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GUEST EDITORIAL

Chronic Kidney Disease with Risk Factor Diabetes: Need for Change in Nomenclature Reflecting Heterogeneity of Kidney Disease in Diabetes

Madhurima Basu[1], Sujoy Ghosh[2*]

The International Diabetes Federation estimates that 537 million individuals around the globe currently have diabetes, and this number is anticipated to rise to approximately 783 million by 2045. About 30% or more of individuals diagnosed with diabetes are more prone to developing chronic kidney disease (CKD), and a considerable portion progresses to renal impairment that requires renal replacement therapy.[1,2]

Type 2 diabetes mellitus (T2DM) is the most prevalent type of diabetes, exceeding 90% of all diagnoses. Even though T2DM is inherently a heterogeneous disease, various clusters have been described with varying risks of developing vascular complications, including nephropathy. In contrast, T1DM is less heterogeneous, with more predictable renal outcomes.[3]

Kidney disease in diabetes was first identified through histological examinations conducted during autopsies of individuals who had diabetes, albuminuria (significant albumin excretion in urine), and renal failure.[4] However, in clinical practice, it is termed diabetic nephropathy and identified as a microvascular complication linked to diabetes.[5]

Classically, diabetic nephropathy is believed to commence with an early rise in glomerular hyperfiltration, which subsequently leads to onset albuminuria. Over time, albuminuria can progress into more severe proteinuria, which may reach the nephrotic range. The estimated glomerular filtration rate (eGFR) typically declines when albuminuria is already present. If no intervention is undertaken, this can lead to advanced stages of CKD. This progression reflects the staging of renal involvement in T1DM as described by Mogensen.[4]

However, recent findings from observational cohort studies, clinical investigations, and mechanistic research examining underlying biological pathways have highlighted the substantial heterogeneity in the presentation and progression of kidney disease in the context of diabetes. These studies reveal distinct patterns in the progression of disease that do not align with the conventional log-linear relationship between urinary albumin excretion, decline in eGFR, and adverse outcomes, particularly in patients with T2DM.[5] Subsequent research has revealed that the classical progression of this pathway in individuals with diabetes and kidney disease is neither linear nor homogeneous and falls short of capturing the full spectrum of biological and clinical heterogeneity.

In the emerging framework, CKD is conceptualized as a complex, multifactorial condition influenced by a wide range of risk factors that extend beyond purely glucocentric considerations. Both modifiable and nonmodifiable factors, such as obesity, hypertension, dyslipidemia, hyperglycemia, smoking, aging, inflammation, low birth weight, low nephron count, oxidative stress, fibrosis, genetic predisposition, previous kidney injury, infectious diseases, environmental exposures, nephrotoxins, and autoimmune conditions, are recognized as contributing risk factors.[4]

Numerous terms, including diabetic nephropathy, diabetic and nondiabetic kidney disease in individuals with diabetes, diabetic and CKD, and nonalbuminuric diabetic kidney disease, are used to describe the complexity and heterogeneity in the diverse manifestations of kidney disease among people with diabetes.[4,5]

For most people with T1DM, diabetes is the main factor leading to kidney disease, and the progression of end-stage kidney disease typically follows a more traditional path after 10–20 years of having diabetes. However, in the case of T2DM, CKD is more multifactorial due to a combination of several CKD risk factors. A retrospective biopsy cohort study found that in 22% of cases, kidney disease was not attributable to diabetes mellitus. Additionally, in 12% of the participants, kidney disease was associated with diabetes and other contributing factors. In this study, 46% of T2DM patients suggested kidney disease was unrelated to diabetes.[6] A systemic review that looked at 40 studies (5,304 data points) of global renal biopsy data between 1977 and 2019 reported that the prevalence of kidney disease due to etiologies unrelated to diabetes, collectively known as nondiabetic kidney disease (NDKD), ranged from 0 to 68.6%, with an average of 40.6%.[7] One of the main criticisms of these retrospective studies is that the observed differences in prevalence may be due to the clinical criteria used by clinicians to perform the renal biopsies. This can introduce a preselection bias, as biopsies are often targeted toward patients with a high clinical suspicion of NDKD.[2]

A prospective cohort study involving untargeted renal biopsies in individuals with T2DM revealed that 35% had a component of NDKD, with NDKD being the sole cause in 18.2% of the cases. This indicates that NDKD is prevalent in T2DM patients with renal involvement. Although multiple studies have indicated that various clinical predictors, such as the duration of diabetes, absence of retinopathy, absence of neuropathy, and presence of hematuria along with RBC casts, can predict NDKD, findings from a prospective study revealed that clinical and laboratory parameters are still inadequate for reliably selecting patients for renal biopsies. Renal biopsy remains the only confirmatory test to distinguish between diabetic kidney disease (DKD) and nondiabetic kidney disease (NDKD) and overlap (both DKD and NDKD).[2] NDKD includes a collection of various kidney disorders that are grouped together under one category, such as IgA nephropathy, membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis (FSGS), and many other causes of kidney disease. NDKD typically leads to a far better prognosis in terms of composite renal outcomes compared to DKD when identified and treated appropriately.[8]

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The Renal Pathology Society's Research Committee has developed a histopathological classification for diabetic kidney disease, creating a consensus system that integrates both type 1 and type 2 diabetic nephropathies (DN). Histopathological classification is based on glomerular, tubular, interstitial inflammation, and vascular involvement, with each parameter having a different grade of involvement. This classification suggests that kidney disease in diabetes is heterogeneous (DKD and NDKD), and even those with DKD are highly heterogeneous, with variable degrees of glomerular, tubular, interstitial, or vascular involvement and different clinical progressions.[9] The follow-up of the prospective biopsy study cohort indicated that combining histopathological features (RPS classes III and IV) with clinical parameters such as proteinuria can help predict worse outcomes in subjects with DKD.[8]

The traditional belief that albuminuria precedes the deterioration of renal function in diabetes has been challenged by the observation of worsening kidney function despite the absence of albuminuria. This condition is referred to as nonalbuminuric kidney disease. Tubulointerstitial pathologies in the kidney have been shown to be associated with renal damage without albuminuria. The prevalence of nonalbuminuric kidney disease is thought to be higher in patients with T2DM than in those with T1DM. Albuminuric DKD is commonly associated with glomerular changes, arteriolar hyalinosis, and interstitial fibrosis, whereas nonalbuminuric DKD more often shows tubular changes and vascular injury. These findings underscore the need for expanding the pathology-based diagnostic framework, which includes alternative mechanisms or pathways of kidney damage and progression in nonalbuminuric types of DKD.[4,5]

Mechanistic studies related to kidney disease in diabetes have revealed that, in addition to hyperglycemia, various other pathological pathways, including epithelial-mesenchymal transition (EMT), fibrosis, which includes transforming growth factor-β–mediated glomerulosclerosis and interstitial fibrosis, chronic inflammation (interleukins and tumor necrosis factor-α), oxidative stress, and tubular injury, are involved, which highlights the heterogeneity in the underlying pathogenesis of the development of the disease.[4,5] More than 80 genetic loci involving both coding and noncoding genes have been identified as contributors to disease onset and progression, resulting in diverse risk profiles.[5]

In 2022, the guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) and the American Diabetes Association–Kidney Disease: Improving Global Outcomes (ADA-KDIGO) introduced the new terminology "diabetes and kidney disease" to describe all kidney-related conditions associated with diabetes, addressing the heterogeneity regarding renal complications in patients living with diabetes.[4] However, nowadays, kidney disease in individuals with diabetes has been reconceptualized as a complex, multifactorial disease, where diabetes is considered a contributing risk factor rather than the sole cause. Reflecting this shift, the KDIGO guidelines have moved away from DKD and coined a new broader term, CKD with risk factor diabetes.[5]

The revised concept of heterogeneity and adoption of the term "CKD with risk factor diabetes" represents not merely a matter of terminology but a pivotal shift toward a better understanding of pathogenesis and management.[5] The primary rationale for addressing disease heterogeneity is to enable disease-specific interventions, including controlling modifiable risk factors through lifestyle modifications. From an intervention perspective, SGLT2 inhibitors (SGLT2i) have been proven to offer renal protection across a range of phenotypes. GLP-1 receptor agonists (GLP-1 RAs) aim to reduce metabolic risk factors and are associated with improved kidney outcomes. In contrast, nonsteroidal mineralocorticoid receptor antagonists (nsMRAs), such as finerenone, provide additional antifibrotic effects and offer potential for precision medicine in patients with diabetes. These medications operate through complementary mechanisms, including regulation of tubuloglomerular feedback, enhancement of natriuresis, and activation of pathways that are anti-inflammatory and antifibrotic, which may result in synergistic benefits when used in combination. Meta-analyses have indicated that the combined use of SGLT2i, GLP-1 RAs, and nsMRAs results in additive renal benefits, underscoring the growing importance of a multimodal therapeutic approach in the management of kidney disease.

To conclude, disease heterogeneity provides deeper insight into the inherent complexity of different subtypes and highlights the need for multi-omics approaches and machine learning algorithms to delineate distinct subtypes to help in diagnosis, prognosis, and determination of specific treatment options.[10]

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ORIGINAL ARTICLE

Atherogenic Indices in Newly Diagnosed Obese and Lean Patients of Type 2 Diabetes Mellitus: A Comparative Study

Edelbert Anthonio Almeida[1], Mohit Mehndiratta[2*], Shanmuga Priya Kirubalenin[3], SV Madhu[4], Rajarshi Kar[5]

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Abstract

Background: Dyslipidemia is one of the driving forces in the pathogenesis of atherosclerosis and its resultant cardiovascular disease. Both these conditions are characterized by an increase in proatherogenic lipids compared to anti-atherogenic lipids. Atherogenic Indices have been developed to predict CVD risk without increasing the cost of testing; however, most of the studies done to date have used these indices in patients who have already suffered a coronary event. Dyslipidemia is most prevalent in cases of type 2 diabetes mellitus (T2DM). Therefore, this study was designed to assess atherogenic risk (via atherogenic indices) in newly diagnosed treatment-naïve obese and lean patients of T2DM.

Materials and methods: Treatment-naïve, newly diagnosed patients of T2DM were recruited and grouped into obese (BMI ≥ 25 kg/m^2) and lean (BMI <18.5 kg/m^2) groups. Blood was collected in a fasting state for the estimation of glycemic parameters and fasting lipid profile. Atherogenic indices (LDL-C/HDL-C, non-HDL-C, TC/HDL-C, atherogenic coefficient, lipoprotein combined index, and atherogenic index of plasma (AIP)) were calculated using predefined formulas.

Results: LDL-C/HDL-C, non-HDL-C, TC/HDL-C, atherogenic coefficient, lipoprotein combined index, and AIP were higher in the obese group compared to the lean group. However, these calculated indices were above the recommended cutoffs in both obese and lean patients with T2DM.

Conclusion: This study is the first to document increased atherogenic risk in both obese and lean patients (newly diagnosed) with T2DM. Although CVD risk is higher among the obese patients, aggressive control of plasma lipids is required in all patients with T2DM, irrespective of BMI.

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Introduction

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion and/or insulin action.[1] The incidence of type 2 diabetes mellitus (T2DM), a subtype of the disease, continues to rise exponentially throughout the globe, riding on the obesity wave.[2] An increase in adiposity can itself lead to derangement of fat metabolism and result in dyslipidemia. Dyslipidemia is also seen in patients with T2DM as a result of disturbance of glucose–insulin homeostasis. Atherosclerosis/cardiovascular disease (CVD), a sequela of dyslipidemia, contributes immensely to the disease morbidity and mortality. Dyslipidemia refers to an imbalance in a patient's fasting lipid profile, marked by low levels of high-density lipoprotein cholesterol (HDL-C) and elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG).[3] Among these, LDL-C has been considered the primary factor in the development of atherosclerosis, often labeled as "bad cholesterol." However, it was noted that even after lowering LDL-C to the suggested levels, 50% remnant CVD risk remained. This forced scientists to rethink their approach and led to the development of numerous lipid ratios/atherogenic indices [LDL-C/HDL-C, non-HDL-C, TC/HDL-C, atherogenic coefficient (AC), lipoprotein combined index, and atherogenic index of plasma (AIP)] for the enhancement of the predictive power of the lipid profile without increasing the cost of testing.[4]

The LDL-C to HDL-C ratio representing the proatherogenic to antiatherogenic potential is a proven CVD risk marker with studies[5,6] documenting a higher level in patients with CVD compared to non-CVD patients. The ratio has also been shown to increase progressively with a decrease in the caliber of coronary vessels.[7] A ratio value greater than 2.517 is considered a sensitive predictor of CVD.

The TC-to-HDL-C ratio represents the ratio of total cholesterol to antiatherogenic cholesterol. It has been shown to correlate strongly with LDL particle number[8] and is documented to be a strong cardiovascular risk marker.[9–11] Non-HDL-C denotes the serum cholesterol of all the apoB-containing lipoproteins. High non-HDL-C may be responsible for the remnant CVD risk seen in individuals despite lowering LDL-C to the recommended ranges. It is calculated by deducting the HDL-C values from TC. Studies[12,13] have reported it to be a better CVD risk predictor in patients with obesity, T2DM, and metabolic disorders displaying atherogenic dyslipidemia.

Atherogenic coefficient or the non-HDL-C/HDL-C ratio denotes the balance between pro-atherogenic and anti-atherogenic lipoproteins and serves as an indicator of lipid dysregulation. It is said to be a better risk predictor for CVD compared to AC.[14] Lipoprotein combined index (LCI) is defined as the ratio of the product of total cholesterol, triglycerides, and LDL-C to HDL-C.[5] It, alongside AIP, i.e., log-transformed TG by HDL-C ratio, is considered to be an accurate marker for CVD risk prediction.[15,16]

Therefore, having compared the metabolic profile in newly diagnosed obese and lean patients of T2DM previously,[17] this study was done to further analyze the levels of nontraditional lipid ratios in newly diagnosed obese (BMI ≥25 kg/m^2) and lean (BMI <18.5 kg/m^2) patients of T2DM before starting antihyperglycemic agents. This is the first study to compare atherogenicity (as measured by atherogenic indexes) across these groups using the Asia-Pacific guidelines for BMI stratification.

Materials and Methods

The study was done in the department of Biochemistry, and patients were recruited from the outpatient department of the Department of Endocrinology of a tertiary care hospital in Delhi, India.

Ethical Aspects

Ethical clearance from the Institutional Ethics Committee-Human Research via diary

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number IEC-HR/2019/41/25. Written informed consent was obtained for all participants, and the study was conducted in lines of the Declaration of Helsinki.

Participant Selection

Newly diagnosed patients of T2DM (age group 20–65 years) were recruited. They were divided based on BMI (WHO Asia-Pacific Guidelines)[18] into obese (BMI ≥25 kg/m^2) and lean (BMI <18.5 kg/m^2). WHO criteria were used for the diagnosis of T2DM.[19] The following patients were excluded: Patients with renal, hepatic, or thyroid disorders, pregnant and lactating women, chronic alcoholics, and those suffering from severe comorbid illnesses. Patients on antihyperglycemic agents were also excluded from the study.

Participant Sampling and Routine Biochemical Testing

Peripheral blood was collected from all participants after an overnight fast of 12 hours. Blood collected in the plain vial was allowed to clot, following which it was centrifuged for 10 minutes at 4000 rpm. The serum thus obtained was used for the estimation of serum analytes (lipid profile and routine biochemical investigations). Blood collected in a fluoride vial was used for the estimation of glucose levels. HbA1c was estimated from blood collected in EDTA tubes on a BIORAD D-10 analyzer. Fasting lipid profile and blood sugar levels were measured by the enzymatic method on the RANDOX RX Imola AutoAnalyzer (RANDOX, UK).

Calculation of Lipid Indices

The following formulas were used for the calculation of lipid Indices:

- LDL-C/HDL-C = LDL-C (mg/dL)/HDL-C (mg/dL).
- TC/HDL-C = TC (mg/dL)/HDL-C (mg/dL).
- Non-HDL-C = TC (mg/dL) –HDL-C (mg/dL).
- Atherogenic Coefficient = Non-HDL-C (mg/dL)/HDL-C (mg/dL).
- Lipoprotein combined index = [TC (mg/dL) × TG (mg/dL) × LDL-C (mg/dL)]/HDL-C (mg/dL).
- AIP = log [TG (mg/dL)/HDL-C (mg/dL)].[20]

Statistical Analysis

SPSS v26.0 (IBM Corporation, USA) software was used to analyze the data. Following testing for normality, unpaired Student's t-test was used to compare parameters between the two groups. A *p*-value of less than 0.05 was considered to be statistically significant.

Results

Each group consisted of 22 male subjects and 8 female subjects. The mean age (years) was 52.1 ± 10.6 in the lean group and 51.5 ± 10.4 in the obese group. The mean BMI (kg/m^2) was 17.9 ± 0.8 in the lean group and 27.2 ± 2.7 in the obese group. Physical and biochemical characteristics of the groups are depicted in Table 1. LDL-C/HDL-C, non-HDL-C, TC/HDL-C, AC, LCI, and AIP ($p = 0.006$) were higher in the obese group compared to the lean group, as depicted in Table 2.

Discussion

Type 2 diabetes mellitus is characterized by hyperglycemia and tends to be associated with dyslipidemia. These metabolic alterations in the plasma serve as a primer for the formation of an atheroma and its sequelae. While the majority of the patients suffering from T2DM tend to be obese, lean patients can also develop the disease. This study was designed to compare the levels of atherogenicity (via atherogenic indexes) in newly diagnosed obese patients (BMI ≥25 kg/m^2) and lean (BMI <18.5 kg/m^2) and of T2DM.

Lipid transport in the body is mainly carried out by lipoproteins. The various types of lipoproteins are differentiated based on their cholesterol-to-triglyceride ratio and apolipoprotein present. A recent review article by Singh and Prabhakaran[21] has highlighted the atherogenic potential of apoB-containing lipoproteins compared to non-apoB-containing molecules. The various atherogenic indices used in this study are also designed to compare the proatherogenic and antiatherogenic potential of lipid molecules. Various atherogenic indices studied showed a similar trend when compared between the two study groups. LDL-C/HDL-C, non-HDL-C, TC/HDL-C, AC, LCI, and AIP were higher in the obese group compared to the lean group. However, only AIP was found to be statistically significant. AIP is the logarithmic transformation of the triglyceride-to-HDL-C ratio and is said to be

Table 1: Comparison of physical and biochemical parameters in obese and lean patients with T2DM

*Variables**	*Obese (n = 30)*	*Lean (n = 30)*	*p-value*
Waist circumference (cm)	100.1 (13.7)	76.7 (6.3)	–
Percentage body fat (%)	35.9 (5.7)	22.1 (5.9)	0.001***
Fasting plasma glucose (mg/dL)	207.28 (73.8)	254.3 (63.1)	0.01**
2-hour postprandial plasma glucose (mg/dL)	329.16 (88.1)	361.2 (76.6)	0.131
HbA1C (%)	9.42 (2.1)	11.5 (2.6)	0.001***
TC (mg/dL)	194.1 (35.4)	187.1 (35.2)	0.43
TG (mg/dL)	146.2 (53.7)	142.6 (66.4)	0.81
LDL-C (mg/dL)	137.5 (36.9)	124.3 (31.1)	0.13
HDL-C (mg/dL)	30.8 (7.5)	34.2 (11.1)	0.16

*values are expressed as mean (SD); **Significant; ***highly significant

Table 2: Comparison of atherogenic indices in obese and lean patients with T2DM

*Variables**	*Obese (n = 30)*	*Lean (n = 30)*	*p-value*	*Recommended cutoffs*
LDL-C/HDL-C	4.8 (2.1)	4.0 (1.6)	0.09	2.517
TC/HDL-C	6.7 (2.4)	5.9 (1.8)	0.14	3.5
Non-HDL-C	163.3 (37.5)	152.8 (34.8)	0.25	<130 mg/dL
Atherogenic coefficient (AC)	5.7 (2.4)	4.9 (1.8)	0.14	3.04
Lipoprotein combined index (LCI)	156253.4 (106258.8)	115817.9 (96340.8)	0.08	78830.7
AIP	0.7 (0.2)	0.6 (0.2)	0.006**	0.2

*values are expressed as mean (SD); **Significant; ***highly significant; values were above recommended levels in both groups

a very sensitive marker of atherogenicity. In addition, it has the following additional benefits compared to traditional indexes. Logarithmic transformation of AIP corrects for the lack of a normal Gaussian distribution and can also serve as an indirect surrogate marker of LDL-C particle size. An interesting finding was that the calculated indices were above the recommended cutoffs in both groups.

This is the first study to demonstrate an increased risk of CVD in both newly diagnosed lean and obese individuals with T2DM. The majority of studies (8–16) to date have utilized these indices to compare CVD risk between patients with established coronary events and control populations, consistently reporting higher levels in those with CVD. However, no previous studies have evaluated these indices specifically in newly diagnosed, treatment-naïve individuals with T2DM.

As previously reported (17), lean individuals with T2DM exhibited poorer glycemic control compared with age-matched obese counterparts, whereas dyslipidemia is more pronounced in the obese group than in lean individuals. This pattern suggests that excess adiposity in obese individuals may confer a greater CVD risk through adverse lipid profiles, potentially exerting a stronger influence than dysglycemia and its sequelae alone.

Nevertheless, as demonstrated in the present study, lean individuals with T2DM also carry a significant risk for CVD and therefore require equally vigilant, structured, and systematic follow-up.

Implications and Future Prospects

Our study demonstrates that obese patients with T2DM are at a higher cardiovascular risk compared to lean patients with T2DM. In addition, both groups were above the recommended threshold of certain lipid ratios, indicating that cardiovascular risk assessment is necessary for all patients with T2DM, irrespective of BMI. Therefore, there is a need to control blood lipid levels aggressively in patients with both lean and obese T2DM to decrease the cardiovascular risk associated with the disease. Future studies are needed to elucidate.

Limitations

A small sample size is a limitation of this study. In addition, matched healthy controls were not recruited.

Statement and Declarations

Source of Funding

None.

Conflict of Interest

None.

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ORIGINAL ARTICLE

Distinct Risk Profiles in Posterior vs Anterior Circulation Strokes: A Prospective Study from Western India

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Abstract

Background: Anterior (ACS) and posterior circulation strokes (PCS) differ in clinical presentation, vascular pathology, and associated risk factors.

Objectives: The aim of the study was to compare vascular risk profiles, clinical characteristics, neuroimaging findings, and outcomes between ACS and PCS patients in a hospital-based cohort.

Methods: A prospective observational study was conducted at a tertiary care hospital, from January to December 2021. Consecutive patients with confirmed anterior or posterior circulation stroke were included. Demographics, National Institutes of Health Stroke Scale (NIHSS) scores, vascular risk factors (hypertension, diabetes, dyslipidemia, smoking, metabolic syndrome), presenting symptoms, computed tomography (CT) imaging findings, and outcomes [modified Rankin Scale (mRS) at discharge, mortality] were recorded. Univariate and multivariate logistic regression analyses were performed.

Results: Among 376 stroke patients analyzed, 274 (72.9%) had ACS and 102 (27.1%) had PCS. PCS patients were significantly younger (54.6 vs 61.2 years; $p = 0.003$), with a higher prevalence of hypertension (78.4 vs 62.8%; $p = 0.008$), current smoking (45.1 vs 28.8%; $p = 0.002$), metabolic syndrome (41.2 vs 28.5%; $p = 0.02$), and poor glycemic control (HbA1c >8% in 51.2 vs 38.6%; $p = 0.04$). PCS presented more often with vertigo (78.4%), ataxia (62.7%), and visual symptoms (54.9%), while ACS typically presented with hemiparesis and aphasia. Despite lower NIHSS scores, brainstem infarcts in PCS accounted for most in-hospital deaths. Multivariate analysis identified hypertension, smoking, age <55, and metabolic syndrome as independent predictors of PCS.

Conclusion: PCS affect a younger demographic and are independently associated with modifiable metabolic and vascular risk factors. Their atypical presentation and distinct risk profile call for targeted screening and prevention strategies, particularly in younger Indian adults.

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Introduction

Stroke remains one of the leading causes of mortality and long-term disability in India, with ischemic strokes accounting for nearly 65.3% of all cases.[1] Among these, anterior circulation strokes (ACS) are more commonly encountered in clinical practice, while posterior circulation strokes (PCS) comprise approximately 17–25% of ischemic strokes.[2] Despite their relatively lower prevalence, PCS are frequently associated with severe outcomes, particularly due to brainstem involvement, and often present with subtle or atypical symptoms, making early diagnosis and timely intervention a clinical challenge.

There is growing recognition that anterior and PCS differ not only in terms of anatomical involvement but also in their underlying pathophysiology and associated risk factors. Studies from East Asian countries such as China and South Korea have highlighted important distinctions. PCS tends to be more frequently associated with metabolic disorders, including hypertension and diabetes mellitus, and often involves intracranial atherosclerosis (ICAS).[3,4] In contrast, ACS has been more strongly linked to traditional atherosclerotic risk factors such as smoking, dyslipidemia, and extracranial carotid artery disease.[5] These differences have implications for both diagnostic approaches and secondary prevention strategies.

However, data from the Indian subcontinent—particularly from hospital-based settings—remain limited. Given India's dual burden of communicable and noncommunicable diseases and a high prevalence of metabolic syndrome, understanding stroke subtype-specific risk factor patterns is of critical importance. Prior studies have largely focused on stroke as a homogeneous entity, often overlooking the nuances that differentiate ACS and PCS in terms of etiology, clinical profile, and vascular pathology.

The present study was conducted to address this knowledge gap by systematically comparing modifiable vascular risk factors, specifically hypertension, diabetes, dyslipidemia, smoking, and metabolic syndrome, between anterior and posterior circulation stroke patients in a tertiary care center in Western India (Fig. 1). We also sought to assess the distribution of intracranial vs extracranial atherosclerotic disease in these two subtypes, given the potential impact of vascular territory on stroke mechanisms and outcomes.

By delineating these patterns in our patient population, we aim to contribute toward a more refined understanding of stroke subtypes in the Indian context. Such insights could facilitate more targeted prevention strategies and individualized risk factor modification, ultimately improving stroke-related outcomes in this high-risk population.

Methods

This hospital-based observational study was conducted in the Department of Internal Medicine at a tertiary care hospital over a 1-year period from January to December 2021. The study was approved by the Institutional Ethics Committee (IEC) (Approval No. IEC/MPGMCJ/2020/179, dated December 15, 2020). Written informed consent was obtained from all participants or their legally authorized representatives prior to inclusion in the study. All procedures were conducted in accordance with the ethical standards of the institutional review board and the Declaration of Helsinki.

We prospectively included consecutive adult patients (aged ≥18 years) who presented with acute stroke, either ischemic or hemorrhagic, confirmed by contrast-enhanced computed tomography (CECT) of the brain with CT angiography. Patients were included if their clinical presentation was consistent with either anterior or posterior circulation involvement and if basic vascular risk factor data were available.

Patients were excluded if they had traumatic intracranial hemorrhage, known

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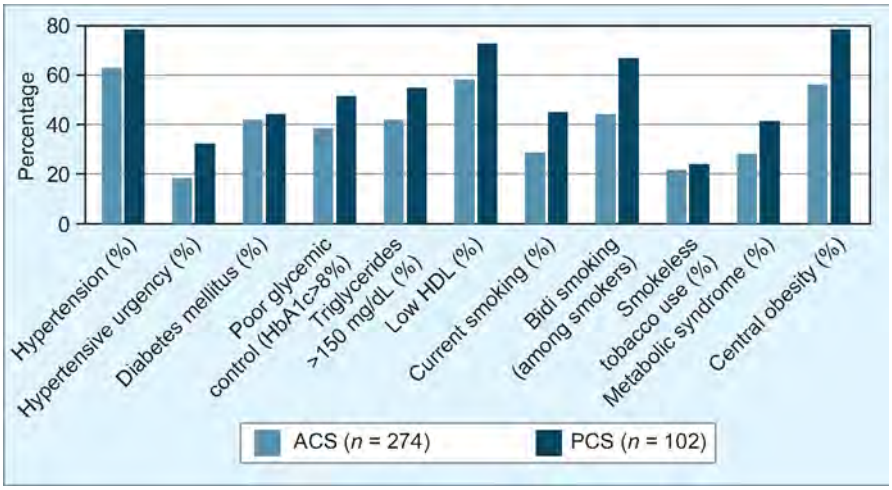

Fig. 1: Comparative prevalence of vascular risk factors in anterior vs posterior circulation stroke

Table 1: Baseline demographic and clinical characteristics of patients with ACS and PCS

Variable	*ACS (n = 274)*	*PCS (n = 102)*	*p-value*
Mean age (years)	61.2 ± 11.8	54.6 ± 10.3	0.003
Age <55 years (%)	25.10	34.60	0.04
Male sex (%)	64.20	58.80	0.34
NIHSS score, median (IQR)	8 (4–14)	5 (2–9)	0.01

cardioembolic stroke sources, such as atrial fibrillation or significant valvular heart disease, terminal illness with poor survival prognosis, or incomplete clinical documentation.

All enrolled patients underwent a structured clinical evaluation, including assessment using the National Institutes of Health Stroke Scale (NIHSS) on admission.[6] Stroke diagnosis and classification were based on CECT of the brain, supplemented by CT angiography of the intracranial and neck vessels to assess vascular territory involvement and underlying arterial pathology. This was performed using a Siemens 16-slice scanner, with findings reviewed by both a radiologist and the treating physician. Standard laboratory investigations were obtained for all patients, including complete blood count, kidney function tests, coagulation profile, fasting blood glucose, HbA1c, lipid profile, renal function tests, and serial blood pressure measurements during hospital stay.

Strokes were classified as ACS if the infarct or hemorrhage involved the territory of the middle cerebral artery (MCA) or anterior cerebral artery. PCS were defined as those affecting the vertebrobasilar system, including the brainstem, cerebellum, or posterior cerebral artery territory.[7]

Risk factors were defined in accordance with established international guidelines. Hypertension was defined as a previously known diagnosis or a systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥80 mm Hg, measured on at least two separate occasions during hospitalization.[8] Diabetes mellitus was defined by a documented prior diagnosis, use of antidiabetic medications, or a fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL, A1C ≥6.5%, or random plasma glucose ≥200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.[9] Dyslipidemia was defined as total cholesterol level >200 mg/dL and/or low-density lipoprotein (LDL) cholesterol >130 mg/dL.[10] Current smoking was defined as the use of any tobacco products (smoked or smokeless) within the preceding 6 months.

Statistical analysis was carried out using IBM SPSS Statistics version 23. Continuous variables were expressed as mean ± standard deviation and compared between groups using the independent-samples *t*-test. Categorical variables were compared using the Chi-squared test. A two-tailed *p*-value of <0.05 was considered statistically significant.

Results

A total of 487 consecutive patients with acute stroke were screened during the study period from January 2021 to December 2022 at Guru Gobind Singh Government Hospital, Jamnagar. After applying the study's inclusion and exclusion criteria, 376 patients were included in the final analysis. The mean age of the cohort was 58.4 ± 12.7 years, with a male predominance (62.5%). Of these, 274 patients (72.9%) had ACS, while 102 (27.1%) were diagnosed with PCS. Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

Patients with ACS were significantly older than those with PCS (61.2 ± 11.8 vs 54.6 ± 10.3 years; $p = 0.003$). Age distribution in ACS showed a unimodal peak between 55 and 70 years (58.4%), whereas PCS demonstrated a bimodal pattern, with peaks in the 45–55-year group (38.2%) and in those aged over 65 years (31.4%). Both subtypes showed male predominance (ACS: 64.2%, PCS: 58.8%; $p = 0.34$), though not statistically significant. Among PCS patients, women presented at a younger age (mean 52.4 years) than men (mean 56.1 years), suggesting possible gender-related differences in risk exposure or pathogenesis.

Hypertension was the most common vascular risk factor and was significantly more prevalent among PCS patients (78.4%) compared to ACS (62.8%; $p = 0.008$). Mean systolic blood pressure at admission was higher in PCS (158.6 ± 24.3 mm Hg) than in ACS (146.2 ± 22.1 mm Hg; $p < 0.001$). Hypertensive urgency (SBP >180 mm Hg or DBP >110 mm Hg) was observed more frequently in PCS (32.4 vs 18.2%; $p = 0.007$), indicating a more labile blood pressure profile among posterior circulation stroke patients. A detailed comparison of vascular risk factors between ACS and PCS is presented in Table 2.

Diabetes mellitus was seen in 42.3% of the total cohort, with no significant difference in prevalence between ACS and PCS groups ($p = 0.68$). However, poor glycemic control (HbA1c > 8%) was significantly more frequent in PCS (51.2 vs 38.6%; $p = 0.04$), suggesting a stronger link between uncontrolled diabetes and posterior circulation pathology.

Dyslipidemia was highly prevalent overall (68.6%), but certain lipid abnormalities were more common in PCS. Triglycerides >150 mg/dL were noted in 54.9% of PCS vs 42.3% of ACS patients ($p = 0.03$), while low high-density lipoprotein (HDL) levels were also more frequent in PCS (72.5 vs 58.4%; $p = 0.01$). These findings support a more pronounced metabolic dysregulation in patients with PCS.

Tobacco use, particularly current smoking, was significantly higher among PCS patients (45.1%) compared to ACS (28.8%; $p = 0.002$). Bidi smoking specifically showed a strong association with PCS [66.7% among PCS smokers vs 44.1% in ACS; odds ratio (OR) 2.34, 95% CI: 1.42–3.86]. The prevalence of smokeless tobacco use was similar between groups (PCS: 23.5%, ACS: 21.5%; $p = 0.68$).

Metabolic syndrome, defined by International Diabetes Federation (IDF) criteria, was present in 41.2% of PCS and 28.5% of ACS patients ($p = 0.02$). Central (abdominal)

Table 2: Comparison of vascular risk factors between with ACS and PCS patients

Risk factor	*ACS (n = 274)*	*PCS (n = 102)*	*p-value*
Hypertension (%)	62.80	78.40	0.008
Systolic BP (mm Hg, mean ± SD)	146.2 ± 22.1	158.6 ± 24.3	<0.001
Hypertensive urgency (%)	18.20	32.40	0.007
Diabetes mellitus (%)	42.30	44.10	0.68
Poor glycemic control (HbA1c >8%)	38.60	51.20	0.04
Triglycerides >150 mg/dL (%)	42.30	54.90	0.03
Low HDL (%)	58.40	72.50	0.01
Current smoking (%)	28.80	45.10	0.002
Bidi smoking (among smokers) (%)	44.10	66.70	0.001
Smokeless tobacco use (%)	21.50	23.50	0.68
Metabolic syndrome (%)	28.50	41.20	0.02
Central obesity (%)	56.30	78.40	0.001

Table 3: Presenting neurological symptoms and signs in ACS and PCS

Clinical feature	*ACS (n = 274)*	*PCS (n = 102)*	*p-value*
Hemiparesis (%)	92.70	37.30	<0.001
Aphasia (%)	48.20	12.70	<0.001
Facial palsy (%)	64.20	29.40	<0.001
Vertigo/dizziness (%)	22.60	78.40	<0.001
Ataxia (%)	18.60	62.70	<0.001
Visual disturbances (%)	9.50	54.90	<0.001
Isolated headache (%)	3.30	18.60	<0.001

Table 4: In-hospital outcomes and prognosis in ACS vs PCS patients

Outcome	*ACS (n = 274)*	*PCS (n = 102)*	*p-value*
Length of stay (days, mean ± SD)	7.2 ± 3.1	5.8 ± 2.7	0.04
mRS 0–2 at discharge (%)	42.30	58.80	0.008
In-hospital mortality (%)	8.40	6.90	0.62
Brainstem death (among PCS) (%)	–	83.3 of PCS deaths	–

Table 5: Multivariate logistic regression analysis for predictors of PCS

Predictor variable	*Adjusted OR (95% CI)*	*p-value*
Hypertension	2.34 (1.42–3.85)	<0.01
Current smoking	1.98 (1.22–3.21)	<0.01
Bidi smoking (among smokers)	2.34 (1.42–3.86)	<0.01
Age <55 years	1.76 (1.12–2.78)	0.02
Metabolic syndrome	1.65 (1.08–2.52)	0.03

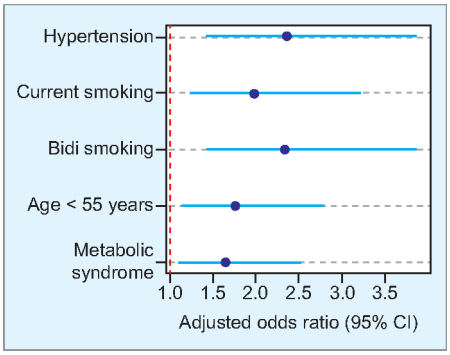

Fig. 2: Forest plot showing adjusted OR with 95% confidence intervals for independent predictors of posterior circulation stroke: hypertension, smoking, bidi smoking, age <55 years, and metabolic syndrome. OR >1 indicates higher likelihood of PCS

obesity was the most common metabolic component in PCS (78.4%), while hypertension was the most frequent component in ACS (92.6% of those with metabolic syndrome), indicating distinct cardiometabolic clustering based on stroke subtype.

Figure 1 illustrates the comparative prevalence of major vascular risk factors between anterior and posterior circulation stroke patients.

Neurological presentation differed significantly. ACS patients most frequently presented with hemiparesis (92.7%), facial palsy (64.2%), and aphasia (48.2%). PCS patients commonly presented with vertigo or dizziness (78.4%), ataxia (62.7%), and visual field disturbances (54.9%). Isolated headache was more common in PCS (18.6%) compared to ACS (3.3%; $p < 0.001$). Stroke severity at presentation was lower in PCS, as reflected by median NIHSS scores [PCS: 5 (IQR 2–9), ACS: 8 (IQR 4–14); $p = 0.01$]. The distribution of presenting neurological symptoms and signs in ACS and PCS is detailed in Table 3.

Neuroimaging findings showed that MCA territory infarcts predominated in ACS (86.5%). Hemorrhagic transformation was noted in 12.4% of ACS and 5.9% of PCS patients ($p = 0.06$). Among PCS patients, cerebellar infarcts were most common (42.2%), followed by brainstem infarcts (38.2%) and multifocal posterior circulation infarcts (19.6%).

The PCS patients had shorter hospital stays compared to ACS (5.8 ± 2.7 vs 7.2 ± 3.1 days; $p = 0.04$). Functional outcomes at discharge, measured by modified Rankin Scale (mRS), were more favorable in PCS, with 58.8% achieving an mRS of 0–2 compared to 42.3% in ACS ($p = 0.008$). In-hospital mortality rates were similar (ACS: 8.4%, PCS: 6.9%; $p = 0.62$); however, brainstem involvement accounted for 83.3% of deaths in PCS. In-hospital outcomes and discharge functional status are summarized in Table 4.

Subgroup analysis showed that younger patients (<45 years) had a higher proportion of PCS (34.6%) compared to older patients (25.1%; $p = 0.04$). In this age-group, current smoking was a particularly strong predictor of PCS (OR 3.12; 95% CI: 1.88–5.18). Gender-specific analysis revealed that women with PCS had a higher prevalence of metabolic syndrome (52.4%) compared to men (34.1%; $p = 0.03$), while smoking was significantly more common in men with PCS ($p = 0.008$), suggesting sex-specific risk factor clustering.

In multivariate logistic regression analysis (Fig. 2), four independent predictors of posterior circulation stroke emerged: hypertension (adjusted OR 2.34; 95% CI: 1.42–3.85; $p < 0.01$), current smoking (OR 1.98; 95% CI: 1.22–3.21; $p < 0.01$), age <55 years (OR 1.76; 95% CI: 1.12–2.78; $p = 0.02$), and metabolic syndrome (OR 1.65; 95% CI: 1.08–2.52; $p = 0.03$). These findings underscore the distinct clinical, metabolic, and vascular profiles that characterize posterior circulation stroke in this Indian cohort. The full multivariate logistic regression model is presented in Table 5.

Discussion

In this hospital-based cohort from Western India, we systematically compared ACS and PCS through a comprehensive analysis of demographic factors, vascular risk profiles, clinical presentations, neuroimaging characteristics, and outcomes. Notably, our findings demonstrated that PCS patients were younger, more hypertensive, more likely

to be current smokers (especially bidi users), and had a higher prevalence of metabolic syndrome compared to those with ACS. This aligns with prior work showing that risk factors are not equally distributed across stroke subtypes and vascular territories.[11–13]

Age and Gender Differences

Our study showed a younger mean age in PCS patients (54.6 vs 61.2 years in ACS), with a significant proportion (34.6%) being under 55 years. This younger age profile is clinically important, underscoring the growing burden of stroke in productive-age adults in India. Similarly, females with PCS presented at a younger age than males, consistent with gender-specific risk factor clustering found in some Chinese studies.[14] These demographic nuances emphasize the need for demographic-tailored prevention efforts.

Hypertension and Blood Pressure Patterns

Hypertension emerged as a powerful predictor of PCS, both in univariate and multivariate analyses. PCS patients had a significantly higher admission systolic blood pressure and greater frequency of hypertensive urgency. Analogous findings have been observed in Chinese and Korean cohorts, where hypertension was characterized as an independent predictor of posterior circulation stroke. The strong association between elevated diastolic pressure and ICAS has also been shown in ICAS patients, supporting the hypothesis that labile hypertension may preferentially damage smaller posterior vessels.[15–17]

Metabolic Syndrome and Dyslipidemia

Our data highlighted significant metabolic dysregulation in PCS patients, evidenced by higher rates of low HDL (72.5%) and hypertriglyceridemia (54.9%), along with increased metabolic syndrome prevalence (41.2 vs 28.5%). These findings echo those in East Asian cohorts where metabolic syndrome was more tightly associated with ICAS in PCS.[18] The higher triglyceride levels and central obesity in our PCS group reinforce a metabolic–atherosclerotic pathway driving these strokes.

Tobacco Use

Tobacco, particularly bidi smoking, was significantly overrepresented in PCS patients. The adjusted OR for PCS in smokers was ~2, with even stronger associations in the younger age subgroup (OR = 3.12). These observations align with population-based studies such as those from Canadian stroke registries, which identified smoking as an important independent risk factor for PCS.[19] Given the higher toxic load and vascular damage from bidis, these findings have particular relevance in South Asian settings where these are commonly used.

Clinical and Neuroimaging Features

We confirmed that PCS often presents with nonlateralizing symptoms such as dizziness, ataxia, and headache, symptoms often misinterpreted as benign, contributing to diagnosis delays. Despite having lower NIHSS scores, PCS patients frequently showed cerebellar, brainstem, or multifocal infarcts on CT. This pattern mirrors findings from both East Asian and Western ICAS registries, where posterior intracranial plaques were prone to adventitia hemorrhage and branch occlusion, complicating clinical recognition and influencing outcomes.[20]

Outcomes and Predictors of Posterior Circulation Strokes

The PCS group had shorter hospital stays and better functional outcomes at discharge (mRS 0–2: 58.8 vs 42.3%). Mortality rates were similar between subtypes, but deaths in PCS predominantly occurred due to brainstem infarction. Notably, multivariate regression identified hypertension, smoking, younger age (<55), and metabolic syndrome as independent predictors of PCS, reflecting a distinct risk profile. These predictors are similar to those reported in multicenter ICAS/ECAS registries, which call for circuit-specific stroke prevention strategies.[14,18]

Clinical Implications

Our findings reinforce that stroke prevention cannot be a "one-size-fits-all" strategy. Prevention of PCS in India, particularly among younger individuals, should be prioritized. Priority should be on aggressive blood pressure control, metabolic syndrome management, and targeted antismoking campaigns, especially for bidi users. Early recognition of atypical symptoms such as vertigo and ataxia is also essential for timely intervention.

Study Limitations

This single-center study using CT (not MRI) may miss small posterior infarcts, and the absence of formal intracranial angiography limits direct classification of ICAS vs ECAS. However, our reliance on initial CT and clinical criteria reflects real-world stroke evaluation in many Indian centers.

Future Directions

Further multicentric studies integrating MR brain and MR angiographic imaging are needed to directly compare ICAS vs ECAS in Indian populations and elucidate genetic predispositions. Additionally, the long-term impact of targeted risk factor modification needs assessment, particularly in younger adults with PCS.

Conclusion

This study demonstrates that PCS differ significantly from ACS in terms of demographics, clinical presentation, and risk factor profile. PCS was more common in younger patients and independently associated with hypertension, smoking, metabolic syndrome, and poor glycemic control. Despite lower NIHSS scores, PCS often presents with atypical symptoms and brainstem or cerebellar involvement. Functional outcomes were better in PCS, though brainstem infarcts carried a high mortality. These findings emphasize the need for territory-specific risk stratification and targeted prevention strategies, particularly in younger, high-risk populations.

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ORIGINAL ARTICLE

Alterations in Serum Electrolytes among Adults with Enteric Fever: A Retrospective Observational Study from a Tertiary Center in New Delhi

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Abstract

Background: Electrolyte abnormalities are frequent in systemic infections such as enteric fever but remain under-recognized in clinical practice. These disturbances may worsen morbidity if not identified and corrected early.

Objective: To determine the prevalence and pattern of serum electrolyte alterations in adult patients hospitalized with enteric fever at a tertiary care center in New Delhi.

Materials and methods: This retrospective observational study analyzed records of 128 adult patients (59 males, 69 females) with laboratory-confirmed enteric fever between January 2023 and March 2024. The first admission values for sodium, potassium, chloride, and bicarbonate were extracted from the hospital laboratory system. Results were categorized as low, normal, or high using standard clinical reference ranges. Descriptive statistics were applied, and gender-based comparisons were performed using Chi-square tests for categorical variables and *t*-tests for continuous measures.

Results: Hyponatremia was present in 58.6% (75/128) of patients, while 57.8% (74/128) had low bicarbonate levels consistent with a trend toward metabolic acidosis. In contrast, potassium and chloride values were predominantly normal, with abnormalities occurring in <10% of patients. The mean ± standard deviation (SD) values (mmol/L) were: sodium 132.7 ± 6.2, potassium 4.3 ± 0.6, chloride 101.1 ± 3.7, and bicarbonate 20.3 ± 4.7. No significant gender differences were detected for mean values or abnormality prevalence (all $p > 0.17$).

Conclusion: Hyponatremia and reduced bicarbonate were the most common electrolyte abnormalities in enteric fever, whereas potassium and chloride disturbances were uncommon. Routine electrolyte monitoring should be incorporated into the management of hospitalized enteric fever patients to enable early correction and improved clinical outcomes.

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Introduction

Enteric fever, caused by *Salmonella enterica* serovars Typhi and Paratyphi, remains a major public health concern in many developing countries, including India. Globally, the World Health Organization (WHO) estimates >11 million cases and 129,000 deaths annually, with the highest burden reported from South Asia and sub-Saharan Africa.[1] In India, the Surveillance for Enteric Fever in India (SEFI) study reported an annual incidence ranging from 360 to 1,200 cases per 100,000 population, underscoring its continued endemicity despite advances in sanitation and antibiotic therapy.[2]

Electrolyte abnormalities are frequently observed in systemic infections and have been associated with worse clinical outcomes, including prolonged hospitalization and mortality.[3] Hyponatremia is particularly common in hospitalized patients with infectious diseases and may result from gastrointestinal fluid loss, renal salt-wasting, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[4] In addition, metabolic acidosis, reflected by low bicarbonate levels, can occur due to dehydration, tissue hypoperfusion, and accumulation of organic acids during systemic illness.[5]

Previous studies have highlighted the relevance of monitoring serum electrolytes in enteric fever. A study from Bangladesh found a high prevalence of hyponatremia among patients with severe typhoid,[6] while Garba et al. in Nigeria reported frequent hyponatremia, hypochloremia, hypokalemia, and metabolic acidosis among 60 laboratory-confirmed typhoid patients.[7] These findings suggest that electrolyte disturbances are a common but under-recognized feature of enteric fever, with potential implications for patient management.

Despite the high burden of disease in India, there is limited contemporary data on the electrolyte profiles of hospitalized adult enteric fever patients. The present study was conducted at a tertiary care center in New Delhi with the aim of characterizing the prevalence and pattern of serum electrolyte abnormalities—specifically sodium, potassium, chloride, and bicarbonate—at admission. By identifying these disturbances early, clinicians may better anticipate complications and optimize supportive care in affected patients.

Materials and Methods

Study Design and Setting

We conducted a retrospective observational study at Max Super Specialty Hospital, Saket, New Delhi, a tertiary care referral center serving both urban and semiurban populations. The study period was from January 2023 to March 2024. Data were obtained from the hospital's laboratory information system (LIS), which records all biochemical and hematological investigations in real time. The study was designed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research.[8]

Participants and Case Definition

All adult patients (≥18 years) with a diagnosis of enteric fever (typhoid or paratyphoid fever) and a complete serum electrolyte panel (sodium, potassium, chloride, bicarbonate) performed at the time of admission were eligible for inclusion. Enteric fever was diagnosed by treating clinicians based on microbiological and/or serological evidence, consistent with prior literature.[3,4] In our setting, this included:

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- Blood culture positive for *Salmonella enterica* serovar Typhi or Paratyphi (gold standard).
- Rapid serological tests, where applicable.
- Patients with only a clinical diagnosis without laboratory confirmation were excluded to minimize misclassification.

After initial extraction of 240 records, duplicate entries and incomplete panels were removed, yielding a final cohort of 128 adult patients. Only the first electrolyte panel at admission was retained to reflect the baseline biochemical profile.

Data Collection and Variables

The following information was extracted: patient registration number, sex, age, hospital location, and electrolyte results. Electrolyte assays were performed using automated biochemistry analyzers following standard laboratory protocols. Each test was conducted with internal and external quality controls in line with institutional policy.

Electrolyte Measurement Methods

- Sodium and potassium were measured using ion-selective electrode (ISE) technology, a widely accepted method for direct quantification of serum electrolytes.[9]
- Chloride concentration was determined *via* a colorimetric method, based on the formation of a colored complex proportional to chloride ion concentration.[10]
- Bicarbonate levels were estimated enzymatically using the modified Forrester method, where bicarbonate reacts with phosphoenolpyruvate in the presence of phosphoenolpyruvate carboxylase (PEPC) and malate dehydrogenase (MDH), with nicotinamide adenine dinucleotide (NADH) oxidation measured spectrophotometrically.[11]

Reference Ranges and Classification

Electrolyte results were categorized as low, normal, or high based on standard clinical ranges used in prior studies[6,7]:

- Sodium (Na^+): 135–155 mmol/L.
- Potassium (K^+): 3.0–5.0 mmol/L.
- Chloride (Cl^-): 98–108 mmol/L.
- Bicarbonate (HCO_3^-): 22–32 mmol/L.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were presented as counts and percentages. Comparisons between male and female patients were performed using Welch's *t*-test for means and Chi-square test for categorical distributions of abnormality (low/high vs normal). A two-sided *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using Python (pandas), and the results are presented as mean ± standard deviation for continuous variables and as counts and percentages for categorical variables.

