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Contents

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Editorial Board (2025–2026)

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EDITORIAL

Including Kidney Health in the National Public Health Agenda: The Time is Now

Sumana Vasishta[1], Vivekanand Jha[2*]

Kidney disease is finally receiving the global attention it deserves. In May 2025, the World Health Assembly adopted a landmark resolution on kidney health on reducing the burden of noncommunicable disease (NCD) through kidney health promotion and prevention, paving the way for its prioritization within the World Health Organization's NCD agenda.[1] For India, which faces an immense and growing burden of kidney disease, this global momentum is a wake-up call to integrate kidney health into our national public health agenda now by strengthening our policies and health systems to combat renal diseases as public health priorities.

Burden of Chronic Kidney Disease in India

Chronic kidney disease (CKD) is a major global health challenge, and India is at its epicenter. The Global Burden of Disease 2017 study estimated that 697 million people had CKD worldwide, with India accounting for approximately 115 million cases—second only to China. This means nearly one in every six people with CKD globally lives in India.[2]

Additionally, the burden is unevenly distributed and is disproportionately high in rural areas (Table 1). A meta-analysis of community surveys conducted between 2011 and 2023 placed national prevalence at 13.2%, with marked heterogeneity across regions.[3] Urban centers are on the lower end of the spectrum: the CARRS study[4] in Delhi and Chennai reported a prevalence of just 7.5%. In mixed urban–rural settings, however, the SEEK study[5] found the rate to be 17.2%, climbing to 18–21% in the rural coastal Uddanam region of Andhra Pradesh among agricultural communities, with most cases attributed to CKD of unknown etiology (CKDu).[6]

Such geographic clustering magnifies the stress on already scarce renal care resources. Government and industry estimate 2,20,000 patients develop new end-stage kidney disease (ESKD) each year, leading to an annual demand of 34 million hemodialysis (HD) sessions. Against this, the country has about 5,000 dialysis centers and 3,340 nephrologists.[7] Even in those who avail state-sponsored free dialysis, sadly, the mortality rate is high due to significantly high indirect costs, resulting in inaccessibility.[8] Consistent with this, the Million Death Study[9] showed a 50% rise in renal failure deaths among 15–69-year-olds between 2001–03 and 2010–13. By 2015, CKD contributed to an estimated 1,36,000 deaths nationwide. In some rural areas where CKD is endemic, CKD has emerged as the leading cause of death in the adult population.[10] The dire financial consequences of kidney care have been documented repeatedly, with high rates of catastrophic healthcare expenditure even in those with mild to moderate stages of CKD.[11,12]

Taken together, these numbers paint a grim picture—CKD in India is common, frequently undiagnosed, heavily skewed toward rural populations with limited access to preventive and therapeutic services, increasingly fatal, and imposes catastrophic financial and human costs.

Risk Factors for Chronic Kidney Disease in India

India's CKD burden is driven by a combination of traditional risk factors and novel context-specific social and environmental risks. Like many countries, the leading causes are type 2 diabetes and hypertension. The SEEK study[5] found that 64.5% of CKD patients had hypertension and 31.6% had diabetes. The ICKD study[13] reported even higher rates—87 and 37%, respectively. India's demographic transition to an aging population compounds this load—the prevalence of CKD rises steeply with age, and projections indicate that the population aged ≥60 years will reach 194 million by 2031, which will further raise the CKD burden.[14] Thus, immediate action is imperative as India stands at a demographic and epidemiological inflection point.

Beyond these, India faces unique factors. In regions like Uddanam in Andhra Pradesh, a substantial fraction of the CKD burden cannot be attributed to diabetes, hypertension, or other known causes of kidney disease.[15] This condition, termed CKDu, disproportionately affects rural agricultural workers. The STOP-CKDu AP study estimated CKD and CKDu prevalence at 21 and 15%, respectively, in the region.[16] Although the exact causes of CKDu remain unclear, recent reviews suggest that heat stress, agricultural pesticides, heavy metals, and water contamination may be contributing factors.[17] Cases with similar disease phenotype have been reported from other parts of India,[15,18] suggesting that the prevalence may be more widespread than that anticipated thus far, suggesting the need for population-level studies (Table 1).

Environmental change-related factors such as extreme heat exposure, dehydration, worsening air pollution, salt intrusion in coastal aquifers, increasing use of ultraprocessed foods, etc., increasingly drive development and progression of kidney diseases, especially among outdoor laborers and low-income groups. Lack of awareness, along with late recognition of CKD, further accelerates the progression. Moreover, Indian studies consistently demonstrate that poverty is an independent driver of advanced CKD. For instance, Raval et al.[19] noted that in rural areas, lower income ($p < 0.01$) and limited access to healthcare ($p < 0.05$) were strongly associated with accelerated CKD progression. In contrast, in urban areas, lower education levels ($p < 0.01$) and unemployment ($p < 0.05$) were the primary socioeconomic factors linked to faster CKD progression. Francis et al. describe this pattern globally and deem it "morally indefensible."[20]

To summarize, the confluence of cardiometabolic, demographic, environmental, and social determinants demonstrates that kidney health must become an explicit part of India's public health agenda. A sole focus on glycemic and blood-pressure control is inadequate. The country needs CKD case finding integrated into current NCD programs, systematic

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Table 1: CKD prevalence in selected community-based studies in India

Study (year)	*Setting (population)*	*Sample size*	*CKD prevalence (%)*
Anand et al. (CARRS, 2015)[4]	Chennai and Delhi (urban)	10,000+	7.5 (95% CI: 6.8–8.2)
Singh et al. (SEEK, 2013)[5]	Multicenter urban/rural (mixed)	5,588	17.2 (95% CI: 16.3–18.1)
Tatapudi et al. (2018)[6]	Uddanam, Andhra Pradesh (rural)	2,210	18.23 (95% CI: 16.4–21.0)
John et al. (STOP-CKDu, 2020)[16]	Uddanam, Andhra Pradesh (rural)	2,419 (67 villages)	21.3 (men), 16.2 (women)
Talukdar et al. (2025)[3]	Pooled data, meta-analysis 2011–2023	18 studies	13.24 (95% CI: 10.52–16.22)

surveillance of CKDu hot spots, rigorous environmental remediation, and social-protection policies strong enough to break the persistent cycle between poverty and kidney disease.

Gaps in India's Current Approach

India's healthcare system currently lacks a coherent kidney disease strategy. Recent public schemes acknowledge the disease, but almost every rupee flows to the last step of the pathway—dialysis and transplant—while prevention, early detection, and basic supportive therapy remain neglected. The Pradhan Mantri National Dialysis Program (PMNDP) delivers free HD in district hospitals, yet peritoneal dialysis (PD)—cheaper, home-based, and formally allowed under PMNDP—accounts for <10% of Indian dialysis patients and is "dying on the ventilator," according to a 2024 national audit by Jeloka et al.[21] Ayushman Bharat PM-JAY offers up to Rs. 5 lakh per family for HD, PD, and transplant, but does not reimburse lifelong immunosuppression or follow-up labs, leaving transplant recipients in chronic financial distress. At the state level, several schemes finance dialysis and transplant, but few fund early-stage care, erythropoietin, and other supportive medication or posttransplant immunosuppressants. Kidney transplantation also remains constrained, with merely 13,642 surgeries performed nationwide in 2023 against >2,00,000 new ESKD cases each year, indicating the huge gap between demand and supply.[22]

The revised National Program for Prevention and Control of NCDs (NP-NCD) finally lists CKD for screening; however, Health and Wellness Centers (HWCs) still lack creatinine meters, urine dipsticks, and treatment algorithms. The other central programs, such as the National Program for Health Care of the Elderly (NPHCE) and the National Rural Health Mission (NRHM), now part of the broader National Health Mission (NHM), unfortunately do not have CKD screening explicitly built in at all.

Challenges at the Primary Care Level

Primary healthcare centers often lack the necessary infrastructure for early CKD detection and management. Essential diagnostic tests, such as serum creatinine and urine protein assessments, are frequently unavailable. Additionally, the availability of generic kidney-protective medications, like angiotensin-converting enzyme (ACE) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and nonsteroidal mineralocorticoid receptor antagonists (nsMRAs), is inconsistent. Consequently, many CKD cases are diagnosed incidentally or at advanced stages and/or are unable to receive effective guideline-directed therapies, limiting the effectiveness of interventions, thereby contributing to high mortality.

Financial Toxicity

Financial constraints remain a major barrier to CKD treatment, often pushing families into severe financial distress. Even among patients accessing state-sponsored free dialysis, dropout rates and resulting mortality remain alarmingly high. This is largely due to substantial out-of-pocket costs for essential treatments, transportation, and other related expenses. In fact, previous studies have shown that the catastrophic cost burden associated with long-term dialysis treatment is a major contributor to cessation of treatment and inequity in access to care.[8,23]

Awareness and Accessibility Issues

Awareness of CKD is limited among both the general population and healthcare providers, particularly in rural areas. This lack of awareness results in late presentations, with many patients seeking care only at advanced stages of the disease. Additionally, nephrology and dialysis services are mainly concentrated in urban centers, further limiting access to specialized care for rural populations.

These gaps highlight the urgent need for innovative and integrated care models. Given the convergence of chronic diseases, a multimorbidity approach is necessary—district-level multidisciplinary NCD clinics could manage diabetes, hypertension, and CKD under one roof. At the primary care level, task-shifting and task-sharing approaches that train frontline health workers, nurses, and medical officers to handle CKD risk assessment, screening, and routine follow-ups, with referral to specialist care being reserved for those requiring it, would help ease the burden on India's limited nephrology workforce while expanding equitable and timely kidney care nationwide. In parallel, developing AI-enabled risk prediction approaches that adapt global risk stratification tools to data derived from Indian CKD cohorts and integrated with interoperable electronic health records would empower tertiary physicians to remotely review laboratory data and provide guided care.

In summary, India's current approach remains reactive and treatment-focused, with limited emphasis on preventive care, inadequate diagnostics at the primary level, and significant financial barriers even for "publicly covered" patients. While the proposed models through the HWCs represent a welcome starting point, sustained investments in policy reform, healthcare infrastructure, and community engagement will be essential to fundamentally transform India's CKD landscape and improve patient outcomes nationwide.

The Case for Policy Integration

CKD in India is not just an NCD issue but a social justice issue—poor, rural, and marginalized groups shoulder the brunt of preventable kidney failure. The ethical imperative is clear—the right to health enshrined in India's constitution demands equitable kidney care for all citizens, making concerted CKD control a moral necessity. At a national level, CKD threatens India's ability to meet its NCD targets. Addressing CKD directly advances the UN Sustainable Development Goals (SDG), particularly SDG 3.4 (reducing premature NCD mortality) and SDG 3.8 (achieving Universal Health Coverage). Economically, unchecked CKD imposes devastating costs, especially when detected late, driving the need for expensive

Table 2: Flagship central health programs relevant to kidney care

Central scheme	*Current initiatives*	*Opportunities*
NP-NCD (national)	Population screening for diabetes, hypertension, common cancers; CKD newly added in 2023 guidelines	Add serum creatinine and urine albumin-to-creatinine ratio (ACR) to the existing screening bundle; incorporate CKD counseling materials
Ayushman Bharat HWCs	Blood pressure (BP), glucose, basic point-of-care tests; no kidney markers	Equip with low-cost creatinine meters and urine dipsticks; automatic estimated glomerular filtration rate (eGFR) reporting
NPHCE (elderly care)	Geriatric package, no explicit kidney focus	Routine CKD screening in those ≥60 years
AB-PM-JAY (insurance)	Dialysis (HD and PD) and transplantation bundles	Empanel more PD and transplant follow-up centers; reimburse erythropoietin, vaccination, and immunosuppressants
PMNDP (dialysis)–national	Free HD in district hospitals; pilot PD rollout	Scale up PD "first policy," link with HWC for risk-factor control

Table 3: Selected state-level programs

State scheme	*Current initiatives*	*Opportunities*
Andhra Pradesh—Dr YSR Aarogyasri + PMNDP	Covers HD, PD, and transplantation	Empanel more PD and transplant follow-up centers; reimburse erythropoietin, vaccination, and immunosuppressants
Tamil Nadu—Chief Minister's Comprehensive Health Insurance Scheme (CMCHIS)	Fixed packages for HD and PD sessions and transplant follow-up; network of >700 empaneled hospitals	Add annual creatinine/ACR screening for CMCHIS card-holders; cover SGLT2 inhibitors and phosphate binders
Kerala—Karunya Arogya Suraksha Padhathi (KASP) + Karunya Benevolent Fund (KBF) + Samaswasam	KASP (AB-PM-JAY equivalent) provides Rs. 5 lakh cover; KBF and Samaswasam offer monthly dialysis subsidy for low-income patients	Empanel more PD and transplant follow-up centers; reimburse erythropoietin, vaccination, and immunosuppressants

dialysis or transplantation—expenses that early detection and preventive care could substantially reduce. Families bear catastrophic out-of-pocket spending, while premature deaths among working-age adults severely diminish workforce and economic productivity. There is, therefore, a compelling and urgent case for including kidney health in India's public health agenda.

