. Saudi J Anaesth 2016;10(2):168–173.
2. Weissman GE, Hubbard RA, Ungar LH, et al. Inclusion of unstructured clinical text improves early prediction of death or prolonged ICU stay. Crit Care Med 2018;46(7):1125–1132.
3. Komorowski M, Celi LA, Badawi O, et al. The artificial intelligence clinician learns optimal treatment strategies for sepsis in intensive care. Nat Med 2018;24(11):1716–1720.
4. Kalın BS, Özçaylak S, Solmaz İ, et al. Assessment of risk factors for mortality in patients in medical intensive care unit of a tertiary hospital. Indian J Crit Care Med 2022;26(1):49–52.
5. Pellathy TP, Pinsky MR, Hravnak M. Intensive care unit scoring systems. Crit Care Nurse 2021;41(4):54–64.
6. Hwang SY, Kim IK, Jeong D, et al. Prognostic performance of sequential organ failure assessment,

acute physiology and chronic health evaluation III, and simplified acute physiology score II scores in patients with suspected infection according to intensive care unit type. J Clin Med 2023;12(19):6402.
7. Keegan MT, Gajic O, Afessa B. Comparison of APACHE III, APACHE IV, SAPS 3, and MPM0III and influence of resuscitation status on model performance. Chest 2012;142(4):851–858.
8. Kumar AA. Mortality prediction in the ICU: the daunting task of predicting the unpredictable. Indian J Crit Care Med 2022;26(1):13–14.
9. Alowais SA, Alghamdi SS, Alsuhebany N, et al. Revolutionizing healthcare: the role of artificial intelligence in clinical practice. BMC Med Educ 2023;23(1):689.
10. Olang O, Mohseni S, Shahabinezhad A, et al. Artificial intelligence-based models for prediction of mortality in ICU patients: a scoping review. J Intensive Care Med 2024:8850666241277134.
11. Xin Y, Li H, Zhou Y, et al. The accuracy of artificial intelligence in predicting COVID-19 patient mortality: a systematic review and meta-analysis. BMC Med Inform Decis Mak 2023;23(1):155.
12. Ortiz-Barrios M, Arias-Fonseca S, Ishizaka A, et al. Artificial intelligence and discrete-event simulation for capacity management of intensive care units during the COVID-19 pandemic: a case study. J Bus Res 2023;160:113806.
13. Pagel C, Banks V, Pope C, et al. Development, implementation and evaluation of a tool for forecasting short term demand for beds in an intensive care unit. Oper Res Health Care 2017;15:19–31.
14. Yinusa A, Faezipour M. Optimizing healthcare delivery: a model for staffing, patient assignment, and resource allocation. Appl Syst Innov 2023;6(5):78.
15. Porcel-Gálvez AM, Fernández-García E, Rafferty AM, et al. Factors that influence nurse staffing levels in acute care hospital settings. J Nurs Scholarsh 2021;53(4):468–478.
16. Stivi T, Padawer D, Dirini N, et al. Using artificial intelligence to predict mechanical ventilation weaning success in patients with respiratory failure, including those with acute respiratory distress syndrome. J Clin Med 2024;13(5):1505.
17. Teng AK, Wilcox AB. A review of predictive analytics solutions for sepsis patients. Appl Clin Inform 2020;11(3):387–398.
18. Rogers P, Boussina AE, Shashikumar SP, et al. Optimizing the implementation of clinical predictive models to minimize national costs: sepsis case study. J Med Internet Res 2023;25:e43486.
19. Ericson O, Hjelmgren J, Sjövall F, et al. The potential cost and cost-effectiveness impact of using a machine learning algorithm for early detection of sepsis in intensive care units in Sweden. J Health Econ Outcomes Res 2022;9(1):101–110.
20. Saqib M, Iftikhar M, Neha F, et al. Artificial intelligence in critical illness and its impact on patient care: a comprehensive review. Front Med (Lausanne) 2023;10:1176192.
21. Mao Z, Liu C, Li Q. et al. Intelligent intensive care unit: current and future trends. Intensive Care Res 2023;3:182–188.
22. Marafino BJ, Boscardin WJ, Dudley RA. Efficient and sparse feature selection for biomedical text classification via the elastic net: application to ICU risk stratification from nursing notes. J Biomed Inform 2015;54:114–120.
23. Pirracchio R, Petersen ML, Carone M, et al. Mortality prediction in intensive care units with the Super ICU Learner Algorithm (SICULA): a population-based study. Lancet Respir Med 2015;3(1):42–52.
24. Awad A, Bader-El-Den M, McNicholas J, et al. Early hospital mortality prediction of intensive care unit patients using an ensemble learning approach. Int J Med Inform 2017;108:185–195.
25. Rajkomar A, Oren E, Chen K, et al. Scalable and accurate deep learning with electronic health records. NPJ Digit Med 2018;1:18.
26. Celi LA, Galvin S, Davidzon G, et al. A database-driven decision support system: customized mortality prediction. J Pers Med 2012;2(4):138–148.
27. Garcia-Gallo JE, Fonseca-Ruiz NJ, Celi LA, et al. A machine learning-based model for 1-year mortality prediction in patients admitted to an intensive care unit with a diagnosis of sepsis. Med Intensiva 2018.
28. Lynch CM, Abdollahi B, Fuqua JD, et al. Prediction of lung cancer patient survival via supervised machine learning classification techniques. Int J Med Inform 2017;108:1–8.
29. Liu Q, Gao J, Luo B, et al. Prediction model for death in patients with pulmonary tuberculosis accompanied by respiratory failure in ICU: retrospective study. Ann Palliat Med 2020;9:2731–2740.
30. Hou N, Li M, He L, et al. Predicting 30-days mortality for MIMIC-III patients with sepsis-3: a machine learning approach using XGboost. J Transl Med 2020;18:462.
31. Nemati S, Holder A, Razmi F, et al. An interpretable machine learning model for accurate prediction of sepsis in the ICU. Crit Care Med 2018;46:547–553.
32. Li G, Xu F, Yin X, et al. Lactic dehydrogenase-lymphocyte ratio for predicting prognosis of severe COVID-19. Medicine (Baltimore) 2021;100(4):e24441.