Results

Study Population

A total of 128 adult patients with laboratory-confirmed enteric fever and complete electrolyte profiles were included in the final analysis. Of these, 59 (46.1%) were male and 69 (53.9%) female.

Distribution of Electrolyte Abnormalities

At admission, sodium and bicarbonate disturbances were most common (Table 1). Specifically, hyponatremia was observed in nearly 6 out of 10 patients (58.6%), making it the most frequent abnormality. Similarly, low bicarbonate levels were recorded in 57.8%, suggestive of a trend toward metabolic acidosis. In contrast, potassium and chloride values remained largely preserved, with over 95% of patients within normal potassium limits and nearly 90% within normal chloride limits. Only a small fraction showed hypokalemia, hyperkalemia, hypochloremia, or hyperchloremia.

Mean Serum Electrolyte Values

The overall mean concentrations reinforced the categorical findings (Table 2). Sodium levels were slightly below the reference threshold, with a mean of 132.7 mmol/L, while bicarbonate averaged 20.3 mmol/L, again falling below the normal lower limit of 22 mmol/L. In contrast, mean potassium (4.3 mmol/L) and chloride (101.1 mmol/L) values were well within the reference ranges.

Gender-based Comparisons

Tables 3 and 4 summarize gender-based analyses. Across all four electrolytes, mean values did not differ significantly between males and females. Although females showed slightly lower average sodium and bicarbonate values, the differences were not statistically significant ($p > 0.17$). Likewise, the distribution

Table 2: Mean serum electrolyte levels at admission

Electrolyte	*Mean ± SD (mmol/L)*
Sodium	132.7 ± 6.2
Bicarbonate	20.3 ± 4.7
Potassium	4.3 ± 0.6
Chloride	101.1 ± 3.7

Table 4: Gender vs electrolyte abnormality (Chi-square tests)

Electrolyte	χ^2	*p-value*
Sodium	1.05 (1)	0.307
Bicarbonate	1.86 (1)	0.172
Potassium	0.04 (1)	0.849
Chloride	<0.01 (1)	0.995

Table 1: Electrolyte distribution ($n = 128$)

Electrolyte	*Low n (%)*	*Normal n (%)*	*High n (%)*
Sodium	75 (58.6)	53 (41.4)	0 (0.0)
Bicarbonate	74 (57.8)	51 (39.8)	3 (2.3)
Potassium	3 (2.3)	122 (95.3)	3 (2.3)
Chloride	7 (5.5)	115 (89.8)	6 (4.7)

Table 3: Mean serum electrolyte levels by gender

Electrolyte	*Male (n = 59) Mean ± SD*	*Female (n = 69) Mean ± SD*	*p-value*
Sodium	133.3 ± 6.3	132.2 ± 6.2	0.314
Bicarbonate	20.9 ± 4.9	19.8 ± 4.6	0.189
Potassium	4.2 ± 0.5	4.4 ± 0.6	0.092
Chloride	100.7 ± 3.7	101.4 ± 3.7	0.314

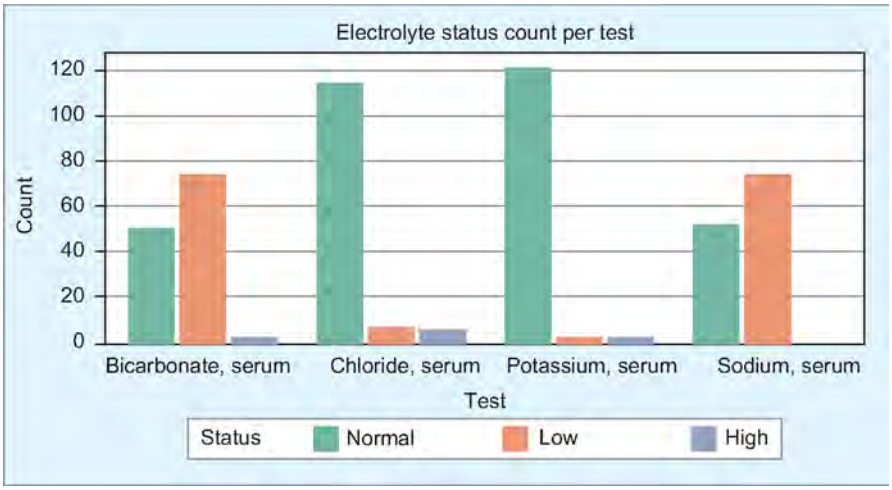

Fig. 1: Distribution of electrolyte abnormalities at admission

of abnormalities (low/high vs normal) did not differ by gender, with Chi-square tests confirming no significant association.

Graphical Presentation

Figure 1 provides a visual overview of the distribution of electrolyte abnormalities. The figure clearly highlights that sodium and bicarbonate imbalances dominate the biochemical profile of enteric fever patients, with more than half of the cohort falling below reference thresholds. In contrast, potassium and chloride abnormalities are far less common, consistent with the tabulated results. This visual representation strengthens the interpretation that targeted monitoring of sodium and bicarbonate may be clinically most relevant in this patient group.

Discussion

This study evaluated electrolyte alterations in 128 adult patients with enteric fever admitted to a tertiary care hospital in New Delhi. The most striking abnormalities observed were hyponatremia (58.6%) and low bicarbonate (57.8%), while potassium and chloride levels were preserved in the majority of cases. These findings indicate that disturbances in sodium and acid–base balance are common features of enteric fever at admission, and they underscore the importance of routine electrolyte monitoring in the clinical management of such patients.

Our results align with previous studies conducted in other endemic regions. Garba et al.[7] reported that 50% of typhoid patients in Nigeria were hyponatremic and 11% exhibited metabolic acidosis, while Chisti et al.[6] in Bangladesh also observed significant sodium disturbances among patients with severe enteric fever. Together with our data, these studies highlight that electrolyte imbalances in enteric fever are not geographically restricted and may represent a consistent pathophysiological response to systemic infection.

The predominance of hyponatremia may be explained by several mechanisms. Gastrointestinal fluid losses (vomiting, diarrhea) contribute to sodium depletion, while SIADH has been reported in systemic infections and may lead to dilutional hyponatremia even in the absence of overt fluid loss.[3,4] Likewise, the high prevalence of low bicarbonate suggests a tendency toward metabolic acidosis, potentially due to dehydration, tissue hypoperfusion, or accumulation of organic acids.[5] However, as we did not measure serum osmolality, urine electrolytes, or arterial blood gases, these mechanisms remain speculative and should be interpreted as plausible rather than confirmed explanations.

Unlike sodium and bicarbonate, potassium and chloride abnormalities were uncommon in our cohort, contrasting with Garba et al.,[7] who reported hypokalemia and hypochloremia in more than one-third of patients. This difference may reflect variations in patient demographics, severity at presentation, or early access to hospital care. Notably, we found no significant gender differences in either mean electrolyte levels or prevalence of abnormalities, consistent with prior reports that biochemical disturbances in typhoid are largely independent of sex.[6,7]

From a clinical perspective, these findings have important implications. Hyponatremia has been linked to neurological complications, prolonged hospital stays, and increased mortality in infectious diseases.[4] Early detection and correction of sodium and bicarbonate disturbances could therefore reduce morbidity and improve patient outcomes. Routine electrolyte panels at admission, particularly in endemic regions, should be integrated into the diagnostic and therapeutic workflow for enteric fever.

Limitations

This study has several limitations. It was conducted at a single center, limiting generalizability. Being retrospective, it relied on available records without the ability to assess longitudinal changes in electrolytes. Clinical outcomes (e.g., complications, duration of hospitalization, mortality) were not captured, precluding analysis of prognostic implications. Furthermore, confounding factors such as hydration status, comorbidities, and prior therapy were not adjusted for. Finally, proposed mechanisms such as SIADH or metabolic acidosis remain hypotheses, as confirmatory investigations (e.g., serum osmolality, arterial blood gases) were not performed.

Conclusion

In summary, this study demonstrates that hyponatremia and low bicarbonate are the most frequent electrolyte abnormalities among adult enteric fever patients admitted to a tertiary hospital in New Delhi, while potassium and chloride remain largely unaffected. These findings emphasize the need for routine monitoring of serum sodium and bicarbonate to guide supportive management. Future multicenter, prospective studies with outcome correlation are warranted to validate these findings and clarify their prognostic significance.

Ethics Approval

The study was approved by the Institutional Ethics Committee of Max Super Specialty Hospital, Saket, New Delhi (approval no. BHR/RS/MSSH/DDF/SKT-2/IEC/IM/26-01/2023).

Consent

Informed consent was waived due to the retrospective nature of the study.

Conflict of Interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

E-health Initiatives for Screening and Management of Anemia in Rural Rajasthan

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Abstract

Introduction: Anemia is considered to be a public health issue of serious concern universally. In the current era of advancing technology, electronic health (e-health) initiatives are being employed in various health programs for disease screening and management. This study was planned to screen for anemia and manage it through a multidimensional approach comprising iron folic acid (IFA) supplementation, deworming among children, and dietary guidance and health education through pop-up videos with the aid of e-health initiatives.

Methods: This was a prospective cohort study. An Android e-application (app) was used on tablets to identify anemia after hemoglobin estimation through the Hemoglobin Color Scale. Accredited Social Health Activists (ASHAs) managed anemia by providing health education and dietary guidance through pop-up videos and IFA supplementation. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 29. Tests of significance in the form of Cochran's Q, McNemar, chi-square, and repeated measures analysis of variance (ANOVA) and independent *t*-test were applied.

Results: The overall prevalence of anemia significantly declined from 46.08% at baseline to 14.65% at the 9th month. Males had a higher anemia prevalence (52.8%) compared to females (39.16%). An overall improvement of 68.2% was observed in the anemia status, with the maximum being in the 1–5-year age-group and females. Mean hemoglobin levels showed a consistent increase across all age-groups, with the maximum being in the 6-month–1-year age-group and females.

Conclusion: This study demonstrated that community-based, sustained, and targeted strategies through the use of e-health initiatives can effectively combat anemia and achieve significant improvements in hemoglobin levels across all age and gender groups.

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Introduction

A low number of red blood cells or hemoglobin concentration below normal is defined as anemia as per the World Health Organization (WHO). Anemia is considered to be a public health issue of serious concern globally. Young children, menstruating adolescent girls and women, and pregnant and postpartum women are at a higher risk of being affected. WHO estimates that children aged 6–59 months, pregnant women, and reproductive-age women suffer from anemia globally in high proportions (40, 37, and 30%, respectively).[1]

Anemia is also widely prevalent in India. Despite a number of government health programs and policies ongoing for a long time, the reports of National Family Health Survey (NFHS)-5 declared a large proportion of the population to be anemic. According to NFHS-5, 57% of reproductive-age women and 25% men were found to be anemic in India, while in the state of Rajasthan, 54.4% women and 23% men were reported to be anemic. These figures were higher in children aged 6–59 months, among whom 67.1% were anemic in India overall and 71.5% in the state of Rajasthan.[2,3]

A multidimensional approach comprising nutrient supplementation, food fortification, prevention and control of parasitic and protozoal infestations, and health education has been endorsed by WHO and United Nations Children's Fund (UNICEF) for the control and prevention of anemia. It has been proven that iron supplementation can prevent <12,500 disability-adjusted life years (DALYs) per year in regions with modest mortality rates, such as the European subregion, to almost 2.5 million DALYs in areas with high adult and child mortality rates, such as in the African and Southeast Asian subregions.[4]

The interventions and strategies, whether for diagnosis or management, are incomplete without the use of e-health in today's era. WHO defines e-health as the use of information and communication technologies for health. Equipping grassroots workers and the use of e-health initiatives have been proven to be beneficial for a number of noncommunicable diseases such as hypertension and diabetes in various studies.[5–7]

Thus, we conducted this research intending to assess anemia prevalence and the effect on anemia after giving 3 months of iron folic acid (IFA) supplementation twice, along with deworming among children and dietary guidance and health education through pop-up videos with the aid of e-health initiatives.

Methods

This was a prospective cohort study funded by Rajasthan University of Health Sciences, Jaipur, and was approved by the ethics committee of the medical college.

Two villages, Lakhesra and Kapoorawala near Jaipur, with difficult access and inadequate health services, were identified for the study. A population of 3,830 individuals above 6 months of age was included in the study. We communicated with Accredited Social Health Activists (ASHAs) in the selected area. Two ASHAs were recognized from each village who consented to work for data collection and follow-up of recruited subjects in the project. Data collection was completed in a year.

An Android e-application (app) was worked on, usable on tablets. The cardinal features were global positioning system (GPS), Skype, and 3G enabled, which helped in live data accumulation and visibility of data at the central location. An essential feature of the app was automatic conveyance of data to a central location.

Pop-up videos on the application, which was an inbuilt feature, could be used for counseling on the assessed problem. These would appear spontaneously for health education on the identification of the risk. For example, for those diagnosed with anemia, a pop-up video would appear on a tablet to be shown to the concerned person about

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the adverse effects of anemia and health education related to it. ASHAs were trained to perform hemoglobin estimation through the Hemoglobin Color Scale (HbCS). The HbCS compares the color of a blood drop, which is absorbed on special chromatography paper. Comparison is done with standard colors on a laminated card, which are displayed in increments of 2 gm/dL. The HbCS has five colors: blood red, barn red, crimson red, firebrick, and Persian red.

Accredited Social Health Activists were trained to perform hemoglobin estimations through training modules and real-time demonstrations using the HbCS. WHO guidelines were used for anemia, which were already fed into the e-application.

Written informed consent was taken from all the heads of the families and participants before recruitment. Collection of baseline data was done by ASHAs in 3 months. For all anemic subjects above 6 months of age, 3 months of IFA, deworming (children), dietary guidance, and health education through pop-up videos in the e-application were done. The hemoglobin estimation was done after 1 month of completion of the course to see the effect. Those who were still anemic were given another 3 months of IFA, and hemoglobin assessment was done after 1 month of completion of the second course.

Those in the age-group of 6 months to 6 years were given liquid formulations of IFA (20 mg elemental iron and 0.1 mg folic acid), while children up to the age of 10 years were given a pediatric dose of IFA (30 mg elemental iron and 250 µg of folic acid per day), along with deworming in all of them. Adolescents and adults were given the adult dose, i.e., 100 mg elemental iron and 0.5 mg folic acid.

Data Collection

The data were transferred directly to the central computer, and reports on various aspects were generated automatically daily through entries in e-application usable on tablets.

Statistical Analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 29 in the form of percentage, mean, standard deviation, and tests of significance in the form of Cochran's Q, McNemar, chi-square for qualitative data, and repeated measures analysis of variance (ANOVA) and independent *t*-test for quantitative data.

Results

A total of 3,830 individuals were included in the study from two villages to assess anemia prevalence and the effect on anemia after follow-up at 5 and 9 months after giving 3 months of IFA treatment twice, along with deworming among children and dietary guidance and health education through pop-up videos in an e-health application.

Distribution of Anemia by Age-group

At baseline, the overall prevalence of anemia was 46.08% (1,765/3,830), which significantly declined to 21.36% at the 5th month and further to 14.65% at the 9th month. The highest anemia prevalence at baseline was observed among the 6-month–1-year age-group (53.09%), while the lowest was among the 5–15 years age-group (40.32%). Change in the number of total anemics at the start and end was found to be statistically significant, as per Table 1.

The greatest improvement in the number of anemics was seen in the 1–5 years group, where prevalence dropped from 46.04 to 10.73%, reflecting a 76.7% change. Conversely, the smallest improvement was in the above 60-year age-group (53.51% change), as evident in Table 1.

The difference in anemia status across three time points in all age-groups was noted and was statistically significant ($p < 0.001$). Change between two specific time points showed significant change in all age-groups in anemia status from baseline to first follow-up at 5th month and baseline to second follow-up at 9th month. But it was not significant in the extreme age-groups, i.e., 6 months to 1 year and above 60-year age-group, from 1st follow-up to the second follow-up, as shown in Table 1.

Distribution of Anemia by Gender

Of the 1,943 males, 52.8% were anemic at baseline, which reduced at 5 months and 9 months, showing an overall 59.85% change. Among females ($n = 1,887$), baseline anemia was lower at 39.16% and showed a greater overall improvement (79.85%), as per Table 2.

The difference in anemia status across the three time points in both genders was statistically significant ($p < 0.001$). Also, change across all two time points was significant ($p < 0.001$).

Change in Mean Hemoglobin across Age-groups

Mean hemoglobin levels showed a consistent increase across all age-groups from baseline to the 5th and 9th months. The mean hemoglobin increased at two follow-ups, as per Table 3, and the difference observed in mean hemoglobin across age-groups at all three time points was found to be statistically significant ($p < 0.001$). Figure 1 shows the comparison of mean hemoglobin level at baseline, at the 5th month, and at the 9th month using a line plot. From the figure, we observe a high improvement in mean hemoglobin level at the two follow-ups.

Table 1: Distribution of anemics as per age-group at start and after F/U5, F/U9 with change in anemia status

Age-group in years	*N*	*Anemia status at start n (%)*	*Anemia status at F/U 5th month n (%)*	*Anemia status at F/U 9th month n (%)*	*Change in status (%)*	*p-value, Cochran's Q (across three time points)*
6 month–1	81	43 (53.09)	22 (27.16)	17 (20.99)	60.46	<0.001
1–5	354	163 (46.04)	66 (18.64)	38 (10.73)	76.7	<0.001
5–15	811	327 (40.32)	167 (20.59)	116 (14.3)	64.53	<0.001
15–45	1,969	915 (46.47)	415 (21.08)	275 (13.97)	69.93	<0.001
45–60	389	203 (52.18)	90 (23.14)	62 (15.94)	69.45	<0.001
Above 60	226	114 (50.44)	58 (25.66)	53 (23.45)	53.51	<0.001
Total	3,830	1,765 (46.08)	818 (21.36)	561 (14.65)	68.21	<0.001

The difference in anemia status across the three time points in all age-groups was statistically significant ($p < 0.001$, Cochran's Q test).
Change between two specific time points showed significant change in all age-groups in anemia status from baseline to first follow-up at the 5th month and baseline to second follow-up at the 9th month ($p < 0.001$, McNemar test).
But it was not significant in the extreme age-groups, i.e., 6 months to 1 year and above 60-year age-group from the first follow-up to second follow-up ($p = 0.131$ and $p = 0.302$, respectively).
Change in the number of total anemics at the start and end was found to be statistically significant ($\chi^2 = 23.36$, df = 1, $p < 0.001$).

Table 2: Distribution of anemics as per gender at the start and after F/U 5th month, 9th month with change in anemia status

Gender	*N*	*Anemia status at start n (%)*	*Anemia status at F/U at 5th month n (%)*	*Anemia status at F/U at 9th month n (%)*	*Change in status (%)*	*p-value, Cochran's Q (across three time points)*
Male	1,943	1,026 (52.8)	555 (28.56)	412 (21.20)	59.85	<0.001
Female	1,887	739 (39.16)	263 (13.94)	149 (7.89)	79.85	<0.001
Total	3,830	1,765 (46.08)	818 (21.36)	561 (14.65)	68.21	<0.001

The difference in anemia status across the three time points in both genders was statistically significant ($p < 0.001$, Cochran's Q test). Also, change across all two time points was also significant ($p < 0.001$, McNemar test).

Table 3: Change in mean Hb across various age-groups

Age-group in years	*N*	*Mean Hb ± SD at start*	*Mean Hb ± SD at F/U 5th month*	*Mean Hb ± SD at F/U 9th month*	*Mean difference from start to end*
6 month–1	43	9.05 ± 1.56	10.67 ± 1.58	11.12 ± 1.14	2.12
1–5	163	9.32 ± 1.15	10.92 ± 1.43	11.35 ± 0.91	2.03
5–15	327	10.05 ± 0.85	11.02 ± 1.31	11.68 ± 0.94	1.63
15–45	915	10.94 ± 1.07	12.23 ± 1.09	12.52 ± 0.92	1.58
45–60	203	10.78 ± 1.08	12.21 ± 1.19	12.52 ± 0.96	1.74
Above 60	114	10.54 ± 1.08	11.95 ± 1.18	12.09 ± 1.04	1.55
Total	1,765	10.53 ± 1.20	11.82 ± 1.33	12.19 ± 1.04	1.66

The difference in Hb level across the three time points in all age-groups was statistically significant (one-way repeated measures ANOVA, df = 2, $p < 0.001$).

Table 4: Change in mean Hb across various gender groups

Gender	*N*	*Mean Hb ± SD at start*	*Mean Hb ± SD at F/U 5th month*	*Mean Hb ± SD at F/U 9th month*	*Mean difference from start to end*
Male	1,026	11.01 ± 1.21	12.13 ± 1.35	12.50 ± 1.08	1.49
Female	738	9.88 ± 0.81	11.41 ± 1.16	11.77 ± 0.83	1.89
Total	1,764	10.53 ± 1.2	11.82 ± 1.33	12.19 ± 1.04	1.66

Both genders had improved Hb levels at follow-ups, more so among females, and this observed difference was statistically significant (independent *t*-test, $t = -6.04$, df = 1762, $p < 0.001$).

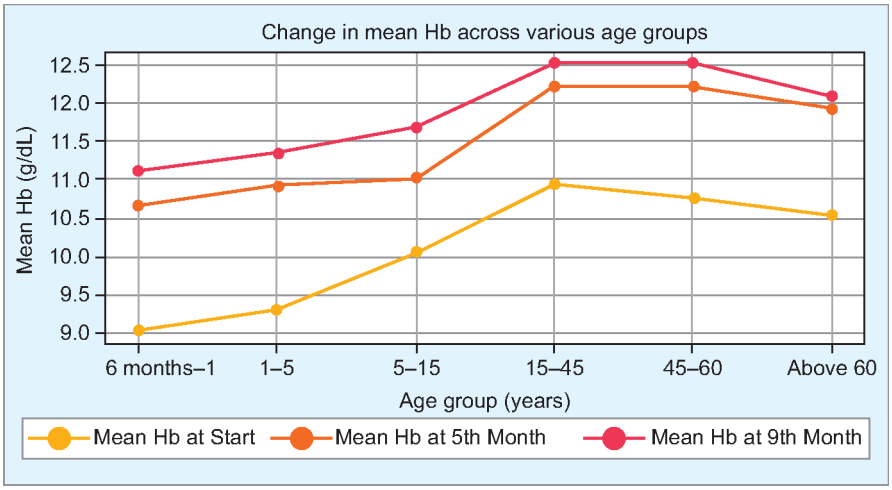

Fig. 1: Comparison of mean Hb level in different age-groups across different time periods

Change in Mean Hemoglobin across Genders

Males had a higher baseline mean hemoglobin compared to females. At the second follow-up at the 9th month, males and females both had improved hemoglobin levels, more so among females, and this observed difference was statistically significant ($p < 0.001$), as per Table 4.

Discussion

This study demonstrated that community-based strategies through the use of e-health initiatives can effectively combat anemia and bring about significant improvements in hemoglobin levels across all age and gender groups by raising awareness and improving adherence to iron supplementation. Similar results were found across various studies among pregnant women and adolescent girls using e-health.[8–11] The results in the form of improvement of the disease condition by e-health initiatives are in line with various other studies using e-health for various health conditions.[6,7,12–14]

This study assessed the prevalence and longitudinal changes in anemia across various age and gender groups following a comprehensive community-based intervention. A significant reduction in anemia prevalence was noted over a 9-month follow-up, from 46.08% at baseline to 14.65%, indicating the potential effectiveness of ongoing interventions such as IFA supplementation, dietary guidance, health education, and deworming. It also highlights that targeted, sustained interventions can improve hemoglobin status in resource-limited settings.

According to the NFHS-5 (2019–2021),[2] anemia prevalence in children aged 6–59 months was 67.1%, in women aged 15–49 years was 57%, and in men aged 15–49 years was 25%. Compared to NFHS data, the baseline prevalence observed in this study

is somewhat lower, possibly due to better coverage, a smaller community, and health awareness among the studied population. This is also evident by better antenatal care (ANC) in the studied area. However, the direction of improvement in hemoglobin status mirrors national efforts like Anemia Mukt Bharat.

The results also contrast with recent NFHS-5 data showing worsening trends in national anemia levels, particularly in children and women.[2] This indicates that while national programs are well-designed, challenges in implementation may limit their impact. In contrast, localized programs with structured follow-up, such as the one in this study, may be better poised to deliver impact.

Younger children (6 months–1 year and 1–5 years) and elderly individuals (above 60 years) showed the highest baseline anemia rates, which is consistent with the known vulnerability of these groups due to factors such as poor dietary intake, higher physiological needs, and comorbidities. Encouragingly, all age-groups demonstrated improvement by the 9th month, with the most substantial change seen in children aged 1–5 years (76.7%). This is consistent with findings from global and Indian studies indicating that children under five are highly responsive to iron interventions. A meta-analysis by Sachdev et al.[15] confirmed that iron supplementation significantly reduces anemia and improves hemoglobin levels among children aged 6–59 months, especially when delivered consistently and combined with deworming and dietary advice. A study by Kapil and Bhavna[16] evaluating anemia control programs in India also reported moderate improvements in anemia status following nutritional supplementation and deworming, particularly among children and pregnant women.

In the current study, all age-groups showed improvement, though the oldest group (>60 years) demonstrated the least change (53.5%). This finding is consistent with research by Chaves et al.,[17] who reported that anemia in elderly populations is often multifactorial—stemming from chronic disease, malnutrition, and inflammatory conditions—which makes it less responsive to standard iron therapy alone. Addressing anemia in older adults may require a more comprehensive diagnostic and management approach, echoing results from the global review by Balarajan et al., who stressed the complexity of anemia in older adults and the need for specialized care beyond iron supplementation.[18]

Although the reduction from baseline to the 5th month was not statistically significant across age-groups, the difference became significant at the 8th month. This suggests that longer follow-up durations may be necessary to observe meaningful improvements in hemoglobin levels and anemia status. It also reinforces the importance of sustained interventions and monitoring over time.

Gender-based analysis revealed a higher initial prevalence of anemia among males (52.8%) compared to females (39.2%), which contrasts with most literature indicating that females, especially of reproductive age, are more affected due to menstruation and pregnancy-related losses.[19] Nevertheless, the greater improvement observed in females (to just 7.89% by 2nd follow-up) likely reflects the benefit of focused programs and improved health-seeking behaviors in female groups as observed with improved ANC in the studied area, which showed among pregnant women IFA consumption, tetanus toxoid (TT) vaccination, and required ANC and postnatal care (PNC) visits were 100%. Also, Janani Suraksha Yojana (JSY) registration was >78%. Bentley and Griffiths[19] previously emphasized the need for gender-sensitive anemia control programs, which may explain this encouraging trend in female improvement.

Further support comes from a recent school-based intervention by Pande et al., where adolescent girls receiving weekly IFA supplementation showed an average increase in hemoglobin of 0.6 gm/dL over just 3 months.[20] Our study recorded a larger increase (1.66 gm/dL) over 8 months, suggesting that longer follow-up and possibly better compliance monitoring may enhance outcomes.

A pragmatic cluster-randomized trial in Karnataka found that integrating community health workers with iron supplementation significantly improved hemoglobin levels and reduced anemia burden more than iron therapy alone.[21] This aligns with our findings and reinforces the effectiveness of integrated, community-led health models.

The significant rise in mean hemoglobin levels across all age and gender groups further supports the effectiveness of interventions. The average hemoglobin improved from 10.53 gm/dL to 12.19 gm/dL overall, with the greatest gains seen in younger children and adult females. The statistically significant differences in mean hemoglobin values across both age and gender groups at all follow-up points ($p < 0.001$) confirm that the observed changes were not by chance.

Our findings on mean hemoglobin changes also align with those reported by Kaur et al.,[22] who found that a school-based iron supplementation program led to an increase of 1.5 gm/dL in mean hemoglobin levels over 6 months among adolescents. In our study, the mean hemoglobin improved by 1.66 gm/dL across the total population over 8 months. The significant gains across all age-groups and genders underscore the efficacy of sustained public health measures.

Conclusion

This study demonstrated that community-based, sustained, and targeted strategies through the use of e-health initiatives can effectively combat anemia and achieve significant improvements in hemoglobin levels across all age and gender groups. The best outcomes were observed in children aged 1–5 years and in females, highlighting the responsiveness of these groups to well-structured interventions. Although older adults showed smaller gains, these findings support the scalability of such models within national programs like Anemia Mukt Bharat. Further research is needed to explore factors affecting persistent anemia in the elderly and ensure long-term adherence to interventions.

This study has several strengths, including a large sample size and comprehensive follow-up, but it also has limitations. Socioeconomic variables, dietary patterns, and comorbidities were not evaluated, which could have influenced outcomes. Also, further evaluation for hemoglobinopathies was beyond the scope of this study. Future studies incorporating these aspects could provide deeper insights into anemia control.

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ORIGINAL ARTICLE

A Prospective 1-Year Study of Renal Recovery in Pigment Nephropathy: Insights Beyond the Acute Phase

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Abstract

Background: Pigment nephropathy is an underrecognized cause of acute kidney injury. Data from northern India is scarce. The present study aims to assess the clinical characteristics and outcomes of pigment nephropathy in this region.

Materials and methods: We analyzed the demographics, etiology, and outcomes of 20 patients with biopsy-proven pigment nephropathy.

Results: The mean age was 27.75 years (range: 13–52), with a male-to-female ratio of 18:2. The average peak serum creatinine was 12.09 mg/dL (range: 0.84–22.3). Rhabdomyolysis was identified in 14 (70%) and hemolysis in 6 patients (30%). The rhabdomyolysis was attributed to hypokalemia, infection, strenuous exercise, physical trauma, inflammatory myositis, neuroleptic malignant syndrome, and heat stroke. The hemolysis was caused by paroxysmal nocturnal hemoglobinuria, thrombotic microangiopathy, transfusion reaction, rifampicin, and physical stress. The majority of patients (85%) required hemodialysis, with a mean of 6 sessions (range: 3–17). The mean duration of hospitalization was 15.3 days (range: 4–30), and the average time to renal recovery was 3.1 weeks (range: 2–6). All 20 patients survived and achieved complete renal recovery. Of the 20 patients, 13 completed at least 1 year of follow-up, 4 were lost to follow-up, and 3 remain under observation. At 1 year, all 13 patients had normal serum creatinine. None progressed to chronic kidney disease.

Conclusion: Of 20 patients (4.1%) with pigment-induced acute kidney injury (AKI), 70% had myoglobin- and 30% hemoglobin-induced nephropathy. Common causes included hypokalemia, infection, strenuous activity, and paroxysmal nocturnal hemoglobinuria. Hemodialysis was required in 85%, with an average hospital stay of 15.3 days. Among 13 patients with a 1-year follow-up, none developed chronic kidney disease. Overall prognosis appears favorable; however, larger studies with extended follow-up are needed to better characterize long-term outcomes in pigment nephropathy.

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Introduction

Pigment nephropathy is an important yet underrecognized entity within the broad spectrum of acute kidney injury (AKI), contributes up-to 10% of AKI.[1] Heme pigments are primarily generated through two processes: rhabdomyolysis and hemolysis. Rhabdomyolysis can be traumatic, exertional, or nonexertional in origin.[2] Hemoglobinopathies, paroxysmal nocturnal hemoglobinuria, malaria, transfusion reactions, prosthetic heart valves, and certain drugs are the important causes of intravascular hemolysis and hemoglobin cast nephropathy.[3–5] Free heme pigments cause direct tubular injury and lead to tubular obstruction via pigment cast formation. Rhabdomyolysis is biochemically characterized by high serum creatine phosphokinase, myoglobin levels, lactate dehydrogenase, and hemolysis by unconjugated hyperbilirubinemia, high serum LDH, and an elevated reticulocyte count. Pathophysiologically, pigment nephropathy is characterized by vasoconstriction, proximal tubular epithelial cell injury, and distal tubule blockage due to pigment cast formation.[2,6] Rhabdomyolysis can present with an asymptomatic rise in creatine phosphokinase to deadly acute kidney injury, though weakness and myalgia are the most common presenting symptoms. As there is no established treatment for pigment nephropathy, the focus remains on prevention. The prognosis of pigment nephropathy is favorable; in the majority, renal function recovers completely.[7,8] However, the studies have shown an increased risk of chronic kidney disease (CKD).[8,9] The etiology and outcomes of pigment nephropathy have been variably reported across studies worldwide, including different regions of India.[7–9] Only a few case reports and retrospective studies have been published from southern India.[4,9] Data from northern India is scarce. The present study aims to analyze the clinical characteristics and outcomes of pigment nephropathy in this region.

Materials and Methods

Study Design

The present study is a prospective, 1-year observational study to evaluate the demographics, etiology, and outcomes of biopsy-proven pigment nephropathy diagnosed between June 2022 and May 2025. This study was approved by the institutional ethics committee on October 16, 2024, via letter number: 233/IEC/IGIMS/2024.

Inclusion and Exclusion Criteria

Patients with AKI and evidence of rhabdomyolysis, defined by raised serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and myoglobin levels or hemolysis indicated by elevated LDH, unconjugated bilirubin, and reticulocyte count, individuals undergoing kidney biopsy were assessed for pigment-induced kidney damage. A total of 20 cases of either myoglobin- or hemoglobin-associated pigment nephropathy were included in the analysis: 14 diagnosed as myoglobin cast nephropathy and 6 as hemoglobin cast nephropathy.

Data Collection

A detailed history for all patients, including information on preceding trauma, strenuous exercise, seizures, alcohol or medication intake, as well as demographic characteristics, was obtained. Comprehensive laboratory investigations, including complete blood count, reticulocyte count, blood urea, serum creatinine, serum electrolytes (sodium, potassium, calcium, phosphate), uric acid, serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), serum myoglobin, liver function tests, urine dipstick and microscopy, and urine protein-to-creatinine ratio were recorded. Treatment details during

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Table 1: Demographic and biochemical characteristics of a patient with pigment nephropathy ($n = 20$)

Parameters	*Value*
Mean age and range (years)	27.75 years (13–52)
Male: female ratio	18:2
Mean serum creatinine at presentation with range (mg/dL)	9.31 (0.84–22.3)
Mean peak serum creatinine (mg/dL)	12.09
Median LDH with interquartile range (IQR) (IU/L)	702.5 (IQR: 381–1154)
Median CPK with interquartile range (IQR) (IU/L)	2198 (IQR: 41–10655)
Median serum myoglobin with interquartile range (IQR) (ng/dL)	396.45 (IQR: 35–1262.5)
Mean serum calcium (mg/dL)	8.10
Mean serum phosphate (mg/dL)	6.96
Mean serum uric acid (mg/dL)	10.07
Mean serum potassium (mEq/L)	4.70
Mean number of hemodialysis	6
Mean duration of hospital stays with range (days)	15.3 (4–30)
Mean recovery time with range (weeks)	3.1 (2–6)

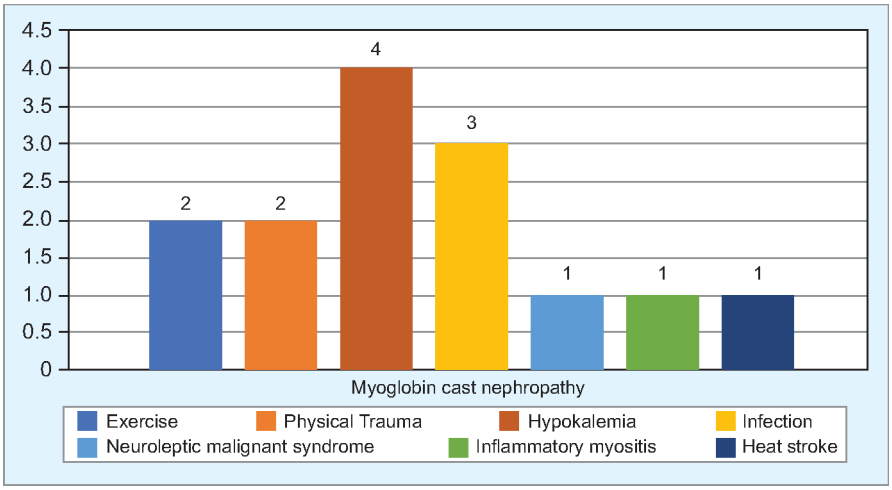

Fig. 2: Etiology of myoglobin cast nephropathy in study population ($n = 14$)

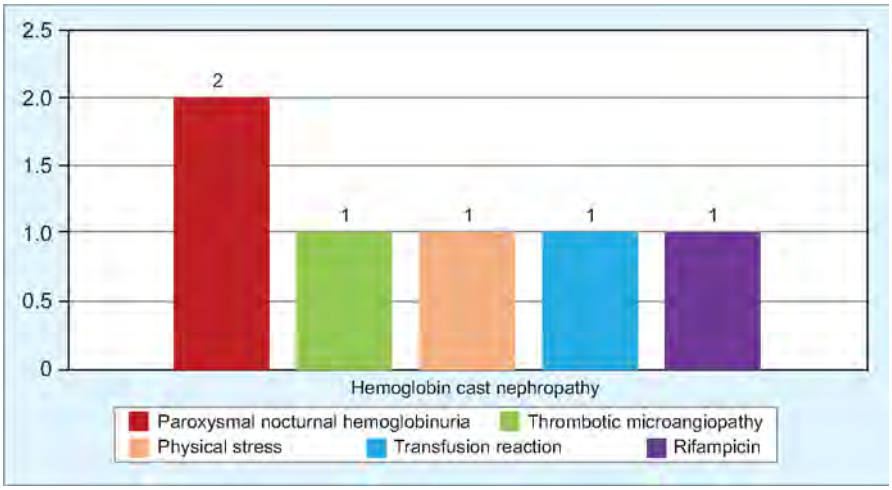

Fig. 3: Etiology of hemoglobin cast nephropathy in study population ($n = 6$)

hospitalization were also documented. Renal biopsy samples were examined under light microscopy using hematoxylin and eosin, Periodic acid–Schiff, trichrome, Periodic acid–Schiff methenamine, and Prussian blue stains. Myoglobin and hemoglobin immunohistochemistry (IHC) were performed on the intratubular pigmented cast. The etiology of rhabdomyolysis and hemolysis was determined by clinical history and laboratory findings. Supportive treatment was provided to all patients, and hemodialysis (HD) was provided to those who required it. The definition of AKI followed the criteria established by the KDIGO guidelines published in 2012.[10] Recovery of renal function was defined as a decline in the serum creatinine to the normal range. Patients were followed for a minimum of 1 year, with renal function tests and urine albumin-to-creatinine ratio measured at 3, 6, and 12 months.

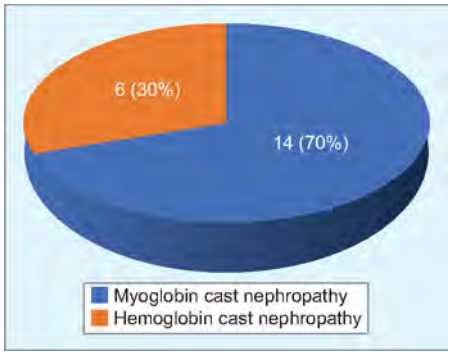

Fig. 1: Types of pigment nephropathy in the study population ($n = 20$)

Statistical Analysis

Mean ± standard deviation is used for normally distributed data, while median with interquartile range (IQR) is used for data that are not normally distributed. Frequencies and percentages are used to present categorical variables.

Results

Out of a total of 481 acute kidney injury cases diagnosed between June 2022 and May 2025, 20 (4.1%) patients with either rhabdomyolysis or hemolysis were included in the analysis. All 20 cases showed histological evidence of pigment nephropathy on tissue biopsy. The mean age was 27.75 years (range: 13–52), with a male-to-female ratio of 18:2. Urine was positive for pigments in 50% of patients, and 50% had oliguria. The average peak serum creatinine was 12.09 mg/dL (range: 0.84–22.3). Other clinical data are presented in Table 1. Rhabdomyolysis was identified in 14 (70%) and hemolysis in 6 patients (30%) (Fig. 1). Cause of rhabdomyolysis were postacute gastroenteritis, persistent hypokalemia (4), infection (3), strenuous exercise (2), physical trauma (2), inflammatory myositis (1), quetiapine and chlorpromazine induced neuroleptic malignant syndrome (1) and heat stroke (Fig. 2).[1] One patient with biopsy-proven inflammatory myositis had

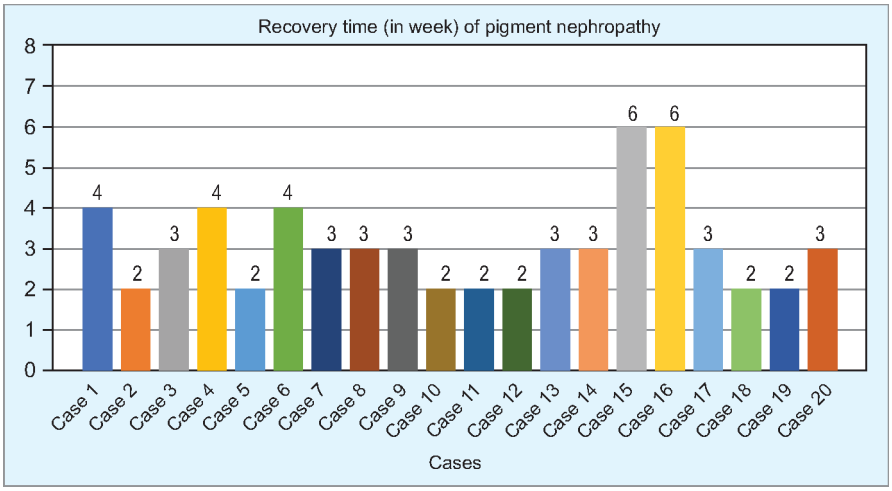

Fig. 4: Recovery time of renal function of patients with pigment nephropathy (n = 20)

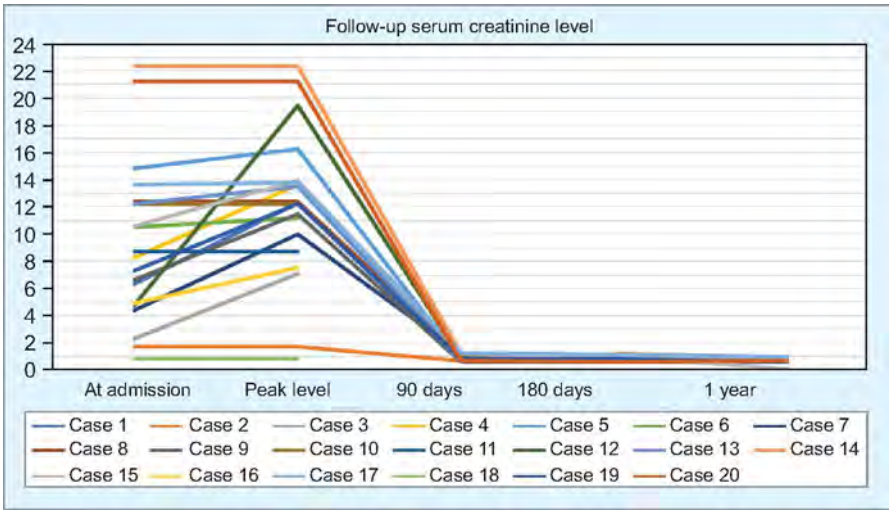

Fig. 5: Serum creatinine level of patients with pigment nephropathy at admission and on follow-up (n = 20)

experienced two prior episodes of recurrent acute kidney injury (AKI) over the past 12 years. Another patient had been on quetiapine (50 mg twice daily) and chlorpromazine (100 mg once daily) for the previous 2 years. The etiologies of hemolysis were paroxysmal nocturnal hemoglobinuria (2), thrombotic microangiopathy (1), transfusion reaction (1), rifampicin (1), and physical stress (Fig. 3).[1] Two patients with paroxysmal nocturnal hemoglobinuria had diffuse intense blue staining on Perl's Prussian Blue technique, indicating hemosiderin deposition. One patient showed histological evidence of thrombotic microangiopathy in addition to pigment nephropathy. In the case of rifampicin-induced hemolysis, the patient had been on daily therapy for 10 days. Another patient developed hemolysis due to physical stress from running. Kidney biopsy showed acute tubular injury with sloughed off epithelial cells, interstitial edema, and pigment casts in all 20 patients. None of the biopsies demonstrated significant glomerulosclerosis, interstitial fibrosis, or tubular atrophy. The majority of patients (85%) required hemodialysis during hospitalization, with a mean of six sessions (range: 3–17). Three patients (15%) did not require dialysis; these included one case each of myoglobin cast nephropathy, paroxysmal nocturnal hemoglobinuria, and thrombotic microangiopathy. The average duration of hospital stay was 15.3 days (range: 4–30), and the average time to renal recovery was 3.1 weeks (range: 2–6) (Fig. 4). All patients survived the acute phase and achieved complete renal recovery with normalization of serum creatinine. Of the 20 patients, 13 completed at least 1 year of follow-up, four were lost to follow-up, and three remain under observation. At the 1-year mark, all 13 had normal serum creatinine; 12 patients had normal urine albumin-to-creatinine ratios (A1) except one had microalbuminuria (A2). None of the patients went into chronic kidney disease (CKD) (Fig. 5).

Discussion

Acute kidney injury is a serious complication of heme pigment-induced kidney injury.[9] It was first described by Meyer-Betz in 1911.[11] Prevalence of AKI in rhabdomyolysis varies from 10 to 50%, and contributes up to one-fourth of AKI.[12,13] In our study, about 4.1% of AKI is contributed by rhabdomyolysis or hemolysis. Pigment nephropathy is most commonly caused by rhabdomyolysis, hemolysis, and bile pigment accumulation. The breakdown of striated muscle in rhabdomyolysis releases myoglobin, a 17.8-kDa heme pigment, into the bloodstream. This condition typically arises following prolonged, intense, or unaccustomed physical activity, especially in hot and humid environments where muscle energy production is compromised due to an imbalance between supply and demand. The mechanism of pigment-induced kidney injury is complex and involves several interrelated processes, including renal vasoconstriction, direct toxicity to proximal tubular epithelial cells, and obstruction of distal tubules by pigment cast formation. In acidic urine, heme pigments readily bind with Tamm-Horsfall protein, promoting the formation of obstructive casts within the distal tubules.[2,6] Rhabdomyolysis causes can be grouped into three categories: traumatic (such as crush injuries, physical trauma, or prolonged immobilization), nontraumatic exertional (including intense physical activity, eccentric exercise, hyperthermia, or underlying metabolic and muscular disorders), and nontraumatic nonexertional (such as drug or toxin exposure, infections, or electrolyte imbalances). In the present study, rhabdomyolysis was observed in approximately 14 patients (70%) and was attributed to various causes, including persistent hypokalemia following diarrhea (4), infections (3), strenuous exercise (2), physical trauma (2), inflammatory myositis (1), neuroleptic malignant syndrome induced by quetiapine and chlorpromazine (1), and heat stroke.[1] Consistent with established classifications, our study observed cases of rhabdomyolysis arising from all three major etiological categories. Rhabdomyolysis results in the leakage of myoglobin, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) into the blood. Although serum myoglobin levels rise early following muscle injury, its rapid and variable metabolism limits its diagnostic sensitivity.[13] Therefore, serum CPK is considered the most sensitive enzymatic marker for detecting muscle injury. Though the threshold for serum CPK to predict the risk of AKI has not been outlined, levels above 5000 U/L are generally

considered to be associated with an increased risk.[14] In contrast, only eight patients (57.1%) in our cohort exhibited such elevated levels. Among the remaining six patients, four had CPK levels ranging from 936 to 3640 IU/L, while two had normal serum CPK levels. Notably, pigment nephropathy was also observed in patients with normal CPK values in the present study. Therefore, a high index of suspicion is essential for timely and accurate diagnosis of pigment nephropathy, regardless of CPK levels.

The second leading cause of pigment nephropathy is intravascular hemolysis. The important causes of intravascular hemolysis are paroxysmal nocturnal hemoglobinuria (PNH), hemoglobinopathies, malaria, transfusion reaction, prosthetic heart valves, and drugs.[4,15,16] Intravascular hemolysis releases hemoglobin into the plasma. When plasma hemoglobin levels exceed the binding capacity of haptoglobin, the concentration of free plasma hemoglobin increases. Free hemoglobin then dissociates into dimeric hemoglobin, which further breaks down into heme and globin. Free heme can pass through the glomerulus and may cause kidney injury. Studies on novel biomarkers have highlighted the role of free iron-mediated kidney injury and identified it as a significant mechanism underlying AKI in patients undergoing cardiopulmonary bypass.[17] Hemolysis was observed in six patients (30%) in our study and was attributed to various causes: paroxysmal nocturnal hemoglobinuria (two patients), thrombotic microangiopathy (1), transfusion reaction (1), rifampicin-induced hemolysis (1), and physical exertion (Fig. 3).[1] Both patients with paroxysmal nocturnal hemoglobinuria exhibited diffuse, intense blue staining with Perl's Prussian Blue stain, indicating hemosiderin deposition. In one patient, pigment nephropathy was caused by hemolysis associated with thrombotic microangiopathy. Rifampicin-induced hemolysis leading to pigment nephropathy was observed in a patient on daily therapy for 10 days. Another patient experienced severe hemolysis following intense running and developed hemoglobin cast nephropathy. Other studies have also reported hemolysis associated with PNH, blood transfusion, and rifampicin therapy.[3–5] Envenomation, poisoning, malaria, infections, and sepsis are common etiologies for both rhabdomyolysis and hemolysis.[6,16] However, in our study, we did not identify envenomation or poisoning as a cause of pigment nephropathy, conditions that are more commonly reported in the southern regions of India. There are no significant histological differences in pigment nephropathy caused by rhabdomyolysis versus hemolysis, except for the presence of hemosiderin deposition in cases of hemoglobin cast nephropathy.[3] In our study, all kidney biopsies showed severe acute tubular necrosis with granular pigment casts. Therefore, it is morphologically challenging to distinguish the underlying cause of pigment nephropathy. Immunohistochemistry for myoglobin and hemoglobin remains the only reliable method for differentiating between myoglobin-induced and hemoglobin-induced kidney injury.