The new WHO resolution on CKD offers an actionable roadmap, calling for earlier detection, stronger prevention, wider treatment access, and more resilient health systems—elements that India can weave into existing platforms. Tables 2 and 3 map the current landscape and gaps and opportunities at the central and state levels, respectively. Building on these foundations, we outline practical upgrades across the prevention-to-post-transplant continuum. Collectively, these steps would close critical gaps, make dialysis genuinely affordable, and move India closer to equitable, sustainable kidney care for every citizen.

Conclusion

The 2025 WHO resolution on CKD presents India with a critical opportunity to act. With one of the highest global burdens, India must urgently shift from a reactive, treatment-heavy model to a proactive, prevention-focused approach. CKD is not only a health issue—it reflects deep social and economic inequities. Integrating kidney care into national NCD programs, strengthening primary care, expanding early detection, and ensuring financial protection are all essential. The path forward is clear. By acting decisively, India can prevent avoidable deaths, mitigate economic losses, and move toward equitable, sustainable kidney care for all, thereby fulfilling both its constitutional duty and global commitments.

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ORIGINAL ARTICLE

Evaluating Pioglitazone for Managing Type 2 Diabetes Mellitus in Patients with Nonalcoholic Fatty Liver Disease

Vijay Panikar[1*], Apoorva Gupta[2], Nikhil Nasikkar[3], Shashank Joshi[4], Sanhita Walwalkar[5], Ishita Sachdev[6], Mangesh Tiwaskar[7], Krish Panikar[8], Aditi Mahajan[9], Narayan Deogaonkar[10], Jimit Vadgama[11], Harshpreet Tuteja[12], Divya Lalwani[13], Samiksha Singh[14], Parveen Kader[15]

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Abstract

Background: Among liver disorders, nonalcoholic fatty liver disease (NAFLD) is the most common and is associated with metabolic syndromes, particularly type 2 diabetes mellitus (T2DM). This study aimed to assess the effectiveness of pioglitazone in the management of T2DM with NAFLD.

Methods: This retrospective, single-center, observational study was carried out at Dr Panikar's Speciality Care Centre from 1st September 2022 to 1st February 2024. The data were collected from the medical records of diabetic patients with NAFLD who received pioglitazone. Patients aged between 18 and 80 years who had diabetes along with NAFLD were included in the study.

Results: A total of 3,350 patients were enrolled in this study, of whom 2,074 were male, with a mean age of 48.6 years. The mean estimated A1C (eA1C) showed a significant reduction at 6 months compared to baseline (6.87 vs 7.6%; mean difference (95% CI): 0.50% (0.39, 0.61); $p < 0.001$). At baseline, the mean controlled attenuation parameter (CAP) was significantly higher than at 6 months ($p = 0.032$). Similarly, the mean cholesterol level was significantly higher at baseline compared to 6 months ($p = 0.020$). A 25.7% decrease in grade 3 fatty liver was noted over the 6-month period from baseline. In terms of the decrease in fibrosis severity, a 37.5% reduction in F2, a 25.8% reduction in F1, and a 17.6% reduction in F4 were observed from baseline to 6 months.

Conclusion: In T2DM patients with NAFLD, pioglitazone improves glycemic control and reduces both fatty liver grades and fibrosis stages.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a liver condition marked by liver damage that is not associated with alcohol consumption. This condition can develop into nonalcoholic steatohepatitis (NASH), which may further advance to severe fibrosis as well as hepatocellular carcinoma (HCC).[1] The rapid rise in NAFLD and NASH is due to several factors. The primary contributors are the epidemic levels of type 2 diabetes mellitus (T2DM), obesity, and various elements of metabolic syndrome.[2] A recent study has shown a high occurrence of hepatic steatosis (75.1%) among patients with T2DM.[3]

As an agonist of peroxisome proliferator-activated receptor (PPAR), pioglitazone may enhance plasma adiponectin concentrations. This elevation is associated with improved insulin sensitivity and helps in mitigating inflammation and fibrosis in the treatment of NAFLD.[4] Among anti-diabetic medications, pioglitazone has the most substantial evidence supporting its effectiveness in NAFLD treatment, demonstrating improvements in liver histology for patients with biopsy-proven NASH.[5] To shed light on this, the current study aimed to assess the effectiveness of pioglitazone in the management of T2DM with NAFLD.

Methods

Study Design

A retrospective, single-center, observational study was carried out at Dr Panikar's Speciality Care Centre from 1st September 2022 to 1st February 2024. The study utilized medical record data from diabetic patients with NAFLD who received pioglitazone therapy.

Inclusion and Exclusion Criteria

This study included patients aged between 18 and 80 years who had diabetes and NAFLD, while those with any other chronic diseases were excluded.

Data Collection

Data on demographic characteristics, disease duration, glycemic and lipid parameters, and liver function tests were obtained from medical records verified by physicians during routine management.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 23. Descriptive statistics were used to present categorical variables as frequency (percentage), and continuous variables were described as mean with standard deviation (SD). Comparison of qualitative data between two groups was performed by applying two independent sample *t*-tests, based on the normality distribution. Paired *t*-tests were conducted to compare the data from baseline to 6 months. *p*-value < 0.05 was considered statistically significant.

Results

A total of 3,350 patients were included in the study. The mean (SD) age was 48.6 (9.2) years. Of the total patients, 2,074 were male. No significant difference was observed in mean weight between baseline and the 6-month follow-up. At baseline, the mean body mass index (BMI) was significantly lower compared to 6 months (25.92 vs 26.55 kg/m^2; mean difference (95% CI): −0.61 kg/m^2 (−0.78, −0.43); $p < 0.001$). At baseline, the mean estimated A1C (eA1C) was significantly higher

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compared to 6 months (7.36 vs 6.87%; mean difference (95% CI): 0.50% (0.39, 0.61); $p < 0.001$). Mean triglyceride (TG) was significantly higher at baseline than at 6 months (160.64 vs 144.04 mg/dL; mean difference (95% CI): 15.97 mg/dL (1.40, 30.54); $p = 0.032$). The mean liver stiffness measurement (LSM) did not show significant changes between baseline and 6 months. No significant change was observed in the average fibrosis index based on four factors (FIB 4) between baseline and 6 months (Table 1).

The average serum glutamic oxaloacetic transaminase (SGOT) was comparable between baseline and 6 months. The mean serum glutamic pyruvic transaminase (SGPT) values showed no significant difference between baseline and the 6-month follow-up. At baseline, the mean controlled attenuation parameter (CAP) was significantly higher compared to 6 months (285.7 vs 273.7 dB/m; $p = 0.032$). The mean glycated hemoglobin (HbA1C) was significantly higher at baseline than at 6 months (7.40 vs 6.20%; $p < 0.001$). The mean cholesterol was significantly higher at baseline than at 6 months (157.04 vs 151.04 mg/dL; $p = 0.020$). No significant differences were observed in the average levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) between baseline and the 6-month follow-up (Table 2).

The severity of fatty liver and fibrosis at subsequent follow-ups is depicted in Table S1. At baseline, 14.9, 23.0, and 47.1% of patients had grade 1, 2, and 3 fatty liver, respectively. The proportion of patients with grade 3 fatty liver decreased from 47.1% at baseline to 35% at the 6-month follow-up, indicating a 25.7% reduction in grade 3 fatty liver over 6 months (Fig. 1). In F2 fibrosis, there was a 37.5% reduction observed from baseline to 6 months (Fig. 2).

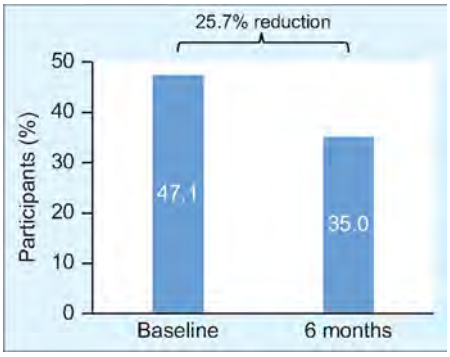

Fig. 1: Change in grade 3 fatty liver from baseline to 6 months

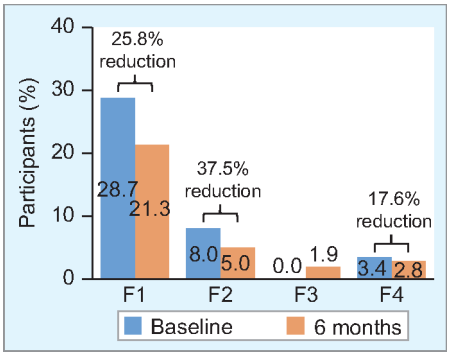

Fig. 2: Severity of fibrosis at baseline and 6 months

Table 1: Comparison of parameters in patients receiving pioglitazone from baseline to 2- and 6-month follow-up ($N = 3350$)

Parameter	*Baseline*	*2 months*	*6 months*	*Mean difference (95% CI); p-value*	
				Baseline to 2 months	*Baseline to 6 months*
Weight (kg)	($n = 3134$) 74.71 (14.22)	($n = 3134$) 74.66 (14.30)	($n = 3130$) 74.76 (14.34)	0.04 (–0.05, 0.14); $p = 0.388$	–0.07 (–0.18, 0.04); $p = 0.212$
BMI (kg/m^2)	($n = 2289$) 25.92 (48.10)	($n = 2289$) 26.12 (48.67)	($n = 2274$) 26.55 (48.67)	–0.20 (–0.30, –0.10); $p < 0.001$	–0.61 (–0.78, –0.43); $p < 0.001$
eA1C (%)	($n = 1887$) 7.36 (2.27)	($n = 1887$) 6.87 (1.62)	($n = 1883$) 6.87 (1.69)	0.50 (0.39, 0.61); $p < 0.001$	0.50 (0.39, 0.61); $p < 0.001$
TG (mg/dL)	($n = 234$) 160.64 (133.34)	($n = 234$) 144.04 (73.57)	($n = 252$) 131.62 (58.80)	16.60 (–1.19, 34.40); $p = 0.067$	15.97 (1.40, 30.54); $p = 0.032$
LSM (kPa)	($n = 4$) 7.58 (2.61)	($n = 4$) 8.65 (2.78)	–	–1.08 (–4.40, 2.25); $p = 0.379$	–
FIB-4	0.98 (0.37)	0.88 (0.30)	0.80 (0.25)	–	0.09 (–0.18, 0.37); $p = 0.365$