33. Woodman RJ, Mangoni AA. A comprehensive review of machine learning algorithms and their application in geriatric medicine: present and future. Aging Clin Exp Res 2023;35(11):2363–2397.
34. Elhaddad M, Hamam S. AI-driven clinical decision support systems: an ongoing pursuit of potential. Cureus 2024;16(4):e57728.
35. Johnson AE, Ghassemi MM, Nemati S, et al. Machine learning and decision support in critical care. Proc IEEE Inst Electr Electron Eng 2016;104(2):444–466.
36. Hao D, Ghassemi MM, Mengling F. The effects of deep network topology on mortality prediction. Conf Proc IEEE Eng Med Biol Soc 2016;2016:2602–2605.
37. Zahid MAH, Lee J (Eds). Mortality prediction with self-normalizing neural networks in intensive care unit patients. In: Proceedings of the 2018 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI); 2018 Mar 4–7; pp. 226–229.
38. Caicedo-Torres W, Gutierrez J. ISeeU: visually interpretable deep learning for mortality prediction inside the ICU. J Biomed Inform 2019;98:103269.
39. Sha Y, Wang MD. Interpretable predictions of clinical outcomes with an attention-based recurrent neural network. ACM BCB 2017;2017:233–240.
40. Cowie MR, Blomster JI, Curtis LH, et al. Electronic health records to facilitate clinical research. Clin Res Cardiol 2017;106(1):1–9.
41. Shickel B, Tighe PJ, Bihorac A, et al. Deep EHR: a survey of recent advances in deep learning techniques for electronic health record (EHR) analysis. IEEE J Biomed Health Inform 2019;22(5):1589–1604.
42. He J, Lin J, Duan M. Application of machine learning to predict acute kidney disease in patients with sepsis associated acute kidney injury. Front Med (Lausanne) 2021;8:792974.
43. Kelly CJ, Karthikesalingam A, Suleyman M, et al. Key challenges for delivering clinical impact with artificial intelligence. BMC Med 2019;17:195.
44. Ahmed MI, Spooner B, Isherwood J, et al. A systematic review of the barriers to the implementation of artificial intelligence in healthcare. Cureus 2023;15(10):e46454.
45. Atallah L, Nabian M, Brochini L, et al. Machine learning for benchmarking critical care outcomes. Healthc Inform Res 2023;29(4):301–314.
46. Saadatmand S, Salimifard K, Mohammadi R, et al. Using machine learning in prediction of ICU admission, mortality, and length of stay in the early stage of admission of COVID-19 patients. Ann Oper Res 2023;328:1043–1071.
47. Syed M, Syed S, Sexton K, et al. Application of machine learning in intensive care unit (ICU) settings using MIMIC dataset: systematic review. Informatics 2021;8(1):16.
48. Kang CY, Yoon JH. Current challenges in adopting machine learning to critical care and emergency medicine. Clin Exp Emerg Med 2023;10(2):132–137.
49. Ayaz M, Pasha MF, Alahmadi TJ, et al. Transforming healthcare analytics with FHIR: a framework for standardizing and analyzing clinical data. Healthcare (Basel) 2023;11(12):1729.
50. Norrie J. The challenge of implementing AI models in the ICU. Lancet Respir Med 2018;6(12):886–888.
51. Che Z, Purushotham S, Khemani R, et al. Interpretable deep models for ICU outcome prediction. AMIA Annu Symp Proc 2017;2016:371–380.
52. Yang J, Soltan AAS, Clifton DA. Machine learning generalizability across healthcare settings: insights from multi-site COVID-19 screening. NPJ Digit Med 2022;5:69.
53. Gerke S, Minssen T, Cohen G. Ethical and legal challenges of artificial intelligence-driven healthcare. Artif Intell Healthc 2020:295–336.
54. Beil M, Proft I, van Heerden D, et al. Ethical considerations about artificial intelligence for prognostication in intensive care. ICMx 2019;7:70.
55. Schneble CO, Elger BS, Shaw DM. Google's Project Nightingale highlights the necessity of data science ethics review. EMBO Mol Med 2020;12(3):e12053.
56. Jawad LA. Security and privacy in digital healthcare systems: challenges and mitigation strategies. Abhigyan 2024;42(1):23–31.
57. YA Amer A, Vranken J, Wouters F, et al. Feature engineering for ICU mortality prediction based on hourly to bi-hourly measurements. Appl Sci 2019;9(17):3525.
58. Massella M, Dri DA, Gramaglia D. Regulatory considerations on the use of machine learning based tools in clinical trials. Health Technol (Berl) 2022;12(6):1085–1096.
59. Gutierrez G. Artificial intelligence in the intensive care unit. Crit Care 2020;24.
60. Habli I, Lawton T, Porter Z. Artificial intelligence in health care: accountability and safety. Bull World Health Organ 2020;98(4):251–256.
61. Maliha G, Gerke S, Cohen IG, et al. Artificial intelligence and liability in medicine: balancing safety and innovation. Milbank Q 2021;99(3):629–647.
62. Ali S, Akhlaq F, Imran AS, et al. The enlightening role of explainable artificial intelligence in medical & healthcare domains: a systematic literature review. Comput Biol Med 2023;166:107555.
63. Lundberg SM, Erion G, Chen H, et al. From local explanations to global understanding with explainable AI for trees. Nat Mach Intell 2020;2(1):56–67.
64. Ho D, Quake SR, McCabe ERB, et al. Enabling technologies for personalized and precision medicine. Trends Biotechnol 2020;38(5):497–518.
65. Habehh H, Gohel S. Machine learning in healthcare. Curr Genomics 2021;22(4):291–300.
66. Roggeveen LF, Hassouni AE, de Grooth HJ, et al. Reinforcement learning for intensive care medicine: actionable clinical insights from novel approaches to reward shaping and off-policy model evaluation. Intensive Care Med Exp 2024;12(1):32.
67. Rogers P, Wang D, Lu Z. Medical information mart for intensive care: a foundation for the fusion of artificial intelligence and real-world data. Front Artif Intell 2021;4:691626.