Pigment nephropathy frequently leads to severe AKI requiring hemodialysis (HD). Currently, there is no definite treatment for pigment nephropathy. Management primarily focuses on preventing AKI in high-risk patients, particularly those with CPK levels exceeding 5000 IU/L.[14] Supportive treatment, such as adequate hydration, maintaining fluid and electrolyte balance, ensuring proper tissue perfusion, and initiating dialysis when indicated, are essential component of care. In our study, the majority of patients (85%) underwent HD, with an average of six sessions (range: 3–17). The remaining three patients (15%) did not require dialysis and showed improvement with conservative management. A study from South India by Sakthirajan et al. reported that approximately 97.8% of patients required HD during hospitalization, with a mean of 9 ± 2 sessions, findings that are broadly comparable to ours.[9] The severity of pigment nephropathy is largely influenced by the underlying disease and the promptness of preventive interventions. Severe AKI is commonly associated with prolonged hospital stays and increased morbidity. The mean peak serum creatinine level of 12.09 mg/dL and the requirement for hemodialysis in 17 patients (85%) indicate the severe nature of AKI in our cohort, which may be attributed to the severity of the underlying disease process and delayed presentation. In our study, the mean hospital stay was 15.3 days (range: 4–30), and the average time to renal recovery was 3.1 weeks (range: 2–6) (Fig. 4). Reported mortality rates in pigment nephropathy range from 3.5 to 22%, depending on several factors such as the severity of the primary illness, AKI-related complications, and the burden of prolonged hospitalization.[2,18,19] Notably, mortality is significantly higher among patients with AKI compared to those without (19.2% vs 3.6%).[9] In our cohort, all patients survived the acute phase and achieved complete renal recovery, evidenced by normalization of serum creatinine. No deaths occurred due to pigment nephropathy. The short-term prognosis of pigment nephropathy is generally favorable, with most patients achieving complete renal recovery.[7,9] However, several studies have shown an increased risk of developing CKD, even in patients who initially recover renal function. In separate cohorts, Sakthirajan et al. and Liapis et al. reported CKD development in 12% and 45% of patients, respectively.[8,9] Of the 20 patients, 13 completed at least 1 year of follow-up. Twelve had normal urine albumin-to-creatinine ratios (A1), while one had microalbuminuria (A2). None of the patients progressed to chronic kidney disease (CKD). This disparity in CKD development risk may be attributed to the shorter follow-up duration in the present study compared to others.

Overall prognosis appears favorable; however, larger studies with extended follow-up are needed to better characterize long-term outcomes in pigment nephropathy.

Limitations of the Study

The present study has several limitations, including a small sample size from a single center and the unavailability of key diagnostic markers such as urine myoglobin, serum haptoglobin, and plasma-free hemoglobin. These factors limit the generalizability of the findings. Furthermore, the short duration of follow-up restricts the ability to assess long-term outcomes.

Conclusion

Pigment nephropathy is often underrecognized cause of acute kidney injury. Total 20 patients (4.1%) were identified with pigment-induced AKI, of whom 14 (70%) had myoglobin-induced pigment nephropathy, and 6 (30%) had hemoglobin-induced pigment nephropathy. Common causes of rhabdomyolysis include hypokalemia, infection, and strenuous activity. Hemolysis was associated with paroxysmal nocturnal hemoglobinuria, thrombotic microangiopathy, transfusion reactions, rifampicin therapy, and physical exertion. Most patients (85%) required hemodialysis, with a mean hospital stay of 15.3 days. All patients survived the acute phase and achieved complete renal recovery, with normalization of serum creatinine in an average of 3.1 weeks. Of the 13 patients with a minimum of 1 year of follow-up, all had normal serum creatinine at 1 year. Twelve had normal urine albumin-to-creatinine ratios (A1), while one had improving microalbuminuria (A2). None progressed to chronic kidney disease. Despite favorable outcomes, larger studies with extended follow-up are needed to clarify long-term prognosis.

Data Availability Statement

The data sets generated and analyzed during the current study are not publicly available

due to patient confidentiality; however, they can be made available upon appropriate request to the corresponding author.

Conflict of Interest

Author do not have any competing either financial or nonfinancial interests to declare.

Informed Consent

Informed consent was obtained from all patients for the collection and utilization of their clinical and laboratory data in research and publication.

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Authors Contributions

Dr Prem Shankar Patel, Dr Prit Pal Singh, Dr Om Kumar, Dr Archana, and Dr Pinki Kumari contributed to the study's conception and design. Data acquisition and analysis were carried out by Dr Prem Shankar Patel, Dr Pinki Kumari, and Dr Archana. The initial draft of the manuscript was written by Dr Prem Shankar Patel and Dr Archana. All authors critically reviewed earlier versions and have read and approved the final manuscript.

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ORIGINAL ARTICLE

Clinicomycological Profile and *In Vitro* Antifungal Activity of Terbinafine and Griseofulvin against Clinical Isolates of Dermatophytes in a Tertiary Care Hospital

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Abstract

Background: Dermatophytes, primarily *Epidermophyton* spp., *Trichophyton* spp., and *Microsporum* spp., are responsible for superficial cutaneous mycoses, estimated to affect 20–25% of the people worldwide. The rise of antifungal resistance, especially to terbinafine, has made treating dermatophytosis increasingly difficult. This study aims to assess the clinical and mycological characteristics of dermatophytosis cases and evaluate the *in vitro* susceptibility of dermatophyte isolates to terbinafine and griseofulvin.

Materials and methods: A total of 118 samples were studied from patients with clinical suspicion of dermatophytosis. The samples were processed for KOH mount and fungal culture for further speciation. Susceptibility to terbinafine and griseofulvin was assessed using the microbroth dilution technique, following the guidelines established by the Clinical and Laboratory Standards Institute (CLSI).

Results: Tinea corporis (57.6%) appeared as the leading symptomatology in our study, followed by tinea cruris (10.2%). KOH positivity was higher (70.3%) compared to positivity by culture (16.9%). *Trichophyton mentagrophytes* was the predominant species (85%) isolated, followed by *Trichophyton violaceum* (10%) and *Microsporum gypseum* (5%). Terbinafine resistance was observed in over 60% of *T. mentagrophytes* isolates, with moderate resistance detected in *T. violaceum*. Griseofulvin showed moderate resistance in *T. mentagrophytes* and higher resistance in *T. violaceum*.

Conclusion: This study highlights the increased resistance of *T. mentagrophytes* to terbinafine and *T. violaceum* to griseofulvin, stressing the critical role of routine susceptibility profiling. The findings highlight the growing challenge of antifungal resistance in dermatophytes and the importance of optimizing diagnostic and treatment strategies to improve patient outcomes.

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Introduction

Dermatophytes, filamentous fungi categorized under the genera *Epidermophyton* spp., *Trichophyton* spp., and *Microsporum* spp., are the primary causative agents of superficial cutaneous mycoses, impacting approximately 20–25% of the global population.[1] These fungi exhibit a unique ability to metabolize keratin, the predominant protein in skin, hair, and nails, which facilitates their role in causing dermatophytosis or ringworm infections. Dermatophytosis manifests as a host response to fungal enzymes released during keratin degradation, leading to inflammation and characteristic clinical presentations.

Globally, dermatophytosis remains a prevalent health concern, particularly in regions with high humidity, dense populations, and substandard hygiene.[2] Additional risk factors include close contact with animals harboring zoonotic dermatophyte infections. Despite the availability of effective antifungal therapies, treatment failures are increasingly reported due to poor adherence to prescribed regimens, improper use of topical steroids, and compromised host immunity. Among these challenges, drug resistance in dermatophytes poses a significant and growing public health threat.

The emergence of resistance to terbinafine, one of the most widely used antifungal agents, is particularly alarming.[3] Specific mutations in the squalene epoxidase (*SQLE* or *SE*) gene, which encodes the essential enzyme for ergosterol synthesis, are key to terbinafine resistance in dermatophytes. These genetic changes reduce the efficacy of terbinafine, thereby complicating treatment outcomes. Moreover, the lack of routine implementation of antifungal susceptibility testing (AFST) in clinical practice contributes to delays in detecting resistant strains and initiating suitable treatment strategies. The lack of antifungal policies in many hospitals worldwide has contributed to the increasing prevalence of antifungal-resistant strains of dermatophytes and inadequate infection control measures. For laboratory-based identification of antifungal resistance, the CLSI document provides guidelines for the broth microdilution method applicable to filamentous fungi. This method calculates the minimum inhibitory concentration (MIC), with higher MIC values indicating relative resistance to a particular drug.[4]

In light of these challenges, this study is designed to investigate both the clinical characteristics and mycological patterns of dermatophytosis in patients treated at a tertiary-care hospital and to evaluate the *in vitro* susceptibility of dermatophyte isolates to terbinafine and griseofulvin. This research addresses the significant gap in regional data on antifungal resistance and highlights the importance of adopting robust diagnostic and sensitivity-testing protocols to guide evidence-based management of dermatophytosis.

Materials and Methods

This hospital-based observational study was undertaken in the Department of Microbiology and Dermatology for a period of 6 months from February 2024 to July 2024, during which skin, hair, and nail samples were collected from clinically suspected cases of dermatophytosis of varying ages and both sexes. However, patients who were initiated on antifungal treatment were excluded from the study.

Institutional Ethics Committee Clearance

Ethical clearance for the study was obtained from the Institutional Ethics Committee under

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the reference number AV/IHEC/2024/006 dated January 3, 2024, prior to the initiation of research.

A total of 118 samples were studied, and patients were enrolled using a nonprobability sampling-convenient sampling technique. Each specimen was divided into two parts: one for a KOH mount and fungal culture. Varying concentrations of potassium hydroxide (KOH), 10%, 20%, and 40% were used for skin, hair, and nails, respectively and samples were subjected to microscopic evaluation to detect fungal elements (Fig. 1). Another part of the specimen was cultured on sabouraud dextrose agar (SDA) supplemented with cycloheximide and incubated at both 37 °C and 25 °C. The SDA slant was checked weekly for up to 4 weeks before being labelled negative for fungal culture (Fig. 2). Species identification was performed macroscopically by observing colony morphology and microscopically using a lactophenol cotton blue mount (LPCB) (Fig. 3).[5]

Antifungal drug susceptibility profile was determined for terbinafine and griseofulvin by microbroth dilution assay according to the CLSI guidelines-document M38-A of filamentous fungi.[6] The stock preparation of the antifungal agents was formulated for susceptibility testing. RPMI-1640 medium, developed by Rose Parker Memorial Institute, was employed as the culture medium for fungal growth. The dermatophyte isolate was subcultured on potato dextrose agar (PDA) to promote the development of conidia. For the inoculation, 100 µL of the conidial suspension in RPMI-1640 was added to each well of a sterile, flat-bottomed 96-well microtiter plate. The wells were then filled with 100 µL of the diluted antifungal drugs. There were control wells with a sterility control that included just RPMI-1640 to validate the lack of contamination and a growth control that contained only the conidial suspension to confirm normal fungal growth. To evaluate the antifungal susceptibility against the investigated drugs, fungal growth was monitored after 48 and 72 hours of incubation at 35 °C in the microtiter plates.

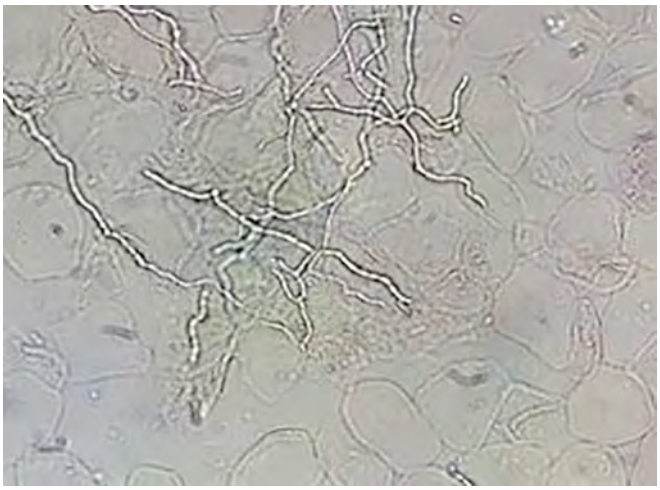
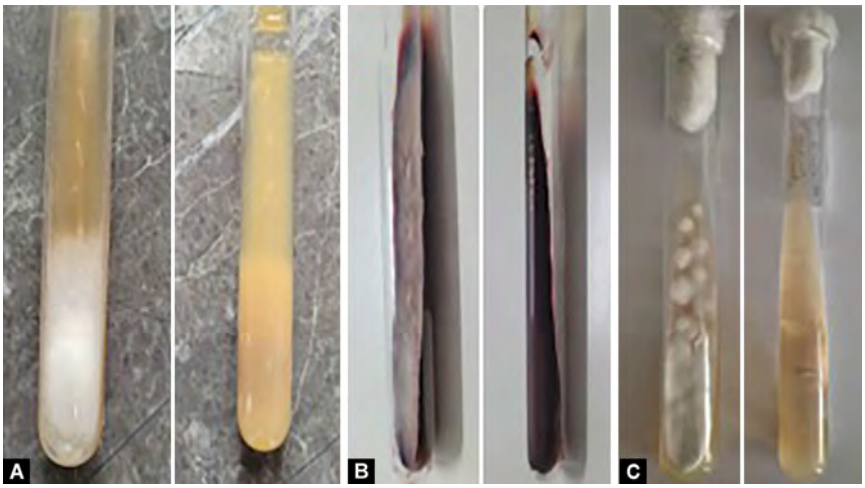


Fig. 1: KOH mount of skin scraping showing fungal filaments (40× magnification)



Figs 2A to C: SDA showing white powdery-cottony growth of *Trichophyton mentagrophytes* (A), wrinkled, purple pigmented colonies of *Trichophyton violaceum* (B), and white powdery colonies of *Microsporum gypseum* (C)

The isolates were further observed visually for 50% (MIC_{50}) and 90% (MIC_{90}) inhibition in growth, and the MIC calculated was established as the concentration at which the growth of dermatophytes was reduced by 80% for antifungal agents when compared to the control strains, *Trichophyton rubrum* PTCC 5143 and *T. mentagrophytes* PTCC 5054. Each test was conducted in triplicate.

Statistical Analysis

Frequency and percentage were used to summarize categorical variables. The mean ± standard deviation was used to describe continuous variables. Data analysis was conducted using SPSS version 28.

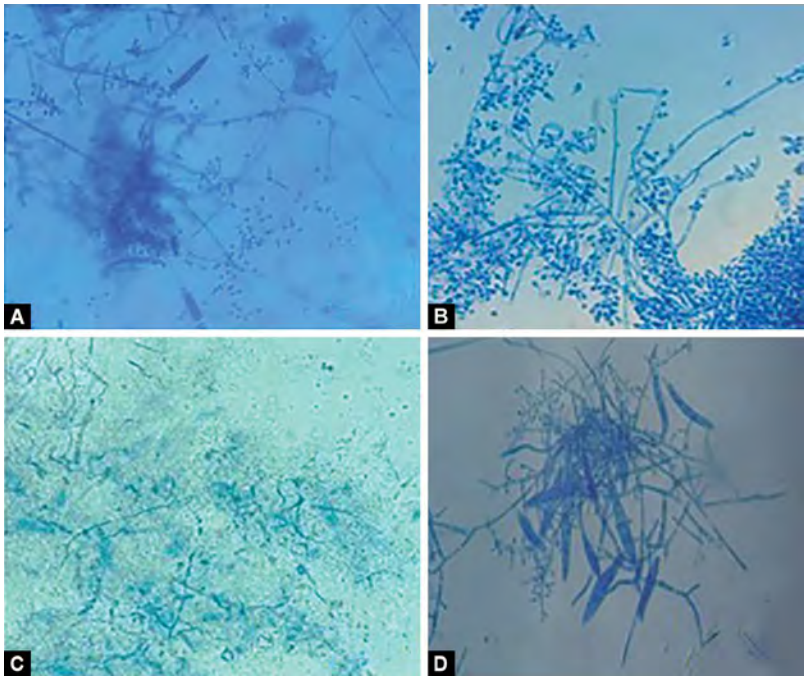
Results

Table 1 illustrates the distribution of individuals by gender across different age groups. The largest group, aged 21–30 years, comprised 25 people, with a nearly equal split between males and females. The 41–50 years group followed with 23 individuals. Age groups 11–20 and 31–40 years had 22 and 20 people, respectively, also showing balanced gender proportions. The 61–70 years group and the 51–60 years had 11 individuals each. The youngest (0–10 years) included only 5, and the oldest (71+ years) recorded just one male. Males generally outnumbered females, except in the 11–20, 51–60, and 61–70 years groups. This shows a very slight male (50.9%) predominance over females (49.1%).

The most commonly encountered clinical presentation was tinea corporis, accounting for 57.6% of cases. This was followed by a combined presentation of tinea corporis and tinea cruris in 13.6% and isolated tinea cruris in 10.2% of cases. Other presentations, such as tinea capitis (7.6%), tinea pedis (4.2%), tinea faciei (3.4%), tinea incognita (1.7%), and tinea barbae (1.7%), were less frequent. These results highlight tinea corporis as the predominant clinical manifestation among the study population (Table 2).

KOH positivity was significantly higher, with 83 samples (70.3%) testing positive, while culture positivity was much lower, with only 20 samples (16.9%) yielding positive results. All those 20 samples which was culture positive were also KOH positive. Out of 83 KOH-positive samples, 63 were culture negative. From the total 118 samples, both KOH and culture-negative were 35 samples (Table 3).

Among 20 culture positive samples *T. mentagrophytes* was the most prevalent species, accounting for 17 isolates (85%). *T. violaceum* was identified in two isolates (10%), and *M. gypseum* was the least common, with only one isolate (5%) (Table 4).



Figs 3A to D: LPCB mount showing grape-like clusters of microconidia, cigar-shaped macroconidia of *Trichophyton mentagrophyte* (A and B), highly distorted hyphae of *Trichophyton violaceum* (C), and numerous spindle-shaped macroconidia of *Microsporum gypseum* (D)

Table 2: Clinical presentation of dermatophytes infection (*n* = 118)

Clinical presentation	*Number*	*Percentage (%)*
Tinea corporis	68	57.6
Tinea cruris	12	10.2
Tinea corporis and cruris	16	13.6
Tinea pedis	5	4.2
Tinea incognita	2	1.7
Tinea capitis	9	7.6
Tinea faciei	4	3.4
Tinea barbae	2	1.7

Table 3: Comparison of KOH and culture results of dermatophytosis

KOH	*Culture*	
	Positive	*Negative*
Positive (83)	20	63
Negative (35)	–	35
Total (118)	20	98

Table 1: Age and sex-wise distribution of cases (*n* = 118)

Age group	*Male*	*Female*	*Total*
0–10 years	3	2	5 (4.2%)
11–20 years	10	12	22 (18.6%)
21–30 years	13	12	25 (21.1%)
31–40 years	10	10	20 (16.9%)
41–50 years	13	10	23 (19.4%)
51–60 years	5	6	11 (9.3%)
61–70 years	5	6	11 (9.3%)
>71 years	1	0	1 (0.8%)
Total	60 (50.9%)	58 (49.1%)	118

Table 4: Isolation rate of dermatophyte species (*n* = 20)

Species	*Number*	*Percentage (%)*
Trichophyton mentagrophytes	17	85
Trichophyton violaceum	2	10
Microsporum gypseum	1	5
Total	20	100

The minimum inhibitory concentration testing for terbinafine showed that *T. mentagrophytes* had MIC_{50} and MIC_{90} values of 4 µg/mL and 8 µg/mL, respectively. *T. violaceum* demonstrated lower MIC_{50} (0.6 µg/mL) and significantly higher MIC_{90} (32 µg/mL) values, indicating variable susceptibility. However, in *M. gypseum*, both MIC_{50} and MIC_{90} were recorded at 8 µg/mL. The findings revealed varied susceptibility patterns to terbinafine among different dermatophyte species. More than 60% of *T. mentagrophytes* (*n* = 17) isolates showed resistance to terbinafine. *T. violaceum* (*n* = 2) and *M. gypseum* (*n* = 1) shows 50% and 100% resistance, respectively (Table 3).

Griseofulvin susceptibility testing showed that *T. mentagrophytes* had MIC_{50} and MIC_{90} values of 4 µg/mL and 16 µg/mL, respectively, indicating moderate resistance. *T. violaceum* demonstrated a higher MIC90 (64 µg/mL) compared to its MIC_{50} (2 µg/mL), suggesting greater resistance at higher concentrations. For *M. gypseum*, both MIC_{50} and MIC_{90} values were 0.5 µg/mL, reflecting good susceptibility to griseofulvin. These findings highlighted significant variations in griseofulvin susceptibility across dermatophyte species (Table 5).

Discussion

Fungal infections of the skin, hair, and nails that result in cutaneous mycoses are caused by dermatophytes. These infections are more prevalent in developing countries and are commonly reported in various regions of India. The warm, humid climate of tropical and subtropical areas is believed to favor their growth and spread. A wide range of antifungal agents has been used for its treatment, but susceptibility varies among different dermatophyte strains. Failure of treatment and emergence of resistance are frequently associated with decreased drug absorption, changes at the phenotypic or genetic level, and increased activity of drug

Table 5: *In vitro* susceptibility testing of terbinafine and griseofulvin antifungal agents against dermatophytes species by microbroth dilution assay ($n = 20$)

Species	*Antifungal drug concentration (µg/mL)*		
		Terbinafine	*Griseofulvin*
T. mentagrophytes ($n = 17$)	Range	0.03–64	0.03–64
	MIC_{50}	4	4
	MIC_{90}	8	16
T. violaceum ($n = 2$)	Range	0.03–64	0.03–64
	MIC_{50}	0.6	2
	MIC_{90}	32	64
M. gypseum ($n = 1$)	Range	0.03–64	0.03–64
	MIC_{50}	8	0.5
	MIC_{90}	8	0.5

efflux systems.[4,7,8] The present study draws attention to the rising concern of antifungal resistance in dermatophytes, with particular interest taken in susceptibility to terbinafine and griseofulvin.

In the present investigation, dermatophytosis was predominantly observed in individuals aged 21–30 years, with a higher incidence among males. These findings are consistent with those documented by Das et al.[8] The observed distribution pattern may be attributed to factors such as increased outdoor exposure and physical activity commonly associated with this age group.[9] Furthermore, tinea corporis emerged as the most frequently encountered clinical manifestation, aligning with the observations reported by Poluri et al.[10]

In the current study, we noted a discrepancy between KOH positivity (70.3%) and culture positivity (16.9%). Such trends have also been reported in another study,[11] where they have substantiated that the elements may fail to grow because of previous antifungal exposure or due to nonviability. The discrepancy between KOH and culture positivity shows the importance of optimizing diagnostic methodologies for accurate identification. In the present study, *T. mentagrophytes* emerged as the most prevalent dermatophyte species, aligning with observations from a study in Western India, where it comprised 47.2% of the total isolates.[12] One of the key findings of this study is the moderate resistance of *T. mentagrophytes* to terbinafine, with MIC_{50} and MIC_{90} values of 4 µg/mL and 8 µg/mL, respectively. This similar pattern of terbinafine resistance in dermatophytes, particularly in *T. mentagrophytes*, has been reported in several other studies.[13–15] The rising occurrence of terbinafine resistance is often associated with mutations in the squalene epoxidase gene, leading to reduced therapeutic effectiveness. The research conducted by Turner and McLellan[16] highlighted that the growing resistance to terbinafine is a major concern in managing dermatophyte infections.

Sensitivity pattern of griseofulvin demonstrated a higher resistance among *T. violaceum* with MIC_{90} of 64 µg/mL. The outcome of the current study matches the study by Van et al.,[17] who reported similar resistance profiles for griseofulvin across different *Trichophyton* species. On the contrary, the study conducted by Sowmya et al.[7] showed 100% susceptibility of the isolates to terbinafine, griseofulvin, and other antifungal agents, and another study by Amin et at.[18] documented lower MIC values for dermatophytes isolated from chronic and recurrent dermatophytosis.

The emergence of antifungal resistance calls for the routine testing of antifungal susceptibility, especially in recurrent dermatophytosis.[19] The performance of broth microdilution testing has been shown to yield reliable and reproducible results, as observed in previous studies,[20] when compared to other methods for AFST.

Conclusion

The findings from this study enhance current knowledge on dermatophyte characterization and resistance trends, which are critical for guiding effective antifungal therapy in dermatophytosis. *T. mentagrophytes* is the most prevalent dermatophyte observed with significant resistance to terbinafine, underscoring a growing concern regarding antifungal resistance in dermatophyte infections. Although griseofulvin remains effective against certain species, such as *M. gypseum*, its efficacy is compromised in others, notably *T. mentagrophytes*, where moderate resistance was detected.

The findings highlight the critical role of performing routine AFST in clinical practice, both to guide evidence-based therapeutic decisions and to ensure the selection of the most effective antifungal agents, thereby improving treatment outcomes. Given the increasing prevalence of dermatophytosis and the rise in antifungal resistance, AFST can aid in tailoring treatment strategies, minimizing treatment failures, and improving patient outcomes. The study also highlights the need for region-specific strategies to combat dermatophytosis, as the prevalence and resistance patterns may vary across different geographical locations. Enhanced diagnostic protocols, regular surveillance of antifungal resistance, and the adoption of more stringent antifungal stewardship practices in clinical settings are crucial to combat the threat of emerging antifungal resistance.

Author's Contributions

- Jaishma Rajni J: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing—Original draft preparation.
- Pramodhini S: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing—Original draft preparation, Supervision, Visualization, Reviewing, and Editing.
- Sheela Kuruvila: Conceptualization, Methodology, Investigation, Resources, Supervision, Visualization, Reviewing, and Editing.
- Latha R: Conceptualization, Methodology, Formal analysis, Supervision, Visualization, Reviewing, and Editing.
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- Sherief Shebeena: Investigation, Resources, Supervision, Visualization, Reviewing, and Editing.

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ORIGINAL ARTICLE

Association between Androgenic Hair Patterns and Prostate Cancer Risk in South Indian Men: A Case-control Study from the Cauvery Delta

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Abstract

Background: Prostate cancer (PCa) is one of the most common malignancies in men worldwide. Androgens influence both prostate growth and hair patterns. Androgenic alopecia (male-pattern baldness) and excessive male-pattern body hair (hypertrichosis) have been hypothesized as clinical markers of long-term androgen exposure. Previous Western studies have reported mixed results on whether early-onset or severe androgenic alopecia correlates with increased prostate cancer risk. Data in South Indian (Dravidian) populations is lacking.

Objective: To examine the association between androgenic hypertrichosis, androgenic alopecia, and prostate cancer in Dravidian men from the Cauvery Delta region of Tamil Nadu, India.

Materials and methods: We conducted an age-stratified, population-based case-control study among men in the Cauvery Delta. The cases consisted of 117 men with pathologically confirmed adenocarcinoma of the prostate (diagnosed 2010–2015). Controls were 123 men with benign prostatic hyperplasia (BPH) from the same hospital registries, frequency-matched by age. Individuals with incomplete data or non-Dravidian (North Indian) ancestry were excluded. Trained investigators performed face-to-face interviews, directly observing and recording postpubertal body hair growth (indicative of androgenic hypertrichosis) and scalp hair loss (androgenic alopecia classified by the Norwood scale). Statistical analysis included multivariate discriminant analysis (Wilks' Lambda), one-way ANOVA for continuous variables, chi-square cross-tabulation, and computation of Cramer's V statistic to assess association strength. A two-tailed *p*-value of <0.05 was considered statistically significant.

Results: The age distributions of cases and controls were comparable. The prevalence of androgenic hypertrichosis and alopecia did not differ significantly between prostate cancer cases and BPH controls. Cramer's V analysis showed that prostate cancer status accounted for only 1.1% of the variance in hypertrichosis (Cramer's V ≈ 0.011) and 1.5% of the variance in alopecia (Cramer's V ≈ 0.015).

Conclusion: In this case-control study of Dravidian men from Tamil Nadu, we observed no significant association between androgenic alopecia or hypertrichosis and prostate cancer. These findings contrast with data from Western cohorts, suggesting that interethnic variation in androgen receptor polymorphisms, follicular sensitivity, and environmental exposures may modulate prostate cancer risk differently. Further research is needed to elucidate how androgenic traits influence prostate carcinogenesis across different ethnic groups.

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Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed cancers in men worldwide. Based on the GLOBOCAN 2022 estimates, PCa ranks as the fourth most common cancer overall and the second most common among men, with around 1.47 million new cases and nearly 397,000 deaths globally.[1] More recent analyses report that age-standardized incidence rates (ASIR) vary over 13-fold between regions, ranging from under 10 per 100,000 in South-Central Asia to over 100 per 100,000 in parts of Northern America and Northern Europe.[2] The median age at diagnosis is approximately 67 years, with over 60% of cases occurring in men aged 65 or older. Established risk factors for PCa include advancing age, family history, race/ethnicity, and certain genetic variations.[3] Notably, men of African ancestry have a higher incidence and mortality than those of European descent.

In India, the incidence of prostate cancer is steadily rising, particularly in metropolitan regions. Prostate cancer ranks second among male cancers in India, with an ASIR of 5.5 per 100,000 men—substantially lower than rates in Western countries (e.g., >100 per 100,000 in the United States). However, this likely reflects underreporting, low screening rates, and limited awareness, rather than the true absence of disease.[4]

Among Indian states, South India—particularly urban regions such as Chennai, Bengaluru, and Thiruvananthapuram—has consistently reported higher prostate cancer incidence. Data from the Population-based Cancer Registries (PBCRs) under the Indian Council of Medical Research - National Centre for Disease Informatics and Research (ICMR-NCDIR) showed that the Chennai PBCR reported an ASIR of 10.8 per 100,000, which is nearly double the national average.[5] Similar trends were observed in the Bengaluru and Thiruvananthapuram registries. This regional variation may reflect greater diagnostic access, lifestyle differences, and possibly unique genetic profiles in the Dravidian population.

Notably, Dravidian men in South India may harbor distinct androgen receptor (AR) polymorphisms, such as shorter CAG repeat lengths, which have been associated with both increased prostate cancer risk and variable androgen sensitivity.[6] This underscores the importance of region-specific research into androgenic traits and their potential role in prostate carcinogenesis, as findings from Western populations may not directly apply to Indian cohorts.

The Cauvery Delta lies in the southeastern part of the Indian peninsula, primarily encompassing the districts of Thanjavur, Tiruvarur, Nagapattinam, and parts of Trichy and Ariyalur in the state of Tamil Nadu. It is formed by the branching of the Cauvery River, which originates in Karnataka and drains into the Bay of Bengal. This fertile region, often referred

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to as the "Rice Bowl of Tamil Nadu," is predominantly agrarian and sustains dense rural populations. Genetically, the population is relatively homogeneous compared to cosmopolitan urban centers, making it a suitable cohort for phenotype–disease association studies.

Androgenic hair changes—namely male-pattern baldness—are driven by dihydrotestosterone (DHT) via the 5α-reductase pathway. In balding scalp follicles, increased local 5α-reductase activity converts testosterone to DHT, which binds androgen receptors and leads to follicular miniaturization and hair thinning.[7] DHT exerts androgenic effects on nonscalp areas, stimulating the development and persistence of terminal hair in androgen-sensitive regions such as the beard, axillae, chest, and limbs.[8]

Androgenetic alopecia (AGA) is extremely common–affecting ~50% of Caucasian men by age 50 and ~80% by age 70. Prevalence is somewhat lower in Asian populations, but still substantial. Given that both prostate cancer and AGA are androgen-dependent, several Western studies have investigated their link. There is limited evidence from India linking androgenic hair patterns to prostate cancer. Given ethnic differences in AR genetics and hair biology, results from Caucasian/Western cohorts may not generalize. It is plausible that Dravidian men manifest androgen effects differently (for example, a genetic propensity to body hair growth) that could uncouple hair phenotypes from cancer risk. To our knowledge, no previous study has assessed both scalp and body hair patterns in relation to prostate cancer in the Tamil population. We therefore undertook this age-stratified, population-based case-control study to evaluate whether androgenic alopecia or hypertrichosis is associated with histologically confirmed prostate cancer among men from the Cauvery Delta region.

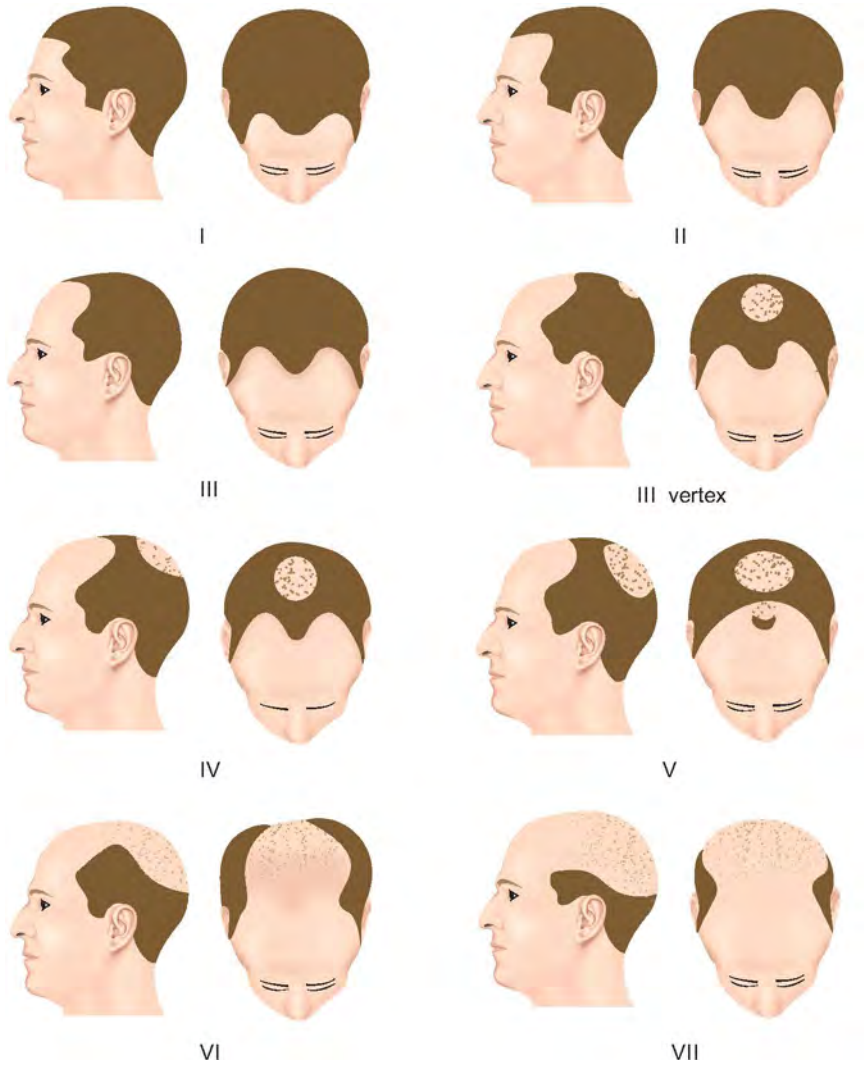

Fig. 1: Hamilton–Norwood classification

Materials and Methods

Study Design and Participants

This was an age-stratified, population-based case-control study conducted in the Cauvery Delta region of Tamil Nadu, India. The source population consisted of adult men of Dravidian (Tamil) ethnicity who sought urological care between 2010 and 2015.

The study included 117 men with histopathologically confirmed adenocarcinoma of the prostate, diagnosed in the Cauvery Delta region between 2010 and 2015. The control group comprised 123 men presenting with lower urinary tract symptoms and diagnosed with benign prostatic hyperplasia (BPH) during the same period at Thanjavur Medical College Hospital and FrontLine Hospital, Trichy. Controls were frequency-matched to cases based on age distribution to minimize confounding.

Men of non-Dravidian (North Indian or other) ethnicity and those with missing clinical or hair data were excluded. All participants provided informed consent for study procedures.

Data Collection

Trained investigators conducted structured, face-to-face interviews with each participant. Demographic information (age, education, occupation), lifestyle factors, medical history, and family history of prostate disease were recorded. The key exposures—androgenic hypertrichosis and androgenic alopecia—were assessed by direct physical examination during the interview:

- Androgenic hypertrichosis: Excessive hair growth in postpubertal males over and above the normal for the age, race of an individual, with normal prepubertal hair distribution. Examiners noted presence or absence of conspicuous body hair in typical androgen-dependent areas (e.g., central chest, shoulders, back). Any man with notably dense male-pattern body hair was classified as hypertrichotic.
- Androgenic alopecia: Assessed using the standardized Hamilton–Norwood classification (Fig. 1). Trained observers determined the Norwood grade of scalp hair loss in each participant. We categorized baldness into vertex (crown) baldness, frontal baldness, or no significant alopecia.

By direct observation (not self-report), the interviewers documented each subject's current hair pattern. All examiners were blinded to the subject's case/control status when assessing hair, to reduce observer bias.

Table 1: Comparison of hypertrichosis and androgenic alopecia scores between prostate cancer and BPH groups

Variables	*Diagnosis*	*No of patients*	*Mean*	*SD*	*SEM*
Hypertrichosis	CA prostate	117	0.06	0.238	0.022
	BPH	123	0.07	0.248	0.022
Androgenic Alopecia	CA prostate	117	0.23	0.423	0.039
	BPH	123	0.24	0.431	0.039

Table 3: Distribution of hypertrichosis among patients with prostate cancer and BPH

Diagnosis	*Hypertrichosis*		*Total*
	No	*Yes*	
CA prostate	110	7	117
BPH	115	8	123
Total	225	15	240

Table 4: Distribution of androgenic alopecia among patients with prostate cancer and BPH

Diagnosis	*Alopecia*		*Total*
	No	*Yes*	
CA prostate	90	27	117
BPH	93	30	123
Total	183	57	240

Statistical Analysis

We performed descriptive analyses comparing cases and controls. Continuous variables (e.g., age) were summarized as means ± standard deviations and compared by one-way ANOVA. Categorical variables (presence/absence of hypertrichosis or alopecia) were analyzed using chi-square tests. The strength of association between hair phenotype and prostate cancer was quantified using Cramer's V coefficient from the cross-tabulation: this gives the percentage of variance in cancer status explained by hair status. A multivariate linear discriminant analysis (Wilks' lambda) was also computed to examine the joint discriminative power of age, hypertrichosis, and alopecia for classifying case vs control. All tests were two-sided with $\alpha = 0.05$. Statistical analyses were conducted using SPSS v22 (IBM, Armonk, NY) and MedCalc v15 (Ostend, Belgium).

Results

Participant Characteristics

The final analysis included 117 prostate cancer cases and 123 BPH controls. Most subjects were aged between 60 and 75 years, reflecting the age distribution of PCa. The mean age (± SD) was almost similar in both groups (cases: 67.2 ± 7.8 years; controls: 66.5 ± 8.2 years). Educational levels and occupational backgrounds did not differ notably. There were no significant differences between cases and controls in known risk factors such as body mass index (BMI) or smoking history.

The mean BMI was 23.8 ± 3.1 kg/m^2 in the prostate cancer group and 23.6 ± 2.9 kg/m^2 in the BPH control group, consistent with regional averages. Approximately 26% of cases and 24% of controls reported current or past smoking, with no significant differences between groups ($p > 0.05$).

Hair Phenotypes

Among cases, hypertrichosis was observed in 6% (7/117), and in controls, 6% (8/123) had hypertrichosis. Baldness was observed in 23% (27/117) of prostate cancer cases and 24% (30/123) of BPH controls. Among these, vertex baldness was more prevalent—seen in 18% (21/117) of cases and 20% (25/123) of controls, while frontal-only baldness was observed in 5% (6/117) and 4% (5/123). This pattern indicates that vertex baldness was the predominant type in both groups.

The one-way ANOVA results (Table 1) indicate that there is no statistically significant difference in the mean scores of hypertrichosis and androgenic alopecia between prostate cancer and BPH groups ($p > 0.05$). This suggests that neither trait effectively differentiates the two diagnostic groups.

Therefore, hypertrichosis and androgenic alopecia are not associated with prostate cancer status in this study population. Prevalence of both traits was similar in cases and controls.

From multidiscriminant analysis (MDA) (Table 2), Wilks' lambda of 1.00 and a nonsignificant chi-square 0.07 ($p > 0.05$) indicate that hypertrichosis and androgenic alopecia do not significantly discriminate between prostate cancer and BPH groups.

Table 2: Results of multidiscriminant analysis

Variables	*Coefficient*
Hypertrichosis (X_1)	2.132
Androgenic alopecia (X_2)	1.886
Constant	−4.599

The results of cross-tabulation between hypertrichosis and diagnosis (carcinoma prostate vs BPH) showed a Cramer's V value of 0.011, indicating a very weak association (Table 3), accounting for only 1.1% of the variance. This confirms that the presence or absence of hypertrichosis is statistically independent of diagnosis at the 5% significance level.

Similarly, cross-tabulation between androgenic alopecia and diagnosis yielded a Cramer's V value of 0.015, indicating a very weak association (Table 4), explaining only 1.5% of the variance. This also confirms that the presence or absence of androgenic alopecia is statistically independent of diagnosis at the 5% significance level.

Discussion

In this first study of its kind in the Cauvery Delta, we found no evidence that androgenic hair phenotypes predict prostate cancer in Tamil men. Both scalp baldness and male-pattern body hair growth were distributed equally among prostate cancer cases and BPH controls. Negligible correlation was observed between hair phenotypes and prostate cancer status.

Consequently, neither androgenic alopecia nor hypertrichosis emerged as risk indicators in this population. These findings contrast with some previous reports in Western cohorts. For example, an Australian age-stratified case-control study[9] found that vertex baldness was significantly associated with higher prostate cancer risk (age-adjusted OR ~1.5 for any vertex balding vs none).

A systematic review[10] of seven case-control studies likewise found that vertex AGA conferred a modestly increased risk (pooled OR ~1.25, $p = 0.002$). No statistically significant association between AGA (any pattern) and prostate cancer was identified (OR 1.03; $p = 0.58$).

A French cohort study[11] reported that men with early-onset baldness (by age 20) had doubled odds of prostate cancer.

These studies suggest shared androgenic pathways between scalp hair follicle miniaturization and prostate tumorigenesis. Proposed mechanisms include chronically elevated DHT levels or heightened 5α-reductase activity, which can both shrink

scalp follicles and promote prostatic epithelial proliferation.

Some studies have reported no positive association between androgenic alopecia and prostate cancer. A Dutch population-based analysis[12] found that early-onset baldness at age 20 or 40 was linked to a slightly reduced risk, and a combined frontal and vertex pattern at age 40 showed a significantly lower risk (*OR* = 0.62). No associations were found with aggressive cancer. These findings align with our study, reinforcing that baldness is not a reliable marker for prostate cancer risk.

A Turkish prospective study[13] reported no significant difference between androgenic alopecia and serum androgen levels in BPH and prostate cancer patients.

Our results are consistent with these null findings, suggesting that hair pattern may be an unreliable surrogate for lifetime androgen exposure or that its association with prostate cancer risk may be influenced by ethnic and genetic factors.

Previous studies suggest that South Indian men tend to carry shorter CAG repeat lengths in the androgen receptor gene, a polymorphism strongly linked to higher prostate cancer risk.

Shorter CAG repeats lead to more sensitive ARs, meaning that prostatic tissue may be hyper-responsive to normal androgen levels.

Paradoxically, this might manifest as increased cancer risk without necessarily causing markedly increased scalp hair loss–especially if other genetic factors (or hair follicle receptor levels) differ. In other words, a man may have high prostatic AR activity but comparatively preserved scalp hair, depending on AR coregulators or local 5α-reductase activity in the skin. Additionally, body hair growth (hypertrichosis) itself reflects androgenic end-organ sensitivity. Increased androgen conversion to DHT by 5α-reductase results in thicker beard and chest hair, often accompanied by scalp hair loss.[14]

A genetic predisposition toward dense body hair in Dravidian men may not necessarily translate into increased prostate cancer risk with prostate cancer risk. Indeed, we found that hypertrichosis itself showed no predictive value. Moreover, androgenic alopecia is highly age-dependent and genetically complex. In Caucasian men, by age 50, about half have noticeable baldness; in Asian men, the prevalence is somewhat lower but still substantial.[15]

Such baseline differences mean that a given degree of alopecia may represent different relative androgen histories across populations.

It is also possible that differences in diet, lifestyle, or environmental exposures in rural Tamil Nadu modulate prostate cancer risk in ways unrelated to hair phenotype. An alternative explanation is methodological: our controls were men with symptomatic BPH, not general population controls. BPH and prostate cancer share some pathophysiology, but their relationship to androgens is complex. If the controls had elevated intraprostatic DHT similar to cases (as might occur in BPH), this could diminish any apparent difference in hair patterns between groups. Indeed, Faydaci et al.[13] found no significant differences in baldness frequency or serum testosterone between BPH and prostate cancer groups, as we did.

Limitations of our study include the moderate sample size and potential for selection bias. Although we used direct clinical observation of hair (a strength over self-report), we did not quantify hormone levels or scalp DHT directly. Also, we did not stratify by tumor grade; some reports suggest AGA may link more strongly to aggressive or early-onset prostate cancer,[9] which we could not evaluate.

Finally, this study was conducted in a geographically confined, ethnolinguistically uniform Dravidian Tamil population from the Cauvery Delta region of South India, allowing for reduced genetic and environmental variability. Results may not apply to other Indian ethnic groups. Despite these limitations, our findings have implications for risk assessment. In the Cauvery Delta, neither male pattern baldness nor excessive body hair should be regarded as independent risk indicators for prostate cancer. This contrasts with some Western data, emphasizing that ethnic context matters. It further suggests that underlying androgen-related cancer mechanisms might differ by population. Future studies should explore genetic markers (e.g., AR polymorphisms, 5α-reductase expression) and include diverse cohorts to understand these differences.

Conclusion

In this case-control study of Dravidian men from Tamil Nadu, we observed no significant association between androgenic alopecia or hypertrichosis and prostate cancer. These findings contrast with data from Western cohorts, suggesting that interethnic variation in androgen receptor polymorphisms, follicular sensitivity, and environmental exposures may modulate prostate cancer risk differently. Further research is needed to elucidate how androgenic traits influence prostate carcinogenesis across different ethnic groups.

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ORIGINAL ARTICLE

Implications of Acetylator Status and Therapeutic Drug Monitoring of Plasma Rifampicin and Isoniazid Concentrations among Indians

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Abstract

Introduction: Low or abnormal plasma concentrations of anti-tuberculosis drugs can be a major reason for treatment failure or the emergence of drug resistance. Acetylator status, which affects drug metabolism, plays a key role in determining drug bioavailability. This study aimed to perform therapeutic drug monitoring (TDM) of rifampicin and isoniazid and to evaluate the correlation between plasma drug concentrations and acetylator status among Indian patients receiving first-line antituberculosis therapy.

Methods: Plasma concentrations of rifampicin and isoniazid were measured using in-house standardized high-performance liquid chromatography methods, while acetylator status was determined by conventional PCR of *NAT2* gene.

Results: Peak concentrations were estimated from 125 patients on first-line tuberculosis (TB) treatment. Among these, 56% exhibited subtherapeutic rifampicin concentrations and 28% had subtherapeutic isoniazid concentrations. Conversely, above normal (potentially toxic) concentrations were seen in 2% and 21% for rifampicin and isoniazid, respectively. Despite receiving the standard TB treatment regimen, only 62% of patients improved clinically, while 38% of patients continued harboring TB signs and symptoms, among which 6 patients (5%) developed rifampicin resistance during the treatment course. About 44% were slow acetylators, followed by 40% intermediate and 16% rapid acetylators. The acetylator status significantly influenced the plasma concentrations of both drugs. Slow acetylators had significantly higher isoniazid concentrations ($p = 0.004$) and lower rifampicin concentrations ($p = 0.01$) as compared to rapid acetylators.

Conclusion: Abnormal concentrations of rifampicin and isoniazid are prevalent and a major concern. Acetylator status influences plasma concentrations of rifampicin and isoniazid. Hence, determining acetylator status and performing TDM could be instrumental in optimizing and improving TB outcomes.

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Introduction

Tuberculosis (TB), caused by *Mycobacterium* species, is one of the oldest known infectious diseases. According to the Global Tuberculosis Report 2022, India is the largest country, accounting for 28% of the total TB cases globally.[1] The treatment for TB requires good patient adherence to combination chemotherapy for a prolonged period. Slow therapeutic response can lead to prolonged infectiousness, extended treatment duration, acquired drug resistance, or recurrence after treatment.[2] The underlying reasons for slow response are diverse, but measurement of serum anti-TB drug concentrations, or therapeutic drug monitoring (TDM), is a potentially useful tool for uncovering the causes of slow response.[2,3]

The bioavailability, pharmacokinetics, and serum concentrations of orally administered antituberculosis drugs can be influenced by several factors, such as patient age, sex, and ethnicity, gastrointestinal disorders, drug formulations, acetylator status, and drug interactions.[4] The *NAT2* gene in humans plays a crucial role in the metabolism of isoniazid. There are a few reports describing the *NAT2* genotype and its association with drug concentrations; however, most of them are from the Western population, and there is limited data on the Indian population.[5] Slow acetylators tend to have increased isoniazid concentrations as compared to intermediate or rapid acetylators.[5] Some studies have also suggested that impaired antimycobacterial drug absorption and bioavailability can delay or lower the cure rates for TB.[6,7] Thus, we aimed to perform TDM of rifampicin and isoniazid in Indian patients suffering from active tuberculosis and on a first-line treatment regimen.

Materials and Methods

Study Participants and Ethical Approval

The study was performed in the biochemistry section of PD Hinduja Hospital and Medical Research Centre with a total of 125 patients (57 males and 68 females) suffering from drug-susceptible TB and on first-line treatment of rifampicin and isoniazid for at least 7 days of therapy. The study protocol was approved by the Institutional Review Board, with written informed consents obtained from all patients prior to enrolment.

The patients were treated with an oral and standard dose of drugs. About 4 mL blood samples (EDTA tube for rifampicin and heparin tube for isoniazid) were collected 2 hours postdose administration (peak concentrations as indicated as C_{max}). The buffy coat from EDTA tubes was used for DNA extraction by the modified Miller et al. method.[8] Plasma was separated, and drug concentrations were analyzed within 1 week to avoid any degradation. Therapeutic ranges for rifampicin were 8–24 mg/L, while those for isoniazid were 3–6 mg/L, as reported in the literature for peak drug concentrations.[2,3]

Drug Level Estimation

The rifampicin and isoniazid concentrations were quantified by an in-house standardized HPLC method. Rifampicin powder (CAS No-13292-46-1) and isoniazid powder (CAS

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No-54-85-3) HPLC grade were obtained from Sigma (St. Louis, MO, USA). The analytical HPLC instrumentation included a Waters 1525 multisolvent delivery system pump and Waters 2487 variable wavelength UV-Vis detector with Empower Version 2 software. MilliQ water was obtained from MilliQ Elix 10® water purification system.