Data presented as mean (SD); BMI, body mass index; eA1C, estimated A1C; FIB-4, fibrosis index based on four factors; LSM, liver stiffness measure; TG, triglycerides

Table 2: Comparison of parameters in patients receiving pioglitazone from baseline to 6-month follow-up

Parameters	*Baseline*	*6 months*	*p-value*
SGOT (U/L)	($n = 295$) 26.16 (12.05)	($n = 709$) 33.32 (152.53)	0.290
SGPT (U/L)	($n = 306$) 29.21 (23.34)	($n = 727$) 31.27 (21.88)	0.114
CAP (dB/m)	($n = 86$) 285.7 (51.2)	($n = 365$) 273.7 (48.0)	0.032
HbA1c (%)	($n = 522$) 7.40 (2.85)	($n = 571$) 6.20 (3.11)	<0.001
Cholesterol (mg/dL)	($n = 697$) 157.04 (43.35)	($n = 919$) 151.04 (36.81)	0.020
HDL-cholesterol (mg/dL)	($n = 650$) 43.96 (13.98)	($n = 877$) 43.82 (15.90)	0.508
LDL-cholesterol (mg/dL)	($n = 644$) 85.77 (33.43)	($n = 868$) 81.96 (29.19)	0.073

Data presented as mean (SD); CAP, controlled attenuation parameter; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Discussion

Among the most prevalent liver conditions, NAFLD is rapidly emerging as a global public health concern,[6] driven by the rising prevalence of obesity and T2DM. This increasing prevalence of NAFLD and NASH cases has led to substantial morbidity and mortality.[7] Management strategies for NAFLD primarily emphasize lifestyle modifications and early treatment of associated metabolic conditions.[8] Pioglitazone is a promising agent for treating NAFLD/NASH.[7]

In the current study, at 6 months, the eA1C was significantly improved compared to baseline ($p < 0.001$). This significant decrease in eA1C indicates improved glycemic control over the study period, which is linked to a reduced likelihood of diabetes-related complications, including neuropathy, retinopathy, and cardiovascular diseases.[9] The present study indicated that the average TG level was significantly higher at baseline compared to the level observed at 6 months. In an earlier study by Belfort et al.,[5] treatment with pioglitazone led to a significant improvement in mean HbA1C levels compared to baseline ($p < 0.001$).[10] Similarly, in the current study, at 6 months, the average HbA1C was significantly improved compared to baseline ($p < 0.001$).

The present study observed that the average CAP score was significantly higher at baseline compared to 6 months ($p = 0.032$). This aligns with the results of a previous study by Chehrehgosha et al., which reported a significantly lower mean CAP score at week 24 compared to baseline ($p < 0.001$).[11] The current study showed that the average HDL-C level was comparable at baseline and at 6 months. Conversely, a previous study by Chehrehgosha et al. reported a statistically significant improvement in HDL-C levels at week 24 compared to baseline in patients treated with pioglitazone.[11]

Conclusion

In patients with T2DM and coexisting NAFLD, pioglitazone was shown to significantly improve glycemic control, reduce liver fat, and regress fibrosis. These results underscore the therapeutic potential of pioglitazone in this population, providing a much-needed tool for managing both diabetes and liver disease in parallel.

Author Contributions

All authors met ICMJE criteria, and all those who fulfilled these criteria are listed as authors. All authors provided direction and comments on the summary, made the final decision about where to publish the summary, and approved submission to the journal.

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Table S1: Severity of fatty liver and fibrosis at subsequent follow-ups

Parameter	*Baseline*	*2 months*	*6 months*
Fatty liver			
Grade 1	14.9	18.0	17.4
Grade 2	23.0	22.8	24.5
Grade 3	47.1	34.1	35.0
Fibrosis			
F1	28.7	23.0	21.3
F2	8.0	6.4	5.0
F3	–	1.51	1.9
F4	3.4	1.51	2.8

Data presented as percentage

ORIGINAL ARTICLE

Oral Iron Absorption Test as a Predictor of Response to Oral Iron Therapy and Gastrointestinal Malabsorption Syndromes in Iron Deficiency Anemia

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Abstract

Background: Iron deficiency anemia (IDA) affects approximately 2 billion individuals globally, yet optimal response to oral iron supplementation remains unpredictable. The oral iron absorption test (OIAT) represents a potentially valuable diagnostic tool for predicting therapeutic response and identifying underlying gastrointestinal malabsorption syndromes.

Materials and methods: This prospective study enrolled 190 IDA patients at a tertiary care center. After collecting baseline hematological parameters, participants underwent OIAT by receiving 60 mg of elemental iron, with serum iron levels measured at baseline and after 2 hours. Patients with abnormal OIAT results underwent additional investigations to identify underlying malabsorption syndromes.

Results: Among the participants (mean age 32.34 ± 11.84 years, 90.5% female), 34.2% demonstrated abnormal OIAT results. Malabsorption was diagnosed in 19.5% of subjects, with *Helicobacter pylori* infection (54.1%), autoimmune gastritis (27.0%), and celiac disease (18.9%) as the predominant etiologies. OIAT showed excellent sensitivity (89.2%), good specificity (79.1%), and exceptional negative predictive value (97.6%) for identifying malabsorption syndromes.

Conclusions: OIAT demonstrates robust diagnostic performance for predicting response to oral iron therapy and identifying malabsorption syndromes in IDA. The high negative predictive value positions OIAT as an effective first-line screening tool, potentially reducing the need for invasive investigations in patients with normal test results.

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Introduction

The World Health Organization (WHO) projects that almost 2 billion people, or 25% of the world's population, are anemic, with roughly half of them having iron deficiency anemia (IDA).[1] In India, according to the National Family Health Survey-5 (2019–2021), anemia affects 63.1% of minors and 57% of women of reproductive age (15–49 years).[2] Iron deficiency contributes significantly to impaired cognitive performance in children, adverse pregnancy outcomes, diminished physical capabilities in adults, and cognitive decline in elderly individuals.[3]

As a leading cause of years lived with disability among women, IDA represents a substantial health burden, particularly in developing nations.[4] Iron, an essential micronutrient, plays crucial roles in cellular growth and differentiation, oxygen transport, enzymatic reactions, immune function, and cognitive development. Its primary function involves the hemoglobinization of erythrocytes, with deficiency resulting in reduced hemoglobinization and subsequent anemia.[5,6]

Oral iron supplementation represents the cornerstone of IDA treatment due to its accessibility, cost-effectiveness, and general safety profile. However, therapeutic response varies considerably among patients, with approximately 72.8% showing positive responses to oral iron therapy while the remainder manifest as nonresponders.[7] Multiple factors influence this variability, including physiological demands, dietary restrictions, chronic blood loss, and reduced iron absorption.[8,9]

The oral iron absorption test (OIAT) has emerged as a potentially valuable tool for assessing intestinal iron absorption and identifying underlying malabsorption syndromes in IDA patients. This simple, noninvasive procedure involves oral administration of a standardized iron dose followed by measurement of serum iron levels at specific intervals. Despite its potential clinical utility, the role of OIAT in guiding therapeutic decisions for IDA management remains underexplored.

This study aimed to investigate the utility of OIAT in predicting response to oral iron therapy and identifying gastrointestinal malabsorption syndromes in patients with IDA, with the goal of enhancing diagnostic efficiency and therapeutic precision in clinical practice.

Materials and Methods

Study Design and Setting

This prospective study was conducted at the department of general medicine in a tertiary care teaching hospital from February 2023 to February 2024. The study received approval from the institutional ethics committee (Ref. No. 544, MC/EC/2023), and written informed consent was obtained from all participants.

Study Population

A total of 190 patients diagnosed with IDA were included based on hemoglobin <13 gm/dL for men and postmenopausal women, <12 gm/dL for premenopausal women, and serum ferritin <15 µg/mL. Exclusion criteria comprised pregnancy, elevated inflammatory markers, gastrointestinal symptoms, evidence of gastrointestinal bleeding, preexisting celiac disease or inflammatory bowel disease, and ongoing iron therapy or packed red cell transfusions within the previous 3 months.

Laboratory Investigations and Oral Iron Absorption Test Protocol

Full blood counts were conducted on EDTA anticoagulated blood samples using an automated Coulter Hematology Analyzer. Serum iron and ferritin levels were measured in all participants. After an overnight fast, baseline blood samples were collected to measure serum iron levels. Participants then received a single oral dose of 60 mg elemental iron as ferrous sulfate. A second blood sample was obtained 2 hours after iron administration. An increase in serum

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iron by at least 100 µg/dL from baseline was considered indicative of adequate iron absorption (normal OIAT), while an increase below this threshold was classified as abnormal.

Follow-up Investigations

Patients with abnormal OIAT results underwent additional investigations, including antitissue transglutaminase (anti-TTG) IgA antibody testing and upper gastrointestinal endoscopy with biopsy to assess for underlying pathologies affecting iron absorption. All endoscopic procedures were performed by an experienced gastroenterologist. Anti-TTG IgA antibody levels were measured using enzyme-linked immunosorbent assay (ELISA), with titers exceeding 15 IU/mL considered positive for potential celiac disease.

Statistical Analysis

Data were analyzed using SPSS software version 24.0 (Chicago, Illinois). Descriptive statistics were calculated for categorical variables (frequencies) and continuous variables (measures of central tendency and dispersion). Chi-square tests were used to analyze categorical variables. Receiver operating characteristic (ROC) curves were generated to calculate the accuracy of OIAT in detecting malabsorption. A p-value < 0.05 was considered statistically significant.

Results

Demographic, Clinical Characteristics, and Laboratory Parameters

The study enrolled 190 participants with a mean age of 32.34 ± 11.84 years (range: 14–60 years) and a strong female predominance (90.5%, n = 172). Baseline laboratory investigations revealed a mean hemoglobin level of 7.71 ± 1.82 gm/dL, mean MCV of 71.17 ± 6.61 fL, and mean ferritin of 4.45 ± 2.57 ng/mL. The mean baseline serum iron was 26.89 ± 24.99 µg/dL, with a post-OIAT mean serum iron of 210.07 ± 86.85 µg/dL after 2 hours (Table 1).

OIAT Results and Malabsorption

Of the 190 participants, 125 (65.8%) demonstrated normal OIAT results, while 65 (34.2%) showed abnormal results. Malabsorption was confirmed in 37 participants (19.5% of the total study population). Among these, *Helicobacter pylori* infection was the most common etiology (54.1%, n = 20), followed by autoimmune gastritis (27.0%, n = 10) and celiac disease (18.9%, n = 7) (Table 2).

Age and Gender Distribution in Malabsorption

In the malabsorption group, the majority (45.9%) were aged 31–40 years, compared to 33.3% in the nonmalabsorption group. Participants aged 51–60 years represented 27.0% of the malabsorption group but only 7.2% of the nonmalabsorption group, suggesting a trend toward increased malabsorption with advancing age, although this difference did not reach statistical significance (p = 0.101). Regarding gender distribution, men represented 21.6% of the malabsorption group compared to 6.5% of the nonmalabsorption group, a trend that approached but did not reach statistical significance (p = 0.079) (Table 3).