POINT OF VIEW

Artificial Intelligence Cannot Be Human, Emotional, or Spiritual

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Abstract

Artificial intelligence (AI) is universally adopted in our day-to-day life, including medical science, and transforming healthcare in various ways, like scientific discovery, collecting and interpreting large data, and gaining insights that might not have been possible by traditional scientific tools. AI also helps learning by geometric understanding, leveraging knowledge, enhanced accuracy and efficiency in diagnostics, imaging, clinical decisions, predictive analysis, drug discovery, virtual assistance, administrative automation, telemedicine, and precision medicine. However, AI lacks emotional consciousness, moral understanding, spiritual insight, and human psychology. AI is a tool to help us and not a human being.

Humanity, sociality, spirituality, and emotions are difficult to define. Human emotions are internal, subjective experiences such as happiness, sadness, anger, fear, love, empathy, and sympathy, deeply rooted in our biological systems, memories, and personal experiences, and AI can simulate these emotions but cannot feel or experience them, while spirituality involves meaning, purpose, and belief in something more than oneself (e.g., God or supreme power). AI has no soul or belief and spiritual practices.

However, concerns persist, including biases ingrained in AI algorithms, lack of transparency in decision-making, potential compromises of patient data, privacy, and safety of AI implementation in clinical settings.

Artificial intelligence has enormous potential in choosing complex regimes, faster calculations, streamlining workflows, and expanding access to healthcare. Nevertheless, AI cannot experience emotions, exercise moral reasoning, or offer genuine spiritual companionship, and successful integration requires AI to function strictly as an assistant to healthcare professionals (HCPs).

"AI has vast potential, but it cannot be human, social, emotional, and spiritual."

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Introduction

Artificial intelligence (AI) is universally occupying a place in our day-to-day life, including medical science. AI is transforming healthcare in various ways, like scientific discoveries, collecting and interpreting large datasets, and gaining insights that might not have been possible by traditional scientific tools. AI helps learning by geometric understanding, leveraging knowledge to enhance accuracy and efficiency by analyzing diverse scientific data, images, sequences, diagnostics, and clinical decisions, drug discovery, administrative automation, mental health screening, and choosing the right drug with precision.[1] However, AI lacks emotional consciousness, moral and social understanding, spiritual insight, and human psychology. AI is a tool to help us and not a human being or sole decision-maker.

Humanity, Sociality, Spirituality, and Emotions

Humanity, sociality, spirituality, and emotions are difficult to define. Still, human emotions are internal, subjective experiences such as happiness, sadness, anger, fear, love, empathy, and sympathy, deeply rooted in our biological systems, social memories, and personal experiences.

Artificial intelligence can simulate emotions, for example, express sympathy or excitement in text, but cannot feel because AI responses are data- and pattern-based and not genuine emotional experiences. AI cannot feel but imitates emotions.

While spirituality involves meaning, purpose, connection, and belief in something more than oneself (e.g., soul, God, universe, or supreme power), which includes consciousness, self-awareness, morality, and existence beyond physical presence. AI has no self-awareness, soul, or belief, cannot seek meaning, contemplate existence, or engage in spiritual practices. AI lacks the essence of spirituality as it has no inner life or existential awareness.

Medical Applications of Artificial Intelligence

Artificial intelligence is useful in many areas of internal medicine and has revolutionized the approach to patients. Here we are enumerating a few of them:

- Diagnostics and imaging: AI models powered by deep learning can interpret radiological, pathological, and retinal scans with high accuracy in diabetic retinopathy and oncology imaging.
- Predictive analytics: Machine learning evaluates large patient datasets to forecast risks of complications or disease progression.
- Personalized medicine: AI algorithms tailor treatment plans based on genetic, phenotypic, lifestyle, and biochemical parameters.[2]
- Drug discovery: AI accelerates identification and optimization of drugs and chemicals, and helps in precision medicine.[2]
- Virtual assistants and telemedicine by monitoring mental health through sentiment and tone analysis, offering support between clinical sessions, and helping in telemedicine.[3]

Discussion

Literature review of 44 studies highlights that AI is enhancing healthcare delivery by more accurate diagnoses, personalized treatment, and efficient resource allocation. However, persistent concerns remain, including biases ingrained in AI algorithms, lack of transparency in decision making, potential compromises of patient data privacy, and safety of AI implementation in clinical settings.