***Rifampicin*:** The separation was performed on a Waters C18 column with a C18 guard column in an isocratic mode at a 1 mL/min flow rate. The mobile phase consisted of 0.05 M dipotassium hydrogen phosphate: acetonitrile in a ratio of 53:47 at pH 4.6, which was adjusted using orthophosphoric acid.[9] Matrix-based calibrators and controls were prepared fresh on the day of assay. A series of working standards with a concentration of 2, 10, 20, 30, and 40 mg/L and the tri-level controls with a concentration of 5, 15, and 35 mg/L were prepared, and protein was precipitated with acetonitrile. The mixture was vortex-mixed and centrifuged at 12,500 rpm for 10 minutes, and 20 µL of the filtered supernatant was injected into the system with UV detection at 340 nm. The method linearity was optimized at 0.2–100 mg/L with the lower limit of detection at 0.1 mg/L. The interday and intraday precision of the controls were within 20% CV. The method is robust, sensitive, and specific for rifampicin.

Isoniazid : The separation was performed on a Waters C8 column with a C8 guard column in an isocratic mode at a 1 mL/min flow rate. The mobile phase consisted of water: methanol in a ratio of 80:20 with 2.5 mL of tetrabutyl ammonium hydroxide and 0.7 mL of 70% perchloric acid. Freshly prepared matrix-based calibrators of concentrations 0.5, 5, 10, 15, and 20 mg/L and tri-level controls of 1, 4, and 17 mg/L were prepared. Plasma proteins were precipitated with para-hydroxybenzaldehyde and trifluoroacetic acid, vortex-mixed, and centrifuged at 14100 rpm for 5 minutes. 20 µL of the filtered supernatant was injected into the system, which passed through the column and a UV detector at 267 nm.[10] The method had a linearity of 0.3–100 mg/L with the lower limit of detection at 0.2 mg/L. The interday and intraday precision of the controls were within 20% CV. The method is robust, sensitive, and specific for isoniazid.

Both the method was validated for all the bioanalytical parameters with an acceptable ± 20% coefficient of variation (CV) for QC samples.[11]

NAT2 Acetylator Status

The *NAT2* acetylator was determined by conventional PCR for the following six SNPs: rs1041983, rs1801280, rs1799929, rs1977730, rs1208, and rs1799931. A web-based server, NAT2PRED, which implements a supervised pattern recognition method to infer NAT2 phenotype from SNPs, was used for the interpretation of acetylator status.[12]

Clinical Outcome

A detailed clinical follow-up was recorded from each patient after 2 months or more of the blood collection to assess their clinical outcome. Compliance was recorded as self-reported or with patient interviews during their clinical follow-up with the treating clinician. As per guidelines from Virginia, patients were regarded as "clinically improved" if they showed an improvement in TB symptoms (i.e., reduced cough/sputum production, no fever, and weight gain), bacteriological reports (TB culture negative), or improvement in imaging reports. Patients with a slow response or no improvement in any of the above factors were classified as "partial responders".[3,13]

Statistical Analysis

Normality testing of the data was performed using the Shapiro–Wilk test. The variables are expressed as mean ± SD when normally distributed and median (range) in all other cases. Statistical analyses (*t*-test and Mann–Whitney test as applicable) and multiple regression analysis for all confounding factors, such as age, weight, dose, etc., were performed using Medcalc version 15.4 software. A *p*-value <0.05 was considered for statistical significance.

Table 1: Demographic and clinical details of patients (*n* = 125)

Patient characteristics	
Age in years, median (range)	28 (12–68)
Gender (Female: Male)	68:57
Weight in kg, median (range)	57.0 (25–99)
Site of TB, *n* (%)	
Pulmonary	54 (43)
Glandular	30 (24)
Spine	12 (10)
Other extra-pulmonary sites	29 (23)
Type of therapy*, *n*	
Combination tablets	88 (70)
Single tablets	37 (30)
Medication in mg/day, median (range)	
Rifampicin dose	600 (300–1050)
Isoniazid dose	300 (125–600)
Medication in mg/kg body weight, mean ± SD	
Rifampicin dose	9.91 ± 1.79
Isoniazid dose	5.48 ± 1.31
Rifampicin levels in mg/L, median (range)	7.1 (0.1–27.3)
Isoniazid levels in mg/L, median (range)	4.1 (0.2–19.8)

*Types of therapy refer to either tablets given in Rifampicin and Isoniazid in a single formulation as combination tablets or two different formulations of each drug as single tablets

Results

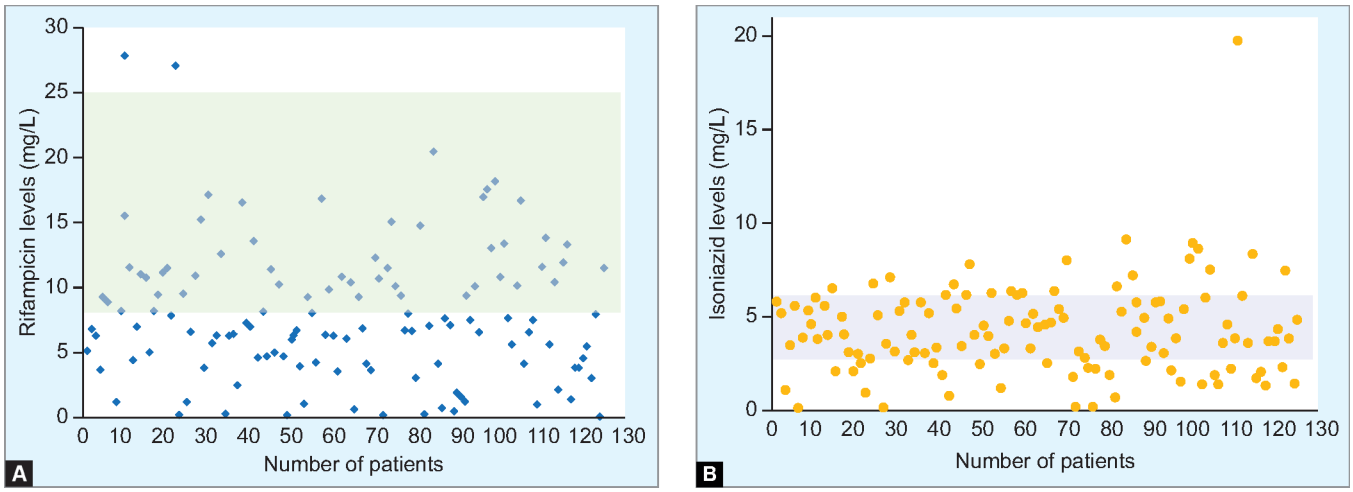
Demographic Details

A total of 125 patients, with a median age of 28 (range, 12–68) years and a median weight of 57 (25–99) kg, were enrolled in the study. Demographic and clinical details of all patients are mentioned in Table 1. None of our patients were suffering from any comorbid conditions such as HIV, while three patients were diabetic.

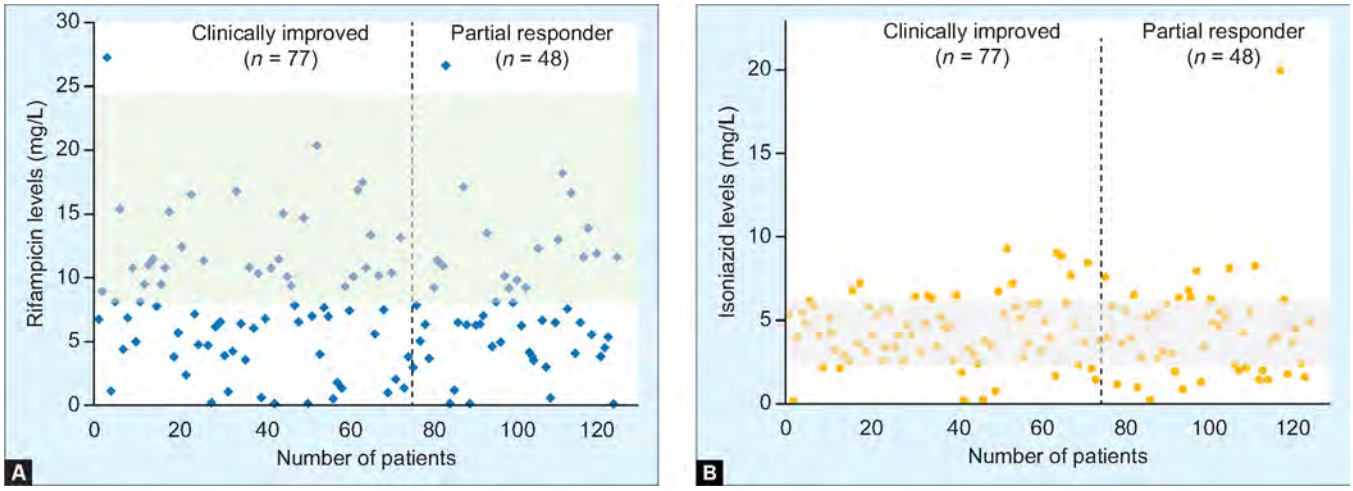
Plasma Rifampicin and Isoniazid Concentrations

Among the study group, on a mean rifampicin dose of 9.91 ± 1.79 mg/kg, a median plasma rifampicin level of 7.1 mg/L was observed. The majority of patients (*n* = 70; 56%) had peak plasma rifampicin concentrations in the subtherapeutic range, while 53 patients (42%) had therapeutic concentrations and 2 patients (2%) were in the toxic range (Fig. 1A).

The patients were on a mean isoniazid dose of 5.48 ± 1.31 mg/kg and had a median plasma level of 4.1 mg/L. Only 51% (*n* = 64) of the study group had isoniazid concentrations in the therapeutic range, while the remaining 49% (*n* = 61) had abnormal isoniazid concentrations. Among these, about 28% (*n* = 35) had subtherapeutic isoniazid concentrations, while 21% (*n* = 26) were in the toxic range for isoniazid (Fig. 1B).



Figs 1A and B: Scatter plot representing plasma drug concentrations observed in the study group (n = 125): (A) Rifampicin concentrations; (B) Isoniazid concentrations. The shaded boxes represent the therapeutic range of the respective drug



Figs 2A and B: Scatter plots representing plasma drug concentrations observed in the study group (n = 125) with clinical outcome: (A) Rifampicin concentrations; (B) Isoniazid concentrations. The shaded boxes represent the therapeutic range of the respective drug

Plasma Drug Concentrations and Clinical Outcome

A detailed clinical follow-up was recorded for all patients after 2 or more months of blood collection. No patient had died during the therapy or follow-up. Among the study group, only 62% of patients (n = 77/125) responded well clinically with improving signs and symptoms of TB, while the remaining 38% patients (n = 48/125) did not improve or had consistent/worsen conditions. These patients were classified as partial/slow responders to therapy. Figure 2 represents the clinical outcome of all patients with their respective rifampicin and isoniazid concentrations. Six patients (5%) had developed resistance to rifampicin during the course of treatment.

In the entire study group, only 18% of patients (n = 23/125) had both the drugs in therapeutic range, while the remaining 82% patients (n = 102/125) had either one or both the drug concentrations in the subtherapeutic range or had abnormal normal values.

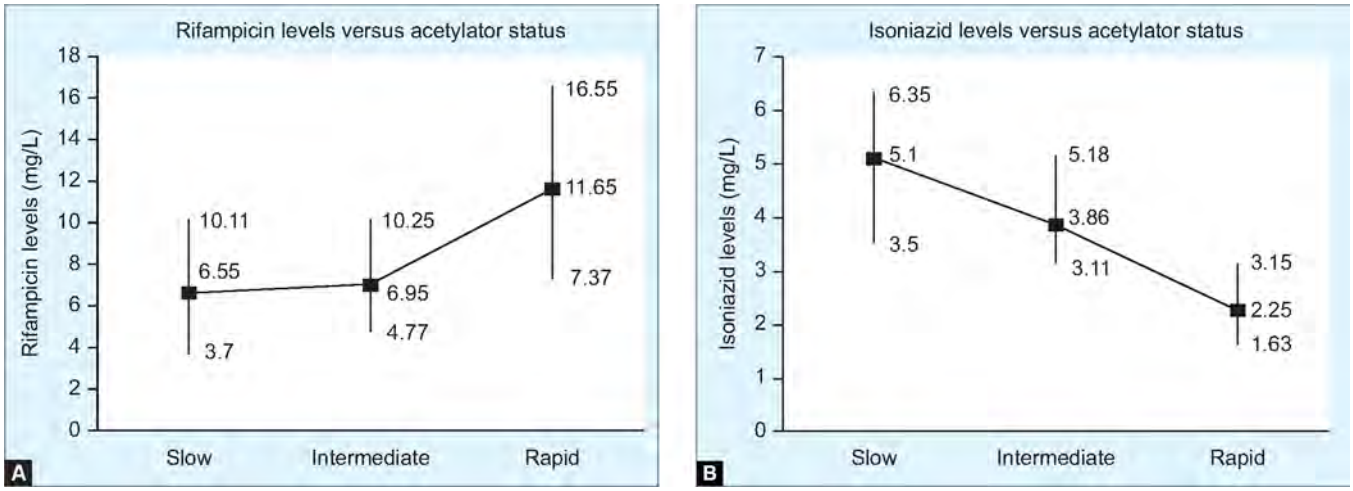
NAT2 Acetylator Status

Based on the genotypes observed from conventional PCR, the acetylator status was determined using the NAT2PRED software. Among the study group, slow acetylators (n = 55; 44%) were the most common, followed by intermediate acetylators (n = 50; 40%), and rapid acetylators being the least (n = 20; 16%). NAT2 acetylator status influences metabolism of isoniazid, thus influencing plasma isoniazid concentrations in the body. Figure 3 shows the trend of plasma concentrations among the acetylator phenotypes. Rapid acetylators had significantly lower isoniazid concentrations as compared to intermediate (p = 0.01) and slow acetylators (p = 0.004) (Fig. 3B). Whilst on comparing plasma rifampicin concentrations were significantly lower in slow (p = 0.01) or intermediate (p = 0.009) acetylators as compared to rapid acetylators (Fig. 3A).

The clinical outcome or plasma concentrations may be influenced by several factors such as age, dose, sex, severity and extent of disease, treatment duration, or the immune function of the patient. No statistical significance was seen on multiple regression analyses of confounding factors like age, sex, body mass index, dose in mg/kg, or duration with plasma rifampicin or isoniazid concentrations.

Discussion

An important finding of this study is that abnormal drug concentrations of rifampicin and isoniazid are common and a major concern. We did observe the majority of patients having low rifampicin concentrations, while isoniazid concentrations were varied between low to normal and supratherapeutic (toxic) concentrations. Interpatient variability is a major concern, warranting the need for therapeutic drug monitoring. This is



Figs 3A and B: Correlation of NAT2 acetylator status with (A) plasma rifampicin concentrations and (B) plasma isoniazid levels among slow, intermediate, and rapid acetylators

consistent with our previously reported findings in a smaller sample size study group.[14] In the present study, too, wide interindividual variability in plasma drug concentrations is seen, with about 56% of patients having subtherapeutic rifampicin concentrations, while 28% with low isoniazid concentrations and 21% with above normal isoniazid concentrations. Our results are also in keeping with a number of studies reporting more than 2–48% patients in the subtherapeutic range for isoniazid and 5–92% for rifampicin.[15–18] These variations in drug concentrations could be attributed to several other factors, such as different doses, drug formulations, comorbid conditions, age, weight, sex, or gastrointestinal abnormalities.[18]

In the present study, peak concentrations were estimated at 2 hours postdose administration for plasma rifampicin and isoniazid concentrations. Literature reports of delayed or malabsorption of rifampicin have doubted the 2-hour as a peak level. In such instances, an additional 6-hour level can help distinguish such patients with poor gastric emptying.[2,3,7] To rule out this possibility, in our laboratory, we have performed a 2-hour and a 6-hour plasma rifampicin level estimation in a small subset of patients wherein no cases of delayed or malabsorption were observed (data not shown). Thus, a 2-hour drug level was an appropriate time point to judge the peak rifampicin level.[14] However, if the patient is suspected of a delayed response, an additional 6-hour level could be taken for information on the rate and completeness of absorption.[7,18]

Several studies have linked low concentrations of anti-tuberculosis drugs to treatment failure, delayed diagnosis or therapy, poor adherence, development of multidrug resistance, HIV co-infection, and other comorbid conditions.[4,7,10,19,20] Patients without these risk factors are expected to respond well to the treatment. Patients who show no clinical or radiographic (or other imaging) improvement and continue to have sputum positive for *Mycobacterium tuberculosis* are classified as slow responders.[21,22] The present study observed the relation with plasma drug concentrations and the clinical outcome. About 62% of patients had improved clinically for symptoms of TB, while 38% were slow responders to standard treatment (partial responders). Drug resistance to rifampicin was seen in six patients (5%) despite receiving adequate doses (mg/kg body weight) and attaining therapeutic concentrations of either one or both the drugs. The extent and severity of disease, good compliance, balanced diet, and most importantly, the immune system of the patient play an important role in effective treatment and positive clinical outcome.[3,19,23] Clinical improvement seen in our patients with abnormal drug concentrations could be attributed to any of the above factors.

The data obtained in this study have important clinical implications. The observed wide variability in both rifampicin and isoniazid concentrations is a major concern. This study brings attention to certain points, such as attaining therapeutic drug concentrations may not be adequate to achieve a positive clinical outcome. Other factors marking symptoms of TB also should be closely monitored. Acetylator status strongly influences the metabolism of drugs thus affecting the plasma concentrations in the body.[24] Isoniazid metabolism is impacted by the activity of the polymorphic enzyme NAT2 influencing its elimination rate and possible development of toxic effects. These acetylation polymorphisms could be associated with inter-individual variability in plasma concentration and half-life of isoniazid.[25] Slow acetylators tend to have higher isoniazid concentrations as compared to intermediate and rapid acetylators. In our study, too, we observed slow acetylators had significantly high isoniazid concentrations. Similar findings have been reported in the South Indian population and other ethnic groups.[5,26,27] None of our patients reported hepatotoxicity despite a few patients having high isoniazid concentrations. However, dosage adjustments should be considered to prevent drug-induced liver injuries and to decrease the cost of managing adverse events, especially if patients tend to have above normal isoniazid concentrations.[28] Drug–drug interaction (DDI) is one common factor known to influence plasma concentrations. Rifampicin and isoniazid are also reported to interact with each other, thus reducing the bioavailability of rifampicin in presence of free isoniazid.[29,30] The primary mechanism of the DDI is not yet clear; however, it could be attributed to the excessive hydrazine formation from the hydrolase pathway. Most DDI are pharmacokinetic in nature thus affecting the bioavailability, absorption or metabolism of the drug. Under acidic conditions in solution, rifampicin undergoes hydrolysis to yield 3-formyl-rifamycin SV (3-FRSV) and 1-amino 4-methylpiperazine which is further aggravated in presence of isoniazid.[31] Thus slow acetylator who tend to retain isoniazid for longer durations, have a higher risk for having a decreased bioavailability of rifampicin and hence a poor clinical response. Rifampicin is a potent liver enzyme inducer while isoniazid is an enzyme inhibitor. Most DDI are due to enzyme inducing effect of rifampicin and the combination dosing can lead to synergistic

hepatotoxicity.[32] Fixed dose combinations can therefore be difficult to handle especially in a slow acetylator phenotype as the risk of reduced bioavailability of rifampicin is high in presence of prolonged exposure to isoniazid. Splitting doses can be beneficial with a monitored time gap to help rifampicin attain their peak level at 2 hours followed by isoniazid dose administration. Also, presence of other factors such as liver disease and age can further increase the risk of adverse effects and poor clinical response. One potential limitation is that the study was limited to 125 samples, and the results can be explored further in a larger sample size. Also, drug pharmacokinetics also include accounting for intra-individual variations which could not be evaluated within the scope of this study.

The correlation between NAT2 acetylator phenotype and rifampicin plasma concentrations remains inadequately studied. In our study, we have observed a strong correlation of plasma rifampicin concentrations with slow acetylators versus intermediate or rapid acetylators. For a majority of patients, the standard regimen of drug doses is adequate; however, it is important to improve the clinical condition in patients with abnormal plasma drug concentrations or vulnerable clinical conditions. On a case-by-case basis, assessment of drug concentrations is certainly helpful.

Conclusion

An abnormal plasma concentration of either of the two drugs was seen in more than half of the study group. Variation in drug concentrations can be attributed to several factors, and therapeutic drug monitoring will help optimize the drug doses needed in the treatment regimen. Treatment strategies based on the acetylator status will help clinicians adjust and prescribe separate or fixed dose combinations of dosages to achieve a better bioavailability and metabolism of both drugs. TDM can help identify patients at high risk of treatment failure or delayed response, enabling timely interventions to optimize treatment outcomes.

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Conflict of interest

All authors declare they have no conflict of interest.

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ORIGINAL ARTICLE

Clinicopathological Spectrum and Biomarker Profile of Male Breast Cancer: A Retrospective Study from a Tertiary Care Center in South India

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Abstract

Introduction: Male breast cancer (MBC) accounts for <1% of breast malignancies yet often presents at advanced stages, particularly in low- and middle-income countries where awareness is limited. This study sought to define the clinicopathological spectrum, biomarker profile, and treatment outcomes of MBC in a South Indian tertiary cancer center.

Objectives: To analyze the demographic features, clinical presentation, pathological characteristics, biomarker distribution, treatment modalities, and outcomes of MBC cases managed at our center between 2019 and 2025.

Materials and methods: We retrospectively analyzed all male patients with histologically confirmed breast carcinoma managed between 2019 and 2025 at ESIC Medical College and Hospital, Hyderabad. Demographic, clinical, pathological, biomarker, and treatment data were retrieved from hospital records and supplemented by follow-up contact.

Results: A total of 15 patients (mean age 60 years, range 31–74) were identified. Median delay from symptom onset to diagnosis was 6 months. All presented with a retroareolar mass, frequently accompanied by nipple retraction or skin changes. Most patients had advanced disease: Stage III (n = 9, 60.0%) and Stage IV (n = 4, 26.7%). Invasive ductal carcinoma was universal. Hormone receptor positivity was seen in 80%, HER2 positivity in 40%, and a triple-positive phenotype in 26.7%. Treatment strategies were stage- and biomarker-driven: 86.7% underwent surgery, endocrine therapy was prescribed for all HR+ cases, HER2-directed therapy was delivered when feasible, and CDK4/6 inhibitors were used in selected advanced HR+ tumors. At last follow-up, 9 patients (60%) remained alive with disease control, while 2 succumbed to progression.

Conclusion: MBC in this cohort was characterized by delayed diagnosis, advanced presentation, and a high prevalence of HER2-positive tumors. Multimodality, biomarker-guided therapy achieved durable control in many patients, underscoring the urgent need for awareness initiatives, earlier detection, and equitable access to targeted therapies in India.

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Introduction

Male breast cancer (MBC) is a rare but clinically consequential malignancy, comprising under 1% of breast cancers and demanding deliberate, guideline-informed care. Late recognition—shaped by stigma, low awareness, and diagnostic inertia—contributes to advanced presentation, particularly in resource-limited settings. Most tumors are hormone receptor–positive, with a meaningful HER2-positive subset; accordingly, endocrine therapy and, when indicated, HER2-targeted treatment are central, though access barriers persist. This review distills current epidemiology, biology, diagnostics, and management, and advances practical, biomarker-driven strategies to enable earlier detection and equitable care.

Materials and Methods

Study Design and Setting

This was a retrospective observational study conducted in the Department of Medical Oncology at a tertiary care center in South India. The study period spanned from 2019 to 2025. All cases of male breast carcinoma diagnosed and managed during this timeframe were included. The study protocol was approved by the Institutional Ethics Committee (IEC No: ESICMC/SNR/IEC-S0401/08–2025) on 29–05–2025 and adhered to all the Declarations of Helsinki. A waiver of informed consent was granted due to the retrospective nature of the study. Patient confidentiality and data privacy were maintained throughout. Data regarding clinical and family history, stage of the disease, histopathological examination, IHC status, and treatment modalities were extracted from electronic hospital medical records, patient files, and chemotherapy logs. Attempts were made to retrieve follow-up information *via* telephonic contact.

Inclusion Criteria

Adult male patients (≥18 years) registered and treated at the Department of Medical Oncology in our institute with histologically confirmed breast carcinoma and availability of baseline demographic, clinical, pathological, and biomarker data were included.

Exclusion Criteria

Benign breast conditions, such as gynecomastia, breast involvement secondary to another primary malignancy, and presence of cardiovascular comorbidities that precluded the use of anti-HER2 therapy were excluded.

Primary Outcome

To describe the clinicopathological characteristics, biomarker profile, and stage distribution.

Secondary Outcomes

To evaluate treatment patterns, including surgery, systemic therapy, endocrine therapy, and HER2-directed therapy.

To assess short-term clinical outcomes, including treatment response and disease status at last follow-up.

To correlate biomarker expression (hormone receptor and HER2 status) with tumor stage and nodal involvement.

To document delays in diagnosis and patterns of loss to follow-up as barriers to optimal care.

Statistical Analysis

Data were compiled from electronic medical records and entered into Microsoft Excel for analysis. Descriptive statistics were used to summarize patient demographics, clinical

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presentation, pathological characteristics, biomarker distribution, treatment modalities, and outcomes. Continuous variables, such as age and diagnostic delay, were expressed as mean, median, and range, while categorical variables, such as stage, histology, biomarker status, and treatment type, were expressed as absolute numbers and percentages. Associations between biomarker expression (hormone receptor and HER2 status) and stage or nodal involvement were descriptively assessed, given the small cohort size precluding formal statistical testing. Survival outcomes were reported narratively as proportions of patients alive, controlled, lost to follow-up, or deceased at last contact. No inferential statistical tests were applied due to the limited sample size.

Results

Fifteen male patients (mean age 60, range 31–74 years) were diagnosed with breast carcinoma, none of whom had a history of familial cancer, estrogen exposure, radiation, or occupational carcinogen exposure. The median time from symptom onset to clinical evaluation was 6 months. All presented with a firm palpable breast mass, predominantly retroareolar, with associated features like nipple retraction, skin thickening, and, in 2 cases, ulcerated fungating tumors. Four patients had systemic symptoms, including cough, dyspnea, bone pain, fatigue, or weight loss. Clinical staging per AJCC 8th edition revealed 2 patients with T1 tumors, 6 with T2–T3 lesions, and 7 with T4 features such as peau d'orange or ulceration. Ipsilateral axillary lymphadenopathy was seen in 13 (86.7%) patients, ranging from mobile to fixed nodes, with no evidence of supraclavicular or contralateral involvement. All patients underwent ultrasound/mammography and core biopsy, confirming invasive ductal carcinoma in all cases. Systemic staging was done via PET-CT as per institution protocols.

- Overall clinical stage distribution was:
- Stage I–II (early-stage): 2 patients (13.3%)
- Stage III (locally advanced): 9 patients (60.0%)
- Stage IV (metastatic): 4 patients (26.7%)

Immunohistochemistry showed hormone receptor positivity in 80%, HER2 positivity in 40%, and a triple-positive profile in 26.7%. The 2 early-stage patients (both *HR+/*HER2–) underwent upfront modified radical mastectomy (MRM) followed by adjuvant endocrine therapy. Among Stage III patients, 6 underwent upfront MRM: 4 *HR+/*HER2– received adjuvant anthracycline–taxane chemotherapy plus endocrine therapy, and 2 HER2+ (one triple-positive, one *HR–/*HER2+) received postoperative trastuzumab-based therapy with chemotherapy. The remaining 3 Stage III patients received neoadjuvant chemotherapy: 2 HER2+ patients (one triple-positive, one *HR–/*HER2+) received dual HER2 blockade with trastuzumab and pertuzumab; 1 *HR+/*HER2– patient with extensive T4b disease received standard chemotherapy. All subsequently underwent MRM and completed biomarker-guided systemic therapy.

Among the 4 Stage IV patients, 2 with de novo HER2+ pulmonary metastases received taxane-based chemotherapy with trastuzumab. Of the 3 HR+ patients, 2 were treated with aromatase inhibitors and CDK4/6 inhibitors (palbociclib), while 1 with endocrine-resistant bone metastasis received fulvestrant. Overall, 13 patients (86.7%) underwent surgery: 11 had MRM, and 2 Stage IV patients underwent palliative toilet mastectomies. Surgical decisions were based on resectability, treatment response, and symptom burden. On follow-up, 9 patients (60%) were alive and under surveillance—5 postcurative treatment, 2 on adjuvant endocrine therapy, and 2 Stage IV patients with stable disease. Four patients (26.7%) were lost to follow-up, and 2 (13.3%) with metastatic disease (one HER2+ and one *HR+/*HER2–) died due to disease progression (Tables 1 and 2).

Table 1: Distribution of TNM stage and biomarker profiles in male breast cancer patients

Parameter	*No. of patients (%)*	*Biomarker profile*
T1	2 (13.3)	HR+/HER2–
T2–T3	6 (40.0)	HR+/HER2– (*n* = 3); Triple+ (*n* = 2); HR–/HER2+ (*n* = 1)
T4b/c	7 (46.7)	HR+/HER2– (*n* = 3); Triple+ (*n* = 1); HR–/HER2+ (*n* = 3)
N0	2 (13.3)	HR+/HER2–
N1–N3	13 (86.7)	All HER2+ and triple+ cases
M0	11 (73.3)	All biomarker subtypes
M1	4 (26.7)	HR+/HER2– (*n* = 2); Triple+ (*n* = 1); HR–/HER2+ (*n* = 1)

Discussion

Male breast cancer is a rare but clinically relevant malignancy, constituting <1% of all breast cancers globally.[1] This retrospective case series from a tertiary center in South India offers valuable insights into the clinical behavior, biomarker patterns, and management challenges of MBC in a low-resource setting. The observed trends largely mirror international data, including a predominance of hormone receptor (HR)–positive tumors, late-stage presentation, and significant barriers to early diagnosis and longitudinal care.

Late Presentation and Diagnostic Limitations

In this cohort of 15 patients, 60.0% (*n* = 9) presented with stage III and 26.7% (*n* = 4) with stage IV disease, indicating that 86.7% (*n* = 13) had either locally advanced or metastatic cancer at diagnosis. This pattern is consistent

Table 2: Treatment approaches by stage and biomarker profile (Non-metastatic)

Stage	*Biomarker profile*	*Chemotherapy*	*HER2 Therapy / Surgical Approach*
Stage I–II (*n* = 2)	HR+/HER2– (*n* = 2)	None	None/Upfront MRM
Stage III (*n* = 6)	HR+/HER2– (*n* = 4)	Adjuvant anthracycline–taxane	None/Upfront MRM
Stage III (*n* = 6)	Triple+ (*n* = 1)	Adjuvant anthracycline–taxane	Trastuzumab (adjuvant)/Upfront MRM
Stage III (*n* = 6)	HR–/HER2+ (*n* = 1)	Adjuvant anthracycline–taxane	Trastuzumab (adjuvant)/Upfront MRM
Stage III (*n* = 3)	Triple+ (*n* = 1)	Neoadjuvant anthracycline–taxane	Trastuzumab + Pertuzumab (neoadjuvant)/MRM post-NACT
Stage III (*n* = 3)	HR–/HER2+ (*n* = 1)	Neoadjuvant anthracycline–taxane	Trastuzumab + Pertuzumab (neoadjuvant)/MRM post-NACT
Stage III (*n* = 3)	HR+/HER2– (*n* = 1)	Neoadjuvant anthracycline–taxane	None/MRM post-NACT

with previous Indian data[2] and highlights delays stemming from low awareness, cultural stigma, and diagnostic inertia among providers. Advanced imaging with PET-CT was performed routinely for staging, providing accurate systemic evaluation. HER2 status was determined by immunohistochemistry (IHC), with dual in situ hybridization (DISH) used for equivocal cases due to unavailability of fluorescence in situ hybridization (FISH). While DISH is an acceptable alternative, limitations in confirmatory HER2 testing can compromise treatment selection in borderline cases.

Biomarker Distribution and Staging Correlation

HR positivity was identified in 80% (n = 12) of patients, consistent with large registry data indicating HR+ rates above 85% in MBC.[3,4] HER2 positivity was identified in 40% (n = 6), and 26.7% (n = 4) were triple-positive (*ER+/*PR+/HER2+). Importantly, HER2-positive and triple-positive tumors correlated with more advanced presentation:

- Among 7 patients with T4 disease, 4 (57%) were HER2+.
- All 13 patients with N1–N3 disease were HER2+ or triple-positive.
- Three of four metastatic cases were HER2+ or triple-positive.

Multimodal Management

MRM was performed in 73.3% (n = 11), consistent with established norms in male breast oncology.[5] Endocrine therapy, primarily tamoxifen, was administered in all HR+ patients. Tamoxifen remains the agent of choice in male patients due to its superior survival benefit compared to aromatase inhibitors.[4] CDK4/6 inhibitors were used in 26.7% (n = 4) with advanced HR+ disease, reflecting integration of contemporary targeted therapies. Recent pooled analyses have shown promising outcomes with CDK4/6 inhibitors in male *HR+/*HER2– breast cancer, with progression-free survival of approximately 20 months.[6]

Neoadjuvant chemotherapy was utilized in only 6.7% of patients, reflecting either stage-inappropriate presentation or limited capacity for treatment monitoring. Sharma et al. similarly reported low neoadjuvant use in Indian MBC populations.[2] Radiotherapy was underutilized, despite evidence that it reduces local recurrence and improves survival in high-risk MBC.[1,7]

Systemic Challenges and Outcomes

Two patients (13.3%) died due to disease progression—both with stage IV disease. Follow-up was complete for all evaluable patients, but 26.7% (n = 4) were lost to follow-up, a common limitation in resource-limited settings. These losses reflect systemic barriers such as travel constraints, treatment fatigue, lack of community support, and financial burden—issues widely reported in LMIC oncology.[2,8]

Strategic Implications

This study reinforces the need for early detection strategies tailored to men and highlights the prognostic significance of HER2 and triple-positive profiles in MBC. Integration of biomarker data with TNM staging enables more informed treatment planning and resource allocation. Current guidelines from NCCN and ESMO recommend dual HER2 blockade in eligible patients,[9,10] but equitable access remains a challenge.

We advocate for national policies that mandate inclusion of male-specific protocols in breast cancer guidelines, such as those by ICMR. Establishing MBC registries and enabling gender-inclusive clinical trials are essential next steps, as recommended in consensus statements from the NIH and global oncology networks.[11]

Conclusion

Male breast cancer in this South Indian cohort was characterized by delayed diagnosis, advanced stage at presentation, and a relatively high rate of HER2 positivity. Biomarker-guided multimodality therapy achieved durable disease control in many patients. These findings underscore the need for earlier detection and awareness, as well as equitable access to HER2-directed and endocrine therapies across resource-limited settings.

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ORIGINAL ARTICLE

Hospital Hyperglycemia is Associated with Adverse Short-term Metabolic and Mortality Outcomes

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Abstract

Introduction: Stress hyperglycemia has been implicated in acute illnesses, but the risk of future diabetes is seldom studied. Hospital hyperglycemia, as defined by in-hospital random blood glucose (RBG) >140 mg/dL, is much less studied. This study aimed to determine the profile and short-term outcome of hospital hyperglycemia patients.

Methods: A descriptive follow-up study was conducted in 50 patients with hospital hyperglycemia. Based on their HbA1c status, patients were categorized into known cases of diabetes (group A, $n = 12$, 24%), undiagnosed diabetes (group B, $n = 13$, 26%), prediabetes (group C, $n = 13$, 26%), and normoglycemic (group D, $n = 12$, 24%). Duration of hospital stay and in-hospital mortality were noted. At 4 weeks post-discharge, HbA1c, along with the glucose tolerance test, was performed for groups C and D, and outcomes were recorded.

Results: Half of the hospital hyperglycemia patients were diabetic, although 26% of the patients with hospital hyperglycemia were unaware of their diabetes status. Average age and BMI were found to be higher in diabetes patients (25.63 ± 5.25 kg/m^2) than prediabetes (22.98 ± 2.24 kg/m^2) and normoglycemic patients (21.38 ± 2.37 kg/m^2). Two deaths were encountered during hospital stay in the prediabetes group.

At 4 weeks post-discharge, in group C, 2 (8.7%) developed diabetes, 4 (17.4%) had impaired fasting glucose, and 3 (13%) had impaired glucose tolerance. One prediabetes patient became normoglycemic. All 12 patients of group D remained normoglycemic.

Conclusion: Hospital hyperglycemia in diabetics as well as prediabetes subjects is associated with a higher age and BMI compared to normoglycemic individuals. Hospital hyperglycemia in prediabetes subjects is associated with higher mortality and greater propensity to develop diabetes in the short-term, compared to normoglycemic individuals.

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Introduction

The American Diabetes Association[1] has defined hyperglycemia in hospitalized patients as blood glucose levels >140 mg/dL (7.8 mmol/L). HbA1c ≥6.5%. can help in differentiating preexisting diabetes from stress hyperglycemia. HbA1c <6.5% with a blood glucose value >140 mg/dL qualifies as stress hyperglycemia.[2] In other words, stress hyperglycemia can be defined as a transient increase in blood glucose during an acute physiological stress in the absence of diabetes. Stress or injury alters normal glucose metabolism and peripheral insulin resistance, thus resulting in stress hyperglycemia. Hospitalization is also an acute stressor, physical and/or mental, and hence, may be considered to contribute to stress hyperglycemia. Patients with hyperglycemia and no previous diagnosis of diabetes have more adverse outcomes compared to patients with preexisting diabetes, for a given degree of hyperglycemia.[3]

Varying rates of hyperglycemia in hospitalized patients have been reported, to the extent that one-third of critically ill patients in tertiary care facilities were reported to be hyperglycemic.[4] Interestingly, one in five adult patients with stress hyperglycemia was reported to have undiagnosed diabetes.[5]

The entity of "hospital hyperglycemia" has not been widely studied, and the follow-up of these patients is hardly available. Keeping in view the importance of hyperglycemia and undiagnosed diabetes in patients getting admitted to hospitals and critical care units, the present study was planned to determine the profile and short-term outcome of patients with hospital hyperglycemia.

Materials and Methods

A descriptive 4-week follow-up study was conducted in a tertiary care hospital in India. A convenient sample of 50 adult (age ≥ 18 years) patients was taken over an 18-month period from January 2021 to June 2022. The study was approved by the Institutional Ethics Committee. Informed written consent was obtained from each patient. Patients presenting to the emergency department of the Medicine were screened for entry into the study, and patients having a random blood glucose level at admission >140 mg/dL were included. Type 1 diabetes patients and patients having severe anemia (Hb <7 gm%) were excluded.

Patient's demographic details along with health-related information, with particular emphasis on details about diabetic status, family history of diabetes, and body mass index (BMI), were recorded in a predesigned, pretested structured proforma. Patients' blood samples (2–3 mL of venous blood) were collected for HbA1c, in addition to other routine investigations, as required for standard of care. Duration of hospital stay and outcome were noted for each patient over a 4-week period. Venous blood was collected for measurement of blood glucose in fluoride vials, and laboratory assessment was done employing the glucose oxidase-peroxidase method, while blood collection was done in an EDTA vial for HbA1c estimation, and the latex agglutination inhibition method was employed in an automated analyzer (Beckman Coulter AU Analyzer).

The patients having hyperglycemia (>140 mg/dL) at admission, who were included in the study, were classified into four groups based on the presence of a history of diabetes diagnosis and HbA1c values at admission:

- Group A: Previously diagnosed type 2 diabetes patients (T2DM) who had RBS > 140 mg/dL.
- Group B: Undiagnosed T2DM. Patients who had RBS > 140 mg/dL at admission, and HbA1c value came out to be ≥6.5%.
- Group C: Prediabetes group—Patients with HbA1c between 5.7 and 6.4% were referred to as the prediabetes group.
- Group D: Nondiabetics—Patients having RBS >140 mg/dL and HbA1c value on testing was < 5.7%.

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After 4 weeks, groups C and D patients were subjected to an oral glucose tolerance test (OGTT) and repeat HbA1c levels. Fasting blood sugar after an overnight 8–12 hours duration fasting and 2-hour post-75 gm glucose (given mixed with 250–300 mL water) blood sugar values were performed in the same sitting for an OGTT. Depending on the values obtained, patients were categorized as normal glucose tolerance, prediabetes (impaired fasting glucose, impaired glucose tolerance), and type 2 diabetes mellitus, as per the ADA classification (Fig. 1).[6]

The collected data was transcribed on to Microsoft Excel spreadsheet on a personal computer. Information is presented as mean ± SD and as proportions and percentages.

Results

Average age of patients of hospital hyperglycemia (n = 50) studied was 43.42 ± 16.41 years. There was a slight female preponderance in the study with a male-to-female ratio of 0.8:1. The average body mass index (BMI) of the study group was 23.99 ± 4.5 kg/m^2 and hospital stay duration was 10.28 ± 4.3 days.

Average age, BMI, and duration of hospital stay in the different groups are outlined in Table 1. Average age as well as the BMI varied, with least being for the subjects of normoglycemia group but increasing in prediabetes to undiagnosed diabetes mellitus, and known cases of diabetes mellitus.

Half of the hospital hyperglycemia patients were diabetics (n = 25), of which 48% (n = 12) were previously diagnosed with diabetes, and 52% (n = 13) had preexisting diabetes (HbA1c ≥ 6.5%), but were unaware of their diabetes status. Only one out of 12 previously known diabetic patients had HbA1c under control, and the rest of the diabetic patients had HbA1c > 6.5%, but none had HbA1c > 8.5%. Patients who were unaware that they had diabetes and were diagnosed at admission had HbA1c values ranging from 6.6 to 12.6%.

At admission, 26% (n = 13) of the study population was prediabetic (group C), while 24% (n = 12) were normoglycemic (group D). On following up groups C and D, to assess for hospital admission-related outcomes, two (8%) patients of group C (prediabetes) expired during in-hospital stay. The cause of death was lung abscess with acute respiratory distress syndrome in one of the patients and tuberculous meningitis in the other. There were no expiries in the other groups.

Duration of hospital stay did not vary significantly, though it was on the higher side (10.42 ± 3.4 days) in patients with higher mean HbA1c as seen in previously known cases of diabetes (7.35 ± 0.6%), compared to 9.25 ± 4.79 days hospital stay in nondiabetic patients with HbA1c < 5.7%.

Table 2 illustrates the outcomes of group C and group D on OGTT at 4-week follow-up (n = 23, excluding two patients who had expired). Two patients (8.7%) were diagnosed to have T2DM, four patients (17.4%) had impaired fasting glucose (IFG), and three patients (12%) had impaired glucose tolerance (IGT). One patient who was having prediabetes (belonging to group C) became normoglycemic, while 12 patients belonging to Group D remained normoglycemic.

Discussion

Acute illnesses can lead to the development of hospital hyperglycemia, but this stress response is presumed to be transient. Stress hyperglycemia typically resolves when the acute illness or the surgical stress is cured.[7] However, the natural course of patients who develop stress hyperglycemia is as yet uncharacterized. Although diabetes patients who present with hyperglycemia at admission have greater adverse outcomes, the same cannot be said categorically for nondiabetic patients. Nondiabetics can have hospital hyperglycemia due to impaired glycemic control as in prediabetes or due to an increase in counter-regulatory hormones such as cortisol, glucagon and growth hormone. Whether stress induced hyperglycemia directly causes harm or is a marker of severity of counter-regulatory hormone release, inflammatory response, and degree of illness is not known.[8] Other risk factors, such as age, family history of diabetes mellitus, and BMI, may also have a contribution.

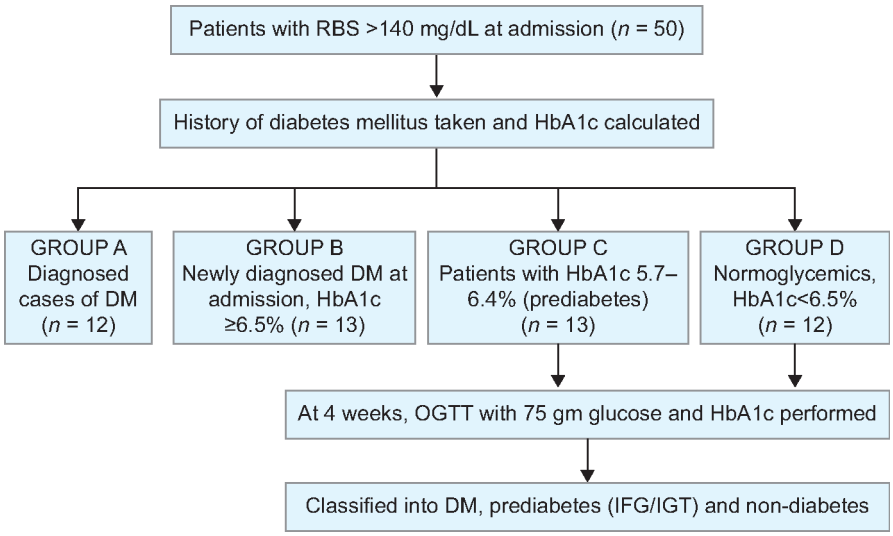

Fig. 1: Flow of patients and distribution in various groups

Table 2: Classification of hospital hyperglycemia patients (admission HbA1c < 6.5%) at 4 weeks follow-up, based on OGTT results

Diabetic status at follow-up	*Frequency*
Normoglycemia	14
Prediabetes (IFG, IGT)	7 (IFG = 4, IGT = 3)
Newly diagnosed T2DM	2
Mortality	2
Total	25

Table 1: Comparison of parameters in the four study groups

Parameters	*Group A Known DM (n = 12)*	*Group B Undiagnosed DM (n = 13)*	*Group C Prediabetes (n = 13)*	*Group D Normoglycemia (n = 12)*
Family history of DM	7 (58.33%)	2 (15.38%)	2 (15.38%)	2 (16.67%)
Age (years)†	56.67 ± 9.63	45.77 ± 15.7	37.62 ± 16.76	33.92 ± 13.96
BMI (kg/m^2)††	26.43 ± 5.05	25.14 ± 5.83	22.98 ± 2.24	21.38 ± 2.37
Duration of hospital stay (days)	10.42 ± 3.4	10.69 ± 4.19	10.69 ± 5.01	9.25 ± 4.79

†p = 0.002; ††p = 0.023 (ANOVA)

In the present study, out of 50 patients with hospital hyperglycemia, 56% (n = 28) were female and 44% (n = 22) were male. In a study conducted by Russo et al.,[2] there were 55% males among hospital hyperglycemia patients. The difference in the result could be due to nonuniform data distribution and a small sample size. In this study on hospital hyperglycemia, mean BMI was higher in diabetic subgroups (25.63 ± 5.25 kg/m^2) compared to nondiabetic subgroups (22.49 ± 2.58 kg/m^2).

The present study revealed that 26% of patients who had hospital hyperglycemia were not aware that they had diabetes, and an equal number had prediabetes. Greci et al.[5] reported that one in five adult patients with stress hyperglycemia as having unrecognized diabetes. O'Sullivan et al.[9] studied 126 patients with hyperglycemia and found that only 11 patients were newly diagnosed diabetics at admission. The lesser number of newly diagnosed patients as compared to our study could be because of the different methodology adopted by them for diagnosing diabetes mellitus. They included patients with RBS >180 mg/dL on two occasions and labelled as newly detected diabetic patients, while the present study used an HbA1c value ≥ 6.5% along with hospital hyperglycemia, i.e., random blood sugar at presentation > 140 mg/dL. Therefore, it is likely that the numbers in O'sullivan's study may be underreported. Further, the higher number of undiagnosed diabetes population among the hospital hyperglycemia patients in the present study could be a reflection of the high prevalence of diabetes among the Indian population. The overall prevalence of type 2 diabetes varies from 8 to 12%, while an equal number of people are in the prediabetes range, as has been evidenced by the ICMR-INDIAB study.[10] Our study highlighted the fact that diabetes mellitus still remains one of the silent comorbidities in patients, irrespective of their illness.

Half of the hospital-hyperglycemia patients in our study were nondiabetic at admission. These patients had RBS > 140 mg/dL at admission but HbA1c < 6.5%. Out of 269 patients of hospital hyperglycemia studied by Tamez-Pérez et al.,[11] 164 (61%) did not have diabetes at presentation, which was slightly higher than the present study, and may be attributed to the high prevalence of diabetes and prediabetes in our population.

In our study, we found that 26% (n = 13) of the studied population were prediabetic at the time of admission. These patients had HbA1c between 5.7 and 6.4%. In a study conducted to find the prevalence of prediabetes among hypertensive patients, the prevalence of prediabetes was 18%.[12] In another study by Mustafa et al.,[13] the prevalence of prediabetes in Malaysian adults was found to be 22.1%.

The variation witnessed in our results when compared to other works, can be attributed to regional and ethnic variations in prevalence of diabetes and atherosclerotic risk factors in south Asia, as also the fact that criteria for hospital hyperglycemia (>140 mg/dL) as enunciated by ADA, which is used in this study is the more stringent one, compared to earlier ones, when the cut-off was higher. Since definitions of hospital hyperglycemia, as well as tools for defining it, as used by various authors, are variable, the results reported in the literature are difficult to compare with our results. Application of a uniform criterion would give a better projection of undiagnosed diabetes in hospital hyperglycemia patients.

In our study, we found that two patients (8.7%) were prediabetics and developed T2DM at follow-up. In a study to determine the incidence of type 2 diabetes among IFG patients, 53 out of 633 patients (8%) developed type 2 diabetes as observed by Forouhi et al.[14] There is a paucity of published literature on the incidence of diabetes mellitus in hospital hyperglycemia patients.

In our study, 2 of 50 patients (4%) diagnosed with hospital hyperglycemia at admission died during the hospital stay. Both these patients belonged to group C (prediabetes group). In another study by Russo et al.[15], the mortality rate at 1 year was 13.24% in stress hyperglycemia patients. However, death in prediabetic subjects in our study was a little intriguing, as there was no mortality witnessed among previously diagnosed (group A) or undiagnosed diabetes patients (group B) in the present study. Chronic hyperglycemia also plays a role by inducing protective cellular conditioning and downregulation of glucose transporters, which would protect cells from unchecked glucose ingress. These protective mechanisms are found to be absent in patients with hospital-related or stress hyperglycemia,[16] and therefore, expiry among the prediabetes patients may be explained on the basis of the lack of these protective mechanisms.

Conclusion

Stress hyperglycemia remains one of the predictable biochemical markers of developing diabetes mellitus in the future. Hence, any patient presenting with hospital hyperglycemia should be thoroughly investigated and followed for a minimum period of 4 weeks for screening for diabetes. Nondiabetic patients with hospital hyperglycemia carry a risk of developing diabetes in the future. Family history of diabetes and BMI shows positive correlation among diabetes patients. Recent onset hyperglycemia carries a greater risk of short-term mortality. Adequate glycemic control, as measured by HbA1c < 5.7%, is associated with lesser morbidity (shorter duration of hospital stay).