Diagnostic Performance of OIAT

Analysis revealed that 33 out of 37 participants (89.2%) with malabsorption had abnormal

Table 1: Demographic and laboratory characteristics of study participants (N = 190)

Characteristic	*Value*
Demographics	
Age (years), mean ± SD	32.34 ± 11.84
Age distribution, *n* (%)	
≤20 years	23 (12.1)
21–30 years	69 (36.3)
31–40 years	68 (35.8)
41–50 years	9 (4.7)
51–60 years	21 (11.1)
Gender, *n* (%)	
Female	172 (90.5)
Male	18 (9.5)
Laboratory parameters	
Hemoglobin (gm/dL), mean ± SD	7.71 ± 1.82
MCV (fL), mean ± SD	71.17 ± 6.61
Serum ferritin (ng/mL), mean ± SD	4.45 ± 2.57
Baseline serum iron (µg/dL), mean ± SD	26.89 ± 24.99
Post-OIAT serum iron (µg/dL), mean ± SD	210.07 ± 86.85
OIAT results and malabsorption	
Normal OIAT, *n* (%)	125 (65.8)
Abnormal OIAT, *n* (%)	65 (34.2)
Malabsorption present, *n* (%)	37 (19.5)
Malabsorption absent, *n* (%)	153 (80.5)

Table 2: Analysis of malabsorption status by demographics and OIAT results

Characteristic	*Malabsorption present, n = 37*	*Malabsorption absent, n = 153*	*p-value*
Age group			0.101
≤20 years	4 (10.8%)	19 (12.4%)	
21–30 years	4 (10.8%)	65 (42.5%)	
31–40 years	17 (45.9%)	51 (33.3%)	
41–50 years	2 (5.4%)	7 (4.6%)	
51–60 years	10 (27.0%)	11 (7.2%)	
Gender			0.079
Female	29 (78.4%)	143 (93.5%)	
Male	8 (21.6%)	10 (6.5%)	
OIAT results			< 0.0001
Abnormal	33 (89.2%)	32 (20.9%)	
Normal	4 (10.8%)	121 (79.1%)	
Etiology of malabsorption (n = 37)			
H. pylori infection	20 (54.1%)	–	
Autoimmune gastritis	10 (27.0%)	–	
Celiac disease	7 (18.9%)	–	

Table 3: Diagnostic performance of OIAT for detecting malabsorption

Parameter	*Value*	*95% confidence interval*
Sensitivity	89.2%	74.6–97.0%
Specificity	79.1%	71.8–85.2%
Positive predictive value	50.0%	39.7–62.7%
Negative predictive value	97.6%	93.1–99.2%
Accuracy	84.2%	78.2–89.1%
AUC for serum ferritin	0.707	0.615–0.800

OIAT results, compared to 32 out of 153 participants (20.9%) without malabsorption. This difference was statistically significant ($p < 0.0001$), demonstrating the strong association between abnormal OIAT results and underlying malabsorption syndromes. The diagnostic performance metrics of OIAT for identifying malabsorption were impressive, with a sensitivity of 89.2%, specificity of 79.1%, positive predictive value (PPV) of 50.0%, negative predictive value (NPV) of 97.6%, and overall accuracy of 84.2%.

Receiver operating characteristic (ROC) curve analysis demonstrated that serum ferritin exhibited moderate discriminative ability for detecting malabsorption, with an area under the curve (AUC) of 0.707 (standard error = 0.047, $p < 0.001$, 95% CI: 0.615–0.800).

Discussion

This study evaluated the utility of the OIAT in predicting response to oral iron therapy and identifying gastrointestinal malabsorption syndromes in patients with IDA. Our findings demonstrate that OIAT represents a valuable diagnostic tool with excellent sensitivity and exceptional negative predictive value for detecting underlying malabsorption in IDA patients.

The demographic profile of our study population, with a mean age of 32.34 years and female predominance (90.5%), reflects the epidemiological pattern of IDA, which disproportionately affects women of reproductive age. This pattern aligns with recent research by Yaman et al., who reported a similar gender distribution (92.6% female) in their study of iron absorption in IDA patients.[10]

Our study revealed that 34.2% of participants demonstrated abnormal OIAT results, indicating impaired iron absorption. This prevalence is comparable to the findings of Loveikyte et al., who reported abnormal OIAT in 59% of their cohort.[11] The difference in prevalence rates may reflect variations in study populations, methodological differences, or regional factors affecting iron absorption patterns.

A key finding from our investigation was the identification of malabsorption in 19.5% of the total study population, with *H. pylori* infection (54.1%), autoimmune gastritis (27.0%), and celiac disease (18.9%) as the predominant etiologies. These findings expand upon the work of Islam et al., who reported similar but not identical prevalence rates for these conditions (*H. pylori* 62%, celiac disease 7.5%, autoimmune gastritis 9.4%).[12] The higher prevalence of autoimmune gastritis and celiac disease in our cohort may reflect regional variations in disease patterns or differences in diagnostic approaches.

The diagnostic performance of OIAT in our study was exceptional, with a sensitivity of 89.2%, specificity of 79.1%, and a notably high negative predictive value of 97.6%. These metrics position OIAT as an excellent first-line screening tool for malabsorption in IDA patients. The high NPV indicates that a normal OIAT result virtually excludes significant malabsorption as a contributing factor to IDA, potentially sparing patients from unnecessary invasive investigations. This aligns with the findings of Gardyn et al., who emphasized OIAT's utility in determining the need for oral versus intravenous iron therapy and further gastrointestinal evaluations.[13]

Although not statistically significant, our data suggested trends toward increased malabsorption in older age groups and among male participants. This observation partially corroborates the findings of Yaman et al., who reported significantly lower iron absorption in male patients ($p = 0.04$) and those of increasing age ($p = 0.02$).[10] Similarly, Silay et al. demonstrated significantly lower OIAT values in older patients compared to younger individuals, suggesting age-related changes in iron absorption capacity.[14]

The moderate discriminative ability of serum ferritin for detecting malabsorption (AUC = 0.707) in our study provides an interesting contrast to the work of Wolff et al., who found that baseline hepcidin levels exhibited a strong negative correlation with transferrin saturation increase following OIAT.[15] These complementary findings suggest that combining multiple biomarkers may enhance diagnostic precision in assessing iron absorption capacity.

Our study has several important clinical implications. First, the high NPV of OIAT suggests that patients with normal test results are unlikely to have significant malabsorption and can be confidently managed with standard oral iron therapy. Second, abnormal OIAT results should prompt further investigation for underlying gastrointestinal pathologies, particularly *H. pylori* infection, autoimmune gastritis, and celiac disease. Third, OIAT represents a cost-effective approach to evaluating iron absorption, potentially reducing the need for more invasive and expensive investigations.

Several limitations of our study warrant mention. The single-center design may limit the generalizability of our findings to other populations with different ethnic or geographic characteristics. The exclusion of patients with elevated inflammatory markers may have resulted in underestimation of malabsorption prevalence, as inflammation can impair iron absorption independent of structural gastrointestinal pathologies. Additionally, the lack of standardized criteria for defining normal versus abnormal OIAT results across studies complicates direct comparisons of diagnostic performance metrics.

Conclusions

The OIAT demonstrates robust diagnostic performance for predicting response to oral iron therapy and identifying gastrointestinal malabsorption syndromes in patients with IDA. The exceptional negative predictive value positions OIAT as an effective first-line screening tool, potentially reducing the need for invasive investigations in patients with normal test results. Among patients with abnormal OIAT and confirmed malabsorption, *H. pylori* infection, autoimmune gastritis, and celiac disease represent the predominant etiologies requiring targeted therapeutic approaches. Early identification of these conditions through OIAT-guided diagnostic algorithms can facilitate more precise treatment strategies, potentially improving outcomes in patients with IDA.

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ORIGINAL ARTICLE

Trends in Glomerular Diseases in Northwest India: Has COVID-19 Altered the Diagnostic Landscape?

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Abstract

Background: Glomerular diseases are a major contributor to chronic kidney disease, with regional variability influenced by genetic, environmental, and healthcare factors. In Northwest India, minimal change disease (MCD) was historically the most common primary glomerular disease (PGD). However, evolving diagnostic capabilities and the disruptions caused by the COVID-19 pandemic may have altered the landscape of glomerular disease presentations and biopsy practices.

Objectives: To reassess the clinicopathologic spectrum of glomerular diseases from 2020 to 2024, compare it with data from 2008 to 2013, and evaluate the impact of the COVID-19 pandemic on biopsy activity and disease distribution.

Methodology: We retrospectively analyzed 925 renal biopsies from 2020 to 2024 and compared them with 622 biopsies from 2008 to 2013. All samples underwent light microscopy (LM) and immunofluorescence (IF) staining (IgA, IgG, IgM, C3, and C4). Diagnoses were categorized into PGD, secondary glomerular disease (SGD), and others. Clinical presentations, including nephrotic syndrome (NS) and acute kidney injury (AKI), were recorded. Statistical comparisons were made using Chi-square (χ^2) and *Z*-tests (SPSS v29), with $p < 0.05$ considered significant.

Results: Glomerulonephritis remained predominant (93.9%) with a significant shift in distribution ($\chi^2 = 121.5$, $p < 0.0001$). IgA nephropathy increased from 7.4 to 15.4%, overtaking MCD (which declined from 21.1 to 8.1%) as the leading PGD. Focal segmental glomerulosclerosis (FSGS) rose to 12.4%, while diabetic nephropathy (DN) increased to 3.1%. Nephrotic syndrome was the most common presentation (59.3%). Biopsy volume declined by 60% in 2020 but rebounded by 2022.

Conclusion: These findings highlight evolving diagnostic trends and underscore the need for broader biopsy access, enhanced diagnostic tools, and a national renal biopsy registry in India.

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Introduction

Glomerular diseases remain the leading cause of chronic kidney disease and end-stage renal disease worldwide; [1,2] their prevalence and patterns vary significantly across regions due to differences in genetics and environment.[3–5] They significantly contribute to the global burden of end-stage kidney disease and require region-specific epidemiological insights for optimal management. In 2016, we published a 5-year retrospective study titled "A Clinicopathologic Study of Glomerular Disease: A Single-Center, Five-Year Retrospective Study from Northwest India," which described biopsy-proven glomerular disease patterns at our center from 2008 to 2013. Our study analyzed 622 renal biopsies performed (2008–2013) at Sawai Man Singh Medical College and Hospital in Jaipur, Rajasthan;[6] we provided the first detailed profile of glomerular diseases in this arid and underserved region of India. Glomerulonephritis dominated renal pathology (93.9%), comprising primary glomerular diseases (PGDs, 79.4%) and secondary glomerular diseases (SGDs, 14.5%). Minimal change disease (MCD, 21.1%) was the most frequent PGD, followed by membranous nephropathy (MGN, 15.0%) and focal segmental glomerulosclerosis (FSGS, 10.5%). Lupus nephritis (LN, 7.6%) and amyloidosis (5.9%) predominated among SGDs. Notably, we highlighted significant regional heterogeneity, contrasting the predominance of MCD in Northwest India with immunoglobulin A nephropathy (IgAN) in Western India, and advocated for a national renal biopsy registry to bridge the data gap.

Since that time, the landscape of glomerular disease has been reshaped by significant global and local shifts.[7–9] Advances in diagnostics, evolving epidemiological trends, and the unprecedented disruption caused by the COVID-19 pandemic have all challenged previous understandings. The pandemic, in particular, disrupted healthcare access, delayed renal biopsies, and may have altered both disease presentation at the time of diagnosis and clinician thresholds for initiating biopsy. Moreover, emerging evidence of immune-mediated kidney injury following SARS-CoV-2 infection or vaccination has introduced new clinical and pathological patterns, prompting the need for updated, region-specific data to guide clinical practice.[10]

In response, we analyzed 925 renal biopsies performed between 2020 and 2024 to update the glomerular disease spectrum at our center. This dataset builds on our earlier work and reflects both evolving diagnostic trends and the impact of the COVID-19 pandemic. While some regional data have emerged, postpandemic biopsy trends from Northwest India remain undocumented. This study addresses that gap by examining temporal shifts in disease patterns over the past decade, with a focus on pandemic-related influences.