Artificial intelligence provides the opportunity for healthcare revolution, it is imperative to address the ethical, regulatory, and safety challenges linked to its integration. Proactive measures are required to ensure that AI technologies are developed and

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deployed responsibly, striking a balance between innovation and safeguarding of patient well-being.[2]

National surveys of healthcare professionals (HCPs) analyzed their concerns and psychology of adopting and integrating AI in medicine, including emotions, worries, attitudes, fears, and difficulties. Addressing comprehensive education and implementation of suitable legislation related to AI may foster AI acceptance.[3]

Digital pathology and computer vision are enabling AI to have positive impact on pathology, including breast pathology. Research using machine learning and the development of algorithms that learn patterns from labeled digital data based on deep learning neural networks and feature-engineered approach to analyze histology have shown promising results.[4]

There is evidence showing the promise and efficiency of AI in clinical medicine both at the research and treatment levels. Many of the obstacles are technical in nature, specifically to develop a better database for optimal parameter adjustments and predictive algorithms. In clinical medicine empathy, sympathy, and emotional touch are important, which cannot be taken care of with any AI, and this justifies the necessity of human monitoring and emotional intervention in clinical medicine. AI cannot replace social, emotional, human, and spiritual behavior of a human being. For example, AI may simulate empathy *via* sentiment analysis or tone adjustment but cannot truly feel or resonate emotionally, and without emotional and motivational empathy, simulated responses seem to be superficial and manipulative.[5]

Clinicians and patient relationship and trust in medicine rely on interpersonal connection, words, gestures, presence, and mutual understanding that AI cannot reproduce. The therapeutic effect of human contact or personal touch contributes significantly, many times tremendously, to healing, which AI cannot. Moral decision-making and responsibility are lacking in AI models. Clinicians must retain control and legal responsibility while using AI. Final clinical judgments or choosing complex regimen options must remain with the clinician.[6]

Artificial intelligence should be rationally guided, transparent, respect the public interest, and impartial. Then and then AI will be fairer, more innovative, and benefit patients and society while preserving human dignity. It can foster accuracy and precision in medicine and reduce the workload by assisting HCPs and will be considered an inspiring innovation.[6]

The potential of AI to streamline clinical work, assist in diagnostics, and enable personalized treatment poses challenges, necessitating exploration of ethical, legal, and regulatory considerations. Approved governance is imperative to accept and successfully implement AI in clinical medicine.

Cultural and contextual understanding is often struggled with by AI in social contexts. It may decontextualize patient stories, missing subtle cues about values, spiritual beliefs, or personal history.[7]

Spiritual Care and Existential Support

- Integration of AI between technology, spirituality, and ethical issues like privacy and empathy calls for a debate on the responsible use of AI. Certain AI tools provide spiritual conversation, but they lack an actual spiritual presence. Digital dialogues about eternity or faith cannot capture authentic spiritual essence.[8]
- Artificial intelligence trained on unrepresentative data can perpetuate inequalities based on race, gender, or socioeconomic status.[3]
- Artificial intelligence has concerns regarding the potential impact on relations of trust in clinical practice. AI cannot be truly reliable and fully trusted as an independent decision-maker. AI lacks accountability for mislabeling or highlighting risks. Clinical systems are more confident even when incorrect, requiring robust oversight.[9]
- Artificial intelligence should assist and never replace clinical judgment. Education, accreditation, legal regulation, and transparent oversight are essential.[6,7]
- Artificial intelligence tools are supposed to free up time and facilitate doctor-patient relations. However, there is little evidence to support this hypothesis. We cannot ignore the importance of empathy and compassion in patient-centered care. Literature review revealed that, besides empathy and compassion, shared decision-making and trust relations are also important. The review also suggested a positive impact on patient-centered doctor relations if AI is used as an assistant and in adapting medical education.[10]

Conclusion

Artificial intelligence has enormous potential to enhance diagnostics, choose complex regimes, address adverse effects, perform faster calculations, streamline workflows, and expand access to healthcare. Nevertheless:

- Artificial intelligence cannot experience emotions, exercise moral reasoning, or offer genuine spiritual companionship.
- The healing dimensions of empathy, trust, cultural understanding, and moral support remain unique to humans only.
- Successful integration of AI requires it to function strictly as an assistant to HCPs, maintaining ultimate responsibility and relationship.
- Finally, "AI has vast potential to assist healthcare, but AI cannot be human, social, emotional, and spiritual," and AI cannot be truly reliable and fully trusted as an independent decision-maker.

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References

1. Wang H, Fu T, Du Y, et al. Scientific discovery in the age of artificial intelligence. Nature 2023;620:47–60.
2. Chustecki M. Benefits and risks of AI in health care: narrative review. Interact J Med Res 2024;13:e53616.
3. Arvai N, Katonai G, Mesko B. Health care professionals' concerns about medical AI and psychological barriers and strategies for successful implementation: scoping review. J Med Internet Res 2025;27:e66986.
4. Yousif M, van Diest PJ, Laurinavicius A, et al. Artificial intelligence applied to breast pathology. Virchows Arch 2022;480(1):191–209.
5. Montemayor C, Halpern J, Fairweather A. In principle obstacles for empathic AI: why we can't replace human empathy in healthcare. AI Soc 2022;37(4):1353–1359.
6. Kahraman F, Aktas A, Bayrakceken S, et al. Physicians' ethical concerns about artificial intelligence in medicine: a qualitative study: "the final decision should rest with a human". Front Public Health 2024;12:1428396.
7. Mennella C, Maniscalco U, De Pietro G, et al. Ethical and regulatory challenges of AI technologies in healthcare: a narrative review. Heliyon 2024;10(4):e26297.
8. Clerici CA, Ferrari A, Proserpio T. Evolving perspectives: exploring the role of artificial intelligence between clinical practice and health pastoral care. Tumori 2025;111(1):6–10.
9. Hatherley JJ. Limits of trust in medical AI. J Med Ethics 2020;46(7):478–481.
10. Sauerbrei A, Kerasidou A, Lucivero F, et al. The impact of artificial intelligence on the person-centered, doctor-patient relationship: some problems and solutions. BMC Med Inform Decis Mak 2023;23(1):73.