Also, diabetes mellitus is still one of the silent comorbidities in asymptomatic patients, as observed in our study.

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ORIGINAL ARTICLE

A Study on Prevalence of Malarial Retinopathy among Malaria Cases and to Determine Its Presence as a Marker of Severe Malaria: Observations from Eastern India

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Abstract

Background: Malarial retinopathy refers to a constellation of changes seen in severe or complicated malaria cases. These include: retinal whitening, vessel changes–whitening, tramlining, retinal hemorrhages, and papilledema. There are very few Indian studies on this entity. Since retina can be easily visualized by direct ophthalmoscopy, this study was done to determine prevalence of malarial retinopathy among malaria cases and to determine relationship between malarial retinopathy and severity of the disease.

Materials and methods: The study was done at Indoor and Outdoor Departments of Tropical Medicine, School of Tropical Medicine (STM), Kolkata, with the support of the Department of Ophthalmology, Regional Institute of Ophthalmology (RIO), Medical College, Kolkata. Adult malaria cases, both complicated/severe and uncomplicated, were included. Patients unable or unwilling to cooperate with eye examination, contraindications to tropicamide eye drops (angle closure glaucoma or known allergy to product), severe corneal scarring or cataracts hindering view by ophthalmoscopy, diabetes mellitus, hypertension, intracranial space occupying lesions, epilepsy, alcohol use, chronic renal failure, age > 60 years and any other known ocular/systemic disease that can cause retinopathy changes were excluded. Severe malaria was diagnosed as per the WHO criteria. Cases with acute febrile illness of other causes were taken in control arm, and normal population subjects were taken as controls. All patients were assessed clinically, followed by appropriate laboratory investigations and then direct ophthalmoscopic examination was done. Ocular findings were be collaborated with severity of illness.

Results: A total of 71 malaria cases were included in our study. Among them, 12 cases were of severe malaria, and rest of the cases were uncomplicated. Of the 12 severe malaria cases, 8 were *Plasmodium vivax*, 3 were *Plasmodium falciparum*, and 1 was mixed. Uncomplicated malaria cases were mostly *P. vivax* (35 out of 59). Features suggestive of malarial retinopathy were noted in 9 out of 12 cases of severe malaria (75%) and 2 out of 59 cases of uncomplicated malaria (3.4%). We noted two cases of retinal changes—one case of retinal whitening in falciparum malaria and one case of vivax malaria with retinal hemorrhage in the uncomplicated group. Both of the cases subsequently needed admission for recurrent vomiting, reduced urine output, and severe weakness 40 dengue cases were included in control arm of AFI cases—20 DHF cases and 20 cases of DF with warning signs. Among them, retinal hemorrhage was noted in one case of DHF (2.5%). Out of 40 sepsis cases, retinal hemorrhage was seen in one case (2.5%). No retinal changes were noted among 40 other AFI cases which included scrub typhus, enteric fever, chikungunya, and acute viral hepatitis. Also, no abnormality was detected on ophthalmoscopy in 40 healthy individuals. The presence of retinopathy was suggestive of severe malaria ($p < 0.05$). We found the sensitivity and specificity of malarial retinopathy as a marker of severe malaria to be 75% and 96.6% with a positive predictive value of 81.8%.

Conclusion: Malarial retinopathy may serve as an important clinical biomarker for predicting severe malaria. All clinicians should be appropriately trained in performing direct ophthalmoscopy to detect the retinopathy changes.

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Introduction

Malaria is a mosquito-borne parasitic infection caused by protozoa of genus *Plasmodium*.[1] It is an important vector-borne disease in tropical and subtropical countries of Asia, Africa, and America.[2] Mainly four species of *Plasmodium*, namely *vivax*, *falciparum*, *ovale*, and *malariae* cause malaria.[3] Plasmodium knowlesi is a recent addition to the list. *Plasmodium falciparum* malaria, especially in children of Africa with Cerebral or severe complicated malaria is reported to cause a cluster of retinal signs[4] collectively known as malarial retinopathy. The severity of malarial retinopathy correlated with mortality and severity of the infection in such cases.[4] Components of malarial retinopathy include: Retinal whitening, vessel changes–whitening, tramlining, retinal hemorrhages and papilledema.[5] Retinopathy is seen in complicated malaria cases only.[6] Among the ocular retinopathy changes, retinal whitening and vessel discoloration are unique to malaria only and not seen in other ocular or systemic conditions.[4,6] Papilledema and retinal hemorrhages can be seen with an ordinary direct ophthalmoscope but distinctive retinal whitening and vessel abnormalities can be seen with indirect ophthalmoscopy as the peripheral retina can be visualised.[7] The pathophysiology behind the retinopathy changes have been postulated to be due to sequestration of infected erythrocytes in the retinal microvasculature.[8] As both the retina and brain have same embryological origin–namely, neuroectoderm, so, the vasculature is similar in both. Breakdown of the blood-tissue barrier, endothelial dysfunction also contributes to the development of the changes.[8]

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In children, severe malaria presents as cerebral malaria, severe anemia, and metabolic acidosis or respiratory distress syndrome. Almost two-thirds of such severe malaria cases had evidence of malarial retinopathy. The large prospective study on Malawian children with cerebral malaria showed that the severity of retinal signs, including number of hemorrhagic spots was related to the outcome and length of coma in the cases.[4] In a study involving Kenyan children, retinal hemorrhage was associated with deeper coma and severe anemia.[9] In children of Mali with malaria, retinopathy was also related to severity of the infection.[10]

Compared to children, severe malaria in adults presents as multisystem involvement, including renal failure, hepatic dysfunction.[5] In studies done on Thai and Indian adults with severe malaria, retinal hemorrhages were detected less frequently than in children.[11–13] In adults, retinal edema and exudate have been reported, instead of the classical retinal whitening seen in children. Macular whitening of retina has been reported in two Malawian adults with cerebral malaria in a study.[14]

Malarial retinopathy changes have been reported to resolve some time after resolution of coma in Cerebral malaria and there no residual persisting retinal abnormalities after that.[15] In a detailed observational study of malarial retinopathy conducted on Bangladeshi adults with *P. falciparum* malaria admitted in hospital, out of 234 study subjects, 85% with cerebral, 67% noncerebral severe and 47% uncomplicated malaria had retinal changes. Moderate to severe retinopathy was found in 6% of those with fatal and 62% of cerebral malaria. They reported resolution of signs to take a median of 2 weeks. The severity of retinopathy correlated with severity of malaria. According to their study, although indirect ophthalmoscopy was more sensitive to detect retinal changes, it provided minimal additional prognostic information when compared to direct ophthalmoscopy.[16]

Malarial retinopathy in adults with severe malaria, although not as common as in children, Medicine and Infectious Disease Specialists should always keep it in mind so as not to miss it. Considering the burden of malaria in our country and scarcity of literature on this topic, this study was undertaken

Aim and Objective

- To determine prevalence of malarial retinopathy among malaria cases.
- To determine relationship between malarial retinopathy and severity of the disease.

Materials and Methods

Study Setting

Indoor and outdoor, Department of Tropical Medicine, School of Tropical Medicine (STM), Kolkata and Department of Ophthalmology, Regional Institute of Ophthalmology (RIO), Medical College, Kolkata, West Bengal, India.

Study Period

12 months.

Definition of Study Population

Malaria parasite found in blood smear, thick and thin.

Sampling Method and Size

The consecutive sampling method was used. A 70 sample size is needed. Considering prevalence rate of malaria, 5.02%.[17]

Inclusion Criteria

Patients >18 years of age of both sexes.

Exclusion Criteria

- Patients are unable or unwilling to cooperate with eye examination.
- Contraindications to tropicamide eye drops (angle closure glaucoma or known allergy to product).
- Severe corneal scarring or cataracts are hindering vision by ophthalmoscopy.
- Diabetes mellitus.
- Hypertension.
- Intracranial space-occupying lesions.
- Epilepsy.
- Alcohol use.
- Chronic renal failure.
- Age > 60 years.
- Any other known ocular/systemic disease that can cause retinopathy changes.

Study Design

Observational study.

Study Tool

- Predesigned proforma for data collection.
- Informed consent document.
- Parameters to be assessed:
  - History taking, clinical examination.
  - CBC, LFT, urea, creatinine, electrolytes—Na^+, K^+.
  - Direct ophthalmoscopy in all cases.
  - Other investigations as per necessity.

Study Technique

- Malaria cases, both complicated/severe and uncomplicated, were taken.
- Severe malaria was diagnosed as per the WHO criteria.[18]
- There were two control groups for comparison. Cases with acute febrile illness of other causes were taken in the control arm group, and normal population subjects were taken as another control group.
- All patients were assessed clinically, followed by appropriate laboratory investigations; direct ophthalmoscopic examination was then performed. Ocular findings were be collaborated with the severity of illness.
- Observations were made by two independent observers, one of them being an ophthalmologist.
- Ophthalmoscopy was done on the day of admission, and in those patients where changes were noted, repeat examination was done at time of discharge and follow-up after 1 month.
- Two drops of tropicamide (0.5 or 1%) eye drops were used to dilate pupil for purpose of examination.
- A subset of patients underwent color fundus/retinal photography when stable enough to be transported to RIO for documentation of the pictures of retinopathy.
- Data was collected and compiled in an MS Excel sheet.

Data Analysis

Descriptive data were represented as mean, standard deviation, range, frequency, or percentages, as applicable. Different levels were expressed at a 95% confidence interval. The normality of the data was assessed using the Shapiro–Wilk test. The continuous variables were compared using the Student's *t*-test. The categorical variables were compared using the chi-squared statistic and Fisher's exact test. Analysis for the various measures was performed using various standard statistical software packages such as Microsoft Excel and GraphPad Prism.

Ethical Issues

- Informed consent was obtained from patient or patient's relatives in all cases
- Management of the patients under the study was not intervened in by any means.
- The proposal was submitted to the Clinical Research Ethics Committee (CRE-STM), School of Tropical Medicine, for approval.
- Patient identity was not disclosed by any means.
- Ethics Committee Approval number: CREC/STM 2022 AS-19 dated December 5, 2022.

Results

A total of 71 malaria cases were included in our study. Among them, 12 cases were of severe malaria and rest cases were uncomplicated. Of the 12 severe malaria cases, 8 were *P. vivax*, 3 were *P. falciparum,* and 1 was mixed. Uncomplicated malaria cases were mostly *P. vivax* (35 out of 59). Tables 1 and 2 show the clinicolaboratory profile of the cases and the clinical profiles of severe malaria cases, respectively.

Severe anemia, hypotension, and hemoglobinuria were noted in one case of falciparum malaria. Two cases of falciparum with renal failure (creatinine >3 mg/dL) with jaundice were seen. Renal failure (creatinine > 3 mg/dL) was seen in a mixed malaria cases as severe malaria.

Features suggestive of malarial retinopathy were noted in 9 out of 12 cases of severe malaria (75%) and 2 out of 59 cases of uncomplicated malaria (3.4%) (Table 3 and Figs 1 to 4)

We noted two cases of retinal changes—one case of retinal whitening in falciparum malaria and one case of vivax malaria with retinal hemorrhage in the uncomplicated group. Both of the cases subsequently needed admission for recurrent vomiting, reduced urine output, and severe weakness.

Forty dengue cases were included in the control arm of AFI cases: 20 DHF cases and 20 cases of DF with warning signs. Among them, retinal hemorrhage was noted in one case of DHF (2.5%).

Out of 40 sepsis cases, retinal hemorrhage was seen in one case (2.5%).

No retinal changes were noted among 40 other AFI cases who needed hospitalization and were admitted indoors, considering disease severity. The cases included 10 cases of scrub typhus, 10 cases of enteric fever, 4 cases of chikungunya, 5 cases of acute viral hepatitis, 4 cases of leptospirosis, and 7 undifferentiated febrile illnesses.

Also, no abnormality was detected on ophthalmoscopy in 40 healthy individuals (Fig. 1). So, the presence of retinopathy was suggestive of severe malaria ($p < 0.05$).

Table 1: Clinicolaboratory profile of study cases

Characteristics	*Uncomplicated malaria (n = 59)*			*Severe/Complicated malaria (n = 12)*			*p-value*
	P. vivax (n = 35)	*P. falciparum (n = 18)*	*Mixed (n = 6)*	*P. vivax (n = 8)*	*P. falciparum (n = 3)*	*Mixed (n = 1)*	
Age (in years)	40.4 ± 13.02	36.7 ± 15.05	36 ± 9.08	32 ± 5.58	39.3 ± 17.56	22	
Sex (M/F)	22/13	12/6	4/2	5/3	2/1	0/1	
Clinical features							
Fever	35	18	6	8	3	1	0.893
Chills	35	18	6	8	3	1	0.893
Headache	11	12	5	6	3	1	0.521
Vomiting	3	4	1	4	2	1	0.688
Diarrhea	2	2	–	1	1	1	> 0.05
Abdominal pain	2	2	–	3	1	1	> 0.05
Decreased urine output	–	–	–	3	2	–	< 0.05
Altered sensorium	–	–	–	2	–	–	< 0.05
Icterus	–	–	–	–	2	–	< 0.05
Hepatomegaly	6	5	2	6	3	1	> 0.05
Laboratory parameters							
Hb	12.32 ± 1.098	12.15 ± 1.28	12.18 ± 0.62	10.39 ± 1.42	8.33 ± 3.23	9.9	0.700
TLC	7150.86 ± 1141.74	7400 ± 800	7633 ± 1284.78	7703.75 ± 1630.10	10166.67 ± 2797.02	6700	0.313
Platelet	1.42 ± 0.17	1.45 ± 0.09	1.54 ± 0.71	1.2 ± 0.2	0.86 ± 0.185	1.51	0.132
Total bilirubin	1.77 ± 0.298	1.89 ± 0.5	1.64 ± 0.39	2.325 ± 0.39	3.1 ± 0.2	3.4	0.351
SGOT	44.4 ± 3.73	44.39 ± 1.54	44.83 ± 6.65	47.75 ± 4.46	53.67 ± 5.03	78	0.148
SGPT	46.28 ± 3.97	46.17 ± 1.76	47 ± 6.98	50 ± 4.14	59.67 ± 2.08	84	0.122
Urea	29.06 ± 5.46	31.17 ± 5.79	33 ± 7.24	43.12 ± 3.14	41.33 ± 3.05	54	0.371
Creatinine	1.21 ± 0.18	1.21 ± 0.17	1.1 ± 0.11	1.77 ± 0.10	1.63 ± 0.15	2.1	0.746

Table 2: Profile of Severe malaria cases ($n = 12$)

Criteria	*No. of cases*
Impaired consciousness (GCS < 11)	2
Prostration (severe generalized weakness with inability to sit, stand, or walk without assistance)	4
Renal failure (serum creatinine > 3 mg/dL)	3
Jaundice (serum bilirubin > 3 mg/dL)	3
Severe anemia (Hb < 5 gm/dL)	1
ARDS	1
Hypoglycemia (plasma glucose < 40 mg/dL)	2
Metabolic acidosis (plasma bicarbonate < 15 mmol/L)	1
Circulatory collapse/shock (BP < 80 mm Hg)	2
Hemoglobinuria	1

Table 3: Malarial retinopathy noted in severe malaria cases

Retinal changes	*Falciparum (n = 3)*	*Vivax (n = 8)*	*Mixed (n = 1)*
Whitening	–	1	1
Hemorrhage	3	2	–
Papilledema	–	2	–

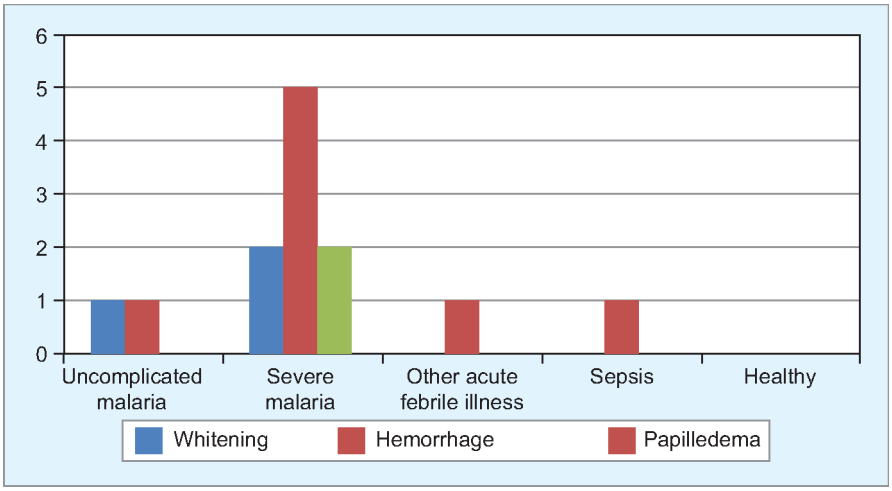

Fig. 1: Retinal changes noted in the study population

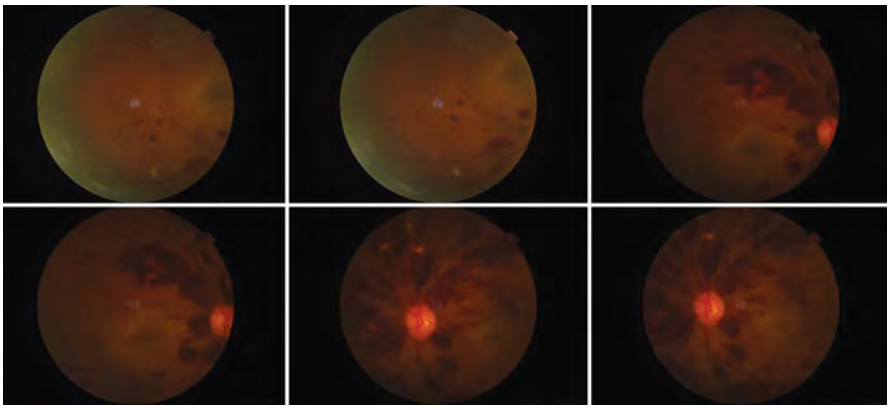

Fig. 2: Serial fundus photo showing multiple intraretinal flame-shaped hemorrhage and a few cotton wool spots centered around the optic disc with dull foveal reflex

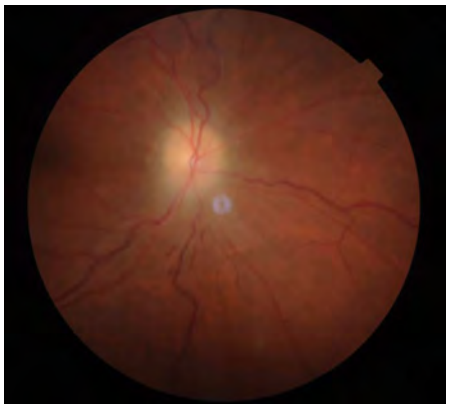

Fig. 3: Blurred disc margin, retinal whitening, with flame-shaped hemorrhage along the inferotemporal vein

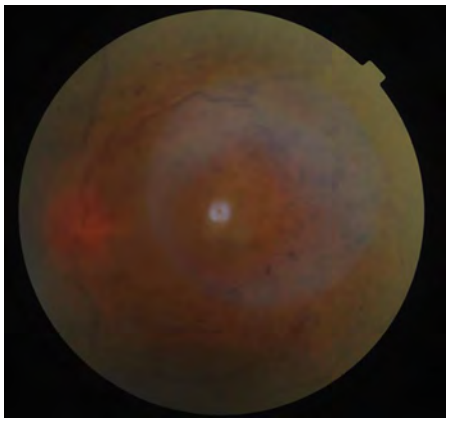

Fig. 4: Fundus photo showing blurred disc margin, mild tortuosity of veins, multiple intraretinal (flame-shaped and dot) hemorrhage in all quadrants with dull foveal reflex

All the retinopathy changes were present at the time of discharge of the patients but resolved at follow-up visit after 1 month.

All the malaria cases were treated according to the National Guidelines. There was one mortality in our study of the *P. vivax* case who developed ARDS, shock, refractory metabolic acidosis, and then renal failure and subsequent multiorgan dysfunction.

Of the eight cases of severe malaria with retinopathy, five cases had headache persisting for up to 1 month. In three cases of them, headache was so excruciating that neuroimaging was needed to exclude other pathologies. Thus, the presence of retinopathy also had a relation with post-malaria headache ($p < 0.05$).

Discussion

Malaria continues to remain an important cause of fever, especially in tropical and subtropical countries.[19]

Despite being a preventable and treatable disease with highly effective drugs such as artemisinin-based combination therapies and injectable artesunate, malaria still leads to mortality and morbidity in developing countries like India. Globally, there were an estimated 241 million cases of malaria in 2020 with 6,27,000 deaths. India accounts for around 4% of global malaria cases, with more than half of the population at risk of malaria.[20]

Although *P. falciparum* has long been associated to be cause of severe malaria, there is emerging evidence that *P. vivax,* which was once considered a benign species, can also cause severe malaria.[21]

In our study, we also found vivax malaria alone to account for 60.6% of the total cases (43/71).

In our study, fever with chills was the most common presenting symptom in all the cases, followed by headache.

A study in North India also reported fever to be the commonest symptom (present in 100% of cases), followed by chills (73.4%), headache (48%), vomiting (46%), abdominal pain (29%), and decreased urine output (20%). Regarding the laboratory parameters, they observed hemoglobin to be significantly lower in falciparum malaria in comparison to vivax or mixed infection and total leukocyte count to be significantly lower in mixed

malaria cases. Other hematological and biochemical parameters were similar among the groups of vivax, falciparum, and mixed malaria. However, AKI, altered sensorium, anemia, thrombocytopenia, and transaminitis were significantly higher in the severe malaria cases compared to the uncomplicated group.[22]

This was consistent with our study also. Decreased urine output, altered sensorium, and icterus were noted only in severe malaria group. In regard to laboratory parameters, hemoglobin and platelet count were lower in severe malaria than in uncomplicated cases, while liver enzymes, bilirubin, urea, and creatinine were higher in the severe malaria group, although the difference was nonsignificant.

Retina being an integral part of the CNS, examination of the retina by easily accessible noninvasive fundoscopy can serve as a surrogate in visualizing inflammatory and obstructive changes in microvasculature occurring in the brain in severe malaria. As both retina and brain tissue have a similar network of vessels and have high metabolic demand, they are vulnerable to sequestration and hypo/nonperfusion. Retinal whitening, hemorrhages, vessel discoloration, and papilledema are components of malarial retinopathy. Hemorrhages are hypothesized to occur as a result of damage or destruction of pericytes, resulting in blood–brain barrier damage leading to rupture of vasculature and subsequent hemorrhage. Adherence of sequestered infected RBCs to endothelium of retinal vessels results in obstruction to blood flow, leading to hypo- and nonperfusion, explaining retinal whitening. Papilledema signifies raised intracranial pressure.[23,24]

A study in Bangladesh included 210 adult subjects, incorporating 75 cerebral malaria cases, 64 severe malaria cases without coma, 31 uncomplicated falciparum malaria cases, 20 vivax malaria cases, and 20 healthy controls. None of the vivax malaria cases and healthy controls had any retinal changes. However, in falciparum malaria cases, indirect ophthalmoscopy detected malarial retinopathy (retinal hemorrhage being the predominant lesion) to be present in 86% of fatal cases, 41% cerebral malaria cases, 25% noncerebral but severe cases. Only 1 out of 31 uncomplicated falciparum cases had a retinal change. On examination by direct ophthalmoscope, only one case of retinopathy was missed, and a lesser number of retinal hemorrhages were detected in comparison to indirect technique. They reported severity of retinopathy to have a significant correlation with severity of malaria. They concluded that malarial retinopathy is an independent predictor of mortality and severity.[25]

Another study from Chittagong, Bangladesh, reported malarial retinopathy to be present in 63% cases of severe malaria, 78% cases with fatal course, 70% with cerebral malaria, 43% noncerebral severe malaria, and 60% uncomplicated malaria cases. 1 out of 5 patients with sepsis had retinopathy changes. Hemorrhage was the most common abnormality, followed by whitening.[26]

An Indian study on 104 adult cases of vivax malaria reported 38% of the severe cases to have retinal changes. On the other hand, only 6% of nonsevere cases had retinopathy. Arteriovenous changes were the commonest change noted, followed by retinal hemorrhage.[27]

In our study, malarial retinopathy was noted in 9 out of 12 cases of severe malaria (75%) and 2 out of 59 cases of uncomplicated malaria (3.4%). Retinal hemorrhage was the most common abnormality in severe malaria. We noted two cases of retinal changes: one case of retinal whitening in falciparum malaria and one case of vivax malaria with retinal hemorrhage in the uncomplicated group. Out of 40 dengue cases included in the control arm, retinal hemorrhage was noted in one case of DHF (2.5%). Out of 40 sepsis cases, retinal hemorrhage was seen in 1 case (2.5%). No retinal changes were noted among 40 other AFI cases, which included scrub typhus, enteric fever, chikungunya, and acute viral hepatitis. Also, no abnormality was detected on ophthalmoscopy in 40 healthy individuals (Fig. 1). Thus, the presence of retinopathy was suggestive of severe malaria ($p < 0.05$).

Another Indian study also reported a significant correlation between retinal changes in malaria patients with mortality and neurological sequelae.[28]

In our study, one mortality was noted in a *P. vivax* case who developed ARDS, shock, refractory metabolic acidosis, and then renal failure and subsequent multiorgan dysfunction. That case had maximum hemorrhagic spots seen on retinal examination. Of the eight cases of severe malaria with retinopathy, five cases had headache persisting for up to 1 month. In three cases, headache was so excruciating that neuroimaging was needed to exclude other pathologies. Thus, the presence of retinopathy also had a relation with post-malaria headache.

So, malarial retinopathy may serve as a bedside clinical biomarker of severe malaria and may be included in the criteria for severe malaria. Early detection of malarial retinopathy may help in the stratification of cases based on severity so that more aggressive treatment may help reduce mortality.

Study Limitations

The small sample size was a major limitation of our study. Moreover, a few cases of malarial retinopathy might have been missed as indirect ophthalmoscopy could not be done in all cases, considering the issue of transport of severe malaria patients. Also, grading of retinopathy was not possible due to the same reason.

Future studies should try to overcome these limitations.

Conclusion

Malarial retinopathy may serve as an important clinical biomarker for predicting severe malaria. We found the sensitivity and specificity of malarial retinopathy as a marker of severe malaria to be 75% and 96.6%, with a positive predictive value of 81.8%. All clinicians should be appropriately trained in performing direct ophthalmoscopy to detect the retinopathy changes.

Source of Support

Nil

Conflicts of Interest

None

Author Declaration

I hereby declare that this study is my original work and has not been presented anywhere in any form, either as part or as a whole study before. I also declare that this article has not been sent anywhere, under consideration for publication, or published.

Authors Contribution

The study was conceptualized by RC and NC. Data collection done by RC, TRB, and IC. Data analyzed by RC and SM. KS and PH provided ophthalmoscope instrument. Others supervised the project.

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ORIGINAL ARTICLE

Early LDL-C Lowering Efficacy of High-intensity Atorvastatin and Ezetimibe Combination Compared with High-intensity Atorvastatin Alone in Acute Coronary Syndrome: The LAI EARLY ACS Study

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Abstract

Background: High-intensity statins are recommended in patients experiencing acute coronary syndrome (ACS) to lower low-density lipoprotein cholesterol (LDL-C) levels, but evidence-based recommended LDL-C goals often remain unmet. We assessed the therapeutic benefit of early LDL-C lowering and the safety of high-intensity atorvastatin and ezetimibe combination versus high-intensity atorvastatin alone in ACS.

Methods: In this investigator-initiated trial, 254 patients admitted with ACS were randomized 1:1 to either atorvastatin 80 mg once daily (group A) or a combination of atorvastatin 80 mg and ezetimibe 10 mg once daily (group B). The first dose was administered orally immediately after diagnosis and then continued daily. The primary and secondary endpoints were percentage reductions in direct LDL-C measurements over the initial 4-week period and at 12 weeks, respectively.

Results: The mean percentage reduction in LDL-C was 8.12% in group A vs 14.43% in group B ($p < 0.001$) at week 1, 16.62% in group A vs 28.34% in group B at 2 weeks ($p < 0.001$), 29.43% in group A vs 45.15% in group B at 4 weeks ($p < 0.001$), and 41.88% in group A vs 60.76% in group B ($p < 0.001$) at 12 weeks. Adverse events were similar in both groups.

Conclusion: Ezetimibe added to high-intensity statin therapy was well tolerated and resulted in an immediate and robust additional decrease in circulating LDL-C concentrations, with a markedly higher proportion of participants achieving LDL-C goals at 4 and 12 weeks. These promising results show that dual therapy started immediately at the diagnosis of ACS has the potential to improve cardiovascular outcomes in ACS.

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Introduction

Patients experiencing an acute coronary syndrome (ACS) face the greatest probability of subsequent cardiac events during the early post-event period,[1] underscoring the importance of prompt initiation of evidence-based preventive strategies. Although the control of conventional risk factors and comorbidities such as hypertension and diabetes is necessary, the management of lipid-associated risk is of extreme importance, as ACS most commonly results from the disruption of vulnerable coronary plaque, which is characterized by a large lipid burden and a structurally fragile fibrous cap. Hence, early robust LDL-C reduction after ACS can reduce adverse CV events by stabilizing the vulnerable plaque.[2]

Increased levels of LDL-C are a well-recognized adjustable determinant influencing both the onset and advancement of atherosclerotic CV disease (ASCVD).[3] Extensive clinical evidence demonstrates that reductions in LDL-C achieved with statin therapy translate into proportional decreases in cardiovascular morbidity and mortality among patients with established ASCVD, thus suggesting that lower LDL-C levels improve outcomes.[4] Clinical trials conducted in the post-ACS setting have shown that initiation of high-intensity statin therapy confers superior cardiovascular protection compared with lower-intensity regimens.[5,6] Further, pretreatment with high-intensity atorvastatin in participants with non-ST-segment elevation ACS being treated with angioplasty followed by atorvastatin 40 mg/day in the ARMYDA-ACS trial significantly lowered the rate of major adverse cardiac outcomes within 30 days, driven primarily by a reduction in myocardial infarction (MI) (5% vs 15%; $p = 0.04$).[7] Additionally, patients randomized to treatment with the non-statin therapies, such as ezetimibe or alirocumab, added to high-intensity statin therapy days to weeks after ACS had lower rates of CV events compared with statin therapy alone.[8,9] Despite these data, real-world utilization of adjunctive non-statin lipid-lowering therapies, such as ezetimibe, remains limited even among patients classified as having extremely high CV risk.

Although statins potently lower LDL-C levels, the addition of non-statin therapy immediately after the index acute coronary event may be required for rapid further LDL-C lowering, which may result in additional reduction in adverse CV events. Recent trials in which subcutaneous evolocumab was initiated within 24 hours of ACS as an adjunct to high-intensity statin treatment demonstrated rapid attainment of markedly low LDL-C concentrations without safety concerns, with most patients achieving guideline-directed LDL-C goals.[10] Further, very early (within 24 hours) initiation of PCSK9 inhibitors with high-intensity statin therapy after ACS is associated with significant plaque regression along with plaque stabilization as evidenced by thickening of the fibrous cap.[11] However, there are many limitations to the integration of PCSK9 inhibitors into clinical practice, including the need for regular injections and high cost, particularly

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in India, where the cost of the medication most commonly is paid directly by the patient due to the absence of insurance coverage [average cost approximately Rs. 50,000 (US $600) per month]. Therefore, there is an unmet need to identify cheaper and more feasible alternatives.

Given that the effectiveness of combination LDL-C lowering with a high potency statin and ezetimibe started immediately at diagnosis of ACS has not been previously reported prospectively, this study—the Lipid Association of India: Ezetimibe Atorvastatin combination for Rapid LDL-C lowering in Acute Coronary Syndrome (LAI EARLY ACS study), analyzed the therapeutic benefit and risk profile of the dual approach of high intensity atorvastatin 80 mg/day with ezetimibe 10 mg/day compared with high intensity atorvastatin 80 mg/day alone in Indian individuals presenting with an acute coronary event.

Materials and Methods

This randomized controlled trial was carried out in the Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, a tertiary care academic hospital associated with Maulana Azad Medical College, New Delhi, India, upon securing ethical approval from the institutional ethics committee in compliance with the Declaration of Helsinki. Consent for participation was taken in writing from all enrolled participants. The study population comprised 254 statin naïve, hemodynamically stable patients with ACS who presented within a 24-hour timeframe of symptom onset and who gave informed consent, between January 2023 and June 2024. Patients were randomized into two groups: atorvastatin 80 mg once daily (group A) or atorvastatin 80 mg plus ezetimibe 10 mg once daily (group B). Both groups were given the first dose of either statin or dual therapy in the emergency ward, along with dual antiplatelet therapy after collecting initial blood samples.

Acute coronary syndrome was defined as acute ischemic chest pain with ischemic ST–T changes on electrocardiogram (ECG) and/or acute elevations in serum cardiac troponin T (cTnT) concentrations. This included patients with acute myocardial infarction (AMI) [both ST-segment elevation (STEMI) and non-ST-segment elevation (NSTEMI)] and unstable angina (UA). The diagnosis of MI was made based on the fourth universal definition of MI.[12] Unstable angina was defined as typical symptoms of myocardial ischemia at rest or on minimal exertion in the absence of ST-elevation or acute cardiomyocyte injury/necrosis, evidenced by a negative troponin t-test. The participants who had a previous diagnosis of coronary artery disease, who were already on any lipid-lowering therapy, or had known moderate-severe hepatic (Child-Pugh class B or C) or renal dysfunction (eGFR less than 45 mL/min/1.73 m^2) were excluded.

Demographic Data and Investigations

Demographic data were recorded along with detailed history, including the presence of risk factors and comorbidities such as smoking, history of hypertension, and diabetes. The electrocardiogram (ECG) was recorded, and 10 mL of blood was collected at emergency triage in an EDTA vacutainer for complete hemogram, in a SST vacutainer for serum levels of transaminases, urea, creatinine, high-sensitivity C-reactive protein (hsCRP), lipid profile tests, and a fluoride vacutainer for blood sugar levels. Routine clinical chemistry and the concentrations of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using a fully automated biochemistry analyzer (Roche Cobas c501). LDL-C levels were measured using direct enzyme assays. The lipoprotein (a) [Lp(a)] concentration was assessed using an isoform-insensitive particle-enhanced immunoturbidometric assay. Complete blood count was assessed using a fully automated hematology analyzer (Sysmex XN1000).

Endpoints

Subjects were followed for a total duration of 12 weeks with on-site visits at 1 week (± 3 days), 2 weeks (± 3 days), 4 weeks (± 3 days), and 12 weeks (± 7 days). During each follow-up visit, vital signs were recorded, and blood samples were collected for measurements of total cholesterol, LDL-C, triglyceride, and HDL-C levels. The concentrations of hsCRP and Lp(a) were assessed initially and at 12 weeks. Blood samples were analyzed blindly, irrespective of the treatment allocation. The primary outcome assessed was decline in LDL-C levels at 4 weeks, and the secondary outcome was decline in LDL-C levels at 12 weeks.

Statistical Analysis

The data obtained were analyzed employing statistical software SPSS version 25 (IBM Corp. Armonk, NY, IBM Corp). Continuous data are described by their means and standard deviations, while categorical data are summarized as frequencies and percentages values. The difference between means of the two groups for patients' baseline characteristics was tested by Student's *t*-test for numerical variables and chi-square test for descriptive data. The linear mixed model was applied with first-order autoregressive covariance structure on the percentage change in lipid variables to compare mean percentage change between the groups at different follow-up time points, with Bonferroni correction. *p*-values < 0.05 were considered statistically significant.

Results

The study comprised of 254 participants. The cohort had a mean age of 53.7 ± 11.9 years; 192 individuals (75.6%) were men. Nearly half of the participants were current or former smokers ($n = 125$, 49.2%), with a mean smoking exposure of 10.2 ± 11.3 pack-years. A history of hypertension was documented in 88 patients (34.6%), while diabetes mellitus was present in 40 patients (15.8%). The majority of patients (161; 63.3%) presented with STEMI, while NSTEMI and unstable angina were the presenting diagnosis in 54 (21.3%) and 39 (15.4%) patients, respectively. The prevalence of STEMI, NSTEMI, and unstable angina did not differ between the groups (Table 1). The follow-up period averaged 94.6 ± 11.2 days, with mean follow-up in group A being 95.4 ± 14.7 days and in group B 93.8 ± 16.7 days, p = NS. Of the enrolled participants, 243 (95.7%) were followed for the entire 3-month study duration. Two patients were lost to follow-up after 1 week, six after 2 weeks, and three after 4 weeks. The baseline profile of both groups is shown in Table 1.

Mean baseline levels of total cholesterol, triglycerides, HDL-C, non-HDL-C, and Lp(a) are given in Table 1. The mean LDL-C level at baseline was 114.7 ± 29.2 mg/dL in group A and 123.2 ± 31.7 mg/dL in group B, $p = 0.03$. Groups A and B were not matched for total cholesterol and LDL-C, resulting in 7.5% higher initial LDL-C levels in the combination therapy group B. Levels of total cholesterol, triglycerides, HDL-C and non-HDL-C at each follow-up visit are shown in Table 2.

The percent LDL-C reduction achieved at each follow-up time was calculated from the baseline LDL-C values using a linear mixed model with a first-order autoregressive correlation that gives the minimum Akaike Information criterion. The interaction was statistically significant ($F = 34.44$, $p < 0.0001$), indicating the pattern of percentage change over time was not similar between the two groups. However, within groups, there was a decrease in the mean LDL-C over time. The intergroup differences in mean percent change in LDL-C were statistically significant at 1 week,

Table 1: Baseline characteristics of the two groups

Baseline characteristics	*Atorvastatin 80 mg daily (group A, n =124)*	*Atorvastatin 80 mg + ezetimibe 10 mg daily (group B, n =130)*	*p-value*
Age, years	53.1 ± 12.2	54.3 ± 11.7	0.43
Females, n (%)	35 (28.2%)	27 (20.8%)	0.17
Males, *n* (%)	89 (71.8%)	103 (79.2%)	
Diabetes, *n* (%)	23 (18.5%)	17 (13.1%)	0.23
Hypertension, *n* (%)	38 (30.6%)	50 (38.5%)	0.19
Body mass index (BMI), kg/m^2	23.57 ± 1.59	23.72 ± 1.69	0.45
Smokers, *n* (%)	59 (47.6%)	66 (50.8%)	0.61
No. of pack-years	10.3 ± 13.2	10.2 ± 11.3	0.95
Systolic blood pressure, mm Hg	133.62 ± 9.62	133.64 ± 11.48	0.99
ACS Presentation			
STEMI, *n* (%)	81 (65.4%)	80 (61.6%)	0.37
NSTEMI, *n* (%)	22 (17.7%)	32 (24.6%)	
Unstable angina, *n* (%)	21 (16.9%)	18 (13.8%)	
Waist circumference, cm	78.39 ± 10.30	80.0 ± 8.53	0.18
Hemoglobin, gm/dL	12.40 ± 1.57	12.66 ± 1.31	0.16
Total leukocyte count, per mm^3	10.46 ± 2.04	10.96 ± 1.81	0.10
Random serum glucose, mg/dL	128.10 ± 40.62	125.36 ± 32.59	0.55
SGOT (AST), U/L	53.05 ± 6.75	53.58 ± 6.56	0.52
SGPT (ALT), U/L	52.20 ± 7.81	52.04 ± 8.64	0.87
Total cholesterol, mg/dL	195.2 ± 43.06	205.08 ± 43.52	0.02
Triglycerides, mg/dL	190.48 ± 69.46	200.85 ± 71.90	0.24
LDL-C, mg/dL	114.66 ± 29.22	123.22 ± 31.74	0.03
HDL-C, mg/dL	35.08 ± 6.68	36.22 ± 7.10	0.19
Non-HDL-C, mg/dL	160.19 ± 44.13	168.86 ± 44.23	0.12
Lipoprotein(a)-(median), mg/dL	35.2	35.7	0.72
hsCRP, mg/L	9.70 ± 2.55	9.61 ± 2.76	0.78

Table 2: Total cholesterol, triglycerides, LDL-C, HDL-C, and non-HDL-C levels at each follow-up visit

Lipid profile (mg/dL)	*1st week*		*2nd week*		*4th week*		*12th week*	
	Group A n = 124	*Group B n = 130*	*Group A n = 123*	*Group B n = 129*	*Group A n = 120*	*Group B n = 126*	*Group A n = 119*	*Group B n = 124*
Total cholesterol	179.11 ± 40.33	181.53 ± 38.72	164.89 ± 36.44	158.54 ± 34.50	145.24 ± 30.37	133.70 ± 25.95	121.33 ± 21.87	109.19 ± 18.29
LDL-C	105.52 ± 27.96	104.95 ± 28.94	96.06 ± 26.52	87.92 ± 24.21	80.83 ± 20.81	67.37 ± 18.32	65.51 ± 15.65	47.29 ± 14.35
Triglycerides	168.00 ± 56.08	170.38 ± 54.21	151.50 ± 45.12	150.23 ± 44.87	133.55 ± 33.85	127.42 ± 30.89	115.63 ± 26.47	104.45 ± 21.45
HDL-C	38.20 ± 5.48	38.84 ± 5.71	39.68 ± 5.06	41.28 ± 5.29	41.81 ± 5.63	43.29 ± 5.70	42.05 ± 5.55	45.12 ± 5.06
Non-HDL-C	140.91 ± 40.98	142.69 ± 39.10	124.20 ± 38.93	116.36 ± 36.11	100.93 ± 34	86.94 ± 32.26	78.62 ± 23.81	63.55 ± 20.01

2 weeks, 4 weeks, and 12 weeks. The mean percentage reduction in LDL-C was 8.12% in group A vs 14.43% in group B ($p < 0.001$) at 1 week, 16.62% in group A and 28.34% in group B at 2 weeks ($p < 0.001$), 29.43% in group A and 45.15% in group B at 4 weeks ($p < 0.001$) and 41.88% in group A and 60.76% in group B ($p < 0.001$) at 12 weeks. Table 3 and Figure 1 show percentage reductions in LDL-C and other lipid parameters at each follow-up. The absolute reductions in LDL-C levels at various time-points were also significantly greater with combination therapy in group B compared to group A. Comparable changes in non-HDL-C were observed.

The proportion of patients achieving LDL-C goals in the two study groups according to various guidelines, American College of Cardiology (LDL-C goal <70 mg/dL), European guidelines (LDL-C goal <55 mg/dL), and Lipid Association of India (LDL-C goal <50 mg/dL) is given in Table 4. The dual therapy of atorvastatin 80 mg and ezetimibe 10 mg once a day led to a significantly greater number of patients achieving LDL-C goals at 4 and 12 weeks (Fig. 2). Median Lp(a) levels at baseline in groups A and B were 35.2 and 35.7 mg/dL, respectively. At 12 weeks, the median Lp(a) levels were 35.6 mg/dL in group A and 37.9 mg/dL in group B (p = NS). The mean baseline hsCRP levels in groups A and B were 9.70 ± 2.55 mg/L and 9.61 ± 2.76 mg/L, respectively. The hsCRP levels significantly decreased to 3.18 ± 1.53 mg/L in group A ($p < 0.0001$ compared to

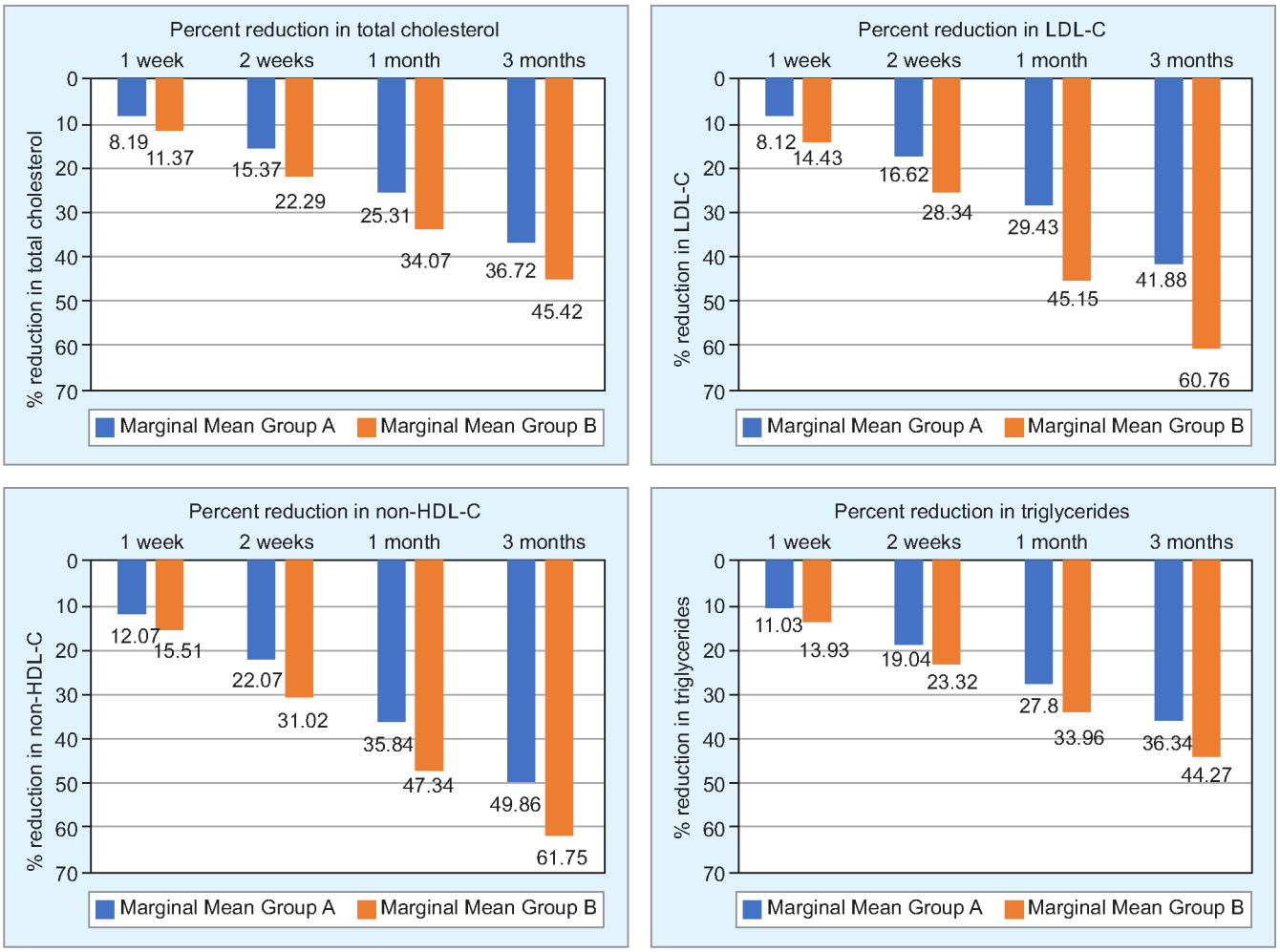

Fig. 1: Percent reduction in lipid parameters at various study visits

Table 3: Percent decrease in LDL-C, total cholesterol, triglycerides, and non-HDL-C at each follow-up

Follow-up time	*Marginal mean (95% CI)*		*Mean intergroup difference of marginal mean (95% CI)*	*p-value with Bonferroni correction*
	Group A	*Group B*		
Percent decrease in LDL-C				
1 week	8.12 (6.73–9.52)	14.43 (13.07–15.80)	6.31 (4.36–8.26)	<0.001
2 weeks	16.62 (15.22–18.02)	28.34 (26.97–29.71)	11.72 (9.76–13.68)	<0.001
4 weeks	29.43 (28.02–30.84)	45.15 (43.76–46.53)	15.72 (13.74–17.69)	<0.001
12 weeks	41.88 (40.46–43.30)	60.76 (59.36–62.15)	18.87 (16.88–20.86)	<0.001
Percent decrease in total cholesterol				
1 week	8.19 (6.91–9.47)	11.37 (10.11–12.62)	3.18 (1.39–4.97)	0.004
2 weeks	15.37 (14.09–16.65)	22.29 (21.03–23.54)	6.92 (5.13–8.71)	<0.001
4 weeks	25.31 (24.02–26.59)	34.07 (32.81–35.34)	8.77 (6.96–10.57)	<0.001
12 weeks	36.72 (35.42–38.02)	45.42 (44.14–46.69)	8.70 (6.88–10.52)	<0.001
Percent decrease in triglycerides				
1 week	11.03 (9.03–13.03)	13.93 (11.97–15.88)	2.90 (0.10–5.70)	0.172
2 weeks	19.04 (17.03–21.05)	23.32 (21.35–25.28)	4.28 (1.47–7.08)	0.012
4 weeks	27.80 (25.78–29.82)	33.96 (31.98–35.94)	6.16 (3.34–8.99)	<0.001
12 weeks	36.34 (34.31–38.37)	44.27 (42.28–46.26)	7.93 (5.09–10.78)	<0.001
Percent decrease in non-HDL-C				
1 week	12.07 (10.38–13.75)	15.51 (13.87–17.15)	3.44 (1.09–5.80)	0.012
2 weeks	22.07 (20.39–23.76)	31.02 (29.37–32.66)	8.94 (6.59–11.30)	<0.001
4 weeks	35.84 (34.14–35.54)	47.34 (45.69–48.50)	11.50 (9.13–3.87)	<0.001
12 weeks	49.86 (48.15–51.57)	61.75 (60.08–63.42)	11.89 (9.50–14.29)	<0.001

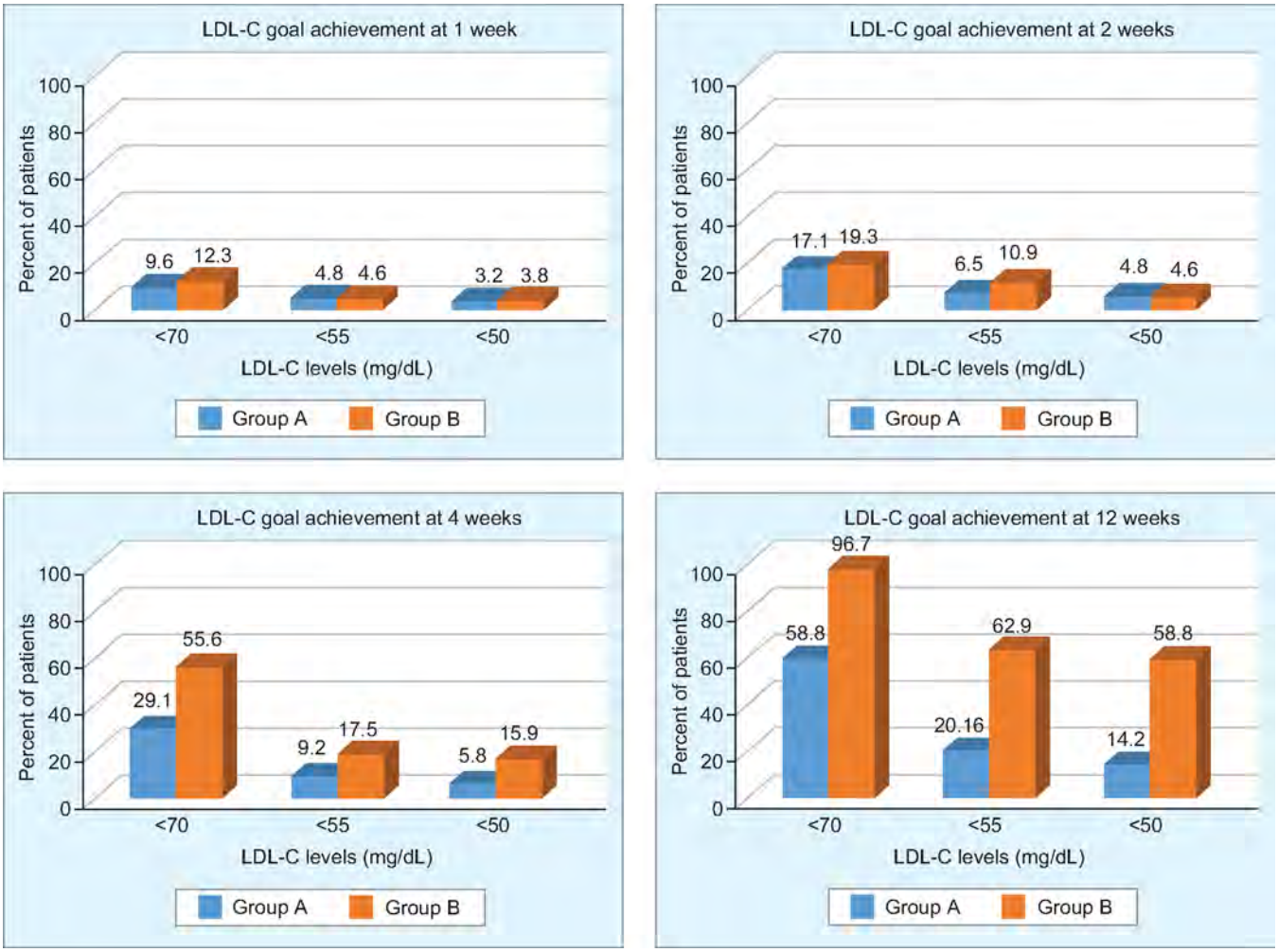

Fig. 2: Percentage of patients in both study groups achieving LDL-C goals according to various guidelines at defined time points

Table 4: Percentage of patients achieving LDL-C goal according to various guidelines

LDL-C at 1 week (mg/dL)	*Group A (n = 124)*	*Group B (n = 130)*	*p-value (group A vs B)*
<70, *n* (%)	12 (9.6%)	16 (12.3%)	0.50
<55, *n* (%)	6 (4.8%)	6 (4.6%)	1.0
<50, *n* (%)	4 (3.2%)	5 (3.8%)	1.0
LDL-C at 2 weeks (mg/dL)	*Group A (n = 123)*	*Group B (n = 129)*	*p-value*
<70, *n* (%)	21 (17.1%)	25 (19.3%)	0.63
<55, *n* (%)	8 (6.5%)	14 (10.9%)	0.22
<50, *n* (%)	6 (4.8%)	6 (4.6%)	1.0
LDL-C at 4 weeks (mg/dL)	*Group A (n = 120)*	*Group B (n = 126)*	*p-value*
<70, *n* (%)	35 (29.1%)	70 (55.6%)	<0.001
<55, *n* (%)	11 (9.2%)	22 (17.5%)	0.05
<50, *n* (%)	7 (5.8%)	20 (15.9%)	0.01
LDL-C at 12 weeks (mg/dL)	*Group A (n = 119)*	*Group B (n = 124)*	*p-value*
<70, *n* (%)	70 (58.8%)	120 (96.7%)	<0.001
<55, *n* (%)	24 (20.16%)	78 (62.9%)	<0.001
<50, *n* (%)	17 (14.2%)	73 (58.8%)	<0.001

baseline) and to 3.17 ± 1.54 mg/L in group B ($p < 0.0001$ compared to baseline) at 12 weeks. The decrease in hsCRP levels was statistically similar between the two groups.