Methodology

This retrospective study was conducted at the Department of Nephrology, Sawai Man Singh (SMS) Medical College and Hospital, Jaipur, Rajasthan—a major tertiary referral center serving the population of Northwest India. We selected two distinct 5-year cohorts (July 2008–June 2013 and January 2020–December 2024) to allow a decade-long comparison of glomerular disease trends. The earlier cohort was previously published and validated, providing a reliable baseline.[6] This design not only facilitated pre- and postpandemic analysis but also captured broader shifts in diagnostic practices, disease presentation, and clinical decision-making that typically evolve over longer periods. Ethical approval was not required, as the study was retrospective in nature and based solely on anonymized, preexisting clinical and histopathological data.

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For the 2008–2013 cohort, 741 renal biopsies were reviewed. Of these, 209 (28.2%) were excluded—80 (10.8%) due to transplant origin or inadequate sampling, and 129 (17.4%) due to nonglomerular diagnoses—resulting in 532 cases for final analysis. For the 2020–2024 cohort, 1,005 renal biopsies were reviewed, with 925 (92.0%) included after applying the same exclusion criteria; 80 biopsies (8.0%) were excluded due to transplant origin, inadequate sampling, or nonglomerular diagnoses.

Renal biopsies were performed using Tru-Cut 14-gauge needles and Bard® disposable core biopsy instrument (Bard Biopsy Systems®), typically yielding two cores—one fixed in formalin for light microscopy (LM), and the other processed for immunofluorescence (IF). Paraffin-embedded sections were stained with hematoxylin and eosin (H and E), periodic acid–Schiff (PAS), Masson trichrome, Congo red, and Jones methenamine silver stains. IF was performed using antibodies against IgA, IgG, IgM, IgE, C3, and C4. Electron microscopy (EM) was not utilized due to its unavailability.

Diagnoses were classified into three groups: PGDs, SGDs, and other conditions such as tubulointerstitial or vascular pathology. PGDs included MCD, FSGS, MGN, IgAN, membranoproliferative glomerulonephritis (MPGN), diffuse proliferative glomerulonephritis (DPGN), and crescentic glomerulonephritis (Crescentic GN). SGDs included LN, renal amyloidosis, diabetic nephropathy (DN), and Monoclonal Immunoglobulin Deposition Disease(MIDD).[11–13]

Clinical data such as serum creatinine, 24-hour proteinuria, hematuria, and hypertension were retrieved from patient records where available. Annual biopsy volumes (2020–2024) were documented to assess temporal trends. To compare disease distribution between the two cohorts, disease frequencies were calculated for both periods. Statistical comparisons were performed using Chi-square (χ^2) tests for overall pattern shifts and two-sample Z-tests to evaluate changes in specific diagnoses. Statistical analysis was conducted using SPSS software (version 29.0), with a p-value < 0.05 considered statistically significant.

Results

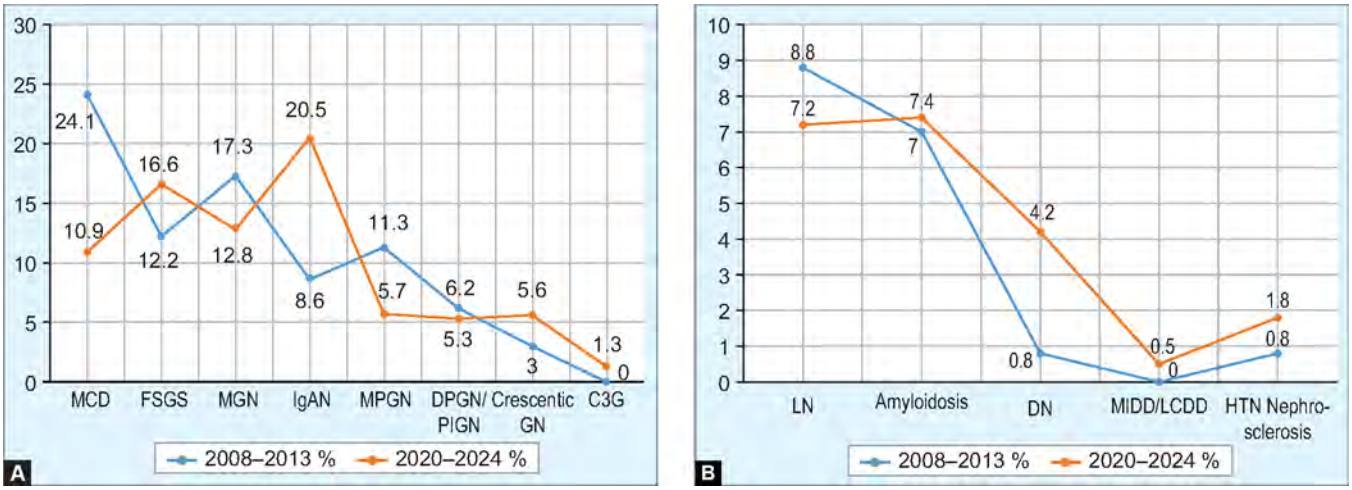
Analysis of 925 renal biopsies performed between 2020 and 2024 revealed significant shifts in the spectrum of glomerular diseases compared to the 2008–2013 cohort. A consolidated summary of these changes is presented in Table 1 and illustrated in Figure 1.

Shifts in Primary Glomerular Diseases

Minimal change disease declined significantly from 128 cases (24.1%) in 2008–2013 to 101 (10.9%) in 2020–2024 (↓13.2%, p < 0.0001). In contrast, IgAN rose markedly

Table 1: Comparative distribution of glomerular diseases in renal biopsies: 2020–2024 vs 2008–2013

Primary /secondary /other	*Diagnosis*	*2008–2013 count (%)*	*2020–2024 count (%)*	*Change (%)*	*p-value*
Primary	MCD	128 (24.1)	101 (10.9)	−13.2	< 0.0001
	FSGS	65 (12.2)	154 (16.6)	4.4	0.174
	MGN	92 (17.3)	118 (12.8)	−4.5	0.0003
	IgAN	46 (8.6)	190 (20.5)	11.9	< 0.0001
	MPGN	60 (11.3)	53 (5.7)	−5.6	< 0.0001
	DPGN	33 (6.2)	49 (5.3)	−0.9	0.192
	Crescentic GN	16 (3.0)	52 (5.6)	2.6	0.08
	C3G	0 (0.0)	12 (1.3)	1.3	0.004
Secondary	LN	47 (8.8)	67 (7.2)	−1.6	0.064
	Amyloidosis	37 (7.0)	68 (7.4)	0.4	0.723
	DN	4 (0.8)	39 (4.2)	3.4	0.0002
	MIDD	0 (0.0)	5 (0.5)	0.5	0.066
	HTN nephrosclerosis	4 (0.8)	17 (1.8)	1	0.123



Figs 1A and B: Comparison of primary and secondary glomerular disease distributions (2008–2013 vs 2020–2024)

from 46 (8.6%) to 190 (20.5%) (↑11.9%, $p <$ 0.0001). MGN also declined from 92 (17.3%) to 118 (12.8%) (↓4.5%, $p = 0.0003$), and MPGN dropped from 60 (11.3%) to 53 (5.7%) (↓5.6%, $p < 0.0001$).

Focal segmental glomerulosclerosis increased from 65 (12.2%) to 154 (16.6%) (↑4.4%) but was not statistically significant ($p = 0.174$). Crescentic GN rose from 16 (3.0%) to 52 (5.6%) (↑2.6%, $p = 0.08$). C3 glomerulopathy (C3G) newly emerged with 12 cases (1.3%) ($p = 0.004$).

Changes in Secondary Glomerular Diseases

Diabetic nephropathy increased significantly from 4 cases (0.8%) to 39 (4.2%) (↑3.4%, $p = 0.0002$). LN declined from 47 (8.8%) to 67 (7.2%) (↓1.6%, $p = 0.064$), approaching significance. Amyloidosis remained stable—37 cases (7.0%) vs 68 (7.4%) (↑0.4%, $p = 0.723$). Hypertensive nephrosclerosis rose from 4 (0.8%) to 17 (1.8%) (↑1.0%, $p = 0.123$). MIDD/LCDD emerged with 5 cases (0.5%) in 2020–2024, though not statistically significant ($p = 0.066$).

Impact of COVID-19 on Biopsy Trends

The trends observed in glomerular disease prevalence from 2020 to 2024 were likely shaped, at least in part, by the impact of the COVID-19 pandemic.[10] With nationwide lockdowns and healthcare services disrupted, access to medical care and timely referrals declined, which may have reduced the number of renal biopsies performed.[11] As a result, milder conditions such as MCD and MPGN may have been underdiagnosed. In contrast, the rise in cases of IgAN and C3G could reflect post-COVID immune responses or a shift toward biopsying only the more severe or atypical presentations during that challenging period.[10,12]

Glomerular Disease Distribution Changes (2008–2013 and 2020–2024)

A Chi-square test of independence was used to assess changes in biopsy-proven glomerular disease distribution. As shown in Figure 2, analysis of ten major diagnoses revealed a significant shift in patterns ($\chi^2 = 121.5$, df =9, $p < 0.0001$). The most marked changes were a decline in MCD (21.1 to 8.1%, ↓13.0%) and a rise in IgAN (7.4 to 15.4%, ↑8.0%). Other notable shifts included declines in MGN (15.0 to 9.5%, ↓5.5%) and MPGN (9.6 to 4.3%, ↓5.3%), and increases in FSGS (10.5 to 12.4%, ↑1.9%) and DN (0.6 to 3.1%, ↑2.5%). These trends may reflect better diagnostics and external factors such as the COVID-19 pandemic.[14]

Key Diagnoses

Z-tests for MCD, IgAN, FSGS, and MGN

Two-sample Z-tests for proportions were performed to assess shifts in four major PGDs—MCD, IgAN, FSGS, and MGN—between 2008–2013 ($n = 622$) and 2020–2024 ($n = 925$), based on χ^2 findings. Significant changes were seen in MCD ($p < 0.0001$), IgAN ($p < 0.0001$), and MGN ($p = 0.0003$), while the increase in FSGS was not significant ($p = 0.174$).

Minimal change disease dropped sharply from 21.1 to 8.1% ($Z = -7.88$), while IgAN rose from 7.4 to 15.4% ($Z = 4.76$), marking the most prominent shifts. MGN declined moderately from 15.0 to 9.5% ($Z = -3.62$), and FSGS showed a slight, nonsignificant rise from 10.5 to 12.4% ($Z = 1.36$). These trends highlight a clear decline in MCD and a notable rise in IgAN as key contributors to the changing glomerular

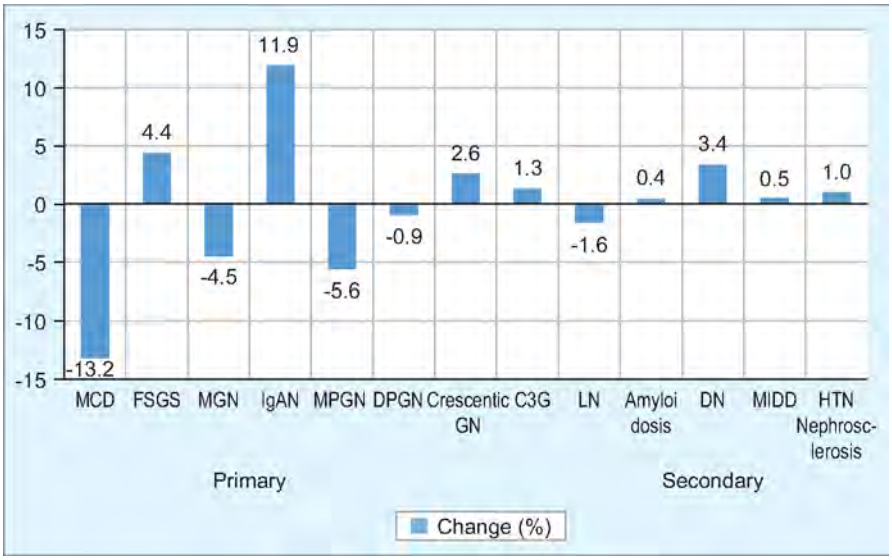


Fig. 2: Percentage change in glomerular disease diagnosed between 2008–2013 and 2020–2024