Black Hairy Tongue

Vijaya Prakash Madesh*

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A 65-year-old man was admitted with left lower-limb cellulitis and an impending abscess. He was a known case of type 2 diabetes mellitus, with hemoglobin A1c (HbA1c) 7.6%, and was started on intravenous piperacillin–tazobactam. Wound debridement was carried out under local anesthesia. At admission, he had stage 1 acute kidney injury as per Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which improved with supportive measures. On the 6th day of therapy, his relatives noticed a black discoloration over his tongue (Fig. 1). Examination revealed a dark coating confined to the dorsal surface of the tongue, with sparing of the tip and lateral borders. There was no associated pain or burning sensation. A diagnosis of black hairy tongue (BHT) was considered, possibly related to piperacillin–tazobactam. The antibiotic was discontinued, and the patient was advised to maintain good oral hygiene and to brush the tongue gently. The discoloration resolved completely within 1 week of these measures.

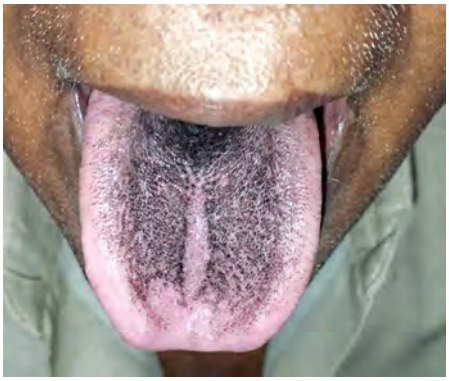

Fig. 1: Black pigmentation and hypertrophy of filiform papillae of tongue

Black hairy tongue is a benign, self-limiting condition characterized by hypertrophy and elongation of the filiform papillae, giving a dark, "hair-like" appearance to the tongue. The pigmentation may vary from brown to black depending on keratin accumulation and microbial colonization. Both external factors (such as smoking, oxidizing mouthwashes, and poor oral hygiene) and systemic factors (including antibiotic exposure, immunosuppression, and diabetes) contribute to its development.[1]

Common antibiotics that are reported to cause BHT are doxycycline, erythromycin, metronidazole, and linezolid. Piperacillin–tazobactam has been reported only rarely as an offending agent. In this patient, the temporal relationship with drug exposure, absence of other predisposing factors, and prompt resolution after drug withdrawal strongly support a causal association. Diagnosis of BHT is clinical and relies on visual recognition of the characteristic tongue changes. Dermoscopy may assist in evaluating papillary morphology, though biopsy is seldom required unless the lesion appears atypical or suspicious for malignancy. Management primarily involves discontinuation of the offending agent, correction of local risk factors, and reinforcement of oral hygiene practices. The overall prognosis is excellent.[2]

Black hairy tongue associated with piperacillin–tazobactam is uncommon. Awareness of this benign and reversible drug reaction helps avoid unnecessary investigations and reassures both patients and clinicians. Regular brushing and withdrawal of the implicated drug usually lead to complete resolution within a few days.

References

1. Ren J, Zheng Y, Du H, et al. Antibiotic-induced black hairy tongue: two case reports and a review of the literature. J Int Med Res 2020;48(10):300060520961279.
2. Schlager E, St. Claire C, Ashack K, et al. Black hairy tongue: predisposing factors, diagnosis, and treatment. Am J Clin Dermatol 2017;18(4):563–569.

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Beyond the White Coat: The Legacy of Dr Bidhan Chandra Roy

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Introduction

Dr Bidhan Chandra Roy, a great physician, statesman and visionary, remains an enduring figure of inspiration for generations of Indians (Fig. 1). As one of the rare personalities to have excelled equally in medicine and politics, his legacy reflects a harmonious confluence of two seemingly disparate worlds.[1] Serving as the second Chief Minister of West Bengal, his contributions to healthcare, education, and infrastructure development left an indelible mark on India's sociopolitical and medical landscape.

Early Life and Medical Prowess

Born on July 1, 1882, in Bankipore, Patna, Dr Roy exhibited academic brilliance from an early age.[2] His journey in medicine began at Calcutta Medical College, where he opted for a career in healing over engineering. A pivotal moment came when his application to study at St Bartholomew's Hospital, London, was initially rejected because he was Indian. Undeterred, he pursued his goal with persistence and eventually gained admission, completing both the Fellowship of the Royal College of Surgeons (FRCS) and the Membership of the Royal College of Physicians (MRCP) within a record 2 years and 3 months.[3] This extraordinary feat not only marked him as a trailblazer but also foreshadowed his future role as a pioneer in India's medical and political arenas.

Returning to India in 1911, Dr Roy's medical career flourished as he established himself as one of the most distinguished physicians and surgeons of his era. He served as a professor at Calcutta Medical College, where his emphasis on medical education laid the groundwork for future generations of doctors. His enduring interest in public welfare later drew him into the realm of politics, where he saw an opportunity to scale his impact from individuals to entire communities. His compassion for patients, combined with his academic rigor, became hallmarks of his approach to medicine and governance alike.