Five patients in group A and six patients in group B reported mild bilateral lower limb muscle pain that resolved after counselling without need to modify the statin dose. Two patients in group A and one patient in group B had recurrent angina; one patient in each group required percutaneous intervention in a nonculprit vessel.

Discussion

This study compared the clinical benefit and tolerability of LDL-C lowering from dual therapy with ezetimibe 10 mg and atorvastatin 80 mg daily versus atorvastatin 80 mg daily, started at admission to the cardiology emergency department in patients presenting with ACS. We demonstrated significantly greater decline in LDL-C with dual therapy compared with atorvastatin alone at all time points studied. Furthermore, the achievement of evidence-based recommended LDL-C goals at 4 weeks and 12 weeks was significantly greater in patients treated with combination therapy compared to monotherapy. This prospective study is the first to report on early achievement of LDL-C lowering shortly after ACS presentation resulting from high-potency statin therapy in combination with ezetimibe.

Acute coronary syndrome is linked to substantial disease burden and death rates. A large retrospective cohort study from Swedish national registries reported that out of 108,315 patients hospitalized with a primary MI, 97,254 (89.8%) survived through the first week following hospital discharge, showing that acute MI is associated with high short-term mortality with standard-of-care treatment.[13] The pathophysiology of ACS is most often linked to plaque disruption, either rupture or erosion, occurring within lesions that possess a substantial lipid component and reduced structural stability, referred to as vulnerable plaque.[14] Hence, plaque stabilization is an important strategy for prevention of complications in ACS management. A multipronged approach that includes risk factor management involving intensive LDL-C lowering, antithrombotic, and anti-inflammatory treatment is necessary. Statins result in significant reductions in adverse CV events, both in ACS patients and stable ASCVD patients, but event rates and mortality remain high when LDL-C levels are persistently elevated despite statin therapy.[5,6,15,16]

Although statin therapy significantly lowers cardiovascular risk, a substantial proportion of adverse events continue to occur in high-risk patients, reflecting the presence of residual risk beyond statin monotherapy, partly due to inadequate LDL-C and non-HDL-C lowering.[17] While high-potency statin therapy reduces LDL-C levels by an average of about 50%, there is great interindividual variability, with many patients not achieving this degree of LDL-C reduction nor achieving evidence-based recommended LDL-C goals. Early reduction of LDL-C after ACS is coupled with reduced rates of reinfarction and adverse CV events.[5,6] Contemporary international guidelines advocate early initiation of high-intensity statins following ACS, with escalation to combination lipid-lowering therapy when LDL-C targets are not promptly achieved. However, the addition of non-statin therapy is often nonexistent or at best delayed, and is typically not started until 4–8 weeks after the index event.[18,19] Such delays may defer optimal LDL-C lowering during a period when patients are particularly vulnerable to recurrent ischemic events.

Recent PCSK9 inhibitor trials in ACS patients have shown that initiation of treatment with evolocumab in combination with statin therapy within 24 hours of ACS presentation results in early achievement of guideline-directed LDL-C goals in the majority of patients without safety concerns versus high-intensity statin therapy alone.[10,20] This strategy also significantly induces plaque regression and fibrous cap thickening over 52 weeks.[11] PCSK9 inhibitor monoclonal antibodies are associated with an early marked reduction in LDL-C levels, but are an injectable therapy and very expensive. Due to the high cost, PCSK9 inhibitors are out of reach of most patients in India, and hence, affordable alternative management pathways are needed that can be easily applied to routine patients. Accordingly, we utilized treatment with high-intensity atorvastatin and ezetimibe.

In the present study, treatment with a high-intensity statin in combination with ezetimibe resulted in LDL-C reductions of 45.15% at 1 month and 60.76% at 3 months. These findings are comparable to those reported in the evolocumab in acute coronary syndrome (EVACS) study, where a 62% reduction in LDL-C at one month was observed with high-intensity statin therapy plus evolocumab.[20]

Given its favorable cost profile and oral administration, ezetimibe represents a practical adjunct to high-intensity statin therapy, offering a well-tolerated and scalable approach to intensifying lipid lowering in ACS [average cost approximately Rs. 1,200 (US $15) per month]. These results further emphasize that clinicians need to consider the benefits of using dual therapy with a high-intensity statin plus ezetimibe in lieu of statin monotherapy in patients with ACS.

Our study results corroborate the Lipid Association of India recommendation to initiate treatment with a combination of high-intensity statin and ezetimibe in ACS patients at emergency triage, soon after initial phlebotomy for laboratory investigations. This recommendation was based on expert opinion in conjunction with extrapolation of data from trials of intensive lipid-lowering therapy in ASCVD patients.[2] This strategy has the potential to reduce adverse CV event rates by stabilizing vulnerable plaque and increasing the fibrous cap thickness.

Study Limitations

There are a few limitations of this study. First, this is a single-center investigator-initiated study enrolling a relatively small number of patients with only 12 weeks of follow-up. However, the study clearly demonstrates the feasibility and efficacy of dual therapy with ezetimibe added to high-intensity atorvastatin in achieving significantly earlier and greater reductions in LDL-C levels compared to statin therapy alone. Second, the impact of further LDL-C lowering with dual therapy on CV events cannot be inferred from this study. Nevertheless, it was proven in other studies that greater LDL-C lowering is associated with lower rates of CV events, regardless of the type of lipid-lowering therapy.[2,8,9]

Conclusion

Our study results demonstrate that the levels of LDL-C and non-HDL-C can be rapidly lowered after ACS by dual therapy with a high-intensity statin in combination with ezetimibe. Although treatment with PCSK9 inhibitors after ACS is proven to rapidly lower LDL-C and non-HDL-C levels and reduce ASCVD events, the high cost of PCSK9 inhibitors are a barrier to access to this treatment, particularly in India. Hence, for many patients, dual therapy with high-intensity statins plus ezetimibe is an affordable and well-tolerated treatment option that will rapidly achieve goal-directed LDL-C levels after ACS.

Author Contributions

VM: Conceptualization, methodology, investigation, validation, data curation, formal analysis, writing—original draft preparation, writing—review and editing, and supervision; NA: Methodology, data curation, resources, investigation, formal analysis, software, and writing—review and editing; PM: Methodology, investigation, data curation, formal analysis, and writing—original draft preparation; PKD: Investigation, validation, and writing—review and editing; NM: Methodology, formal analysis, and writing—review and editing; JY: Data curation, validation, and writing—review and editing; SS: writing—review and editing; SS: Writing—review and editing; MDG: Writing—review and editing; SK: methodology, and writing—review and editing; SK: Methodology, and writing—review and editing; AK: Writing—review and editing; PBD: Writing—review and editing; KKP: Writing—review and editing; RP: Conceptualization, methodology, software, and writing—review and editing.

Source of Support

This research received no external funding.

Informed Consent Statement

Informed consent was obtained from all the subjects.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare no conflicts of interest related to this manuscript. However, other industry affiliations are reported as follows:

- Vimal Mehta: Institutional Research Grants from Novo Nordisk, Eli Lilly, LIB Therapeutics, AstraZeneca.
- Pratishtha Mehra: Speaker/Advisory activities—Novo Nordisk, Eli Lilly.
- P Barton Duell: Advisory activities—Akcea/Ionis, Esperion, Regeneron, Kaneka, Novo Nordisk. Institutional grants: Regeneron, Regenxbio, Retrophin/Travere.
- Other authors have no conflict of interest.

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ANNOUNCEMENT

ICP ACADEMIC CALENDAR YEAR – 2026

Indian College of Physicians (ICP) plans to undertake the following academic activities during the year 2026:

A. ICP Advanced Clinical Certification (IACC)

Total 8 courses:

1. **Electrolyte, Acid Base and Fluid Disorders**
   Course Director – Dr Sanjay Pandya, Rajkot
2. **Artificial Intelligence for Physicians**
   Course Director – Dr Alok Modi, Mumbai
3. **Thyroid Disorders**
   Course Director – Dr Prakash Keswani, Jaipur
4. **Obesity**
   Course Director – Dr Puneet Saxena, Jaipur
5. **Tropical Diseases**
   Course Director – Dr Anupam Prakash, New Delhi
6. **Clinical Report Interpretation Course (CRIC)**
   Course Director – Dr Amit Saraf, Mumbai
7. **Common Medical Emergencies**
   Course Director – Dr Saumitra Ghosh, Kolkata
8. **Toxicology and Envenomation**
   Course Director – Dr Divendu Bhushan, Patna

- All certificate courses will be done on virtual platform.
- Every course will have 10 sessions.
- Each session will be held on a fixed day of every week.
- An assessment test will be conducted at the end of each course based on MCQ questionnaire.
- All attendees will be provided with a certificate by ICP.
- Maximum two certificate courses will run simultaneously to give the opportunity to attendees to attend maximum number of courses.

B. ICP Clinical Case Dialogues

Convenor – Dr Nandini Chatterjee, Kolkata

- It will be a CASE-BASED DISCUSSION SERIES on virtual platform.
- Total 10 sessions.
- Each session will be held once in a month.
- A postgraduate student will present a case of clinical interest, which will be discussed by 3–4 experts.

C. ICP Roundtable

Convenor – Dr L Sreenivasmurthy

- It will be a series of PANEL DISCUSSIONS on virtual platform.
- Total 10 sessions.
- Each session once in a month.
- ICP roundtable will be on subjects of clinical importance.
- There will be one moderator and 3–4 experts of national repute.

D. ICP Academic Outreach Program

Convenor – Dr Ashutosh Chaturvedi

- ICP academic outreach program is a program focused on teaching of postgraduate students.
- Physical classes will be held at medical colleges of different states.
- At least two medical colleges from each state will be chosen.
- There will be one local faculty and one national faculty.
- Expenses of national faculty will be borne by ICP.
- Each medical college will have the freedom to choose the subject and faculty.
- A state coordinator from each state will oversee the program.

State Coordinators

1. Rajasthan – Dr Sanjeev Maheshwari
2. West Bengal – Dr Nandini Chatterjee
3. Bihar and Jharkhand – Dr Amit Das
4. Haryana – Dr Munish Prabhakar
5. Northeast – Dr Sekhar Chakraborty
6. Gujarat – Dr Anil Kulshreshtha
7. Delhi – Dr Anupam Prakash
8. Odisha – Dr Jayant panda
9. Tamil Nadu – Dr Palaniappan
10. Karnataka – Dr Ravikeerthi
11. Andhra Pradesh – Dr Jawahar Swaroop
12. Telangana – Dr Naval Chandra
13. Maharashtra – Dr Rakesh Bhadade
14. Uttar Pradesh – Dr AK Gupta
15. Kerala – Dr Chandni Sanjeevan
16. Punjab – Dr RK Bansal
17. Madhya Pradesh – Dr RK Jha
18. Chhattisgarh – Dr Prabhat Pandey
19. Tripura – Dr Pradeep Bhowmik
20. Assam – Dr Dwijen Das
21. Goa – Dr Digamber Naik
22. Uttarakhand – Dr Ghanshyam Pangtey
23. Himachal Pradesh – Dr Rajesh Bhawani

E. Insights by the Masters

Virtue CME programs by eminent experts on clinically relevant subjects.

F. Cross-border CME

In association with Global forum, CME programs will be organized inviting international speakers.

G. ICP Medtalk

Experts in their specialties will be invited to record podcast on subjects of clinical interest in medicine. These podcasts will be uploaded on ICP website.

H. ICP Monographs

4–5 Monographs will be published during the year on subjects of clinical significance.

I. ICP Knowledge League (IKL)

Convenor – Dr Sanjeev Maheshwari
Quiz master – Dr Mukesh Bhatia, New Delhi

- It will be a postgraduate quiz program starting from the state level to zonal and national level.

Regards
Dr Girish Mathur
Dean, Indian College of Physicians

ORIGINAL ARTICLE

Prevalence and Predictors of Neurocognitive Impairment, Fatigue, and Health-related Quality of Life in Patients with HIV/AIDS

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Abstract

Background: People living with human immunodeficiency virus (PLHIV) are known to have decreased quality of life (QoL), increased fatigue, and neurocognitive dysfunction. In India, the prevalence and predictors of the same are not explored. We aim to determine the prevalence and predictors of neurocognitive impairment (NCI), fatigue, and health-related QoL among PLHIV in India.

Setting: The study was conducted among people attending an antiretroviral therapy center in a tertiary care hospital in New Delhi after ethical approval.

Materials and methods: We enrolled consented patients and used the Montreal Cognitive Assessment (MoCA), Multidimensional Assessment of Fatigue (MAF) scale, and 36-item Short Form (SF-36) survey to assess NCI, fatigue, and health-related QoL (HRQoL), respectively.

Results: A total of 100 PLHIV with a mean age of 42.0 ± 9.6 years were enrolled, with 48% females. 47 patients (47%) had NCI with a MoCA score <26. Male gender, PLHIV with <5 years of treatment, and <50 years of age had higher MoCA scores. MoCA scores had a negative correlation with age and MAF scores and a positive correlation with SF-36 scores. 55 patients (55%) suffered from fatigue, with lesser fatigue scores for males. Fatigue scores had a negative correlation with SF-36 scores. 71 patients (71%) had total SF-36 scores >50 with males having higher scores. Fatigue had a negative correlation on QoL, $r = -0.831$.

Conclusion: In India, the prevalence of NCI, fatigue, and decreased QoL is higher compared to other populations. Management strategies in HIV require interventions to improve NCI, fatigue, and QoL along with antiretroviral therapy.

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Introduction

Acquired immunodeficiency syndrome (AIDS) is defined by the occurrence of any of the more than 20 life-threatening cancers or "opportunistic infections" due to the immune system weakening. According to the WHO, advanced human immunodeficiency virus (HIV) disease (AHD) is defined as a condition with a CD4 count of < 200 cells/mm^3 or with the presence of WHO clinical stage 3 or stage 4 disease in the adolescent and adult population. Children < 5 years of age living with HIV infection are also considered as advanced HIV disease.[1] At the end of 2023, 39.9 million and 2.5 million people were living with HIV across the world and in India, respectively. In 2023, an estimated 1.3 million people worldwide were diagnosed with HIV, highlighting the global disease burden. The same year, around 630,000 patients diagnosed with HIV died due to HIV-related causes.[2]

Human immunodeficiency virus has neuroinvasive, neurotrophic, and neurovirulent properties with central nervous system (CNS) infection causing a myriad of clinical manifestations. However, neurological manifestations in people living with HIV (PLHIV) can result from the direct infection of CNS or opportunistic infections or tumors or due to treatment (side effects and immune reconstitution inflammatory syndrome (IRIS)). Chronic neurodegenerative conditions in PLHIV is referred to as HIV-associated neurocognitive disorders (HAND) with abnormalities in cognitive, behavioral, and motor function. HAND ranges from asymptomatic to minor neurocognitive disorder to HIV-associated dementia (HAD). Although patients with HIV-associated dementia have declined with the advent of highly active antiretroviral therapy (HAART), the prevalence of less severe HIV-associated neurocognitive impairment is rising.[3,4]

Mini-Mental Status Examination (MMSE) and HIV dementia scale are simple bedside cognitive tests used to assess HAD. However, these are inadequate for less severe HIV-associated neurocognitive impairment. MMSE was less sensitive in individuals with a college education and less specific in individuals with less education.[3,5] Montreal Cognitive Assessment (MoCA) is widely used for assessing neurocognitive impairment (NCI) in PLHIV because of its improved accuracy and low false positive rate.[6]

Health-related quality of life (HRQoL) gives data on the physical and mental health status and the impact of disease on the ability to function in daily life. HRQoL is a good indicator for patients who have chronic illnesses like HIV/AIDS. A greater understanding of the predictors that affect the HRQoL may help identify targets for improving HRQoL in PLHIV. Chronic fatigue is not only highly prevalent among people living with HIV/AIDS, but also one of the most disabling symptoms, significantly impacting the day-to-day functioning of the patient and overall quality of life. In PLHIV, fatigue is strongly linked to psychological factors such as depression, anxiety, and emotional distress.[7,8]

In the Indian context, neurocognitive impairment, HRQoL, and fatigue among PLHIV are not widely explored. We plan to find the prevalence and predictors of fatigue, neurocognitive dysfunction, and HRQoL in PLHIV in India.

Materials and Methods

Study Design and Site

The study was conducted as a cross-sectional, observational study among all adult PLHIV with age > 18 years on HAART for >1 year under the outpatient department follow-up of the Department of Medicine at our center, a tertiary care teaching hospital in New Delhi, India. Those with a history of opportunistic

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infections within the past 6 months, all cases with a prediagnosed generalized anxiety disorder or depression, any recent demise in the family, or any disease requiring hospitalization in the last year, history of head injury or CNS infection or seizure disorder anytime in the past were excluded.

Objective

The study was planned to determine the prevalence and predictors of neurocognitive disorders, fatigue, and health-related quality of life (QoL) in PLHIV using the MoCA, Multidimensional Assessment of Fatigue (MAF) scale, and 36-item Short Form Survey (SF-36), respectively.

Ethical Approval

The study was initiated after ethical approval from the Institute Ethics Committee. Patients were explained about the study using a bilingual participant information sheet, and informed written consent was obtained.

Sample Size

We calculated the sample size by the expected prevalence of fatigue in PLHIV as 65% based on the results of a previous study,[8] with 10% absolute precision and 90% confidence interval, using a standard online tool.[9] This yielded a sample size of 91 individuals. To adjust for the diversity of opinions, a 10% sample was taken extra, yielding a sample size of 100.

Data Collection

The data collection instrument consisted of sociodemographic parameters, including gender, age, marital status, level of education, and employment, along with the MoCA test, MAF scale, and SF-36 questionnaire. MAF and SF-36 questionnaires were translated into the local language (Hindi) and were validated before use. A prevalidated Hindi version of the MoCA test was used in the study.

The MoCA test was used to assess the neuropsychological function of PLHIV, and scores less than 26/30 were considered abnormal. The assessment evaluates seven key domains of neurocognitive functions, namely visuospatial and executive skills, memory including delayed recall, naming ability, language, attention, abstract thinking, and orientation (Table 1).[10] Mild, moderate, and severe cognitive dysfunction were defined by a MoCA score of 18–25, 10–17, and <10, respectively.[11]

Health-related QoL was assessed using the SF-36 questionnaire. The questionnaire consists of 36 items that assess eight domains of health: (1) limitations in physical activities due to health problems, (2) limitations in social activities caused by physical or emotional issues, (3) bodily pain, (4) general mental health—including psychological distress and well-being, (5) restrictions in usual role activities due to physical health, (6) energy and fatigue, (7) limitations in role activities due to emotional problems, and (8) overall perceptions of general health.[12] The eight domains of SF-36 are divided into two groups, physical dominion (comprising of functional capacity, general health status, pain, and physical aspects), to measure the impact of limitations in physical activity of everyday life on HRQoL and the mental health dominion (encompasses multiple areas related to psychological well-being, including mental health, vitality, social functioning, and emotional aspects), analyses the mental health impact. Each domain score was determined, and the global SF-36 score was calculated as the average of the domain scores. Higher SF-36 scores indicate better health status and overall quality of life.[13]

The MAF scale consists of 16 items designed to evaluate four key dimensions of fatigue, namely severity of fatigue, distress, interference of fatigue on daily activities, and timing. Among the 16 items, 14 use a numerical rating scale, while the remaining two are multiple-choice.[14] On evaluation using the MAF scale, patients were asked to reflect on the pattern of fatigue for the past week and also on the effect of fatigue on their day-to-day activities. For every question posed, patients were asked to circle the number from 1 to 10 that most closely indicates how they felt during the past week, with 1 being the least and 10 being the highest degree. Responses 1 and 2 were considered "nil" fatigue, while responses 9 and 10 were considered "a great deal" of fatigue.

Statistical Analysis

Data were collected and stored with a Microsoft Excel spreadsheet. Descriptive statistics are presented as mean with standard deviation in continuous variables and median with interquartile range in categorical variables. Non-normally distributed data (confidence scores) were analyzed using the Mann–Whitney test, while normally distributed data were analyzed using Student's *t*-tests. Correlation among variables was done using the Pearson or Spearman correlation coefficient. The data were analyzed with SPSS software (Version 25.0, Armonk, NY: IBM Corp).

Results

A total of 100 PLHIV visiting the outpatient department were enrolled. Out of 100, 48% were females. The patients had a mean age of 42.0 ± 9.6 years with an average duration of antiretroviral therapy use of 4.7 ± 2.3 years.

Neurocognitive Impairment

The mean MoCA score was 20.4 ± 5.6 (68.1%). Males had a significantly higher mean MoCA score (27.6 ± 7.2) than females (24.1 ± 6.8), *p*-value = 0.015. Those with duration of ART <5 years had significantly higher mean MoCA score, 27.4 ± 7.0, compared to those with duration of ART >5 years, 24.3 ± 7.1, *p*-value = 0.028. The age of the patient affected the MoCA score significantly, with patients with age >50 years having a mean MoCA score of 19.7 ± 6.4, and those with age <50 years had a mean MoCA score of 27.2 ± 6.7, *p*-value < 0.01.

Among the different domains of MoCA, the language domain was the most affected in PLHIV, with a 42.3% decrease, followed by memory and delayed recall, which decreased by 40.6%. Similarly, orientation was the least affected domain among PLHIV with a 14.2% decrease. Table 1 shows the different domains of the MoCA test with the maximum score achievable in each domain and the mean score of patients in each domain.

Table 1: Domain-wise mean and maximum achievable MoCA score of PLHIV

Domain	*Maximum score achievable*	*Mean score of the patients*	*Mean percentage score*
Visuospatial/executive	5	3.17 ± 1.24	63.4
Naming animals	3	2.45 ± 0.74	81.7
Attention	6	3.72 ± 1.38	62.0
Language	3	1.73 ± 0.78	57.7
Abstraction	2	1.25 ± 0.82	62.5
Memory and delayed recall	5	2.97 ± 1.13	59.4
Orientation	6	5.15 ± 0.99	85.8

A total of 47 patients (47%) had cognitive impairment (MoCA score <26), with 35, 11, and 1 PLHIV having mild, moderate, and severe cognitive impairment, respectively. PLHIV with normal MoCA scores (n = 53) had higher SF-36 scores (mean = 70.8 ± 21.9) than those with cognitive dysfunction (n = 47) (mean = 54.2 ± 33.3), p-value < 0.01. People with MoCA scores ≥ 26 had a mean MAF score of 14.2 ± 15.7, significantly lower than the mean MAF score (21.4 ± 18.9) of those with MoCA scores < 26 (p-value = 0.04). MoCA scores have a significant negative correlation with the age of patients (r = −0.433, p-value < 0.0001). Similarly, MoCA scores have a significant negative correlation with the MAF scores (r = −0.337, p-value = 0.001). MoCA scores significantly correlated with SF-36 scores and its mental health domain, r = 0.451, p-value < 0.0001, and r = 0.476, p-value < 0.0001, respectively.

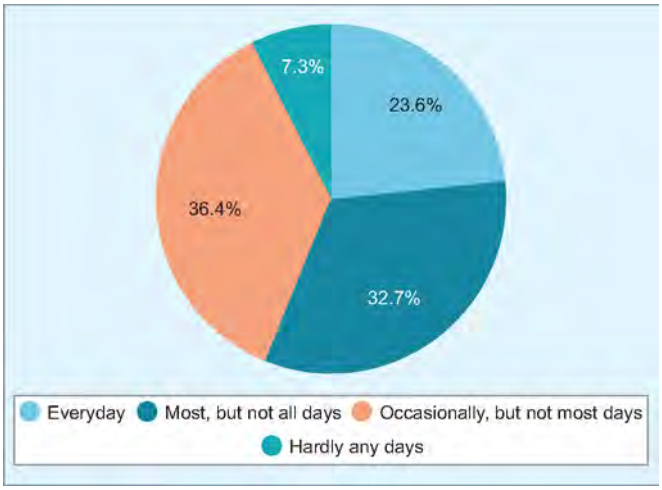

Fig. 1: Pie chart showing the responses of patients on the MAF questionnaire for fatigue

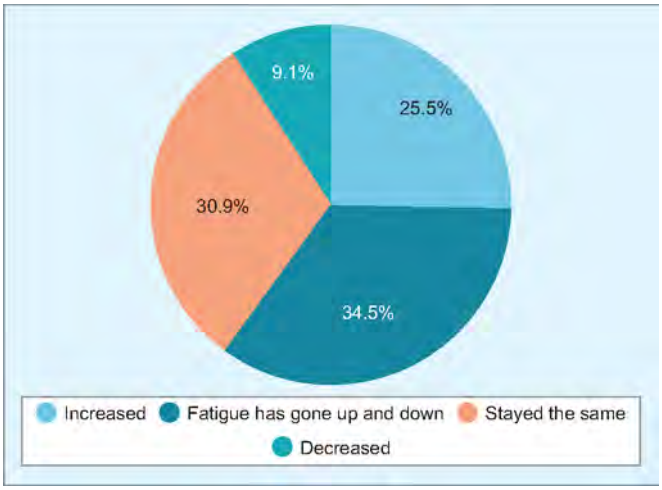

Fig. 2: Pie chart showing the change in the severity of fatigue in the last week

Fatigue

Out of 100 patients, 55 patients (55%) reported suffering from fatigue in the past week. The mean MAF score among fatigued patients was 31.9 ± 10.1. Out of the 55 patients who reported having suffered fatigue in the past week, 13 (23.6%) reported that they suffered fatigue daily, and four reported that they had fatigue on hardly any days in the past week (Fig. 1). Of the 55 patients who reported having suffered fatigue, 14 (25.5%) reported that their fatigue increased during the last week, fatigue went up and down in 19 patients (34.5%), stayed the same in 17 (30.9%), while it decreased in 5 (9.1%) (Fig. 2). Among different aspects of fatigue, "exercise other than walking and engaging in sexual activity" was the most opted aspect, 32.7% (n = 18) and "dress" was the least opted aspect, 5.4% (n = 3) (Table 2).

Males reported a significantly lower (mean = 11 ± 14.1) MAF score compared to females (mean = 24.5 ± 18.5), p-value < 0.01. MAF scores were unaffected by the patient's age and duration of ART. There were no significant differences in the MoCA scores of the patients who reported fatigue and those who did not. The mean SF-36 scores

Table 2: Different ratings for each question given by the patients who are suffering from fatigue, calculated with the MAF questionnaire

Questions asked	*The mean degree of fatigue in that aspect (n = 55)*	*Percentage of patients who reported "a great deal" in that aspect (n = 55)*
To what degree have you experienced fatigue	6.16 ± 2.28	12.7
How severe is the fatigue that you have been experiencing	6.29 ± 2.08	9.0
To what degree has fatigue caused you distress	6.65 ± 2.41	10.9
Do household chores	5.49 ± 2.37	7.3
Cook	4.56 ± 3.08	7.3
Bath or wash	4.07 ± 2.67	7.3
Dress	3.44 ± 2.84	5.5
Work	6.58 ± 2.28	10.9
Visit or socialize with friends or family	6.44 ± 2.67	12.7
Engage in sexual activity	7.62 ± 2.49	32.7
Engage in leisure activities	6.62 ± 2.44	14.5
Shop and do errands	6.76 ± 2.25	14.5
Walk	6.40 ± 2.30	9.0
Exercise other than walking	8.18 ± 1.91	32.7

Table 3: Descriptive analysis of eight different domains of the SF-36 questionnaire

Domains of health-related quality of life	*Mean ± standard deviation (n = 100)*
Physical health problems	67.15 ± 33
Emotional health problems	62.09 ± 25.79
Social activities	65.38 ± 25.92
Pain	66.00 ± 29.04
Role limitations due to physical health problems	65.25 ± 45.07
Role limitations due to personal or emotional problems	69.00 ± 44.76
Energy/fatigue	57.20 ± 26.45
General health perceptions	51.95 ± 27.14

were significantly higher in people with no fatigue (mean = 83.5 ± 14.3) than in those who reported fatigue (mean = 46.2 ± 27.0) (p-value < 0.01). Fatigue scores had a strong negative correlation with SF-36 scores and its physical and mental health domains, $r = -0.831$, p-value < 0.0001, $r = -0.84$, $p < 0.0001$, and $r = -0.795$, p-value < 0.0001, respectively.

Health-related Quality of Life

The overall mean global SF-36 score was 63.0 ± 28.9. The mean global SF-36 score was significantly higher in males (74.1 ± 23.4) compared to females (50.9 ± 29.6), $p < 0.01$. However, the mean SF-36 scores were unaffected by age and duration of the ART. A total of 71 patients had total SF-36 scores >50. patients with SF-36 score >50 had higher MoCA scores (mean = 27.8 ± 6.5) than those with SF-36 <50 (mean = 21.2 ± 6.7, p-value < 0.01). Patients with SF-36 scores >50 had significantly lower MAF scores (mean = 9.9 ± 12.8) compared to those with SF-36 scores <50 (mean = 37.6 ± 10.1, p-value < 0.01). The physical health domain was more affected compared to mental health, with a mean score in the mental health domain of 82.5 ± 34.4 and 77.0 ± 35.8 in the physical health domain.

Among different domains of SF-36, general health perceptions were the most affected in PLHIV, with a mean score of 51.9 ± 27.1, and "role limitations due to personal or emotional problems" were the least affected (mean = 69.0 ± 44.7) (Table 3). 13 (13%) patients reported better general health compared to their health 1 year ago, while eight (8%) reported worsened general health.

Twenty-five (25%) of patients reported facing no bodily pain in the past 4 weeks, while 5% reported facing very severe bodily pain. A total of 31 patients (31%) reported that the emotional problems had no impact on their routine social interactions with the family, friends, neighbors, or community groups. Ten and three patients reported that emotional problems caused very severe and severe interference in their normal social activities with family, friends, neighbors, or groups, respectively. Out of the 100 patients, 25% felt that their physical health or emotional problems had no impact on their social activities, while 4% of the patients reported that it interfered with their social activities all of the time.

Discussion

In this hospital-based cross-sectional study, we explored the prevalence of neurocognitive dysfunction, quality of life, and fatigue in PLHIV on ART for more than 1 year. In the Indian population, the prevalence and factors affecting the former were not explored. With the reduced mortality largely due to the widespread use of HAART, the QoL and its factors gain more importance. We report the higher prevalence of fatigue and neurocognitive dysfunction in PLHIV and the urgent need to improve their QoL.

The Montreal Cognitive Assessment is a widely used and accepted tool for assessing NCI. In our study, the prevalence of neurocognitive dysfunction was 47%. Studies from India reported lesser MCI among the Indian population: In diabetic patients, the prevalence of NCI was 35.6% with a median age of 58 years,[15] while in the normal population, the NCI was 58% with a median age of 70 years.[15] Compared with these, the prevalence of NCI is very high in PLHIV, especially with 42 years as the mean age for NCI in PLHIV. Various studies have shown a higher prevalence of NCI among PLHIV.[15] The mean MoCA score was lesser compared with other studies in PLHIV. There was a significant gender difference in MoCA scores in our study, probably due to the differences in mental health, hormonal, and genetic differences between males and females.[16] NCI was found to increase significantly with increasing duration of ART. However, longer disease duration is associated with a rise in the incidence of HAND.[15] The increased prevalence of NCI may indicate that newer strategies need to be devised to prevent HAND in patients who have been infected for a long duration apart from ART.

Neurocognitive impairment has an independent association with depressed mood, and in our study, MoCA scores had a significant positive correlation with the mental health domain of SF-36.[15] Cognitive dysfunction was also associated with increased severity of fatigue. NCI had a significant negative correlation with fatigue, and NCI can be one of the factors for fatigue among PLHIV; vice versa may not be true. In people with poor HRQoL, cognitive dysfunction and fatigue were found to be significantly increased, which indicates that QoL has a positive impact on physical, mental, and cognitive health. PLHIV with cognitive dysfunction had a poor quality of life, with a significant positive correlation, warranting strategies that reduce cognitive dysfunction to improve HRQoL.

Fatigue is among the most prevalent and distressing symptoms experienced by individuals living with HIV, with reported prevalence rates ranging from 33 to 88%.[17] Gender has a significant effect on fatigue, with females having higher fatigue scores. In the Indian population, this could be attributed to hormonal changes, iron deficiency, lifestyle, lack of self-care, poor quality of sleep, and psychological stress.[18] The result, however, indicates the need for better preventive strategies oriented toward females. The duration of ART did not affect MAF scores, indicating that PLHIV may face fatigue even during initial phases of diagnosis and treatment. The QoL is better among nonfatigued patients, indicating that the interventions targeting fatigue in the Indian population can significantly improve the QoL of patients with HIV infection. With the reports of fatigue due to ART can potentially interfere with treatment adherence; measures to target fatigue can help in improving treatment adherence.[19] People with fatigue did not have a significant increase in NCI, indicating that the cognitive dysfunction may have caused fatigue; the vice-versa may not hold.

The mean SF-36 score in our study was lower than that measured for the normal Indian population and also lower compared to other populations affected with HIV.[20] This decline in QoL could be attributed to the struggles associated with PLHIV, differences in the perceptions of a good QoL, and the nonavailability of a social support system in India for PLHIV.[21] Males have higher SF-36 scores as reported by other studies in the past.[21] This could be because females are physiologically more prone to emotional and physical stress and they have lesser family and institutional support compared to males in India.[10,22]

The duration of ART taken did not affect HRQoL in our study. Similar studies from Pakistan and Kenya found that the

time since diagnosis of HIV infection and the duration of ART negatively affected HRQoL, respectively, while a similar study from India found the same was better in people taking ART for a longer duration.[23–25] These differences may be because of the differences in the perceptions of subjective indices like QoL.

This study paves the way for exploring deeper into the issues of increased fatigue, NCI, and decreased QoL among PLHIV in India. This also asserts the need for a more proactive and dynamic social support system for PLHIV in India, and also key interventions focusing not just on medically managing HIV infection and opportunistic infections, but comprehensively intervening in the patients as a whole. A qualitative study focusing on what patients need can help in guiding the interventions as per the needs of the population. More studies focusing on patient-reported outcomes are warranted in India. Routine use of these patient-reported outcomes with medical care in ART centers can improve adherence and overall life of PLHIV in India.

This study has potential limitations. The data were collected in a single interview with the patients and could not be compared with baseline deficits in HRQoL, neurocognitive dysfunction, and fatigue present in the patients before HIV infection. The limitation is common in similar studies, especially in resource-limited settings. The influence of the disease severity, opportunistic infections, and the effect of polypharmacy is not known from this study. Being a single-center study from a tertiary hospital in New Delhi, the results may not be generalizable to the broader Indian population, especially those from rural settings or managed at primary-level facilities. However, single-center studies remain valuable for hypothesis generation and baseline data collection in under-researched contexts. The cross-sectional study design is unable to establish causal relationships between NCI, fatigue, and HRQoL; nonetheless, the strength and direction of the correlations provide a rationale for future longitudinal research. Fatigue and HRQoL were self-reported in our study, which may have introduced a potential recall bias. Selection bias may also have occurred because all participants were on ART for >1 year; thus, early-stage or ART-naïve patients were not included. This was intentional to reduce confounding by acute illness, but may underestimate variability in earlier disease stages. Though the MoCA <26 cut-off is internationally accepted, it may be influenced by cultural and educational factors in the Indian context; future studies should validate local thresholds. Also, the predictors were assessed mainly through correlation and bivariate analyses; multivariate regression could have been better controlled for confounding. This was limited by the modest sample size, but it will be prioritized in follow-up studies. ART regimen-specific effects on fatigue and NCI were not examined in our study; incorporating regimen type, duration, and side effects may yield more targeted clinical recommendations. Qualitative data exploring patient perspectives were not collected; integrating such insights into future mixed-method studies could enrich understanding and guide patient-centered interventions.

Despite these limitations, our study contributes novel data on the burden and correlates of NCI, fatigue, and HRQoL among Indian PLHIV—a population in which such relationships are underexplored. The findings underscore the need for multicenter, longitudinal, and mixed-method research to develop targeted interventions, as well as integrating neurocognitive and psychosocial screening into routine HIV care in India.

Information on Previous Presentation/Publication

NA.

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No funding was required.

Conflicts of Interest

The authors have no conflicts of interest.

Use of Artificial Intelligence

Artificial intelligence was not used.

Data Availability Statement

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

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ORIGINAL ARTICLE

Study of Thyroid Function in Newly Diagnosed Human Immunodeficiency Virus Patients and Effect of Antiretroviral Therapy on Thyroid Function

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Abstract

Background: Thyroid dysfunction is a frequently overlooked yet clinically significant comorbidity in human immunodeficiency virus (HIV)-infected individuals. The introduction of antiretroviral therapy (ART) has improved life expectancy but has also been associated with metabolic and endocrine disturbances, including thyroid abnormalities. Thyroid dysfunctions such as subclinical hypothyroidism, sick euthyroid syndrome, and overt hypothyroidism are increasingly recognized in both treatment-naïve and ART-experienced patients. However, limited data are available on thyroid function at the time of HIV diagnosis and its evolution following ART initiation, especially in the Indian population.

Materials and methods: This prospective observational study was conducted at Moti Lal Nehru Medical College, Prayagraj, including 100 newly diagnosed HIV patients aged ≥18 years. Baseline free T3, free T4, TSH, and CD4 were measured prior and 3 months after the start of ART. Statistical analysis was performed using SPSS version 27.0, with paired *t*-tests, analysis of variance (ANOVA), and Pearson correlation test to assess the changes and associations between thyroid parameters and ART, CD4 count, and demographic variables.

Results: The study focused on measuring serum free T3, free T4, and TSH levels at baseline and after ART initiation and analyzing their relationship with immunological status as indicated by CD4 count. The study population consisted of 100 individuals with a mean age of 37.29 ± 13.01 years, predominantly male (70%). At baseline, 62% of patients were euthyroid, while the remaining 38% showed thyroid dysfunction, primarily subclinical hypothyroidism and subclinical hyperthyroidism. Following 3 months of ART, the prevalence of thyroid dysfunction increased: euthyroid patients decreased to 41%, and cases of subclinical hypothyroidism, clinical hypothyroidism, and subclinical hyperthyroidism rose noticeably. This shift in thyroid status distribution was statistically significant (Chi-squared test, $p = 0.028$), suggesting a potential impact of ART on thyroid physiology.

In terms of hormone levels, the study observed a statistically significant increase in mean TSH values (from 4.23 ± 4.13 µIU/mL to 7.50 ± 7.85 µIU/mL, $p < 0.001$) and a significant decrease in free T3 levels (from 2.92 ± 0.88 pg/mL to 2.45 ± 1.00 pg/mL, $p = 0.005$) post-ART. Free T4 levels did not show a significant change ($p = 0.337$). These results align with existing literature suggesting that ART may unmask or exacerbate subclinical thyroid dysfunction, possibly through immune reconstitution or direct effects on thyroid metabolism.

Correlation analysis demonstrated a significant negative association between CD4 count and TSH levels both before and after ART ($\rho = -0.28$ and -0.34, respectively), and a positive correlation between CD4 and both free T3 and free T4.

Conclusion: This study establishes that ART is associated with significant changes in thyroid hormone profiles, particularly an increase in TSH and a decline in free T3 levels, reflecting emerging thyroid dysfunction. The results underscore the importance of regular thyroid function monitoring in HIV patients, particularly after initiating ART, to facilitate early detection and management of evolving endocrine disturbances.

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Introduction

Since its discovery in 1983, human immunodeficiency virus (HIV) has killed about 40.4 million people globally as of 2022. This figure is startling, and HIV might develop into a worldwide health emergency if unchecked. HIV belongs to the *Lentivirus* genus, Retroviridae family. The virus primarily attacks CD4+ T-lymphocyte helper cells, which results in severe immunological suppression and ongoing cell death. Numerous clinical symptoms result from this suppression, which also impairs the immune system. HIV eventually develops into AIDS if left untreated. At this point, opportunistic infections cause death because the immune system is unable to stop infections. HIV-1 and HIV-2 are the two primary forms of HIV. Numerous bodily fluids, including blood, amniotic fluid, breast milk, semen, rectal fluids, and vaginal fluids, can spread HIV. Sexual contact, pregnancy and childbirth, and fomites—such as needles or reusable medical equipment—can all spread HIV.[1]

By secreting thyroid hormones, the thyroid gland plays a crucial part in controlling growth, development, and metabolism. These hormones, triiodothyronine (T3) and thyroxine (T4), influence almost all organ systems and regulate a vast range of physiological functions. Thyroid disorders can have serious clinical repercussions that affect metabolism, mental clarity, cardiovascular health, and general quality of life. Significant changes in thyroid function and other aspects of the endocrine system can occur in the setting of chronic disorders like HIV infection. Comprehensive management of afflicted people requires an understanding of the interactions among HIV, antiretroviral medication (ART), and thyroid function.

Thyroid dysfunction in HIV-positive people is becoming more well recognized. These patients exhibit a wide range of thyroid abnormalities, from overt thyroid illness to subclinical hypothyroidism and euthyroid sick syndrome. Numerous theories have been put out to account for these changes, including autoimmune reactions, opportunistic thyroid infections, direct viral impacts on the thyroid gland, and the metabolic effects of long-term sickness.[2] Additionally, despite being life-saving, ART has been linked to the emergence of metabolic disorders, such as thyroid dysfunction.

Many HIV-positive individuals show symptoms of nonthyroidal illness syndrome before starting ART, which is typified by low serum T3 levels and normal or low thyroid-stimulating hormone (TSH) and T4 levels. Instead of being a primary thyroid

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disease, this disorder is an adaptive reaction to a systemic ailment. After starting ART, a complicated series of changes could take place. Hashimoto's thyroiditis and Graves' disease are two autoimmune thyroid conditions that might be concealed by immunological reconstitution inflammatory syndrome (IRIS).[3] Furthermore, direct thyroidal effects have been linked to some antiretroviral medications, while the precise pathways are still being studied. Geographic location, stage of HIV infection, ART regimen, and the presence of opportunistic infections are some of the factors that affect the prevalence rates of thyroid dysfunction in HIV-positive populations, according to epidemiological research.

Aims and Objectives

- To measure serum free T3, serum free T4, and serum TSH levels in newly diagnosed HIV patients to be started on ART.
- To study the association between thyroid hormone levels and ART regimen in newly diagnosed HIV patients.
- To study thyroid function after 3 months of initiating ART.

Materials and Methods

Before the study, proper ethical clearance was obtained from the institute.

Place of Study

This prospective observational study was conducted at SRN Hospital, MLN Medical College, Prayagraj.

Duration of Study

The study was carried out over a 12-month period from 1st March 2024 to 1st March 2025.

Type of Study

Prospective observational study.

Study Population

Newly diagnosed HIV patients (aged ≥18 years) enrolled from OPD and IPD of the Department of Medicine and ART Center.

Sample Size

Hundred.

Sample Size Calculation

Based on the study by Dev et al. (2015), reporting prevalence rates of thyroid dysfunction between 30 and 75%. For conservative estimation, a prevalence (p) of 30% (0.30) was selected as the expected proportion.

For a proportion-based study design, the following formula was used:

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

Where:

n = required sample size

Z = Z-score corresponding to the desired confidence level (1.96 for 95%)

p = expected prevalence/proportion (0.30)

d = desired margin of error or precision (0.10 i.e., 10%)

$n = (1.96)^2 \times 0.30 \times (1 - 0.30) / (0.10)^2$

$n = 3.8416 \times 0.30 \times 0.70 / 0.01$

$n = 0.806736 / 0.01$

$n = 80.67 \approx 81$ patients

To account for a potential dropout rate of 20%, the sample size was adjusted:

Final sample size = $81 \times 1.20 = 97.2 \approx 100$ patients

Inclusion Criteria

- Newly diagnosed HIV cases aged ≥18 years.

Exclusion Criteria

- Patients on medications such as amiodarone, lithium, and immunosuppressants.
- Pregnant and lactating females.

Study Procedure

After obtaining informed written consent from each participant, newly diagnosed HIV-positive patients were systematically enrolled into the study. A detailed history was recorded, focusing on the presence of any known thyroid disorder, current pregnancy or lactation status, and any prior exposure to antiretroviral therapy (ART). This was followed by a comprehensive physical examination and a full general and systemic examination to assess the clinical status of the patient.

Relevant laboratory investigations were conducted, including thyroid function tests (free T3, free T4, and serum TSH), HIV-1 and HIV-2 confirmation, CD4 lymphocyte count, complete blood count parameters (hemoglobin, total leukocyte count, platelet count, MCH, MCHC, MCV), liver function tests (SGOT/AST, SGPT/ALT), and renal function tests (serum urea and creatinine). All clinical and biochemical findings were meticulously documented to evaluate the baseline health profile of the participants and to facilitate follow-up analysis of thyroid function after the initiation of ART.

Statistical Analysis

Statistical analysis was performed using SPSS software version 27.0. Descriptive statistics, including mean and standard deviation, were applied to summarize demographic variables, hematological, biochemical, and immunological parameters. Paired t-tests were used to compare thyroid hormone levels (free T3, free T4, and TSH) before and after 3 months of ART, assessing the significance of observed changes. The Chi-squared test was utilized to evaluate changes in the categorical distribution of thyroid status (euthyroid, hypothyroid, and hyperthyroid) pre- and post-ART. Spearman's rank correlation coefficient was employed to analyze the association between CD4 count and thyroid parameters, both at baseline and post-ART, including delta (Δ) changes. Lastly, multivariate logistic regression analysis was conducted to identify independent predictors of thyroid dysfunction post-ART. A p-value of <0.05 was considered statistically significant.

Results

The age distribution of the study participants (n = 100) shows that the majority belonged to the younger age-groups, with the highest proportion (34%) aged between 20–29 years (n = 34), followed by 25% in the 30–39 years category (n = 25). Participants aged 40–49 years constituted 19% (n = 19), while those in the 50–59 years and 60–70 years comprised 11% (n = 11) and 8% (n = 8), respectively. Only 3 participants (3%) were below 20 years of age. The overall mean age of the cohort was 37.29 years with a standard deviation of ±13.01, indicating a fairly wide age spread and a predominant representation of individuals in early to mid-adulthood, as shown in Table 1 and its graphical representation in Figure 1.

The sex distribution of the study population (n = 100) reveals a male predominance, with 70% of the participants (n = 70) being male and 30% (n = 30) being female, as shown in Table 2 and its graphical representation as a pie chart in Figure 2.