Table 2: Clinical syndromes and corresponding histological diagnoses in renal biopsies (2020–2024)

Primary/secondary	*Renal disease*	*Number (%)*	*NS (%)*	*AGN (%)*	*RPRF (%)*	*AUA (%)*	*CKD (%)*
Primary	MCD	101 (10.9)	91 (16.6)	7 (5.1)	0 (0.0)	3 (3.4)	0 (0.0)
	FSGS	154 (16.6)	146 (26.6)	8 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)
	MGN	118 (12.8)	107 (19.5)	3 (2.2)	0 (0.0)	7 (8.0)	1 (1.4)
	IgAN	190 (20.5)	32 (5.8)	55 (40.1)	11 (14.3)	64 (72.7)	28 (37.8)
	MPGN	53 (5.7)	35 (6.4)	12 (8.8)	3 (3.9)	3 (3.4)	0 (0.0)
	DPGN	49 (5.3)	24 (4.4)	20 (14.6)	5 (6.5)	0 (0.0)	0 (0.0)
	Crescentic GN	52 (5.6)	13 (2.4)	3 (2.2)	30 (39.0)	0 (0.0)	6 (8.1)
	C3G	12 (1.3)	3 (0.5)	6 (4.4)	1 (1.3)	0 (0.0)	2 (2.7)
Secondary	LN	67 (7.2)	16 (2.9)	20 (14.6)	27 (35.1)	0 (0.0)	4 (5.4)
	Amyloidosis	68 (7.4)	60 (10.9)	0 (0.0)	0 (0.0)	3 (3.4)	5 (6.8)
	DN	39 (4.2)	19 (3.5)	3 (2.2)	0 (0.0)	8 (9.1)	9 (12.2)
	MIDD	5 (0.5)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)
	HTN nephrosclerosis	17 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (23.0)
	Totals	925 (100.0)	549 (100.0)	137 (100.0)	77 (100.0)	88 (100.0)	74 (100.0)

disease spectrum, with MGN also playing a significant role.

Clinical Syndromes Associated with Histological Diagnoses (2020–2024)

We analyzed the clinical presentations of biopsy-proven renal diseases from 2020 to 2024 (Table 2). Nephrotic syndrome was the most common indication for biopsy, seen in 549 of 925 cases (59.3%). Among PGDs, FSGS was predominant (146 cases, 26.6%), followed by MGN (107, 19.5%), MCD (91, 16.6%), and IgAN (32, 5.8%).

Immunoglobulin A nephropathy was the most frequent PGD overall (190 cases, 20.5%), leading to acute glomerulonephritis (AGN, 40.1%) and contributing significantly to rapidly progressive renal failure (14.3%) and chronic kidney disease (CKD, 37.8%).

Acute glomerulonephritis was identified in 137 cases (14.8%), predominantly due to IgAN (40.1%), DPGN (14.6%), and MPGN (8.8%). Rapidly progressive renal failure (8.3%) was mainly caused by crescentic GN (39.0%) and LN (35.1%). CKD (8.0%) was frequently associated with hypertensive nephrosclerosis (23.0%) and DN (12.2%). Asymptomatic urinary abnormalities (AUA) were noted in 88 cases (9.5%), mostly due to IgAN (72.7%).

Discussion

This study provides an updated clinicopathologic profile of glomerular diseases based on 925 renal biopsies performed from 2020 to 2024 at our tertiary care center in Northwest India, compared to 622 biopsies from 2008 to 2013. By examining two distinct cohorts separated by a decade, we identified significant temporal shifts reflecting evolving nephrology practices and the impact of the COVID-19 pandemic. A χ^2 analysis confirmed substantial changes in disease distribution ($\chi^2 = 121.5$, df = 9, $p < 0.0001$).

The most notable finding was the sharp decline in MCD from 24.1 to 10.9% ($p < 0.0001$) and the rise of IgAN from 8.6 to 20.5% ($p < 0.0001$). This made it the leading PGD. Other significant changes included a decline in MGN from 17.3 to 12.8% ($p = 0.0003$) and MPGN from 11.3 to 5.7% ($p < 0.0001$). In contrast, FSGS increased from 12.2 to 16.6% ($p = 0.174$), although this change was not statistically significant. Among SGDs, DN increased from 0.8 to 4.2% ($p = 0.0002$). This indicated rising diabetes prevalence in India.[13,14] LN remained stable at 7.2% ($p = 0.064$). Amyloidosis showed only a modest increase from 7.0 to 7.4% ($p = 0.723$).

The evolution of glomerular disease patterns at our center over the past 15 years tells a compelling story—one shaped by improved diagnostics, shifts in clinical decision-making, and the sweeping global impact of the COVID-19 pandemic. Our comparison of renal biopsy data from 2008 to 2013 and 2020 to 2024 reveals both expected trends and new insights that mirror changes in nephrology across India and globally.

Perhaps the most striking shift has been the sharp decline in MCD, from 24.1 to just 10.9%. This is consistent with data from other Indian centers, where similar drops have been observed over time.[15] The decrease likely stems from a more conservative biopsy approach in patients with classic steroid-sensitive NS—especially in children and young adults—who are now often treated empirically with corticosteroids.[16] At the same time, improvements in histopathology and IF have enabled clearer differentiation between MCD, early FSGS, and IgAN, leading to diagnostic reclassification in many cases.[15,16] The COVID-19 pandemic only accelerated this trend, as biopsy activity declined and clinicians prioritized patients with atypical or steroid-resistant features.[17]

In contrast, IgAN emerged as the most common PGD in our recent cohort, rising from 8.6 to 20.5%. This increase likely reflects both a true epidemiological shift and enhanced diagnostic recognition due to greater awareness and improved biopsy practices. At our center, renal biopsies are routinely performed in patients with CKD who present with active urinary sediments and normal-sized kidneys, and a substantial proportion of these cases were diagnosed as IgAN. The Oxford classification has brought greater uniformity and precision to the diagnosis and prognostication of IgAN.[18] IF has become more routinely available, leading to better detection of mesangial IgA deposition. A recent systematic review from India estimates the prevalence of IgAN at 16.5%, higher than in Western populations but lower than in East Asian countries.[13] Interestingly, recent case reports suggest that COVID-19 may also serve as a trigger for new-onset or relapsing IgAN, possibly via immune dysregulation.[19]

We also noted a significant decline in MPGN, from 11.3 to 5.7%, which aligns with recent advances in our understanding of complement-mediated glomerular diseases. Many cases once labeled as MPGN are now being subclassified as C3G, a pathogenic subset within the MPGN pattern, based on dominant C3 staining and complement dysregulation, owing to improved availability of immunohistochemistry and complement pathway analysis.[20] These tools have enhanced diagnostic accuracy and provided a more mechanistic framework for understanding disease progression.[21] However, in many centers such as ours, access to EM remains limited, creating challenges in accurately subtyping these diseases.[22]

A parallel decline was observed in MGN, which fell from 17.3 to 12.8%. This likely reflects a shift in diagnostic strategies. The increased use of antiphospholipase A2 receptor (PLA2R) antibody testing has reduced the reliance on biopsy for typical cases of primary MGN.[23,24] In addition, widespread hepatitis B vaccination and improved antiviral therapy have led to a decrease in secondary MGN, especially in regions such as ours where hepatitis B was once endemic.[25]

Secondary glomerular diseases showed evolving patterns as well. DN increased from 0.8 to 4.2%, in line with India's growing burden of type 2 diabetes.[13,14] LN remained relatively stable at 7.2%, and amyloidosis saw only a modest rise from 7.0 to 7.4%. These numbers highlight how public health trends and improved survival may be influencing biopsy findings.

The COVID-19 pandemic had a clear, though temporary, impact on biopsy activity and disease patterns. In 2020, the number of renal biopsies at our center dropped by 60% (95 cases) compared to the prepandemic average of 234 per year, due to lockdowns and healthcare disruptions. A recovery began in 2021 (185 biopsies), followed by a peak in 2022 (267 biopsies), suggesting a catch-up effect from delayed diagnoses. This period also coincided with increased detection of IgAN and C3G, supporting the hypothesis of postviral immune activation following COVID-19.[19,26] SARS-CoV-2 infection has been linked to a wide range of glomerular pathologies, including MGN, crescentic GN, podocytopathy, and thrombotic microangiopathy largely attributed to direct viral injury and immune dysregulation.[27] In patients with preexisting glomerular diseases, COVID-19 was associated with acute kidney injury (AKI) in approximately 16.9% of cases, with worse outcomes among older patients, males, and those receiving corticosteroids or presenting with hypoalbuminemia.[28]

Focal segmental glomerulosclerosis showed a mild increase in prevalence from 12.2 to 16.6%, although this change was not statistically significant. However, the trend may reflect a growing recognition of FSGS, particularly as more patients with steroid-resistant NS are being biopsied. This observation is consistent with global patterns, notably in East Asia and Europe, where FSGS has been increasingly identified as a major cause of NS.[5,29] Additionally, the COVID-19 pandemic brought attention to collapsing glomerulopathy (COVAN), a distinct variant of

FSGS, especially among patients with high-risk APOL1 genotypes.[26]

As expected, the clinical presentations closely reflected the underlying histological patterns. Nephrotic syndrome was the most common presentation in podocytopathies such as MGN, FSGS, MCD, and amyloidosis, where damage to the glomerular filtration barrier leads to heavy proteinuria.[30] C3 glomerulopathy, driven by dysregulation of the complement pathway, is typically presented as AGN, consistent with its pathophysiological mechanism.[31] Interestingly, only 33.7% of IgAN cases in our cohort presented with AUA, a notable decline from historical figures exceeding 50%. This may reflect pandemic-era biopsy practices, where patients with milder urinary findings were often managed conservatively.[32] Hypertensive nephrosclerosis consistently presented with CKD, reflecting its silent progression. CKD was also the predominant presentation in chronic immune complex-mediated diseases such as MPGN and LN, suggesting delays in diagnosis or evolving referral patterns.

Limitations

This was a single-center, retrospective study, potentially limiting generalizability. EM and complement assays were unavailable, restricting diagnostic precision for certain conditions. Pandemic-related selection bias in biopsy decisions may have influenced disease prevalence data.

Conclusion

The evolving spectrum of glomerular diseases highlights significant shifts in nephrology practice, diagnostics, and public health trends. Our findings emphasize the need to improve renal biopsy access and strengthen advanced diagnostics, including IF, complement assays, and EM. Crucially, our results support earlier recommendations to establish a national renal biopsy registry, such as the Indian TrANslational GlomerulonephrItis BioLogy nEtwork (I-TANGIBLE), currently underway in India.[33] This initiative would allow standardized tracking of disease patterns, validate our observed trends nationally, and guide evidence-based nephrology care.

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ORIGINAL ARTICLE

Retrospective Observational Electronic Medical Records-based Real World Study to Assess the Prevalence and Treatment of Dyslipidemia in Indian Patients

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Abstract

Background: Dyslipidemia is an imbalance of lipids—total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL). The aim of this observational electronic medical records (EMR)-based study was to evaluate the prevalence, comorbidities, and treatment pattern in dyslipidemia patients.

Methodology: This was a retrospective, EMR-based longitudinal study that used anonymized data. Data were analyzed for dyslipidemia patients of either gender, age ≥18 years, prescribed lipid-lowering agents. Follow-up data were captured at 3 months (±30 days) from the baseline visit. There were records of 77,57,513 adult patients in the EMR database from January 2018 to 2023. Of these, 15,20,319 (19.6%) patients were diagnosed with dyslipidemia, of which 90,933 (5.98%) were treatment-naïve patients, that is, newly diagnosed, and 65,535 (72.07%) patients had follow-up within 3 months (±1 month).