Fig. 1: A commemorative sketch of Dr Bidhan Chandra Roy, portraying his composed demeanor as both a physician and a statesman. Artist: Dr Sugata Dasgupta

The Unlikely Bridge between Medicine and Politics

Dr Roy's foray into politics was driven by his profound belief in the symbiosis of health and national development. He maintained that "Swaraj (self-rule) would remain a mere dream unless the citizens were healthy and strong in mind and body." This conviction motivated him to join the Indian National Congress and contest the 1925 elections. His initial service as an elected member of the Calcutta Corporation saw him rise to the position of mayor in 1933, where he spearheaded reforms in public health, sanitation, and municipal governance.[2]

His tenure as the second Chief Minister of West Bengal (1948–1962) was transformative. Taking office just after India's independence, he was tasked with stabilizing a state struggling with refugee influxes and economic instability. Under his leadership, West Bengal witnessed industrial expansion, including the establishment of the Durgapur Steel Plant and the Kalyani engineering hub, developments that played a pivotal role in the state's postindependence industrialization.[1]

But perhaps his most lasting contribution was his visionary approach to urban planning. The development of Salt Lake City (Bidhannagar), now one of Kolkata's most prominent residential and commercial hubs, exemplifies his foresight. His influence extended to education as well, with the establishment of educational institutions like the Indian Institute of Technology (IIT) Kharagpur, India's first IIT. These initiatives reflected his deep understanding of the role of education and urban development in fostering long-term societal progress.

Healthcare Reformer and Visionary

Dr Roy's role in healthcare reform is unparalleled. As a physician-turned-politician, he placed health at the heart of governance. During his tenure as Chief Minister, the number of health centers in West Bengal grew from 70 to 271. He championed the establishment of 96 maternity centers, 92 leprosy clinics, 16 malaria control units, and one of India's first polio clinics.[3] His deep

concern for women's and children's health led to the creation of institutions like the Chittaranjan Seva Sadan for women and children, as well as the Chittaranjan Cancer Hospital, which became one of the country's leading cancer treatment centers.

Dr Roy's administrative acumen extended to the medical profession itself. He played a seminal role in the establishment of the Medical Council of India (MCI) and the Indian Medical Association (IMA).[1] As the first president of the MCI, he laid the foundation for medical ethics, professional standards and the regulation of medical education in India, a legacy that still endures. His tenure also saw improvements in mental healthcare, with the establishment of dedicated mental health facilities and infectious disease hospitals. Through his vision, healthcare in India was no longer viewed in isolation but as an integrated part of nation-building.

The Ethos of Leadership

What set Dr Roy apart from his contemporaries was his ethos of selfless service. His leadership was not confined to policy or administration but was characterized by a personal commitment to public welfare.[4] Known to attend to patients in the morning before addressing affairs of state, he epitomized the concept of "service before self." His convocation address at Lucknow University in 1956 captures the essence of his philosophy: "My young friends, you are soldiers in the struggle for freedom from want, fear, ignorance, frustration, and helplessness. Through dedicated efforts for the country, carried out in a spirit of selfless service, may you proceed with hope and courage."

His dedication was not only symbolic but also deeply practical. During his tenure as Chief Minister, he displayed political dexterity in managing communal tensions, ensuring the resettlement of refugees after the partition, and promoting policies to improve the lives of marginalized communities. His approach to governance was inclusive, balancing the demands of rapid industrialization with the needs of the underprivileged.[5]

Recognition and Legacy

Dr Roy's contributions to India's medical, educational, and political landscape did not go unrecognized. In 1961, he was awarded the Bharat Ratna, India's highest civilian honor, for his unparalleled service to the nation. In a symbolic gesture, India's National Doctor's Day is celebrated every year on July 1, his birth and death anniversary, to honor his contributions to the medical profession.[6]

The impact of Dr Roy's legacy extends far beyond his lifetime. As a physician, he redefined medical education, emphasizing the role of ethics and empathy. As a political leader, he proved that governance need not be divorced from compassion. Today, Salt Lake City, Chittaranjan Cancer Hospital, IMA, MCI, and IIT Kharagpur stand as living monuments to his vision. His life serves as a blueprint for future generations, demonstrating how dedicated leadership can drive tangible social progress.

Conclusion

Dr Bidhan Chandra Roy's life is a testament to the power of a singular vision that bridges two distinct domains, medicine and politics, for the betterment of society. His work continues to inspire doctors, policymakers, and leaders alike. At a time when the world seeks role models who embody service, resilience, and vision, Dr Roy's story remains profoundly relevant. As India's "doctor-statesman," he exemplified how one person's dedication can shape the destiny of a nation. His life reminds us that the most profound impact lies not in individual success but in collective progress, a lesson that resonates deeply in our world today.

Contributorship Statement

All the authors prepared the manuscript with adequate planning and execution. All the authors contributed to review of literature, critical revision of content, and final approval of manuscript. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Johnson S, Rajan H, Shaikh S, et al. A tribute to the legendary physician and politician: Dr. Bidhan Chandra Roy. Cureus 2024;16(11):e73222.
2. History Today in Medicine—Dr. Bidhan Chandra Roy. Available from: https://cmeindia.in/history-today-in-medicine-dr-bidhan-chandra-roy/. [Accessed on December 18, 2024].
3. Bharadwaj HR, Bone M. Statue of Dr Bidhan Chandra Roy (1882–1962): an epitome of healthcare in politics. J Med Biogr 2023;31(4):280–281.
4. Dr Bidhan Chandra Roy—A Leader Par Excellence. Available from: https://www.expresshealthcare.in/blogs/guest-blogs-healthcare/dr-bidhan-chandra-roy-a-leader-par-excellence/444287/. [Accessed on December 17, 2024].
5. Kumar R. The leadership crisis of medical profession in India: ongoing impact on the health system. J Family Med Prim Care 2015;4(2):159–161.
6. National Doctor's Day Special—Celebrating Dr Bidhan Chandra Roy. Available from: https://medicaldialogues.in/articles/national-doctors-day-special-celebrating-dr-bidhan-chandra-roy-least-explored-journalist-of-india-130956. [Accessed on December 18, 2024].