The comparison of thyroid hormone levels before and after 3 months of ART reveals significant changes, particularly in TSH and free T3 values. The mean free T3 level declined from 2.92 ± 0.88 pg/mL at baseline to 2.45 ± 1.00 pg/mL post-ART, a statistically significant decrease (t = 2.877, p = 0.005), indicating a potential suppression of triiodothyronine levels following ART initiation. Free T4 levels, however, showed only a mild, statistically nonsignificant reduction from 1.19 ± 0.37 ng/mL to 1.10 ± 0.38 ng/mL (t = 0.965, p = 0.337), suggesting relatively stable thyroxine levels. In contrast, TSH levels demonstrated a marked increase from 4.23 ± 4.13 µIU/mL at baseline to 7.50 ± 7.85 µIU/mL post-ART, a highly significant change (t = −6.518, $p < 0.001$), indicating a potential shift toward hypothyroid status or subclinical thyroid dysfunction posttreatment. These results underscore the need for close thyroid function monitoring in patients undergoing ART, as shown in Table 3 and its graphical representation in Figure 3.

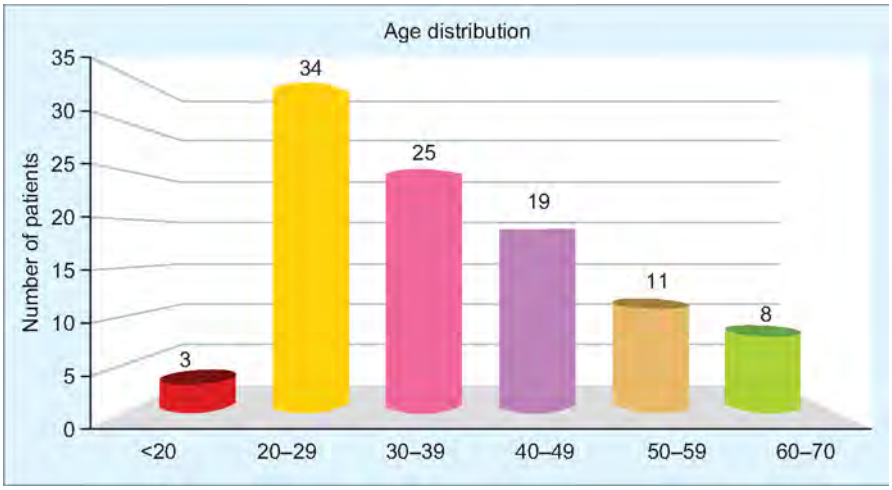


Fig. 1: Graphical representations of age distribution of enrolled patients

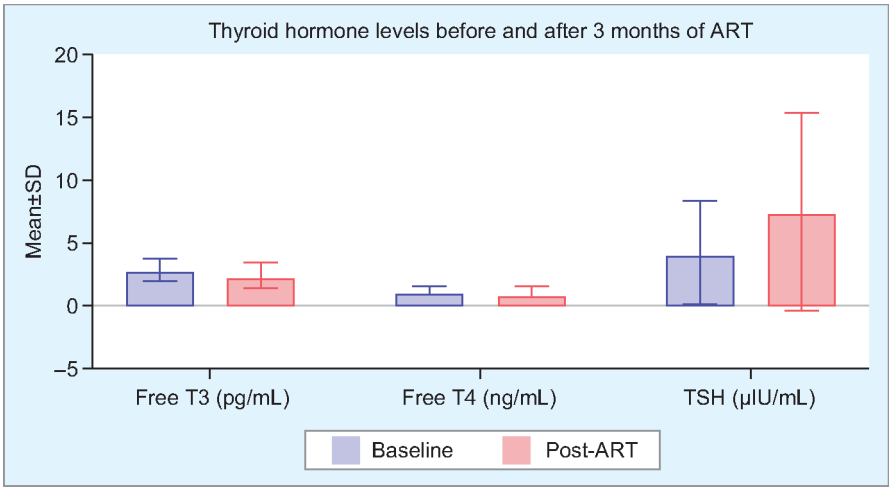


Fig. 3: Graphical representations of thyroid hormone levels before and after 3 months of ART

The distribution of patients according to thyroid status before and after ART demonstrates a statistically significant shift ($\chi^2 = 9.10$, $p = 0.028$), indicating that ART has an impact on thyroid function. At baseline, the majority of participants (62.0%) were euthyroid, but this proportion declined significantly to 41.0% post-ART. Conversely, there was a rise in all categories of thyroid dysfunction after therapy: subclinical hypothyroidism increased from 11.0 to 17.0%, clinical hypothyroidism rose from 14.0 to 19.0%, and subclinical hyperthyroidism showed the most pronounced increase from 13.0 to 23.0%, as shown in Table 4 and its graphical representation in Figure 4. These findings suggest that ART may unmask or induce thyroid dysfunction in a subset of patients, with a trend toward both hypothyroid and hyperthyroid changes.

At baseline, CD4 counts had a moderate negative correlation with TSH ($\rho = -0.28$, $p = 0.004$), indicating that lower immune status was associated with higher TSH levels. In contrast, free T3 and free T4 levels were positively correlated with baseline CD4 counts ($\rho = +0.35$ and $+0.31$, respectively, both $p \leq 0.002$), suggesting better thyroid hormone levels in individuals with higher immune function.

Following ART, these trends became more pronounced. The negative correlation between CD4 and TSH strengthened ($\rho = -0.34$, $p = 0.001$), while the positive correlation of CD4 with free T3 and free T4 also intensified ($\rho = +0.41$ and $+0.36$, respectively, both $p \leq 0.001$), reflecting improved thyroid function with immune restoration.

When examining the delta (Δ) values—representing changes from pre- to post-ART—a statistically significant inverse relationship was observed between ΔCD4 and ΔTSH ($\rho = -0.30$, $p = 0.003$), implying that increases in CD4 counts were linked to reductions in TSH levels. Likewise, positive correlations were noted between ΔCD4 and Δ free T3 ($\rho = +0.33$, $p = 0.002$) and Δ free T4 ($\rho = +0.29$, $p = 0.005$), as shown in Table 5 and their graphical representation in Figures 5A to C, indicating that immune recovery was associated with parallel improvements in thyroid hormone levels.

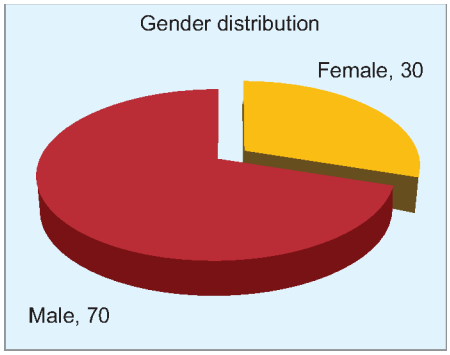


Fig. 2: Graphical representations of gender-wise distribution of enrolled patients

Table 1: Age-wise distribution of participants

Age distribution	*N*	*%*
<20	3	3.00%
20–29	34	34.00%
30–39	25	25.00%
40–49	19	19.00%
50–59	11	11.00%
60–70	8	8.00%
Mean ± SD	37.29 ± 13.01	

Table 2: Gender-wise distribution of enrolled patients

Gender distribution	*N*	*%*
Female	30	30.00%
Male	70	70.00%

The multivariate logistic regression model evaluating predictors of thyroid dysfunction after ART among 100 patients did not identify any statistically significant independent variables. The intercept had a coefficient of −0.180 ($p = 0.887$), indicating no baseline risk in the absence of predictors. Age had a negative coefficient (−0.010, $p = 0.574$), suggesting a minimal and nonsignificant inverse association with thyroid dysfunction risk. Similarly, CD4 count was not a significant predictor ($\beta = 0.0001$, $p = 0.913$), showing no meaningful contribution despite its univariate correlation in prior analysis.

Among the thyroid-related predictors, TSH ($\beta = +0.035$, $p = 0.588$), free T3 ($\beta = -0.219$, $p = 0.333$), and free T4 ($\beta = +0.543$, $p = 0.347$) also failed to reach statistical significance, as all 95% confidence intervals crossed zero, as shown in Table 6. This indicates that when modeled together, none of these variables independently explained the variability in thyroid dysfunction risk post-ART.

Table 3: Thyroid hormone levels before and after 3 months of ART

Parameter	*Baseline (mean ± SD)*	*Post-ART (mean ± SD)*	*t-value*	*p-value*
Free T3 (pg/mL)	2.92 ± 0.88	2.45 ± 1.00	2.877	0.005
Free T4 (ng/mL)	1.19 ± 0.37	1.10 ± 0.38	0.965	0.337
TSH (µIU/mL)	4.23 ± 4.13	7.50 ± 7.85	–6.518	**<0.001**

Bold value shows the marked significance of the value

Table 4: Distribution of patients according to thyroid status before and after ART

Thyroid status	*Baseline (n = 100)*	*Post-ART (n = 100)*	*p-value*
Euthyroid	62 (62.0%)	41 (41.0%)	$X = 9.10$
Subclinical hypothyroidism	11 (11.0%)	17 (17.0%)	$p = 0.028$
Clinical hypothyroidism	14 (14.0%)	19 (19.0%)	
Subclinical hyperthyroidism	13 (13.0%)	23 (23.0%)	

Table 5: Correlation of CD4 count with thyroid parameters before and after ART

Correlation pair	*Spearman's ρ*	*p-value*	*95% CI (lower–upper)*	*Interpretation*
Baseline CD4 vs baseline TSH	–0.28	0.004	–0.45 to –0.09	Significant negative correlation
Baseline CD4 vs Baseline free T3	+0.35	0.001	+0.16 to +0.52	Significant positive correlation
Baseline CD4 vs Baseline free T4	+0.31	0.002	+0.12 to +0.49	Moderate positive correlation
Post-ART CD4 vs post-ART TSH	–0.34	0.001	–0.51 to –0.15	Stronger negative correlation post-ART
Post-ART CD4 vs post-ART free T3	+0.41	<0.001	+0.23 to +0.57	Strong positive correlation
Post-ART CD4 vs post-ART free T4	+0.36	0.001	+0.18 to +0.53	Significant positive correlation
ΔCD4 vs ΔTSH	–0.30	0.003	–0.48 to –0.10	CD4 rise linked to TSH decline
ΔCD4 vs Δfree T3	+0.33	0.002	+0.14 to +0.51	Immune recovery linked to T3 increase
ΔCD4 vs Δfree T4	+0.29	0.005	+0.10 to +0.47	Mild but significant association

Table 6: Multivariate logistic regression for predicting thyroid dysfunction post-ART (n = 100)

Predictor	*Coefficient (β)*	*Standard error*	*z-value*	*p-value*	*95% CI (lower–upper)*
Intercept	–0.180	1.263	–0.142	0.887	–2.66 to 2.30
Age (years)	–0.010	0.018	–0.562	0.574	–0.046 to 0.026
CD4 count	0.0001	0.0009	+0.109	0.913	–0.0017 to 0.0019
TSH (µIU/mL)	+0.035	0.064	+0.541	0.588	–0.091 to 0.160
Free T3 (pg/mL)	–0.219	0.227	–0.968	0.333	–0.663 to 0.225
Free T4 (ng/mL)	0.543	0.578	+0.940	0.347	–0.589 to 1.675

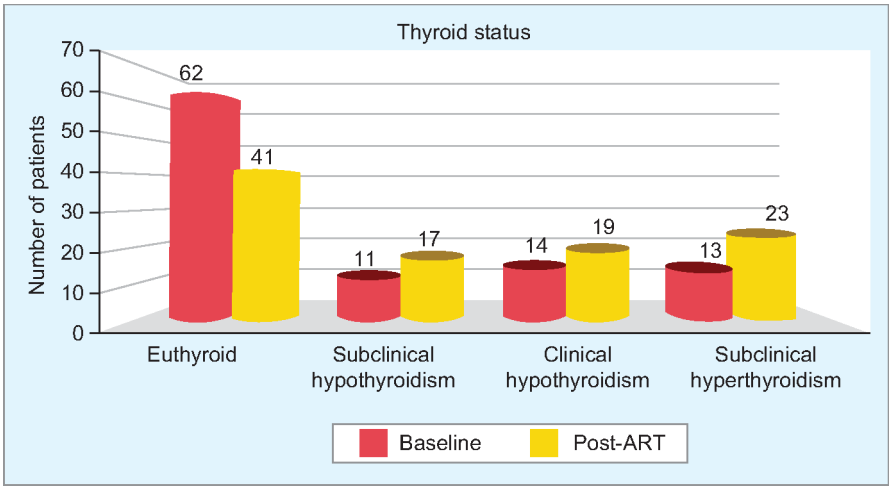
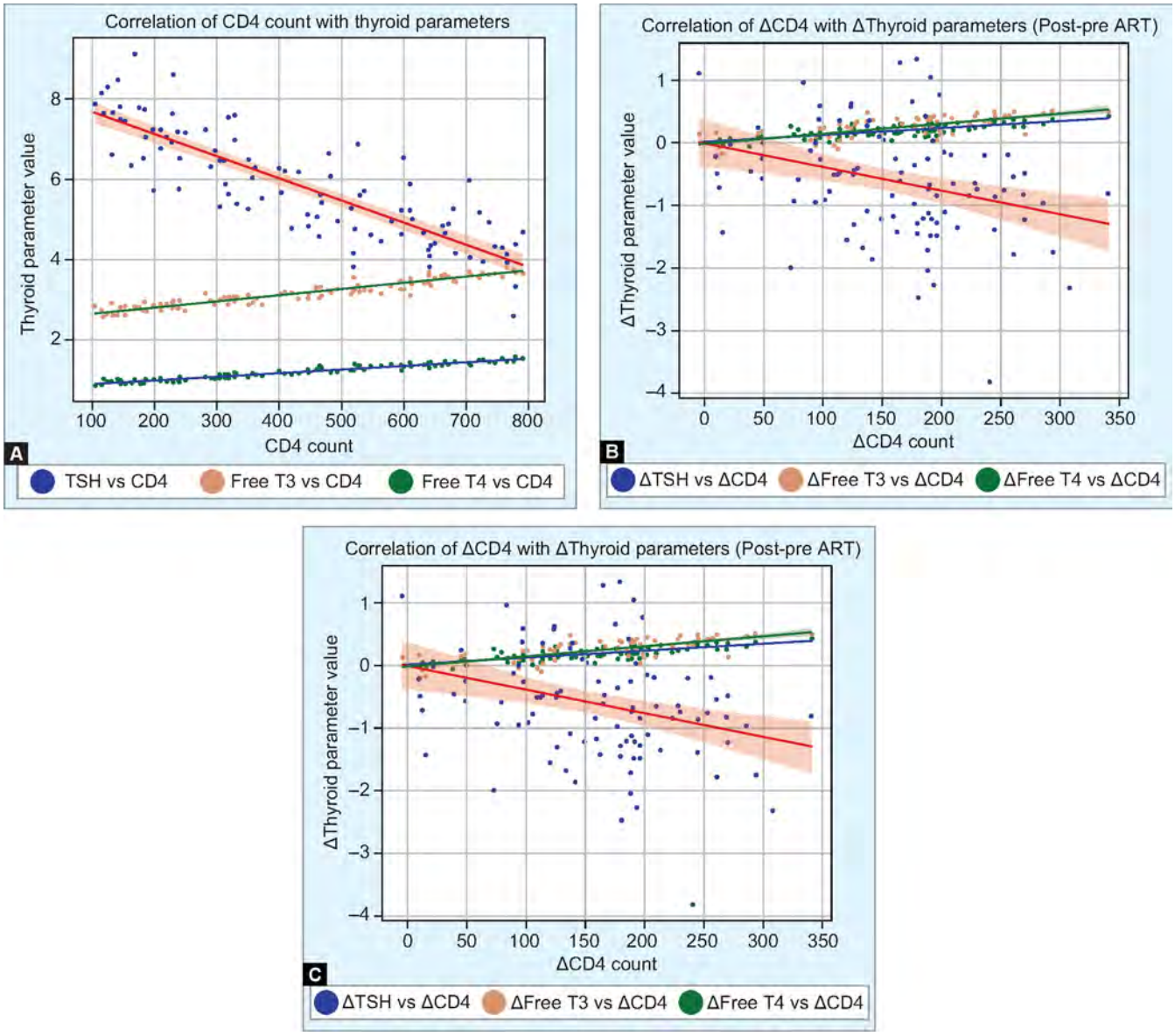


Fig. 4: Graphical representations of distribution of patients according to thyroid status before and after ART

Discussion

The purpose of this research is to measure thyroid function in newly diagnosed HIV patients before starting ART and to analyze changes in thyroid hormone levels following 3 months of treatment. We aimed to investigate how ART affects thyroid function in the early phases of treatment by examining important markers like TSH, free T3, and free T4. Our results contribute to the ongoing debate on the necessity of routine thyroid monitoring in people with HIV, especially when initiating ART.

The bulk of participants in our cohort were young to middle-aged individuals, with the largest percentage (34%) in the 20–29 age range and 25% in the 30–39 age range. Dev et al.[4] closely match the mean age of our



Figs 5A to C: (A) Graphical representations of correlation of CD4 count with thyroid parameters before and after ART; (B) Graphical representations of post-ART correlation of CD4 count with thyroid parameters (with random variation); (C) Graphical representations of correlation of ΔCD4 with thyroid parameters (post–pre ART)

sample, indicating that HIV infection primarily affects people in their early to midadult years.

After 3 months of ART, our study observed that TSH levels significantly increased (4.23 ± 4.13 to 7.50 ± 7.85 µIU/ml, $p < 0.001$) and free T3 levels significantly decreased (2.92 ± 0.88 to 2.45 ± 1.00 pg/mL, $p = 0.005$), indicating possible hypothyroid or subclinical thyroid dysfunction. Free T4 levels remained largely constant. These changes highlight the importance of regular thyroid monitoring in HIV patients receiving ART.

Similarly, Nasution et al.[5] documented comparable alterations in thyroid function in their cohort, where TSH levels rose from 1.44 ± 0.68 µIU/mL to 1.76 ± 0.91 µIU/mL following 3 months of ART, while mean free T4 levels dropped from 1.03 ± 0.14 ng/dL to 0.87 ± 0.13 ng/dL ($p = 0.006$). These changes were statistically significant, lending further support to the potential thyroid function alterations observed in our study. Like our results, their findings point to a trend toward elevated TSH and decreased free T4 during ART, which may indicate subclinical thyroid disease or early-stage hypothyroidism.

Dev et al.[4] emphasized the significance of monitoring TSH levels in HIV-positive patients, particularly when subclinical hypothyroidism is suspected. According to Bongiovanni et al.,[6] Surks et al.,[7] and Kong et al.,[8] TSH levels above 10 mU/L should be treated, while values between 4.5 and 10 mU/L may also require intervention.

According to Dutta and Kalita,[9] thyroid dysfunction was present in 36.84% of their HIV-infected patients, with subclinical hypothyroidism being the most prevalent anomaly. Overt hypothyroidism was more common in women (42.3%) than in men (35.8%). These results align with the higher TSH and lower free T3 levels observed in our study after ART, particularly among patients with thyroid dysfunction.

The impact of ART on thyroid function was further highlighted by our study, which revealed a significant shift in thyroid status after therapy. Subclinical hyperthyroidism increased from 13.0 to 23.0%, subclinical hypothyroidism from 11.0 to 17.0%, and clinical hypothyroidism from 14.0 to 19.0%, while euthyroid patients decreased from 62.0 to 41.0%. These findings are consistent with Madeddu et al.,[10] who reported a similar

pattern of elevated subclinical hypothyroidism in ART-treated HIV patients.

Our observation of a rise in hypothyroid cases after ART aligns with Dev et al.,[4] who reported a high frequency of thyroid abnormalities (75.5%) in HIV-positive patients, with subclinical hypothyroidism being the most prevalent (53%). Although the percentage of overt hypothyroidism was higher in our cohort, Dev et al.[4] reported a lower incidence of overt hypothyroidism (8.4%), consistent with our observed increase in clinical hypothyroidism. Additionally, Dutta and Kalita[9] found a greater prevalence of subclinical hypothyroidism in HIV-positive individuals, supporting our findings of thyroid dysfunction after ART.

Conclusion

This prospective observational study aimed to assess thyroid function in newly diagnosed HIV patients and to evaluate the effect of ART over a period of 3 months. Specifically, the study focused on measuring serum free T3, free T4, and TSH levels at baseline and after ART initiation, and analyzing their relationship with immunological status as indicated by CD4 count. The study population consisted of 100 individuals with a mean age of 37.29 ± 13.01 years, predominantly male (70%). At baseline, 62% of patients were euthyroid, while the remaining 38% showed thyroid dysfunction, primarily subclinical hypothyroidism and subclinical hyperthyroidism. Following 3 months of ART, the prevalence of thyroid dysfunction increased: euthyroid patients decreased to 41%, and cases of subclinical hypothyroidism, clinical hypothyroidism, and subclinical hyperthyroidism rose noticeably. This shift in thyroid status distribution was statistically significant (Chi-squared test, $p = 0.028$), suggesting a potential impact of ART on thyroid physiology.

In terms of hormone levels, the study observed a statistically significant increase in mean TSH values (from 4.23 ± 4.13 µIU/mL to 7.50 ± 7.85 µIU/mL, $p < 0.001$) and a significant decrease in free T3 levels (from 2.92 ± 0.88 pg/mL to 2.45 ± 1.00 pg/mL, $p = 0.005$) post-ART. Free T4 levels did not show a significant change ($p = 0.337$). These results align with existing literature suggesting that ART may unmask or exacerbate subclinical thyroid dysfunction, possibly through immune reconstitution or direct effects on thyroid metabolism.

Correlation analysis demonstrated a significant negative association between CD4 count and TSH levels both before and after ART ($\rho = -0.28$ and -0.34, respectively) and a positive correlation between CD4 and both free T3 and free T4. These findings indicate that patients with lower immune function may be more prone to thyroid abnormalities and that immune recovery post-ART may influence thyroid hormone trends.

In conclusion, this study establishes that ART is associated with significant changes in thyroid hormone profiles, particularly an increase in TSH and a decline in free T3 levels, reflecting emerging thyroid dysfunction. The results underscore the importance of regular thyroid function monitoring in HIV patients, particularly after initiating ART, to facilitate early detection and management of evolving endocrine disturbances.

Limitations

The study was conducted with a relatively small sample size of 100 participants, which limits the generalizability of the findings to a larger population.

Thyroid function was only assessed after 3 months of ART, which may not be sufficient to observe long-term effects or trends in thyroid dysfunction.

Other potential confounding variables, such as nutrition, lifestyle factors, and comorbidities, were not systematically controlled for, which may have influenced thyroid function independently of ART.

Although the study evaluated changes pre- and post-ART, it did not provide a longitudinal analysis of thyroid function over an extended period, limiting insights into the long-term effects of ART on thyroid health.

Recommendations

Future studies should include a larger sample size to improve statistical power and ensure that the findings are more broadly applicable to diverse populations.

Longer follow-up periods should be implemented to better understand the sustained effects of ART on thyroid function and to detect any long-term thyroid dysfunction.

The inclusion of additional confounders, such as dietary habits, comorbid conditions, and concurrent medications, should be considered to better isolate the effects of ART on thyroid health.

A more comprehensive, multicenter approach could enhance the generalizability of the findings, allowing for a broader range of HIV patients from different geographical and socioeconomic backgrounds.

Public and Patient Involvement

During the study, all subjects were educated about thyroid dysfunction and the effects of ART on thyroid function. The results of the study were shared with HIV support groups to create awareness about thyroid dysfunction in HIV patients, and the importance of proper screening of thyroid function was explained to all HIV patients on ART.

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ORIGINAL ARTICLE

Diabetic Retinopathy: Does 12 Weeks of Intensive Lifestyle Intervention Cause Any Improvement?

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Abstract

Introduction: Diabetic retinopathy (DR) is a microvascular disorder occurring due to the long-term effects of diabetes mellitus and is the most common cause of severe vision loss in adults. Diabetic retinopathy may lead to vision-threatening damage to the retina, eventually leading to blindness.

Aim: To study the effect of 12 weeks of intensive lifestyle intervention program on diabetic retinopathy using OCT and VEP.

Setting and design: Quasi-experimental study conducted in the Department of Physiology in collaboration with the Department of Ophthalmology at AIIMS, Nagpur.

Materials and methods: 75 patients of type 2 diabetes mellitus with a duration of >5 years were recruited as per the inclusion and exclusion criteria. After taking clinical history and anthropometry parameters, visual evoked potential and optical coherence tomography were done. Then, a 1.5-hour lifestyle intervention session was conducted. Followed by follow-up visits on 15th, 30th, and 45th days, done with biweekly follow-up in between through telephonic/ WhatsApp group.

Results: Modification in dietary pattern, regular exercise, healthy sleep schedule, and stress management showed a reduction in latencies and no major changes in amplitudes, but overall mild improvement was observed in PRVEP and FVEP. Also, in the retinal nerve fiber layer, mild changes along with a reduction in the severity of thickening of the retinal nerve fiber layer (RNFL) of both eyes were seen, but no major changes in central macula thickness were observed.

Conclusion: Lifestyle modifications play a crucial role in the improvement of diabetic retinopathy.

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Introduction

India is known as the diabetic capital of the world, and there is a growing incidence of DM in the age group between 20 and 70 years. The reason for the rising prevalence of diabetes and other noncommunicable diseases is due to various factors such as rapid urbanization, sedentary lifestyles, unhealthy diet, and stress. In India, the prevalence of diabetes mellitus is 9.3% among individuals aged 18–69 years.[1] Diabetes mellitus is a chronic, metabolic disease characterized by elevated levels of blood glucose, which leads to serious damage to the heart, blood vessels, eyes, kidneys, and nerves.[2] One of the microvascular complications of diabetes is diabetic retinopathy, that damage the blood vessels in the tissue of the retina. In our study, visual evoked potential (VEP) gives important diagnostic information regarding the neural functional integrity of the visual system. It is done by light flash VEP or pattern VEP stimulus, which can be used to see the damage in the visual pathway, which includes retina, optic nerve, optic chiasm, optic radiations, and occipital cortex.

Optical coherence tomography (OCT)—a noninvasive imaging method that uses reflected light to create pictures of the retina, which helps in the early diagnosis of DR by providing anatomical information about retinal nerve fiber layers, macula foveal dip, and thickness of macula, which tells us about disease progression.[3] Lifestyle medicine is a medical specialty that uses lifestyle interventions as a primary modality to treat chronic conditions, including cardiovascular diseases, type 2 DM, and obesity. Lifestyle medicine clinicians are certified professionals trained to apply evidence-based, prescriptive lifestyle changes to treat and reverse chronic conditions. Applying the pillars of lifestyle medicine, which are a whole-food plant-based diet, physical activity, restorative sleep, stress management, and positive social connection, provides effective modes of prevention for these chronic diseases.[4] Standard treatment protocols are insufficient to manage long-standing DM and its complications. Incorporating lifestyle modifications along with standard treatment protocol increases the chances of better control over blood glucose and reduces the effects of hyperglycemia on other organ systems, causing improvement in diabetes and its complications. Hence, this study was undertaken to assess the effect of 12 weeks of a structured lifestyle intervention program on diabetic retinopathy using OCT and VEP.

Materials and Methods

This was a quasi-experimental study (pre- and post-comparison without control) of 1-year duration conducted in the Department of Physiology (Lifestyle Intervention Clinic) in collaboration with the Department of Ophthalmology at All India Institute of Medical Sciences (AIIMS), Nagpur. Seventy-five patients with type 2 diabetes mellitus of >5 years' duration were recruited under the following criteria.

Inclusion Criteria

- Age between 18 and 60 years of either gender.
- Known case of type 2 diabetes mellitus of >5 years duration.
- HbA1c between 6.5 and 9.9%.
- The patient should be on a stable dose of oral antidiabetic medications during the study period.
- Nonhypertensive, nonsmoker, nonalcoholic.

Exclusion Criteria

- Recently diagnosed with diabetes mellitus.
- HbA1C >10%.
- Pregnant and lactating women.
- Presence of associated psychiatric illness.
- Undergone recent surgery.
- Patients taking steroids.
- Failure to give informed consent.

In the lifestyle intervention clinic, participants meeting the inclusion criteria—diagnosed with type 2 diabetes mellitus were enrolled after obtaining informed consent. Clinical history and anthropometric measurements were documented, followed by baseline assessments using VEP to assess visual pathway function and OCT to evaluate retinal structural changes. A structured 1.5-hour lifestyle intervention session was

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Table 1: Visual evoked potential (Pattern)

VEP (Pattern)	*Latencies (ms)*		*Amplitudes (mV)*		*Normal*		*Abnormal*	
	Pre-I	*Post-I*	*Pre-I*	*Post-I*	*Pre-I (%)*	*Post-I (%)*	*Pre-I (%)*	*Post-I (%)*
Right eye	113.19 ± 33.75	114.25 ± 35.27	6.14 ± 4.24	5.88 ± 3.24	21 (28)	22 (29)	54 (72)	53 (71)
Left eye	114.15 ± 34.14	112.64 ± 35.56*	5.33 ± 3.23	5.21 ± 2.65	20 (27)	20 (27)	55 (73)	55 (73)

Pre-I, preintervention; post-I, postintervention; *statistically significant (< 0.05)

Table 2: Visual evoked potential (Flash)

VEP(Pattern)	*Latencies(ms)*		*Amplitudes (mV)*		*Normal*		*Abnormal*	
	Pre-I	*Post-I*	*Pre-I*	*Post-I*	*Pre-I (%)*	*Post-I (%)*	*Pre-I (%)*	*Post-I (%)*
Right eye	123 ± 32.18	123.51 ± 28.52	7.17 ± 3.61	7.69 ± 3.77*	45 (60)	47 (63)	30 (40)	28 (37)
Left eye	123.07 ± 36.84	119.59 ± 33.89*	7.34 ± 3.55	6.99 ± 3.66*	47 (63)	44 (59)	28 (37)	31 (41)

Pre-I, preintervention; post-I, postintervention; *statistically significant (<0.05)

Table 3: Optical coherence tomography: retinal nerve fiber layer

Variables	*Right eye (RNFL)*		*Left eye (RNFL)*	
	Preintervention (%)	*Postintervention (%)*	*Preintervention (%)*	*Postintervention (%)*
Normal	49 (65.33)	54 (72)	53 (70.67)	57 (76.00)
Thinning	13 (17.33)	16 (21.33)	10 (13.33)	8 (10.67)
Thickening	13 (17.33)	5 (6.67)	10 (13.33)	8 (10.67)
Cataract	0 (0.00)	0 (0.00)	2 (2.67)	2 (2.67)

Table 4: Optical coherence tomography (OCT): Central macula thickness (µm)

Variables	*Preintervention Mdn (IQR)*	*Postintervention Mdn (IQR)*	*Mean difference*
Right eye	262 (36)	261 (30)*	1.5
Left eye	261 (33)	261 (33.5)	1.5

*Statistically significant (<0.05)

then conducted, emphasizing evidence-based modifications in dietary habits, physical activity, sleep hygiene, stress management, and social connectivity. Follow-up assessments were conducted on Days 15, 30, and 45, with additional biweekly check-ins via telephone or WhatsApp to reinforce adherence, address concerns, and monitor ongoing progress throughout the intervention period.

Statistical Analysis

The collected data was entered into a Microsoft excel spreadsheet. Jamovi 2.3.28 was used for data analysis. Depending on the normality tests, parametric and nonparametric paired *t*-test applied, that is student's *t*-test and the Wilcoxon signed–rank test, respectively for comparing pre(baseline) and postintervention parameters. *p*-value <0.05 will be considered as statistically significant.

Results

The results are presented in Tables 1 to 4.

Discussion

Diabetic retinopathy (DR) is a devastating complication and can lead to blindness due to microangiopathy and optic neuropathy because of metabolic abnormalities and intraneural blood flow disorders. T2DM leads to microvascular alterations in the retinal capillary network, microaneurysms, intraretinal microvascular abnormalities, and neovascularization.[5] Applying the pillars of lifestyle medicine—a whole-food plant-based diet, regular physical activity, restorative sleep pattern, stress management, and having positive social connections—provides effective prevention for these conditions.[3] In our study, assessment of diabetic retinopathy was done by fundus examination and OCT, whereas for visual pathway impairment, assessment was done by VEP. The study by Sala-Vila et al. and Aro et al. reported that dietary involvement of long-chain ω-3 polyunsaturated fatty acid (LCω3PUFA), lifestyle changes with involvement of exercise and healthy diet, is associated with a reduced incidence of severe DR in individuals with type 2 diabetes and can lead to a significant reduction of retinal microaneurysm and macular edema.[6] Dietary changes, such as including nitrates, a dietary source found in dark leafy greens (represents 80% of nitrate intake), are converted to nitric oxide once ingested. Nitric oxide has a protective action against DR as it causes vasodilation and increased blood flow to the eye vessels. Omega-3 fatty acids in the diet also improve systemic microcirculation and ocular blood flow, which leads to improved ocular health. Another study by She et al. reported that oxidative stress causes optic nerve injury, so the fruits and vegetables with high antioxidants act as neuroprotection from oxidative stress, affecting the cell and tissue morphology and its functions, leading to cell death, which has an important role in the pathogenesis of retinal diseases.[7] The study by Soleimani et al. and Pan et al. each reported that 5,000 steps daily or two and a half hours of nonsedentary life reduced the visual field progression significantly by 10%.[8] Every additional 10 minutes of evening activity per day leads to a slowing of the rate of ganglion cell-inner plexiform layer thinning.[9] And exercise also improves blood flow throughout the body, including the eyes, which helps in delivering nutrients for collagen production. Stress reduction techniques like yoga and meditation have a positive impact on eye health because of high stress, hormones such as cortisol and adrenaline that cause insulin resistance, which can raise your blood sugar and increase the risk of diabetic retinopathy.[10]

So, relaxation techniques, such as meditation, yoga, deep breathing, and mindfulness, along with positive social connection with family and friends and good sleep can help individuals to relax the body and manage their pain in a better way.

However, other advantages were incidentally noted. Dosage of medications was reduced with a decrease in economic burden related to treatment for diabetes. Patients experienced more positivity and a good mood to do day-to-day activities. Through this study, in many patients who were asymptomatic of complications, early detection of complications was possible so that further precautions could be taken, which reduced the risk of complications of diabetes, along with a positive impact and better quality of life[11] experienced by patients.

One of the primary limitations of our study is the relatively short duration of the intervention, which lasted only 12 weeks. Although mild improvements in PRVEP and FVEP latencies and RNFL thickening were observed, the limited timeframe may not have been sufficient to capture more substantial or long-term changes in visual function or retinal structure. Additionally, no significant changes were noted in the central macular thickness, suggesting that longer follow-up periods may be necessary to detect meaningful structural improvements. Lastly, variability in participant adherence, despite regular follow-up via telephonic and WhatsApp-based check-ins, may have influenced the consistency of intervention effects.

Overall, we concluded that in a sample size of 75 patients, diet and lifestyle modification (regular physical exercise, restorative sleep pattern, stress management, and positive social connection) ought to be included in the first line of the management of diabetes. Reduction in the dosage of medications with early detection of complications was possible, reducing the financial burden on the patients. But for more significant changes to be observed, follow-up of more than 12 weeks is required.

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REVIEW ARTICLE

Thyrotropin Controversy in Subclinical Thyroid Disorders

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Abstract

Aim: The thyrotropin controversy in subclinical thyroid disorders (STDs) is among the most common endocrine disorders globally. In India, approximately 42 million people suffer from thyroid disorders, with subclinical hypothyroidism (SCH) affecting about 9.4% of the population. SCH is more prevalent in females (11.4%) compared to males (6.2%).

Discussion: The diagnosis and treatment of SCH and subclinical hyperthyroidism (SHT) are controversial. SCH is often diagnosed based on biochemical markers, as patients may be asymptomatic or exhibit vague symptoms. Thyrotropin (TSH) levels may be elevated or decreased, while triiodothyronine (T3) and thyroxine (T4) remain within the normal reference range or near the lower or upper limits. STDs refers to an abnormal TSH with normal thyroxine (FT4) and free triiodothyronine (FT3) levels. It includes STDs and individuals at high risk for disease progression or adverse outcomes, with unclear prognosis. Progression of SCH to overt hypothyroidism depends on initial serum TSH levels, thyroid peroxidase antibodies (TPO), family history of thyroid disorders, previous radiation, and smoking. Controversies surround SCH and its association with cardiovascular diseases (CVD), pregnancy outcomes, neuropsychiatric issues, metabolic syndrome, dyslipidemia, and diabetes. Assay interference is a problem in interpreting thyroid function tests (TFTs), occurring in 1% of cases. The health package investigation systems often overlooks the impact of drug intake and assay interference. Various methods for measuring TFTs, such as radioimmunoassay, immunometric assay, and ELISA, differ in sensitivity, specificity, and standardization, leading to methodological variability. Common causes of assay interference include human antimurine antibodies (HAMA), thyroid hormone autoantibodies (THAAbs), rheumatoid factor, antistreptavidin, and antiruthenium antibodies. When diagnosing SCH, it is crucial to rule out other causes of elevated TSH, such as autoantibodies, goiter, and rare conditions such as thyroid hormone resistance (THR), diagnosed by serum glycoprotein alpha subunit (α-GSU) and family history. Biotin, a common supplement, can affect TFT assays, leading to spurious results. It can cause falsely high T4 and T3 levels and low TSH, leading to misdiagnosis of SCH.

Conclusion and recommendations: The timing of TFTs, whether fasting, postprandial, or random, remains a debated issue. Assay interference and biotin intake should be considered when analyzing TFTs. The role of iodine and iodine supplementation during pregnancy and its impact on STDs are not yet fully conceptualized. Large randomized clinical and epidemiological studies are needed to establish a consensus on the diagnostic threshold for TSH. These studies should include diverse populations and medical conditions to improve our understanding of the disease and patient outcomes. In practice, avoid rushing to treat elevated TSH levels between 4 and 10 mIU/L or low TSH between 0.5 and 0.1 mIU/L without confirming the diagnosis with additional tests (T3, T4, FT4, FT3, and TPO). TSH alone should not be the sole decision-maker; consider other TFTs and sequential testing from the same laboratory and time to make more informed decisions. While TSH levels can be affected by time and prandial state, FT3 and FT4 levels remain stable, suggesting all three TFTs may aid in accurate diagnosis and treatment decisions.

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Introduction

Thyroid disorders (TD) are one of the most common endocrine disorders globally. In India, about 42 million people suffering from TD and subclinical hypothyroidism (SCH) are about 9.4% with female preponderance; 11.4% compared to 6.2% in men.[1,2] Incidence and prevalence vary in sample population as environmental and regional differences are there regarding iodine content of the water, salt iodination, and we know that hilly areas have higher incidence of iodine deficiency disorders (IDD) compared to non-hilly areas. Hypothyroidism and hyperthyroidism prevalence is between 1–2% and 0.5–2% and 10 times more prevalent in women than in men. Studies suggest that 1% of males and 5% females have thyroid nodules, and the frequency increases with age and iodine-deficient populations. Developing countries are equally affected as developed ones, and globally, TD is common, and hypothyroidism and SCH in the Pakistani population are 4.1 and 5.4% with female preponderance,[3] 4–8% in Brazil,[4] 3–8% in the USA.[5,6] Kumar et al. reported SCH about 30% in India. Prevalence in school-going children of Pakistan is 8.43%[7] higher compared to 1.7% children in USA[8].

Discussion

There are few most controversial issues in the endocrine world such as diagnostic cut offs of plasma glucose in gestational diabetes mellitus (GDM), metformin in pregnancy; prediabetes to be treated or not and diagnosis of SCH and treatment decision of SCH because diagnosis of subclinical thyroid disorders (STDs) are more of a biochemical nature as most often but not patients with STDs are asymptomatic or have vague symptomatology and thyrotropin or thyroid stimulating hormone (TSH) is elevated or decreased and thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4) and free triiodothyronine (FT3) are within normal reference range or at lower or upper border of normal.[9,10]

A slightly raised TSH is the most common thyroid function (TF) abnormality worldwide. SCH is also known as mild hypothyroidism, early thyroid failure, preclinical hypothyroidism, or decreased thyroid reserve.[11] SCH prevalence is 3–8% and increases with age have female dominance, and lately around the sixth decade in males.[12,13] Presence of thyroid peroxidase antibody (TPO) increases the risk of developing SCH and progression of SCH to overt hypothyroidism. The role of Iodine supplementation is controversial, and iodine-sufficient areas have a higher incidence of SCH than iodine-insufficient regions, according to European studies.[14]

Subclinical thyroid dysfunction or disorder (STDs) is defined as an abnormal TSH with normal T3, T4, FT4, and FT3. Persons who are at high risk of disease progression and or adverse clinical outcomes and whose prognosis is not well understood are included in STDs. Initial serum TSH, TPO positivity, family history of TD, history of radiation, pollution, and smoking are the risk factors for SCH progressing to overt hypothyroidism. SCH has various outcome issues, such as cardiovascular disease risk (CVD), pregnancy

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outcomes, neuropsychiatric problems, metabolic syndrome, dyslipidemia, and diabetes. Type 2 diabetes mellitus (T2DM) patients are more likely to develop STDs, specifically SCT.[1516]

There is minimal data to support routine thyroxine replacement of STDs (serum TSH 0.1–0.45 mIU/L or 4.5–10.0 mIU/L), and recommendations are against routine treatment of such patients.[17]

Why STD are Important?

Poor understanding of STDs may lead to over or under treatment of people with these biochemical abnormalities. Cohort review of 500 patients with SCH at Mayo Clinic in 1995–1996 revealed 38.7% of patients with TSH between 5.1 and 10.0 mIU/L received treatment.[18] There is a difference of opinion regarding treating asymptomatic SCH or subclinical hyperthyroidism (SCHY).

Vary important fact to be remembered is that TSH varies with the time of sample collection and relation to food. Study of 57 patients with three groups: group I with normal T4 and TSH; group II with SCH with increased TSH and normal FT4, and group III with overt hypothyroid with low FT4 and high TSH; thyroid function tests (TFT), FT4, and TSH were done in fasting and 2-hour postmeal samples. TSH was found to be low in all three groups in postmeal samples irrespective of the fasting levels while FT4 values did not change significantly. This has led to reclassification of 15 out of 20 (75%) subjects as SCH based on fasting values, otherwise normal TSH in the postprandial sample.[19–22] Possible explanation for low TSH in postmeal sample may be foods causing an increase in serum somatostatin levels, which suppresses TSH secretion from the pituitary.[21–24] Another big controversy is about consensus on the timings of TFT and assay methodology, and is really confusing everyone, patients, biochemist and clinicians.[19] We all know TSH levels are highest in the early morning but decrease with prandial state, and one may argue that random testing may leave some SCH undiagnosed; quite right! And at the same time opponent may use this fact in their favor that fasting sample may overdiagnose SCH, which is also correct and scientific.

Hypothyroidism is mostly caused by autoimmune chronic lymphocytic thyroiditis, and TPO antibodies are the test required to confirm the diagnosis after TSH in the Western World. Elevated TSH with normal T4 is a controversial issue to treat or not, and levothyroxine replacement may be beneficial in some cases. Iodine supplementation is recommended routinely to women planning a pregnancy unless contraindicated,[20] though the routine iodine supplementation is also a controversial issue requiring large-scale studies and more data.

Thyroid disorders are usually benign and present with varied manifestations. About one-third of the global population lives in iodine-deficient areas despite a whole lot of efforts to increase iodine intake by way of iodizing salt or iodine fortification of oil, and at the same time, TD are common in iodine-repleted areas. Another important factor is that TDs are usually autoimmune in nature, such as primary atrophic hypothyroidism, Hashimoto's thyroiditis, and Graves' disease. In iodine-repleted areas, congenital hypothyroidism affects one in 3,500–4,000 births, and the routine screening is recommended universally with a heel-prick blood sample. Controversy also persists about healthy adults' screening for TD as the prevalence of overt TD is low, but STDs are significant, 10% SCH, and 1% with subclinical hyperthyroidism SCHY.[25]

Assay Interference

Assay interference is another issue in TFT interpretation. About 1% of all TFTs have assay interference. Health package investigation system by various corporate organizations, hospitals, and laboratories does not pay enough attention to the possible intake of drugs, timing of sample, which may cause assay interference.

Assay interference is an important consideration because of several methods to assess TFT, such as radioimmunoassay, immunometric assay, tandem mass spectrometry, and ELISA. Differences in their sensitivity, specificity, and standardization can result in significant methodological variability.

Other causes of assay interference leading to high TSH are human antimurine antibodies (HAMA), thyroid hormone autoantibodies (THAAbs), rheumatoid arthritis (RA) factor, antistreptavidin and antiruthenium antibodies[4]; and rare incidences of thyroid hormone resistance (THR) having serum glycoprotein alpha subunit (α-GSU) along with a family history of the disorder**.**

Biotin is another element interfering with TFT assays, a common health supplement for skin ailments, *per se,* that does not affect thyroid function, but certain TFT assays for TSH, T3, T4, and thyroglobulin. Biotin causes spuriously high T4 and T3 and low TSH, leading to misdiagnosis of SCHY.[3]

As per Helfand's review, TSH is a widely available, reliable, and acceptable test to detect the STDs with a sensitivity of more than 98% and specificity of more than 92%. However, it remained unclear whether treating patients with STDs would reduce morbidity or not.[26]

Thyroid disorders are an important cause of adverse pregnancy outcomes; hence trimester-specific reference range was laid down by various guidelines with controversies, but consensus is on lower cut-offs for TSH throughout pregnancy. American Thyroid Association (ATA), Endocrine Society clinical practice guideline[5,6] gave TSH cutoffs as 0.1–2.5 Miu/L in the first, 0.2–3.0 mIU/L in the second, and 0.3–3 mIU/L in the third trimester. ATA 2017 recommended the upper cutoff 0.5 mIU/L less than the preconception TSH value or 4.0 mIU/L when local population-specific reference range is not available.[27,28]

Conclusion

- STDs and overt thyroid disorders are common with varied presentations.
- No universally accepted guideline for the diagnosis and treatment of STDs and SCH.
- Assay interference and biotin intake should always be at the back of mind while analyzing TFT.
- The role of iodine supplementation during pregnancy and otherwise in STDs has not yet been conceptualized.
- Pregnancy cutoffs and trimester-specific ranges are still a debatable issue, but consensus is on lower cutoffs for TSH and no controversy on TSH < 2.0 mIU/L for SCH and 0.1 mIU/L for SCHY.
- Controversy regarding the timing of TFT persists, whether fasting, postprandial, or a random sample is still a debatable issue.
- Routine healthy adult population screening for TD is controversial, as the prevalence of STDs is significant, 10% SCH, and 1% with subclinical hyperthyroidism SCHY.
- Another controversial issue is the population-specific reference range recommended by some of the guidelines.

Recommendations

- Large randomized clinical and epidemiological studies are required to solve the various controversial issues discussed above.
- TSH alone is a double-edged sword as it is highest in the early morning but decreases with meals, and one may argue that random testing may leave some SCH undiagnosed; quite right! And at the same time opponent may use this fact in their favor that a fasting sample may overdiagnose SCH, which is also scientifically correct.
- What we can understand with the review of literature and infer and recommend is not rush to treat raised TSH in the range of

4.0–10 mIU/L or TSH below 0.5 mIU/L without confirming the diagnosis and taking into consideration the clinical presentation and T3, T4, FT4, FT3, and TPO testing.

- TSH alone should not be a decision maker but the other TFTs and sequential TFTs from the same laboratory and time may help you decide better as we have seen that TSH level is affected by prandial state but not the FT3 and FT4 so TFT including other parameters such as TSH and T3, T4, FT3, FT4 and TPO can be useful to correctly diagnose or exclude thyroid dysfunction.
- In person, I also recommend writing thyrotoxic in place of hyperthyroidism in clinical practice as there are minor differences in spelling of hypothyroidism and hyperthyroidism, which may confuse the patient if handwriting is not clear, which most of the time is…! Here, I would like to clarify that while recommending this narrative, I know the difference between hyperthyroidism and thyrotoxicosis.

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REVIEW ARTICLE

Happy Heart Syndrome: A Review of Takotsubo Cardiomyopathy Triggered by Positive Emotional Stressors

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Abstract

Takotsubo cardiomyopathy, or "broken heart syndrome," is a condition characterized by transient left ventricular dysfunction, typically triggered by intense emotional or physical stress. While initially thought to follow primarily negative life events, such as grief or fear, a subset of cases now recognized as "happy heart syndrome" occur instead after positive emotional triggers, such as celebrations, romantic moments, or good news. This review summarizes the current understanding of takotsubo syndrome (TTS) precipitated by joyful events, focusing on novel insights from the largest registry analysis to date of 37 "happy heart" cases from the international, multicenter GEIST registry. Compared with the more common negative emotional trigger group, these patients had a higher prevalence of men and atypical midventricular ballooning patterns. While event rates trended lower, likely due to the small sample size, acute complications, such as pulmonary edema, and long-term mortality did not definitively differ. The pathophysiology of "happy heart syndrome" remains unclear but implicates differences in central autonomic processing and peripheral catecholamine responses to positive vs negative emotional stimuli. Several key outstanding questions are highlighted, including understanding susceptibility factors, confirming prognostic differences, and leveraging insights into underlying brain–heart circuitry. Ultimately, dedicated research into this rare but fascinating condition could provide broader mechanistic insights and therapeutic opportunities for the prevention and management of all takotsubo phenotypes at the nexus of mind, brain, and heart.

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Introduction

Takotsubo cardiomyopathy, also known as stress cardiomyopathy or broken heart syndrome, is a fascinating condition characterized by transient left ventricular dysfunction that mimics an acute myocardial infarction. It was first described in 1990 in Japan, with the name "takotsubo" referring to the distinct apical ballooning appearance of the left ventricle that resembles a Japanese octopus trap.[1] While initially thought to occur primarily following negative emotional stressors, such as grief, fear, or anger, more recent evidence shows takotsubo can also be triggered by positive emotional events, dubbed "happy heart syndrome."[2,3]

This review summarizes the current understanding of takotsubo syndrome (TTS) precipitated by joyful life events, with a focus on novel insights from a large international registry study.[4] The pathophysiology, clinical characteristics, prognosis, and outstanding knowledge gaps of this intriguing condition are discussed.