Results: The prevalence of dyslipidemia was 19.6% with a greater number of males. Diabetes and hypertension (HTN) were the top comorbidities. HDL was in the normal range (44.8 ± 9.7 mg/dL), LDL and TC were borderline high (140.5 ± 38.8 and 222.8 ± 42.8 mg/dL), TG were high (203.8 ± 94.7 mg/dL), and VLDL was close to the normal range (29.2 ± 8.5 mg/dL) at baseline. About >50% of dyslipidemia patients with diabetes, HTN, or diabetes and HTN with LDL >100 mg/dL at baseline achieved LDL <100 mg/dL at follow-up. In dyslipidemia patients with coronary artery disease (CAD), 47.54% of patients had LDL >100 mg/dL at follow-up, and only 4.92% of patients had LDL <55 mg/dL at follow-up. A number of 66.7% of dyslipidemia patients with chronic kidney disease (CKD) had LDL <100 mg/dL at follow-up. Low- to moderate-dose rosuvastatin and atorvastatin were the mostly prescribed drugs.

Conclusion: Statins significantly reduced LDL, TC, and TG in patients with CAD and LDL in patients with CKD. Despite being on lipid-lowering drugs, probably due to low doses, a significant proportion of patients did not achieve the recommended LDL levels.

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Introduction

This was a retrospective, electronic medical records (EMR)-based, longitudinal database study. The study protocol was approved by the Royal Pune Independent Ethics Committee (RPIEC240823) on August 18, 2023. A waiver for informed consent was obtained as it involved anonymized data. The study was also registered on the Clinical Trials Registry of India (CTRI/2023/09/057954). Data were analyzed for dyslipidemia patients of either gender, age ≥18 years, prescribed lipid-lowering agents, and who had a baseline and a follow-up visit within 3 months (±1 month) from baseline.

The baseline visit (visit 1) was when the patient was diagnosed with dyslipidemia and prescribed a lipid-lowering agent. For visit 1, data on demographic characteristics such as age, gender, body mass index (BMI), comorbidities, lipid-lowering agents, their doses, and lipid profile [total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and serum triglycerides (TG)] were extracted.

The follow-up visit was recorded at 3 months (±1 month) from baseline. During this visit, data on lipid profile were extracted and the change from baseline was assessed. Patients with LDL >100 mg/dL at baseline and with follow-up data at 3 months (±1 month) from baseline were assessed to determine the number of patients who achieved target LDL levels defined in the subsequent sections.

The primary outcome measures were to determine the prevalence of dyslipidemia, incidence of newly diagnosed dyslipidemia, assess demographic characteristics, number and percentage of newly diagnosed dyslipidemia patients with different comorbidities, and assessment of lipid profiles.

The secondary outcome measures were to assess the lipid profile in newly diagnosed dyslipidemia patients with different comorbidities at baseline and follow-up, and to assess the number and percentage of newly diagnosed dyslipidemia patients achieving target LDL levels according to International Guidelines [European Society of Cardiology (ESC), American Stroke Association (ASA)/ American Heart Association (AHA)] and the Lipid Association of India (LAI) consensus statement.

The current study, being an observational and database study, involved no additional tests or interventions. Data management was done in accordance with applicable regulatory requirements to ensure the integrity of the data, for example, removing errors and inconsistencies in the data. The data from the EMR were collected using the data collection forms.

Statistical Analysis

Continuous variables were summarized using descriptive statistics [sample size(*n*), mean, standard deviation (SD)]. Categorical variables were presented as the number and

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percentage of patients. Unless otherwise noted, percentages were based on the number of patients from the population, as appropriate. All statistical tests were conducted at a two-sided 5% significance level. A paired *t*-test was used to compare the follow-up values with the baseline values.

Results

Patient Flow

There were records of 77,57,513 adult patients in the EMR database from January 2018 to 2023. Of these, 15,20,319 (19.6%) patients were diagnosed with dyslipidemia, of which 90,933 (5.98%) were treatment-naïve patients, that is, newly diagnosed, and 26,968 patients had follow-up within 3 months (±1 month). The mean duration between baseline and follow-up visit was 85.98 days. The prevalence of dyslipidemia was 19.6%, and the incidence of newly diagnosed dyslipidemia was 1.17% (based on total adult patients on EMR) and 5.98% (based on total adult patients diagnosed with dyslipidemia)

Demographic Characteristics

Of the 90,933 patients, the majority of patients (68.2%) belonged to the 40–64 years age-group, followed by 18% patients between 18 and 39 years, and 13.8% belonged to ≥65 years. The mean ± SD age of patients was 50.9 ± 11.96 years. Males comprised 53.4% and females were 46.6%. Most of the patients (71.7%) had a BMI of ≥25 kg/m^2, 27.5% had their BMI in the normal range, while 0.8% patients were underweight. In patients newly diagnosed with dyslipidemia, diabetes (58.38%) and hypertension (HTN) (46.95%) were the most common comorbidities observed. Table 1 gives a summary of patient demographic characteristics.

Table 1: Summary of demographic characteristics

Parameter	*Category (years)*	*Percent (%)*
Age (years)	18–39	18.0
	40–64	68.2
	≥65	13.8
	Overall	–
Gender	Female	46.6
	Male	53.4
Newly diagnosed dyslipidemia patients with comorbidity at baseline	Diabetes	58.38
	HTN	46.95
	MI	0.48
	CAD	2.71
	CKD	1.67

Patients with Low-density Lipoprotein ≥100 mg/dL at Baseline (by Drug Molecules)

Of the patients who had LDL ≥100 mg/dL at baseline, 746, 100, and 282 patients were on rosuvastatin 20, 10, and 5 mg, and of them, 70 (70%), 424 (56%), and 133 (47%) achieved LDL <100 mg/dL at follow-up, respectively. Clearly, the response was dose-dependent. Of 80 patients on atorvastatin 20 mg, 38 (46%) achieved LDL <100 mg/dL at follow-up. Among 1,208 patients on statins with LDL ≥100 mg/dL at baseline, 664 (54.97%) achieved LDL <100 mg/dL at follow-up. Table 1 of Supplementary file.

Analysis of Actual and Change from Baseline in Lipid Profiles by Comorbid Conditions

In dyslipidemia patients with diabetes, HTN, or both, there was a statistically significant ($p < 0.05$) reduction in LDL, TC, TG, and VLDL from baseline to follow-up.

In patients with dyslipidemia, coronary artery disease (CAD), and chronic kidney disease (CKD), there was a statistically significant ($p < 0.05$) reduction in LDL, TC, and TG from baseline to follow-up visit; however, change in VLDL was not statistically significant.

In patients diagnosed with dyslipidemia and having coexistent conditions like CAD, diabetes, HTN, or both, HDL reduced from baseline to follow-up, while HDL improved in dyslipidemia patients with CKD and myocardial infarction (MI). Table 2 of Supplementary file.

Analysis of Change in Lipid Profile from Baseline to Follow-up

There was a statistically significant reduction in levels of LDL, TC, TG, and VLDL from baseline to follow-up. The mean ± SD values for HDL, LDL, TC, TG, and VLDL at baseline were 45.2 ± 10.6, 140 ± 38.8, 222.8 ± 42.8, 203.8 ± 94.7, and 29.2 ± 8.5 mg/dL, respectively. The mean values for the same at the follow-up were 44.4 ± 10.4, 97.1 ± 36.4, 173.3 ± 42.2, 153 ± 50.7, and 24.7 ± 7.9 mg/dL, respectively. The mean ± SD change from baseline to follow-up for HDL, LDL, TC, TG, and VLDL was observed to be 0.9 ± 10, 43.4 ± 44.1, 49.5 ± 47.7, 50.7 ± 91.1, and 4.6 ± 9 mg/dL, respectively.

Analysis of Change in Lipid Profile from Baseline to Follow-up (for 3 Most Prescribed Lipid Lowering Agents)

A statistically significant ($p < 0.05$) reduction was observed for LDL, TC, TG, and VLDL from baseline. The mean ± SD change from baseline in LDL, TC, TG, and VLDL with rosuvastatin was 49.6 ± 43, 55.1 ± 43.5, 28.8 ± 74.4, and 3.8 ± 8.5 mg/dL, respectively. The mean ± SD change from baseline in LDL, TC, TG, and VLDL with atorvastatin was 43.1 ± 37.3, 50.7 ± 47.3, 27.2 ± 73.9, and 3.6 ± 9 mg/dL, respectively. The mean ± SD change from baseline in LDL, TC, TG, and VLDL with fenofibrate + rosuvastatin was 34.1 ± 44.9, 42.9 ± 56.7, 120.1 ± 101.3, and 11.3 ± 9.2 mg/dL, respectively.

Change in Lipid Profiles by Comorbid Conditions

In dyslipidemia patients with CAD, the mean reduction in LDL from baseline was 34.2 mg/dL with rosuvastatin and 34 mg/dL with atorvastatin, and the mean reduction in TG with fenofibrate + rosuvastatin and rosuvastatin was 68.2 and 21.4 mg/dL, respectively. The mean reduction in LDL from baseline in dyslipidemia patients with CKD with fenofibrate + rosuvastatin, rosuvastatin, and atorvastatin were 110.7, 58.3, and 52.2 mg/dL, respectively, and the mean reduction in TG from baseline with fenofibrate + rosuvastatin and rosuvastatin were 196.3 and 21.4 mg/dL, respectively. In dyslipidemia patients with DM, the mean reduction in LDL with rosuvastatin and atorvastatin was 46.5 and 37.6 mg/dL, respectively, and the mean reduction in TG from baseline was 127.3 mg/dL with fenofibrate + rosuvastatin and 32.2 mg/dL with atorvastatin. In dyslipidemia patients with HTN, the mean reduction in LDL with rosuvastatin and atorvastatin was 53.3 and 42.8 mg/dL, respectively, and for TG with fenofibrate + rosuvastatin and rosuvastatin, it was 113.1 and 31.1 mg/dL, respectively. Refer to Tables 3 and 4 in the Supplementary file.

Discussion

Dyslipidemia is a major risk factor for cardiovascular disease (CVD) and a leading cause of mortality and morbidity globally. LDL and its oxidized form cause progression of atherosclerosis, as LDL delivers cholesterol to the vascular artery wall. In clinical settings, statins are the first choice for lowering LDL levels.[1] In the present EMR-based observational study, the prevalence of dyslipidemia was 19.6% with a greater number of males. Diabetes and HTN were the most common comorbidities in the current study. These findings align with existing evidence on the high prevalence of diabetes and HTN in dyslipidemia patients.

This study reports that 44.2, 20.4, 5.3, and 1.8% of patients belonged to overweight, obesity class I, II, and extremely obese, respectively, with 27.5% having BMI in the normal range. Around 0.8% of patients were

classified as underweight. The dysregulation of lipoprotein metabolism in obese patients causes increased production of VLDL and breakdown of HDL, which are associated with higher risk of CV and renal diseases. Hence, in addition to lipid-lowering therapy, the importance of regular physical activity and dietary modifications should be emphasized to the patients to prevent CVD and CKD. A higher number of patients with obesity might have also been a reason for the decrease in HDL levels from baseline to follow-up, as evidence suggests that HDL decreases with increasing BMI.[2] Dyslipidemia and obesity are highly prevalent among South Asians, likely due to the higher socioeconomic status associated with higher consumption of a calorie-rich diet and a sedentary lifestyle. The most prescribed drugs for dyslipidemia are statins (62.7%), where rosuvastatin 10 mg [*n* = 24,956 (27.4%)] was mostly prescribed, followed by atorvastatin 10 mg (14.3%), rosuvastatin 5 mg (8.9%), and rosuvastatin 20 mg in 5.4% of patients. Most patients were on moderate statin therapy (atorvastatin 10 mg and rosuvastatin 10 mg), which was sufficient to decrease LDL levels below 100 mg/dL.[3] In this study, 56% of patients on rosuvastatin 10 mg, 70% of patients on rosuvastatin 20 mg, and 46% on atorvastatin 20 mg achieved LDL <100 mg/dL at follow-up.