The Epigenome–Microbiome Axis: Host Regulation of Gut Ecology

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Emerging evidence reveals a dynamic epigenome–microbiome axis, whereby the host's epigenetic machinery shapes gut ecology and reciprocally the microbiota influences host gene regulation. This bidirectional interaction, particularly in the gut, holds profound implications for gastroenterology.

A seminal study demonstrated that microbial colonization alters global histone acetylation and methylation across multiple host tissues, contingent on diet. Short-chain fatty acids (SCFAs) produced through microbial fermentation were sufficient to recreate colonization-like chromatin states in germ-free mice on a polysaccharide-rich diet but not when mice were fed a Western-style diet.[1] SCFAs, especially butyrate, function as histone deacetylase inhibitors (HDACi), inducing histone hyperacetylation and transcriptional activation in intestinal epithelial cells (IECs) and systemic tissues. Aside from SCFAs, diet- and microbiome-derived metabolites—including folate, acetyl-CoA, and one-carbon cycle intermediates—contribute essential methyl and acetyl donors, influencing both deoxyribonucleic acid (DNA) methylation and histone modifications.[2]

Functionally, colonization triggers ten–eleven translocation (TET) 2/3-mediated

Table 1: Key studies that elucidate key host–microbiota epigenetic mechanisms

Study (year)	*Model/tissue*	*Mechanism*	*Key findings*
Krautkramer et al., (2016)[1]	Mice (IECs, liver)	Microbial SCFAs → HDAC inhibition	Butyrate restored histone acetylation and transcription of colonization pathways
Ansari et al., (2020)[5]	Mice colon crypts	Microbiota → TET2/3-mediated DNA demethylation	Colonization induced hypomethylation of inflammation-related loci; dysbiosis worsened colitis
Pan et al., (2018)[6]	Postnatal IECs	Microbiota-dependent methylome establishment	Gut microbes directed methylome and transcriptome maturation during development
Qin et al., (2018)[7]	Human IECs	Obesity-associated dysbiosis → histone changes	Obesity-altered microbiome reshaped epigenetic landscapes in colonic IECs

DNA demethylation in IECs, a process absent in germ-free mice. Antibiotic-induced dysbiosis suppresses TET3 expression, while intestinal insults prompt microbiota-dependent hypomethylation at key regulatory loci (e.g., *cd177*, *Pla2g2a*, *Lpo*) that modulate inflammation and barrier integrity.[3] These epigenetic programs are crucial to maintaining homeostasis and may hinder neoplastic progression. Table 1 summarizes recent studies that elucidate key host–microbiota epigenetic mechanisms.

Collectively, these findings implicate epigenetic–microbiome interplay in inflammatory bowel disease (IBD), obesity, and colorectal cancer (CRC). For example, obesity-associated dysbiosis correlates with altered epigenetic marks in colonic IECs, mediated through histone modifications. In CRC, microbial modulation of TET enzymes and histone writers/readers establishes an environment permissive to malignant transformation.

These mechanisms carry several clinical implications. First, SCFA-enriched diets or targeted probiotics—such as *Faecalibacterium prausnitzii* and *Roseburia* spp.—could beneficially reshape IEC epigenomes, improving barrier function and reducing inflammation.[4] Second, developing stool- or IEC-derived epigenetic biomarkers (e.g., histone marks, DNA methylation patterns) may enhance risk stratification for IBD or CRC. Third, combined therapeutic strategies employing epigenetic drugs (e.g., HDACi), and microbiome-targeting interventions could synergize to restore epithelial homeostasis and modulate host immunity.

Given these observations, future gastroenterology research should prioritize longitudinal, multiomic studies in at-risk or diseased cohorts, aiming to dissect causality and identify therapeutic windows. Interventional trials testing nutrient-based or microbial epigenome modulators, alone or with epigenetic drugs, are the logical next steps. Moreover, the development and validation of minimally invasive epigenetic biosensors are necessary to tailor personalized interventions.

In conclusion, the epigenome–microbiome axis represents a paradigm shift in our understanding of host–microbe crosstalk in gut health. By exploring how host epigenetic states govern microbial ecology and vice versa, we can begin to craft targeted therapies and diagnostics that modulate this relationship for better patient outcomes in a range of gastrointestinal diseases.

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References

1. Krautkramer KA, Kreznar JH, Romano KA, et al. Diet-microbiota interactions mediate global epigenetic programming in multiple host tissues. Mol Cell 2016;64(5):982–992.
2. Miro-Blanch J, Yanes O. Epigenetic regulation at the interplay between gut microbiota and host metabolism. Front Genet 2019;10:638.
3. Zouggar A, Haebe JR, Benoit YD. Intestinal microbiota influences DNA methylome and susceptibility to colorectal cancer. Genes (Basel) 2020;11(7):808.
4. Licciardi PV, Wong SS, Tang ML, et al. Epigenome targeting by probiotic metabolites. Gut Pathog 2010;2(1):24.
5. Ansari I, Raddatz G, Gutekunst J, et al. The microbiota programs DNA methylation to control intestinal homeostasis and inflammation. Nat Microbiol 2020;5(4):610–619.
6. Pan WH, Sommer F, Falk-Paulsen M, et al. Exposure to the gut microbiota drives distinct methylome and transcriptome changes in intestinal epithelial cells during postnatal development. Genome Med 2018;10(1):27.
7. Qin Y, Roberts JD, Grimm SA, et al. An obesity-associated gut microbiome reprograms the intestinal epigenome and leads to altered colonic gene expression. Genome Biol 2018;19(1):7.