Background

Takotsubo syndrome accounts for an estimated 1–3% of suspected acute coronary syndrome cases.[5] While the exact mechanisms are unclear, the leading hypothesis proposes that an exaggerated release of catecholamines (adrenaline and noradrenaline) in response to intense emotional or physical stress triggers negative inotropic, metabolic, and vasomotor effects that impair myocardial function.[6] This "brain–heart" interaction, likely mediated by the sympathetic nervous system, appears to induce the characteristic regional wall motion abnormalities seen in TTS, most commonly apical ballooning.[7]

Emotional stressors have long been recognized as common precipitants of TTS, accounting for roughly one-third of cases in registry studies.[8,9] Early reports focused on negative emotional triggers, like grief, fear, anxiety, or interpersonal conflicts, coining the term "broken heart syndrome."[10] However, in 2005, a seminal case series from the International Takotsubo Registry identified a subset of patients in whom TTS was precipitated instead by positive life events, like celebrations, romantic moments, or good news—so-called "happy heart syndrome."[2]

Epidemiology and Triggers

In the largest registry study to date from the international, multicenter GEIST registry published in 2023, just 37 of 2,482 TTS cases (1.5%) were attributed to positive emotional triggers, while 873 cases (35%) had negative emotional triggers.[4] Thus, while "broken heart syndrome" is 20–30 times more common, "happy heart syndrome" does appear to represent a distinct clinical entity.

The specific positive emotional triggers identified included birthday and family celebrations, romantic moments, weddings, receiving good news, public performances, family reunions, vacations, and other joyous occasions.[4] This diversity underscores that a variety of pleasant life events have the potential to provoke the catecholamine surge believed to induce TTS in susceptible individuals.

While the overwhelming majority of TTS cases occur in postmenopausal women, a notable 18.9% of "happy heart" cases were men, compared to only 5% of "broken heart" cases.[4] The reasons for this gender disparity are uncertain, but could relate to differences in physical vs emotional trigger prevalence, or biological susceptibility between men and women.

Clinical Characteristics

Aside from a higher proportion of male patients, the baseline demographic and clinical characteristics, such as cardiovascular risk factors, clinical presentation, and ejection fraction, were similar between the "happy heart" and "broken heart" groups in the GEIST study.[4] However, atypical nonapical ballooning patterns, especially midventricular, were significantly more common with positive emotional triggers (27 vs 12.5% in the negative group).

The mechanisms underlying these distinct regional ballooning patterns are unknown but could involve differences in the temporal dynamics, magnitude, or regional distribution of catecholamine release in response to positive vs negative emotional stressors.[4] Variable regional myocardial beta-

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adrenoreceptor expression and downstream signal transduction effects may also play a role.[11]

Prognosis

Due to the relatively small number of "happy heart" cases, the GEIST study was likely underpowered to definitively assess differences in outcomes compared to the "broken heart" group. Nevertheless, there was a clear trend toward lower rates of inhospital complications, such as pulmonary edema, cardiogenic shock, and death, in the positive emotional trigger group, albeit not reaching statistical significance (8.1 vs 12.3%).[4] Long-term mortality over a mean 3.4 year follow-up was also numerically lower at 2.7% compared to 8.8% in "broken hearts," again a nonsignificant difference.[4]

Potential explanations for a more benign clinical course with positive emotional triggers could include lower stroke volumes or rates of catecholamine release, more frequent atypical ballooning patterns, which have been associated with better outcomes in some studies,[12] or an impact of the emotional milieu itself on neurohormonal recovery pathways. However, larger prospective studies are needed to confirm any prognostic implications of the emotional trigger in TTS.

Pathophysiology

While the exact pathophysiology of TTS remains poorly understood, the leading hypothesis centers on exaggerated catecholamine toxicity in a susceptible myocardium, likely triggered by brain–heart neural signaling pathways.[6,7] Proposed mechanisms of catecholamine-mediated myocardial stunning include direct toxic effects, switching of beta-adrenoreceptor signal transduction from positive to negative inotropic pathways, microvascular spasm, and metabolic disturbances.[13]

Why positive emotional events might trigger a similar process is unclear but could relate to differential activation of central autonomic control centers or divergent peripheral effector pathways compared to negative emotional stress. Interestingly, some neuroimaging studies have revealed distinct patterns of brain activity in response to pleasant vs unpleasant stimuli.[14]

The observed differences in regional ballooning patterns between "happy" and "broken" hearts also raise intriguing questions about potential heterogeneity in sympathetic innervation, beta-receptor distribution, or signal transduction effects across different myocardial segments.[4,11] Ultimately, dedicated mechanistic studies will be needed to dissect these pathways and explain the clinical diversity of TTS phenotypes.

Unanswered Questions

While the GEIST study represents the most comprehensive analysis of "happy heart syndrome" to date, several key questions remain:

- Why do only a small minority of intense positive emotions trigger TTS, while many more cases follow negative emotional stress? Are there distinct central nervous system processes that modulate the peripheral catecholaminergic response?
- What are the pathophysiologic bases for the observed clinical differences, like gender distribution and ballooning patterns, based on the emotional trigger?
- Do "happy heart" cases truly have more benign acute complications and long-term prognosis, as suggested by GEIST? Larger prospective cohort studies are needed.
- Can improved understanding of "happy heart" cases provide broader insights into the general pathophysiology and therapeutic prevention or management of TTS?
- Are there reliable ways to predict which emotional milieu (positive or negative) might trigger TTS in a given susceptible patient? Can biomarker or neuroimaging approaches help elucidate individual risk?

Conclusion

In summary, while takotsubo cardiomyopathy or "broken heart syndrome" classically follows negative emotional stressors, a subset of around 1–2% of cases appears to be precipitated by positive emotional triggers, termed "happy heart syndrome."[2–4] The largest analysis to date from the GEIST International Registry confirms several distinct clinical characteristics of this rare condition, including a higher prevalence in men and atypical midventricular ballooning patterns compared to the more common negative emotion–triggered cases.[4]

"Happy heart syndrome" highlights the complex brain–heart interactions that likely underlie all cases of takotsubo cardiomyopathy, with differences in autonomic processing of positive vs negative emotional stimuli potentially translating into divergent patterns of regional myocardial injury.[4,6,7] While preliminary GEIST data suggest "happy hearts" may have a more benign clinical course, larger prospective studies are still needed.[4]

Ultimately, dedicated research into this unique subgroup could provide broader insights into TTS pathophysiology and heterogeneity. A deeper understanding of how the heart processes and responds to various emotional stressors, whether positive or negative, could uncover novel prevention and management strategies for this fascinating cardiomyopathy at the intersection of mind, brain, and heart.

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REVIEW ARTICLE

The Essential Role of Bedside Training in Undergraduate Medical Education: A Systematic Review

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Abstract

This systematic review examined the role of bedside teaching (BST) in undergraduate medical education, focusing on its impact on clinical competence and professional growth. The review included 15 studies that investigated the effects of BST on physical examination skills, diagnostic abilities, communication skills, and confidence among medical students. The results showed that BST significantly improved physical examination skills, diagnostic abilities, and communication skills, and increased confidence among students. BST was also found to enhance empathy and professionalism among students. However, the review highlighted several challenges in implementing BST, including time constraints, lack of trained faculty, and declining opportunities for BST. To address these challenges, the review recommended integrating BST into the medical curriculum, providing faculty development programs, and utilizing technology-enhanced learning tools. The findings of this systematic review underscore the importance of BST in undergraduate medical education, emphasizing its potential to enhance clinical competence and professional growth among future healthcare professionals.

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Introduction

Bedside teaching (BST) has been central to medical education, offering students hands-on experience in clinical settings. It integrates theoretical knowledge with practical skills, helping students develop a patient-centered approach. Historically, BST gained prominence in the 19th century with Sir William Osler, but recent decades have seen a decline due to challenges such as time constraints, large student groups, and technological shifts. Despite these challenges, BST's benefits—improved diagnostic skills, communication, and empathy—underscore its continued relevance. Reintegrating BST into medical curricula through blended learning and faculty training is crucial to developing well-rounded physicians.

Objective

Bedside teaching is a cornerstone of medical education, offering a unique and immersive learning experience that enhances the clinical skills of undergraduate medical students. The direct patient interaction facilitated by BST allows students to practice and refine essential clinical skills such as history taking, physical examination, and diagnostic reasoning in a real-world setting.[1] BST provides an authentic environment for students to develop their abilities in history taking and physical examination. Engaging with patients in a clinical setting allows students to hone their interviewing techniques and improve their examination skills, which are critical components of medical practice. This hands-on experience is invaluable in bridging the gap between theoretical knowledge and practical application.[1] By observing and participating in patient assessments, students learn to integrate clinical findings with theoretical knowledge, enhancing their diagnostic reasoning skills. BST encourages critical thinking and problem-solving, as students must analyze patient information, consider differential diagnoses, and formulate management plans under the guidance of experienced clinicians.[2] In addition to cognitive skills, BST also emphasizes the acquisition of practical skills such as performing procedures, interpreting diagnostic tests, and managing patient care. The supervised clinical environment ensures that students receive immediate feedback and support, which is crucial for their skill development and confidence building.[1] BST plays a vital role in the professional development of medical students by fostering essential attributes such as professionalism, communication, and empathy. Engaging in BST allows students to observe and emulate the professional behaviors demonstrated by their mentors. They learn about ethical practice, patient confidentiality, and the importance of maintaining a professional demeanor in clinical settings. This exposure helps inculcate a sense of responsibility and integrity that is fundamental to medical practice.[2] Effective communication is a critical competency for healthcare providers. BST provides a platform for students to practice and enhance their communication skills by interacting with patients, families, and healthcare teams. This interaction helps students develop the ability to convey information clearly, listen actively, and establish rapport with patients, which is essential for patient-centered care.[3] Direct patient contact during BST fosters empathy and compassion in medical students. By experiencing patients' perspectives and understanding their concerns, students learn to provide holistic and patient-centered care. This empathetic approach not only improves patient satisfaction but also enhances the therapeutic relationship between doctors and patients.[1]

Despite its numerous benefits, BST faces several challenges that can hinder its effective implementation. This review identifies these challenges and proposes practical solutions to overcome them. One of the primary challenges in implementing BST is the limited time available for teaching amidst the busy schedules of clinical educators and trainees. The demanding nature of clinical practice often leaves little room for dedicated teaching sessions, making it difficult to integrate BST into the curriculum.[2] There is often a lack of standardized curricula and assessment methods for BST, leading to variability in the quality and consistency of training. Without standardized protocols, it becomes challenging to ensure that all students receive a comprehensive and uniform learning experience.[1] Ensuring patient privacy and obtaining informed consent for educational activities during BST sessions

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is crucial but can be challenging. Patients may feel uncomfortable or reluctant to participate in teaching sessions, which can limit the opportunities for students to engage in bedside learning.[4] Effective BST requires skilled educators who are not only proficient clinicians but also adept at teaching. However, many clinicians may lack formal training in educational methodologies, which can impact the quality of BST. Additionally, insufficient institutional support and recognition for teaching efforts can discourage faculty involvement in BST.[3] To address time constraints, BST should be formally integrated into the medical curriculum with designated time slots for teaching activities. This approach ensures that BST is a prioritized component of medical education rather than an optional or ad-hoc activity. Institutions can also consider reducing clinical workloads or providing protected teaching time for educators to facilitate BST sessions.[5] Developing standardized curricula and assessment tools for BST can help ensure consistency and quality in training. Institutions should establish clear learning objectives, structured teaching modules, and uniform assessment criteria to guide BST sessions. Regular evaluations and feedback mechanisms can further enhance the effectiveness of BST.[1] Educators must prioritize patient privacy and obtain informed consent for BST activities. Clear communication with patients about the educational purpose of BST and the potential benefits for future healthcare providers can help alleviate concerns. Institutions should also develop guidelines to address ethical considerations and protect patient rights during teaching sessions.[4] Providing faculty development programs that focus on teaching methodologies and educational skills can enhance the effectiveness of BST. Institutions should offer training workshops, mentorship programs, and resources to support educators in their teaching roles. Recognizing and rewarding faculty contributions to medical education through promotions, awards, and incentives can further encourage faculty engagement in BST.[3] Incorporating technology and blended learning approaches can complement traditional BST and address some of its challenges. Virtual simulations, online modules, and video-based learning can provide additional avenues for skill development and reinforce BST concepts. These tools can also offer flexibility in scheduling and allow for self-paced learning, making BST more accessible and efficient.[6]

Methodology

A systematic review of BST in medical education was conducted using PubMed, ResearchGate, ScienceDirect, and SpringerLink, selected for their extensive peer-reviewed medical and educational research collections.

Keywords and Search Terms

The search strategy employed specific keywords and search terms designed to capture a wide range of relevant studies. The primary keywords included "bedside teaching," "undergraduate medical education," "clinical skills," "professional development," "medical training," and "bedside rounds." These keywords were used both individually and in combination using Boolean operators (AND, OR) to ensure a thorough search of the literature. For instance, searches such as "bedside teaching AND undergraduate medical education" and "clinical skills OR professional development AND medical training" were performed to gather diverse and comprehensive data.

Inclusion Criteria

Types of Studies

The review included various types of studies such as systematic reviews, meta-analyses, original research articles, and literature reviews. This was to ensure a broad perspective on the topic, capturing both quantitative and qualitative data.

Publication Date

Studies published within the last 15 years were included to ensure the review covered contemporary practices and developments in BST.

Language

Only studies published in English were considered, due to the language proficiency of the reviewers and the prevalence of English in scientific literature.

Relevance to Objectives

Studies that specifically addressed the impact of BST on clinical skills, professional development, or educational methodologies in undergraduate medical education were included.

Exclusion Criteria

Nonpeer-reviewed Articles

Articles that were not peer-reviewed, such as opinion pieces, editorials, and nonscholarly sources, were excluded to maintain the quality and reliability of the data.

Irrelevant Topics

Studies that did not directly pertain to BST or undergraduate medical education, or those focusing solely on postgraduate or continuing medical education, were excluded.

Outdated Research

Studies published >15 years ago were excluded unless they were seminal works frequently cited in recent literature, ensuring the review remained current and relevant.

Data Extraction and Analysis

The data extraction and analysis process involved several steps to ensure the systematic and unbiased collection of relevant information from the selected studies.

Initial Screening

Titles and abstracts of the identified articles were screened to exclude studies that did not meet the inclusion criteria.

Full-text Review

Full texts of the remaining articles were retrieved and reviewed in detail. During this phase, key information related to the study objectives, methodology, findings, and conclusions were extracted.

Data Extraction Tool

A standardized data extraction form was used to collect information systematically. This form included sections for study characteristics (e.g., authors, year of publication, study design), participant details, intervention specifics (e.g., nature and duration of BST), outcomes measured, and key results.

Criteria for Assessing Study Quality

Study Design

The study design was evaluated to determine the level of evidence provided. Systematic reviews and meta-analyses were given higher weight due to their comprehensive nature and methodological rigor.

Sample Size and Population

The adequacy of the sample size and the representativeness of the study population were considered. Studies with larger, more diverse samples were deemed more reliable.

Intervention Clarity

The clarity and detail with which the BST intervention was described were assessed. Studies that provided explicit descriptions of the teaching methods, duration, and context were considered more informative.

Outcome Measures

The relevance and validity of the outcome measures used in the studies were evaluated. Preference was given to studies that used validated tools and clearly defined metrics for assessing clinical skills and professional development.

Bias and Confounding Factors

Potential sources of bias and confounding factors were identified. Studies that employed strategies to minimize bias (e.g., randomization, control groups) and accounted for confounding variables were rated higher.

Results

The systematic review evaluated 15 key studies that investigated the impact of BST on undergraduate medical education. These studies were meticulously selected based on their methodological quality, relevance to the topic, and the depth of insights they provided into the role of BST in enhancing medical education outcomes. The sample sizes in the included studies varied from 50 to 300 participants, encompassing a diverse group of medical students at different stages of their training. The studies utilized a range of research designs, including randomized controlled trials (RCTs), cohort studies, cross-sectional analyses, and qualitative studies. Many studies adopted mixed-methods approaches, integrating both quantitative assessments of clinical skills and qualitative evaluations of student experiences and perceptions.

A prominent theme across the reviewed studies was the substantial improvement in physical examination skills among students engaged in BST. Bedside training provides an invaluable opportunity for hands-on practice, enabling students to refine their examination techniques in real clinical settings. For example, Ratelle et al.[1] conducted an RCT that demonstrated significant enhancements in the physical examination skills of students who participated in BST compared to those who only engaged in classroom-based learning.

Bedside teaching also plays a critical role in augmenting diagnostic abilities and clinical reasoning skills. Direct interaction with patients under the supervision of experienced clinicians allows students to integrate clinical findings, formulate differential diagnoses, and make informed clinical decisions. A comprehensive literature review by Narayanan (2020) highlighted that BST sessions are instrumental in developing the critical thinking skills necessary for accurate diagnosis and effective patient management.[7]

Bedside teaching significantly contributes to the development of essential communication and interpersonal skills. During BST sessions, students engage directly with patients, their families, and the healthcare team, enhancing their ability to communicate effectively and empathetically. According to Shetty (2021) study, BST fosters the development of soft skills such as active listening, empathy, and professional bedside manner, which are crucial for effective patient care.[5]

Participation in BST is associated with increased confidence among medical students in clinical settings. Studies reported that students who underwent BST felt more prepared and self-assured when performing clinical tasks independently. This boost in confidence is attributed to the supportive learning environment provided by BST, where students receive immediate feedback and guidance from instructors. Additionally, BST enhances students' empathy toward patients, as it allows them to witness and understand the patient's perspective firsthand.[5]

Despite its proven benefits, BST has experienced a decline in recent years due to various factors. Changes in healthcare delivery models, increased patient acuity, and administrative burdens have limited opportunities for BST. For instance, Delungahawatta (2022) noted that the emphasis on efficiency and throughput in hospitals often leads to reduced time for educational activities such as BST.[8]

The review also identified several barriers to the effective implementation of BST. Time constraints were a recurring theme, as both students and clinicians face demanding schedules that make it challenging to allocate time for BST. Additionally, the lack of adequately trained faculty was highlighted as a significant obstacle. Many clinicians may lack formal training in educational techniques, which can impact the quality of BST sessions. Zheng (2023) emphasized the need for faculty development programs to equip clinicians with the necessary skills to deliver effective bedside education.[9,10]

Thus, this systematic review underscores the vital role of BST in undergraduate medical education. It reveals significant improvements in clinical competence, particularly in physical examination skills and diagnostic abilities, facilitated by BST. Moreover, BST contributes to professional growth by enhancing communication skills, confidence, and empathy among medical students. However, the implementation of BST faces several challenges, including declining opportunities, time constraints, and the need for better-trained faculty. Addressing these challenges is crucial for maximizing the benefits of BST and ensuring its continued integration into medical education (Tables 1 to 5).

Table 1: Comparison of physical examination skills pre- and postbedside teaching

Study	*Preteaching score (%)*	*Post-teaching score (%)*	*Improvement (%)*
Narayanan et al. (2020)[7]	60	85	+25
Shetty et al. (2021)[5]	55	80	+25

Table 2: Enhancement of diagnostic abilities following bedside teaching

Study	*Preteaching score (%)*	*Post-teaching score (%)*	*Improvement (%)*
Salam et al.[4]	65	90	+25
Blaschke et al.[9]	70	95	+25

Table 3: Growth in communication skills postbedside teaching

Study	*Preteaching score (%)*	*Post-teaching score (%)*	*Improvement (%)*
Narayanan et al.[7]	70	90	+20
Blaschke et al.[9]	75	95	+20

Table 4: Boost in confidence and empathy

Study	*Preteaching confidence level*	*Post-teaching confidence level*	*Empathy enhancement*
Salam et al.[4]	Low	High	Moderate
Shetty et al. (2021)	Moderate	High	High

Table 5: Challenges in implementing bedside teaching

Factor	*Description*
Time constraints	Limited availability of time for bedside teaching sessions due to demanding schedules
Faculty training	Lack of adequately trained faculty to conduct effective bedside teaching

Discussion

This systematic review fostered the concept that BST plays a pivotal role in undergraduate medical education, serving as a cornerstone for the development of clinical competence and professional growth among future physicians. Several studies have underscored its significance, emphasizing that BST facilitates experiential learning, fosters patient-centered care, and enhances students' ability to integrate theoretical knowledge with practical skills.[1] Furthermore, discussions highlighted that BST can aid competency-based education models and cannot be replaced by simulation-based education.[1] By immersing students in real-life clinical scenarios, BST cultivates critical thinking, diagnostic acumen, and interpersonal communication skills essential for delivering high-quality patient care.

While simulation-based education offers controlled environments for skill acquisition, BST offers unique advantages by exposing students to the complexities of patient care in real-time settings. Studies have shown that BST enhances students' clinical reasoning abilities and foster a deeper understanding of disease pathology and treatment strategies.[4] Additionally, BST promotes the development of empathy and professionalism by allowing students to observe and interact with patients in authentic clinical settings, which may be lacking in simulated environments.

To optimize the benefits of BST, medical educators must implement strategic approaches to integrate BST into the curriculum seamlessly. This includes incorporating structured BST sessions into clinical rotations, ensuring adequate faculty supervision, and providing opportunities for reflective practice and feedback.[4] Moreover, fostering interdisciplinary collaboration and utilizing technology-enhanced learning tools can enhance the effectiveness of BST and cater to diverse learning styles among students.

Faculty development programs play a crucial role in equipping educators with the necessary skills and knowledge to facilitate effective BST sessions. Training programs should focus on enhancing faculty's clinical teaching skills, communication techniques, and feedback delivery methods.[2] Additionally, promoting a culture of lifelong learning and providing ongoing support and mentorship can empower faculty to create engaging and enriching learning experiences for students during BST sessions.

One limitation of this systematic review is the potential for selection bias, as only studies available in the selected databases were included. Additionally, the quality and rigor of individual studies may vary, leading to potential biases in the interpretation of findings. Future reviews should aim to include a broader range of sources and employ rigorous quality assessment criteria to minimize bias and ensure the robustness of conclusions.

Despite the wealth of literature supporting the benefits of BST, there remain significant gaps in our understanding of its optimal implementation and impact on student learning outcomes. Future research should focus on evaluating the long-term effects of BST on clinical practice and patient outcomes, exploring innovative teaching strategies to enhance its effectiveness, and identifying barriers to its implementation in different healthcare settings.

Thus, BST plays an indispensable role in undergraduate medical education, offering unparalleled opportunities for experiential learning, skill development, and professional growth among future healthcare professionals. By recognizing its significance, implementing effective integration strategies, and investing in faculty development, medical educators can ensure that BST remains a cornerstone of medical education, nurturing competent and compassionate physicians equipped to meet the evolving needs of patients and society.

Conclusion

Bedside teaching is vital in medical education, offering hands-on learning, skill development, and professional growth opportunities. This systematic review highlights its significant role in enhancing clinical skills, including diagnostic, procedural, and communication abilities. BST also fosters professionalism and empathy, shaping students into patient-centered healthcare professionals. Feedback from students, clinicians, and patients supports its continued integration into medical curricula.

While current evidence shows BST's positive impact, further research is needed. Future studies should compare BST with alternative teaching methods, such as simulation-based education, to assess strengths and limitations. Longitudinal studies could evaluate the long-term effects of BST on clinical performance, career trajectories, and patient outcomes. Additionally, investigating patients' perspectives on BST will provide insights into its influence on patient care and curriculum development.

In conclusion, BST is a powerful educational tool in medical training. Continued exploration of its benefits, refining of teaching methods, and assessment of its long-term effects will ensure it remains integral to shaping compassionate and competent healthcare professionals for future generations.

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Semaglutide Hype or Hope: Evidence-based Review in Diabesity

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Abstract

India is struggling with the twin epidemics of diabetes and weight issues, holding the second position globally in the former and third in the latter. Despite multiple advancements with therapies that offer glycemic control and weight benefits, there has remained a gap for a comprehensive drug for the management of "diabesity." Semaglutide, since its global approval in 2017, has become a blockbuster, owing to the popularity of "Ozempic." While Ozempic has been traditionally approved for glycemic control in type 2 diabetes mellitus (T2DM), it does offer significant other benefits powerful weight loss, cardiovascular benefits, renal protection benefits, and functional improvement in peripheral arterial disease. The drug is approved in India for first-line use in adults with T2DM as an adjunct to diet and exercise. The long use of semaglutide globally and in India has ensured adequate data on efficacy and safety, ensuring confidence and trust. Gastrointestinal side effects are the most common adverse events seen with the molecule, as with other GLP-1 drugs. This review highlights the global clinical data and practicalities of the use of Ozempic in diabesity in the Indian context.

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Diabesity and Diabetes–Problem Statement in India

Type 2 diabetes (T2D) and obesity are two interconnected pandemics and are together called "Diabesity." In India, obesity and overweight issues are responsible for approximately 70% of T2D cases, and even more in many other countries.[1] India now has an estimated 101 million adults with diabetes and 136 million with prediabetes, corresponding to an adult dysglycemia prevalence of roughly 25%.[2] National Family Health Survey-5 (2019–2021) data indicate that about 24% of women and 22.9% of men aged 15–49 years are overweight or have obesity (BMI ≥25 kg/m^2), with a two- to three-fold increase in prevalence since NFHS-3.[3] In two large prospective cohorts, higher BMI was a dominant predictor of T2D: in women (*n* = 114,281; 14-year follow-up), obesity was associated with ~30–90× higher diabetes risk vs normal weight; even small BMI increases were linked to large risk jumps (e.g., BMI 33.0–34.9 kg/m^2 had 13.7× higher risk than BMI 31.0–32.9 kg/m^2); a similar graded pattern was seen in men, with obesity associated with ~8–50× higher risk.[4,5] These findings confirm a substantial overlap between diabetes and excess adiposity, contributing to a large pool of individuals with "diabesity" along with multiple metabolic risk factors.

The illustration of diagnostic criteria for diabetes/prediabetes and for overweight/obesity is given in Figure 1. Overlaps define diabesity (diabetes + obesity) and prediabesity (prediabetes + overweight), which represent cardiometabolically high-risk phenotypes.

Contemporary guidelines for T2D management (e.g., ADA Standards of Care 2026; RSSDI clinical practice recommendations 2022) therefore emphasize early use of glucose-lowering agents that provide sustained glycemic control, meaningful weight loss, and cardiorenal risk reduction.[6,7] In this context, the choice of first-line pharmacotherapy for type 2 diabetes in India should be driven by good evidence for both efficacy on hyperglycemia and weight issues and for prevention of cardiovascular and renal complications.

Characteristics of an Ideal First-line Agent for Diabesity

The ideal first-line therapy for T2D (especially in patients with weight issues) should fulfill several key criteria (Table 1).[8,9]

Unmet Needs with Current First-line Therapies in India

In practice, the most common first-line pharmacotherapy for T2D in India has traditionally been metformin, with sulfonylureas often added as second-line (due to low cost), with newer classes like DPP-4 inhibitors or SGLT-2 inhibitors being increasingly used (Fig. 2). However, each of these options has limitations when tackling diabesity.[8,9]

- *Metformin*: Weight-neutral, but many patients experience gastrointestinal side effects. Monotherapy may not achieve sufficient HbA1c reduction in moderate-to-severe hyperglycemia, and it provides no cardiovascular or other end-organ risk reduction proven in trials. Further, metformin is contraindicated in advanced renal impairment and has been associated with vitamin B_{12} deficiency.
- *Sulfonylureas (SUs)*: These insulin secretagogues (e.g., glimepiride, gliclazide) are effective at lowering glucose initially, but they often cause weight gain and carry a significant risk of hypoglycemia. Moreover, they have not shown CV benefits; some studies raise concerns about their long-term CV safety. Long-term use of SUs has been associated with exhaustion of pancreatic beta cells, leading to potential ineffectiveness.
- *DPP-4 inhibitors*: These drugs (e.g., sitagliptin, vildagliptin) are weight-neutral and well-tolerated, but their glycemic efficacy is modest (average reduction ~0.6–0.8%). They have not demonstrated a major reduction in adverse cardiovascular events in large trials (they are considered CV-neutral), and their effect on weight or other organ outcomes is minimal. DPP-4 inhibitors may be insufficient as first-line monotherapy.
- *SGLT-2 inhibitors*: These drugs (e.g., empagliflozin, dapagliflozin) do offer multiple benefits, including moderate glucose lowering and modest weight loss (~2–3 kg), along with proven reductions in heart failure and CKD progression. However, as an initial therapy, they have

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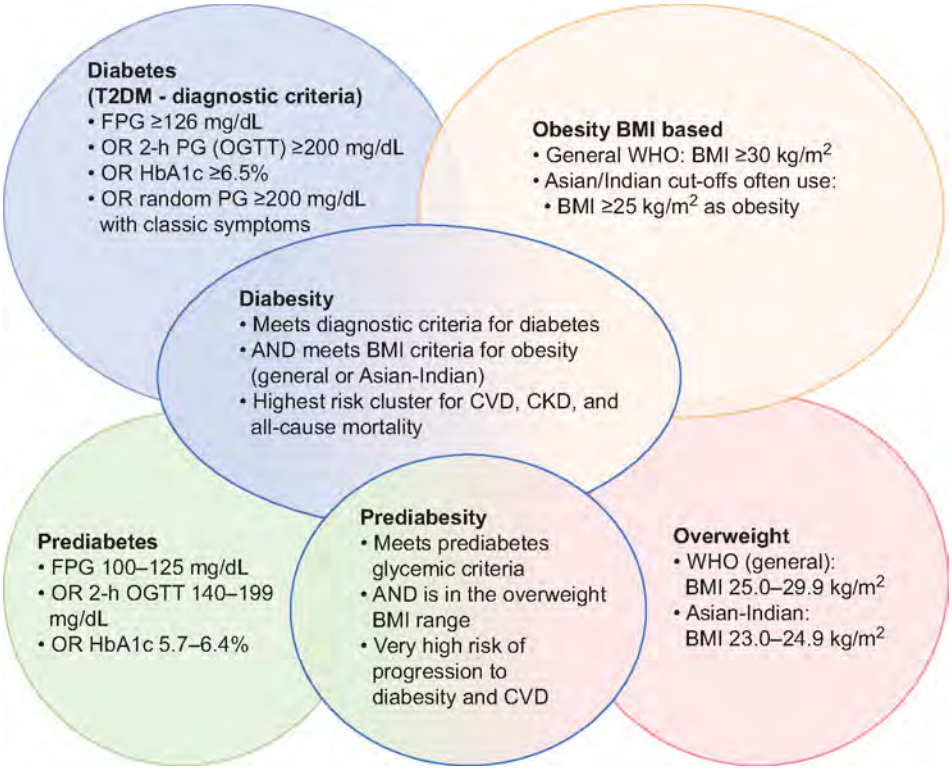

Fig. 1: Diagnostic overlap of diabetes, obesity, prediabetes, and overweight: Defining "diabesity" and "prediabesity." While these are defined overlaps, there are also other overlaps that exist in the real-world clinical setting

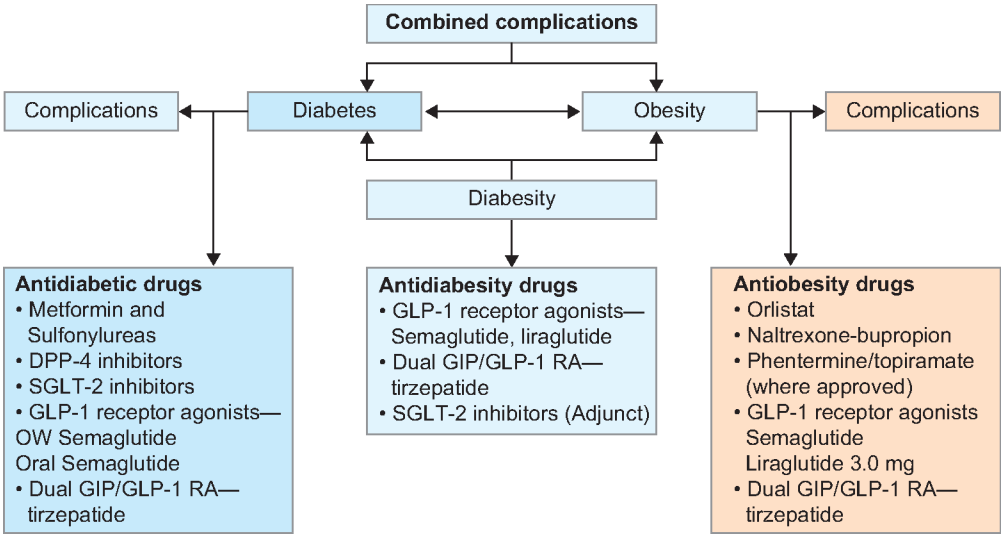

Fig. 2: Relationship between diabetes, obesity, and "diabesity" and corresponding treatment classes

some drawbacks: HbA1c reduction is mild to moderate (~0.5–1.0%), and can cause genitourinary infections.

Collectively, these limitations mean that Indian patients on these first-line agents fail to achieve optimal outcomes in diabesity management. There remains an unmet need for a first-line medication that can simultaneously deliver potent glucose-lowering, promote weight loss, and improve long-term cardiovascular and renal outcomes.

Semaglutide as an Ideal First-line Solution vs Current Options

This review focuses on weekly injectable semaglutide 1.0 mg (titrated upwards from 0.25 mg and 0.5 mg)–known popularly with the brand name of Ozempic® from Novo Nordisk. Across the SUSTAIN phase 3 program, once-weekly injectable semaglutide 1.0 mg produced mean HbA1c reductions of ~1.5–1.8% with substantial weight loss over ~30–56 weeks, clearly exceeding the glycemic and weight effects of DPP-4 inhibitors (~0.6–0.8% HbA1c, weight-neutral) and SGLT2 inhibitors (~0.5–1.0% HbA1c, ~2–3 kg weight loss), and avoiding the weight gain and hypoglycemia seen with sulfonylureas. In SUSTAIN 2, 3, and 4, semaglutide was consistently superior to sitagliptin, once-weekly exenatide, and insulin glargine, respectively, for HbA1c and weight outcomes when added to metformin, with or without other oral agents.[10–12] These data position semaglutide as a single agent

Table 1: Key characteristics of an ideal first-line pharmacologic agent for diabesity (diabetes with weight issues)

Criterion	*Requirement/definition*	*Rationale in diabesity context*
Potent glycemic control	Produces substantial HbA1c reduction and durable glycemic control	Reduces risk of microvascular complications (retinopathy, nephropathy, neuropathy) in high-risk patients
Weight reduction	Induces clinically meaningful weight loss	Addresses obesity as a core driver of insulin resistance and cardiometabolic risk
Convenient dosing and adherence	Simple regimen (e.g., once-daily or once-weekly) with low treatment burden	Enhances long-term adherence in a chronic, lifelong disease
Risk of hypoglycemic events	Low inherent risk of hypoglycemia	Addresses the key barrier of hypoglycemia in the management of diabetes and diabesity, potentially improving adherence in the long term
Long-term organ protection	Demonstrates improvement in cardiovascular and renal outcomes, plus reduction in major adverse events and mortality	Aligns with guideline shift from "glucose-centric" to "cardiorenal risk-centric" diabetes management
Proven safety profile	Acceptable GI/other AEs, no major organ-specific toxicity; supported by RCTs and real-world data	Suitable for early, long-term use in broad populations, including older adults and those with comorbidities

Table 2: How current first-line classes and semaglutide meet key "diabesity" criteria

Drug class	*Strong HbA1c lowering*	*Significant weight loss*	*Proven CV benefit (MACE reduction)*	*Proven renal protection*	*Low hypoglycemia risk*	*Simple dosing*
Metformin	✓	Δ (neutral)	Δ (legacy only)	Δ (does not provide benefit)	✓	✓ (daily)
Sulfonylureas	✓	× (gain)	×/Δ (uncertain)	×	×	✓ (daily)
DPP-4 inhibitors	Δ (modest)	× (neutral)	× (CV-neutral)	×	✓	✓ (daily)
SGLT-2 inhibitors	Δ (moderate)	✓	✓ (mainly HF/ at-risk)	✓	✓	✓ (daily)
Semaglutide 1.0 mg	✓✓ (very high)	✓✓ (marked)	✓ (↓ MACE in SUSTAIN-6)	✓ (FLOW, albuminuria ↓)	✓ (intrinsic low hypoglycemia)	✓ (weekly)

✓✓, clearly superior/strong effect; ✓, clearly meets criterion; Δ, partial/limited; ×, does not meet criterion or opposite effect

capable of equitably achieving targets for both glycemia and body weight, in contrast to current first-line drugs, which typically optimize one domain at the expense of the other (Table 2).

Further, data from the SUSTAIN 6 cardiovascular outcomes trial shows a 26% reduction of 3-point major adverse cardiovascular events in people with established ASCVD or at high risk of ASCVD. The FLOW trial, a dedicated renal outcomes trial with semaglutide, showed a significant 24% risk reduction of renal end-points. Also, the STRIDE trial has shown a 13% functional improvement in peripheral arterial disease (PAD) outcomes with semaglutide.

Contemporary guidelines position semaglutide ahead of other molecules: ADA/EASD and AACE recommend GLP-1 RAs with proven CV benefit (including semaglutide) as preferred early therapy in people with type 2 diabetes and established ASCVD, high CV risk or obesity, independent of metformin use; ADA standards 2026 also position GLP-1 RAs as the 4th pillar of CKD management (based on FLOW results); RSSDI guidance similarly highlights GLP-1 RAs in Indians living with obesity/overweight and type 2 diabetes mellitus (T2DM) with added cardiorenal risk. Thus, semaglutide aligns closely with the "ideal" first-line diabesity agent with high glycemic control efficacy, significant weight loss, low hypoglycemia risk, and outcome benefits.

The ADA 2026 and RSSDI 2022 recommendations endorse early use of GLP-1 RAs and SGLT-2 inhibitors with proven CV and renal benefit, particularly in people with obesity, ASCVD, or CKD, rather than focusing only on metformin-based HbA1c control.[6,7] Reflecting this evidence, the 2025 update of the WHO Model List of Essential Medicines added semaglutide, dulaglutide, liraglutide, and tirzepatide for adults with T2DM, established cardiovascular or chronic kidney disease, and obesity (BMI ≥ 30 kg/m^2), based on data showing improved glycemic control, weight loss, and reduced premature mortality with GLP-1-based therapy.[13]

Clinical Evidence: Efficacy and Outcomes with Semaglutide

Glycemic Control

In SUSTAIN 1 (drug-naïve T2DM), semaglutide reduced HbA1c by 1.55% at 30 weeks; 80% of patients achieved HbA1c < 7%.[14] In SUSTAIN 2, semaglutide added to metformin ± TZD reduced HbA1c by 1.6% vs 0.5% with sitagliptin.[10] Similar advantages were seen versus once-weekly and insulin glargine.[11,12,15,16] Subgroup analyses of SUSTAIN results reveal up to 2.8% mean reduction of HbA1c in people with high baseline HbA1c of more than 9%. Real-world SURE studies report HbA1c reductions of ~ 1.5% in routine practice.[17]

Weight Loss

Across SUSTAIN 1 to 4, semaglutide produced a mean weight loss of ~4–6 kg, versus ~1–2 kg with sitagliptin or canagliflozin, and weight gain with basal insulin and sulfonylureas.[10,14,18] In SUSTAIN 2, weight change was–6.1 kg with semaglutide vs–1.9 kg with sitagliptin.[10] Approximately two-thirds of patients achieved ≥5% (clinically meaningful) weight loss with semaglutide. Subanalysis data of SUSTAIN show that the mean weight loss reached up to ~8 kg in people with high baseline BMI. It is important to note that achieving weight loss in T2D is always challenging (as evident from studies in nondiabetic people with obesity, where the weight loss magnitude is much higher): roughly half of body-weight variability is attributed to genetic factors and half to environmental influences (e.g., energy-dense diets and lower physical activity), and body weight is tightly defended by interacting hormonal, metabolic, and neural mechanisms. After diet-induced weight loss, adaptive biological responses

tend to increase appetite and favor weight regain, contributing to plateaus and making sustained weight reduction more difficult in people with diabetes.[19]

Cardiovascular Outcomes

In SUSTAIN-6, semaglutide (0.5 or 1.0 mg weekly) in T2D (with established ASCVD or high risk of ASCVD) reduced 3-point MACE by 26% vs placebo over a median 2.1 years (HR 0.74; 95% CI 0.58–0.95), with a marked reduction in nonfatal stroke.[11]

Renal Outcomes

In SUSTAIN-6, semaglutide reduced the composite kidney outcome (new or worsening nephropathy) by 36% (HR 0.64; 95% CI 0.46–0.88), mainly via lower incidence of new macroalbuminuria.[11] The dedicated FLOW trial in T2DM with CKD (eGFR 25–75 mL/min/1.73 m^2 and albuminuria) reported that semaglutide reduced the primary composite kidney outcome (sustained ≥50% eGFR decline, kidney failure, or renal/CV death) by 24%.[20,21] Additionally, UACR improvement was seen by around 32% vs placebo. These results translated roughly to 5 additional years of high-quality life before ESRD development.

Peripheral Artery Disease and Limb Outcomes

The STRIDE study focused on people with T2D and early peripheral artery disease (PAD). Semaglutide led to a significant improvement in functional capacity. Over 12 months, semaglutide improved maximal treadmill walking distance by ~40 meters on average (~13% improvement from baseline). Patients also reported better leg pain symptoms and quality of life. These signals position semaglutide as a therapy that may reduce limb-related complications (possibly even amputations, as suggested by some observational data) in addition to protecting the heart and kidneys.[22,23]

Weekly Convenience, Safety, and Legacy

Semaglutide's convenient once-weekly regimen (0.25 mg initially for 4 weeks, 0.5 mg for the next 4 weeks, and then 1.0 mg) reduces dosing burden. Patient-reported outcomes demonstrate greater treatment satisfaction and preference for once-weekly semaglutide vs once-daily injections in SUSTAIN and SURE studies.[24]

Safety profile is typical of GLP-1 RAs: gastrointestinal AEs (nausea, vomiting, diarrhea) are the most frequent, generally mild to moderate, transient, and mitigated by stepwise titration; hypoglycemia is rare unless combined with insulin or sulfonylureas. In SUSTAIN-6, an increased risk of diabetic retinopathy complications was observed in patients with preexisting advanced retinopathy who achieved large, rapid HbA1c reductions in a short duration.[11] This is also in line with large-scale studies such as DCCT and UKPDS, wherein a sudden lowering of sugars led to a temporary worsening of retinopathy in high-risk patients. However, improvement in microvascular complications (including retinopathy) in the long run has been shown in these studies with continued intensive control. There have been isolated reports of the association of GLP-1 RAs with NAION (non-arteritic anterior ischemic optic neuropathy/neuritis). These reports are predominantly from centers that are ophthalmic centers, where there is a potential identification bias–NAION has risk factors including obesity, overweight, hypertension, T2D, and concomitant PDE-5 inhibitor use. Pooled analysis of data (presented at EASD 2025) from semaglutide RCTs shows a comparable incidence of NAION versus placebo, indicating no clear causal association with semaglutide. EMA has recommended a label update in the EU to include NAION as a "very rare" adverse drug reaction (incidence of up to 1 in 10,000). As a cautionary measure, high-risk people can undergo an ophthalmic examination to rule out potential risk factors, including a crowded optic cup–disk ratio.[11]

No consistent signal has been seen for pancreatitis or medullary thyroid carcinoma in human data. The broader GLP-1 RA class (liraglutide, dulaglutide) has independently demonstrated CV and renal benefits, and semaglutide extends this class legacy with greater potency for HbA1c/weight and now dedicated kidney and obesity/CV evidence.[11,20,25–28]

Summary and Conclusion—Semaglutide as an Ideal First-line Agent in India

For Indian patients, where diabesity is common and cardiorenal complications drive morbidity and cost, a first-line therapy that simultaneously and robustly addresses glycemia, weight, and cardiorenal risk is desirable. Semaglutide delivers large HbA1c reductions, clinically meaningful weight loss, risk reductions in MACE, and slower kidney disease progression, additional PAD functional improvement, with inherently low hypoglycemic risk and an acceptable, predictable safety profile. With generic versions lined up for launch in India, the use of semaglutide is bound to increase, although the safety, quality, and consistency of generic semaglutide have yet to be time-tested. The innovator molecule, Ozempic® has stood the test of time since its US-FDA approval in 2017. Compared with traditional first-line drugs, Ozempic® offers the most comprehensive "diabesity" management profile in a single agent. The "Ozempic hype" is not merely just hype but rather gives substantial hope to Indian clinicians and patients alike as a worthy tool to correct the grim cardiometabolic picture in India and globally.

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All authors have contributed to concepts, design, definition of intellectual content, investigation, and manuscript writing equally.

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Letter to the Editor Regarding "A Clinicoradiological and Bacteriological Profile of Community-acquired Pneumonia in a Tertiary Care Center in Eastern India"

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Dear Editor,

We read with great interest the article titled "A Clinicoradiological and Bacteriological Profile of Community-acquired Pneumonia in a Tertiary Care Center in Eastern India" by Hati et al. [Journal of the Association of Physicians of India 2025;73(3):25–29]. The study provides valuable insights into the clinico-bacteriological landscape of community-acquired pneumonia (CAP) in the Indian context. The study focuses on a very relevant topic in today's scenario of rising cases of community-acquired pneumonia with sepsis, which manifests as a major task of managing critically ill patients. The inclusion and exclusion criteria fit the study well. Data collection has been done in a comprehensive manner. The role of procalcitonin and its utility have been highlighted, which is relevant in recent times. Comparison of Indian and international studies has been done for a broader perspective. However, we would like to highlight a few limitations that warrant consideration for future research.

1. The study offers valuable regional insights; however, the results may not be broadly applicable to the general population as they might be due to sample bias introduced by selecting participants from a single tertiary care center. In order to capture the variability in the clinical and microbiological characteristics of CAP across various hospitals and centers, multicenter studies are better.[1]
2. Although comorbidities such as diabetes and hypertension are included in the study, a comparison of the clinical severity, microbiological pattern, and biomarker levels in people with and without these illnesses has not been explained in the study. This is a lost chance to increase the therapeutic relevance of findings because comorbidities such as diabetes mellitus, chronic lung disease, and immunosuppressive status are known risk factors for severe CAP and also affect pathogen distribution and outcome.[2] Comorbidity-based outcome stratification would have provided insightful information for individualized risk assessment and management.
3. The diagnostic yield was severely limited by the study's exclusive reliance on aerobic culture techniques. This could help to explain the observed 48% culture-negative rate. A single culture method used alone may result in false negatives, overlooking possible infections. Notably, traditional aerobic cultures alone are not a reliable way to detect respiratory viruses, anaerobic bacteria, or atypical organisms (including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp.).[3] In order to increase the etiological yield and overall diagnostic accuracy, this constraint emphasizes the necessity of implementing other diagnostic modalities, such as anaerobic culture, polymerase chain reaction (PCR)-based multiplex panels, and BioFire respiratory panels.[4]
4. The study does not use additional validated measures like the Pneumonia Severity Index (PSI) or qSOFA; instead, it uses the CURB-65 score alone to determine the severity of pneumonia. Despite being useful and simple to use, CURB-65 may not work as well for some patient populations, especially the elderly or those with several comorbidities.[5] The PSI has been demonstrated to have better prediction accuracy for mortality and provides a more thorough risk stratification by taking into account laboratory data, age, and concomitant diseases. Multiple severity scores could help guide triage decisions more successfully and offer a more thorough picture of clinical outcomes.[6]
5. A significant limitation of the study is the absence of antibiotic resistance data for the bacterial isolates. In the context of rising antimicrobial resistance (AMR) both globally and within India, reporting susceptibility patterns is essential for guiding empirical therapy and updating clinical guidelines. Without this information, it is difficult to determine whether the identified organisms were multidrug resistant (MDR) or sensitive to standard first-line agents. Studies from India and other developing regions have documented increasing resistance to macrolides, beta-lactams, and fluoroquinolones among *Streptococcus pneumoniae* and *Klebsiella pneumoniae*, two of the most common CAP pathogens.[7] The inclusion of resistance profiles would have significantly enhanced the clinical utility of the findings and supported antimicrobial stewardship efforts.[8]
6. The study did not incorporate any advanced radiological investigations, such as computed tomography (CT) scans, relying solely on chest X-rays for evaluating pulmonary involvement. While chest radiography is widely used and accessible, it has limited sensitivity for detecting early or subtle infiltrates, small pleural effusions, or complications such as cavitation or empyema.[9] Several studies have demonstrated that chest CT offers superior diagnostic accuracy, especially in patients with equivocal or normal chest X-ray findings or when differentiating infectious from noninfectious causes of opacities.[10] The absence of CT-based imaging in this study may have led to underestimation of disease extent or misinterpretation of radiological patterns.
7. Another notable omission in the study is the lack of data on the requirement for invasive supports, such as mechanical ventilation, vasopressor therapy, or intensive care unit (ICU) admission. These outcomes are crucial for validating severity scoring systems like CURB-65 and assessing the real-world burden of severe CAP. Including such endpoints would have enhanced the study's prognostic relevance and clinical applicability.[11] Previous studies have demonstrated that markers such as procalcitonin, multilobar infiltrates, and higher CURB-65 or PSI scores correlate strongly with the need for intensive care and advanced support.[12] The absence of this information limits the interpretation of severity and treatment outcomes in the current cohort.
8. The study's microbiological assessment was limited to aerobic bacterial cultures, which likely resulted in the underrepresentation of important pathogens such as respiratory viruses, fungi, and anaerobic bacteria. These organisms are well-documented contributors to CAP, particularly among the elderly, immunocompromised patients, and those with chronic diseases.[13] The absence of diagnostic modalities like viral PCR assays, fungal cultures, or anaerobic culture techniques may have led to an

incomplete etiological profile. Notably, pathogens such as influenza viruses, respiratory syncytial virus (RSV), Aspergillus spp., and anaerobic flora involved in aspiration pneumonia could have been missed.[14] Broader microbiological testing should be considered in future studies to improve diagnostic accuracy and inform more targeted therapy.

9. The study does not provide differentiation between patients who received prior antibiotic therapy in outpatient settings or were referred from other healthcare facilities. This is an important omission, as prehospital antibiotic exposure is a well-known factor that reduces culture positivity, alters clinical presentation, and may promote the development of antibiotic-resistant organisms.[15] In many parts of India and other low- and middle-income countries, the irrational use of antibiotics—including over-the-counter availability and incomplete courses—remains a significant concern.[16] Accounting for this subgroup would have added depth to the microbiological findings and informed local antimicrobial stewardship strategies.
10. Future studies should aim to incorporate advanced molecular diagnostic tools such as multiplex PCR assays, BioFire respiratory panels, and real-time PCR (RT-PCR) to improve pathogen detection in CAP. These technologies offer significantly higher sensitivity and faster turnaround times than conventional culture, particularly in patients who are partially treated, immunocompromised, or present with atypical or viral infections.[17] Incorporation of these modalities can substantially reduce the proportion of culture-negative cases, detect coinfections, and contribute to a more comprehensive microbial profile.[18]

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