Comment on: "Sitosterolemia: Case Series of a Rare Genetic Disorder from India"

Ahmad Alam

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We read with great interest the article by Umapathy and Subbaiah, "Sitosterolemia: Case Series of a Rare Genetic Disorder from India" (JAPI, July 2025;73(7):12–14). The authors deserve appreciation for highlighting this underdiagnosed lipid disorder and for emphasizing the value of peripheral blood smear findings in guiding diagnosis.[1]

We wish to respectfully comment on the next-generation sequencing (NGS) findings, particularly in case 4, where a diagnosis of sitosterolemia was made despite identifying only a heterozygous variant in the *ABCG8* gene. As acknowledged by the authors, sitosterolemia is an autosomal recessive disorder, and clinical disease usually results from biallelic pathogenic variants, either homozygous or compound heterozygous mutations in *ABCG5* or *ABCG8*. A single heterozygous mutation does not typically explain the clinical phenotype and raises important questions:

- Was the variant classified using a recognized variant classification system such as the American College of Medical Genetics and Genomics–Association for Molecular Pathology (ACMG–AMP) guidelines?
- Was it a pathogenic or likely pathogenic variant, or possibly a variant of uncertain significance (VUS)?

Table 1: Typical structured variant report following ACMG-AMP guidelines

Gene (transcript)	*Location*	*Variant*	*Zygosity*	*Classification*
ABCG8 (NM_022437.3)	Exon 5	c.490G>A (p.Arg164His)	Homozygous	Pathogenic

- Was copy number variation (CNV) analysis or deletion/duplication testing performed to identify a second allele that NGS might miss?
- Importantly, plasma plant sterol levels—a biochemical hallmark of sitosterolemia—were not measured. This would have been especially helpful in validating the diagnosis in a borderline genetic case.

For clarity, a typical structured variant report might look like the following (Table 1):

This format illustrates the importance of including transcript IDs, Human Genome Variation Society (HGVS)-compliant variant descriptions, zygosity, and pathogenicity classification using ACMG criteria. Such standardized reporting strengthens diagnostic confidence and clinical utility.[2,3]

We commend the authors for adding to the limited Indian literature on sitosterolemia. However, we suggest that in future publications involving genetic data, key details such as variant classification, evidence of pathogenicity, reporting system used, and whether parental/family segregation or biochemical confirmation was attempted be explicitly mentioned.

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References

1. Umapathy V, Subbaiah RM. Sitosterolemia: case series of a rare genetic disorder from India. J Assoc Physicians India 2025;73(7S):12–14.
2. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS recommendations for the description of sequence variants: 2016 update. Hum Mutat 2016;37(6):564–569.
3. Ramachandran SK, Edavana S, Moolath S, et al. Primary adrenal insufficiency with normal male external genitalia in a boy with CYP11A1 deficiency. BMJ Case Rep 2024;17(9):e261512.

Letter to Editor: A Clinical Study to Evaluate the Anti-inflammatory Effect of Lactoferrin + Disodium Guanosine Monophosphate Therapy in the Patients with Chronic Kidney Disease

Abhijeet V Tilak[1], Bhalchandra Rane[2], Nitin Gawari[3], Aadil S Shah[4]

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Dear Editor,

We read with interest the article titled "A Clinical Study to Evaluate the Anti-inflammatory Effect of Lactoferrin + Disodium Guanosine Monophosphate Therapy in the Patients with Chronic Kidney Disease" published in our esteemed journal.[1]

We would like to congratulate the authors for a well-conducted study. As highlighted by the authors, a very small population and short duration are major limitations of this study. Considering the huge disease burden of chronic kidney disease (CKD) in India, various drugs along with nutritional supplement therapy for improving quality of life in patients with CKD have been studied; however, double-blind, randomized studies with larger populations and longer durations are needed.[2–4]

The authors have reported a significant reduction of tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and IL-10 in the test group compared to baseline. However, baseline values of the control group and between-group comparison at various times are not reported. Improvement in hemoglobin and estimated glomerular filtration rate (eGFR) in the test group, although nonsignificant, is a promising finding compared to their decrease in the control group. Changes in other renal parameters are not mentioned in the study. These details would add to the knowledge and help in further exploration and future study design of this combination.

The authors have used lactoferrin 100 mg and guanosine monophosphate (GMP) 10 mg; however, we could not find the details about the dosage form used, frequency of dose, and source of drug procurement in the article. Patient compliance is significantly important and at times challenging in chronic conditions; assessing compliance and its effect on efficacy also needs to be monitored in future studies.[5,6]

Thanking you.

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References

1. Yadav R, Sangha SS, Yadav S, et al. A clinical study to evaluate the anti-inflammatory effect of lactoferrin + disodium guanosine monophosphate therapy in the patients with chronic kidney disease. J Assoc Physicians India 2025;73(1):18–22.
2. Rajapurkar MM, John GT, Kirpalani AL, et al. What do we know about chronic kidney disease in India: first report of the Indian CKD registry. BMC Nephrol 2012;13:10.
3. Chopra HK, Khullar D, Nair T, et al. Consensus statement from India on the renal benefits of ARNi, SGLT-2i, and bisoprolol in chronic kidney disease. J Assoc Physicians India 2024;72(5):77–88.
4. Shah A, Bhoite R, Immadisetti P, et al. Impact of oral nutritional supplementation in chronic kidney disease patients on maintenance hemodialysis: an open-label, single-arm study among Indian patients. J Assoc Physicians India 2024;72(4):38–43.
5. Sharma D, Goel NK, Cheema YS, et al. Medication adherence and its predictors among type 2 diabetes mellitus patients: a cross-sectional study. Indian J Community Med 2023;48(5):781–785.
6. Shah MH, Honnekeri AS, Samat DA, et al. Digging deep: medication adherence in chronic diseases and its association with patient satisfaction and stress in an Indian metropolis. Cureus 2023;15(10):e46493.

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