In patients with LDL ≥100 mg/dL at baseline, 45% reduction in LDL levels was seen in 9.55% of patients on fenofibrate 160 mg + rosuvastatin 10 mg, 7.5% of patients on atorvastatin 20 mg, 9% of patients on rosuvastatin 10 mg, and 7% of patients on rosuvastatin 20 mg. Similarly, in a trial where patients were randomized to receive atorvastatin 10 or 20 mg and rosuvastatin 10 or 20 mg, there was a decrease in LDL by 45–50% with rosuvastatin and 40–47% with atorvastatin.[3]

As per the American Diabetes Association (ADA), for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD), the recommended target LDL reduction is >50% from baseline, and LDL goal is <55 mg/dL. In diabetes patients with no history of CV disease or risk factor, the target LDL is <100 mg/dL, and with a CV risk factor (HTN, smoking), the target LDL is <70 mg/dL, and for others it is <100 mg/dL. In this study, over 50% of dyslipidemia patients with diabetes, HTN, or both with baseline LDL >100 mg/dL achieved LDL <100 mg/dL at follow-up, while only 8.48, 8.76, and 10.33% of them had LDL <55 mg/dL at follow-up. In dyslipidemia patients with CAD, 47.54% had LDL >100 mg/dL at follow-up, and only 4.92% reached the target LDL <55 mg/dL. As per the ESC guidelines, for very high-risk patients with CKD (stage 4 or 5), the target LDL is <70 mg/dL, while it is <100 mg/dL regardless of CKD stage.[2] In this study, 66.7% of dyslipidemia patients with CKD had LDL <100 mg/dL at follow-up.

As per the AHA/American College of Cardiology (ACC) guidelines, statins are recommended for diabetes patients of 40–75 years of age with dyslipidemia and without ASCVD.[4] Irrespective of the three most prescribed antihyperlipidemic agents (rosuvastatin, atorvastatin, and fenofibrate + rosuvastatin), there was a slight reduction in HDL from baseline to follow-up, likely because the quantitative lipid changes in diabetes patients can reduce HDL.[5] There was a significant reduction in LDL and TG with all three drugs; however, there was a higher reduction in TG with fenofibrate + rosuvastatin (127.2 mg/dL) compared to rosuvastatin (28.6 mg/dL) and atorvastatin (32.2 mg/dL). Studies have shown that rosuvastatin, either alone or in combination with fenofibrate, effectively reduces TG and LDL. A slight reduction in HDL was noted in dyslipidemia patients with HTN, potentially due to impaired HDL synthesis and turnover and changes in HDL function and composition due to HTN and antihypertensive drugs. There was an increase in HDL in dyslipidemia patients with CAD with rosuvastatin, while there was a decrease in HDL with atorvastatin and fenofibrate + rosuvastatin. This is consistent with other studies showing rosuvastatin's ability to increase mean HDL levels.

The strength of the current study lies in its extensive dataset encompassing over 90,000 patient data at baseline and over 25,000 for follow-up, from patients across India.

This highlights the need for continued efforts to improve dyslipidemia management, particularly in those with CV risk factors. As the prevalence of dyslipidemia is high in India, creating awareness is essential. Overall, the study demonstrates that appropriate pharmacotherapy can effectively lower lipid levels, but further interventions may be required for patients with more complex conditions.

Supplementary Material

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

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ORIGINAL ARTICLE

Effect of Sleep Quality on Heart Rate Variability in Medical Students: A Cross-sectional Study

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Abstract

Background: Globally, medical students had demonstrated poor sleep quality. Poor sleep can negatively affect cardiovascular functions. The autonomic nervous system (ANS) regulates cardiovascular function during the sleep-wake cycle and can be monitored by heart rate variability (HRV). The primary objective was to determine any association between sleep quality and HRV parameters in medical students.

Materials and methods: A cross-sectional study was conducted at a single institution in North India. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality. HRV was recorded using Power Lab AD Instrument (Australia). The correlation between HRV variables and sleep parameters was estimated using Pearson's correlation coefficient and Spearman correlation based on the normality test.

Results: A total of 84 medical students (54 males and 30 females) participated in the study. The mean total PSQI score was 6.44 (SD = 2.62). There was a statistically significant negative correlation between PSQI global score and HRV indices high frequency (HF), root mean square successive difference (RMSSD), and the proportion of differences in consecutive RR intervals that are longer than 50 ms in % (pRR50). A statistically significant positive correlation between PSQI global score and low frequency (LF), and LF/HF ratio was found.

Conclusion: The present study found that parasympathetic-related indices (RMSSD, pRR50, and HF) were inversely correlated to poor sleep quality and directly related to sympathetic indices (LF and LF/HF). This suggests that the poorer the sleep quality, the less is the parasympathetic activity and the more is the sympathetic activity.

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Introduction

Sleep is a biological circadian phenomenon that is related to physical and mental functions.[1] The medical curriculum is one of the stressful courses worldwide and presents increased academic demands and stress levels. Various studies worldwide have found that medical students have poor sleep quality.[2]

Various evidence shows that poor sleep negatively affects not only cognitive functions but also cardiovascular functions.[3] The effect of alteration in sleep on the cardiovascular system may be partially mediated through the autonomic nervous system (ANS).[4] ANS plays a vital role in sleep and can be monitored by heart rate variability (HRV).[5] HRV refers to the variation in time intervals between consecutive heartbeats, which is determined by the duration of interbeat periods.[6] The Pittsburgh Sleep Quality Index (PSQI) is a gold standard questionnaire for evaluating sleep quality and is validated across various populations.[2]

In the literature search, we found studies on sleep quality and HRV conducted in other countries, but not much has been done in India, especially focusing on medical students.[7,8] Therefore, we aimed to study the effect of sleep quality on various parameters of HRV in medical students. The hypothesis in this study was that medical students would indicate low sleep quality and that it would correlate with HRV parameters. The primary objective was to determine any association between sleep quality and HRV parameters in medical students.

Materials and Methods

This descriptive cross-sectional study was conducted in the Autonomic Function Lab of the Department of Physiology, University College of Medical Sciences, Delhi, India, from September 2023 to November 2023. Approval from the Institutional Ethics Committee (IECHR-2023-60-7-R1) was obtained before the initiation of the study.

Study Population

First- and second-year students pursuing the undergraduate medical course were considered because final-year students may possess improved coping mechanisms for their studies.[2]

Inclusion Criteria

- Age between 18 and 25 years.
- Normal body mass index (BMI) (18.5–24.9 kg/m^2).

Exclusion Criteria

- On medication known to affect ANS (antihypertensive, antiepileptic, anxiolytics, and beta-blockers).
- History of diabetes mellitus, hypertension, mental illness, hormonal disorders, and other disorders known to affect ANS.
- Students who are currently smoking, consuming alcohol, or on regular physical activity.

Sample Size

Based on the primary objective, a sample of 84 subjects was required. The sample size was estimated using G*Power 3.1 software, assuming a low correlation of 0.3, a level of significance of 5%, a two-tailed alternative hypothesis, and a power of 0.8.[9] The sampling method used was nonrandom convenience sampling.

Study Tools

The questionnaire consists of two sections: the first section contains demographics such as age, gender, academic year, and residence, and the second section contains the Pittsburgh Sleep Quality Index (PSQI).

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index questionnaire assesses sleep quality over a 1-month time interval. It consists of 19 items and evaluates seven key areas: sleep latency, subjective sleep quality, habitual sleep efficiency, sleep duration, sleep disturbances, use of sleeping medication, and daytime dysfunction experienced in the past month. Each item is scored on a scale of 1–3, with

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3 indicating the most severe sleep issues. The total score on the PSQI can range from 0 to 21. A combined score of all seven components is known as the "global score of PSQI." A global PSQI score of 5 or higher suggests poor sleep quality, while a lower score indicates better sleep quality. The PSQI has demonstrated internal consistency and reliability, with a Cronbach's alpha coefficient of 0.83 for its seven components.[10] In the current study, the Cronbach's alpha was found to be 0.64. This indicates that the questionnaire is a reliable tool for assessing sleep quality.

Recording of Heart Rate Variability

Heart rate variability was recorded in the Autonomic Function Lab of the department using Power Lab AD Instrument (Australia) equipment. Participants were advised to refrain from caffeine for 24 hours before the recording. Recordings were done with subjects in loose clothing and after voiding urine.[11]

For recording HRV, the standard limb lead II position was obtained by firmly placing disposable electrodes over the nonhairy, cleaned skin at three sites: right wrist (–ve lead), left foot (+ve lead), and right foot (ground lead). HRV recording was done for 10 minutes. From the recording, 5-minute ECG segments were selected for analysis of HRV in all subjects after ruling out gross ECG abnormalities, if any, and the auto-computed results were analyzed for the time- and frequency-domain parameters of HRV.[11,12] Time-domain measures and frequency-domain measures of HRV are summarized in Tables 1 and 2.

Time Domain Measures

Frequency Domain Methods

Statistical Analysis

The data were analyzed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 26.0. Descriptive analysis was performed. After testing assumptions for correlational analysis between HRV variables and sleep parameters, Pearson's correlation coefficient test was used; otherwise, the Spearman correlation test was used.

Results

Demographic Characteristics

Out of 84 participants, the proportion of male and female students was 54 (64.28%) and 30 (35.71%), respectively. The average age of participants was 20.19 ± 1.36 [mean ± standard deviation (SD)], with an average BMI of 21.76 ± 1.86 kg/m^2. Table 3 shows the demographic characteristics of participants. The proportion of good sleepers (PSQI global scores <5) was 20 (23.81%), and poor sleepers (PSQI global scores ≥5) were 64 (76.19%).

Descriptive Statistics

Table 4 shows the mean values of PSQI global scores and its seven components, and HRV variables. The mean PSQI global score was 6.44 (SD = 2.62). Sleep duration, sleep latency, daytime dysfunction, and subjective sleep quality had means above 1, contributing most to the overall PSQI score. Sleep disturbance, sleep efficiency, and the use of sleep medication had means below 1.

The majority of participants (n = 63, 75.00%) had >85% sleep efficiency. The results of sleep latency showed that one-third of the participants (n = 29, 34.52%) took 16–30 minutes to fall asleep. Among the 84 participants, more than half (n = 51, 60.71%) rated their sleep quality as fairly good. The majority of participants (n = 76, 90.47%) complained of daytime dysfunction.

Assumption Testing

HRV variables and PSQI scores were assessed for normality. Data followed a normal distribution as determined from skewness, kurtosis, and the Z test (skewness and kurtosis), except for sleep disturbance, sleep efficiency, sleep medication, and LF/HF.[13] LF/HF was log-transformed. A few outliers were present in the data, which were replaced with the 5th or 95th percentile values.

Correlation between Heart Rate Variability and Sleep Parameters

Table 5 shows the correlation between sleep and HRV parameters. There was a statistically significant negative correlation between PSQI global score and HF ($r = -0.358$, $p < 0.01$), RMSSD ($r = -0.227$, $p < 0.05$), and pRR50 ($r = -0.288$, $p < 0.01$). A statistically significant positive correlation between PSQI global score and LF/HF ($r = 0.390$, $p < 0.01$) and LF ($r = 0.375$, $p < 0.01$) was found. SDRR ($r = -0.223$, $p < 0.05$), RMSSD ($r = -0.258$, $p < 0.05$), and pRR50 ($r = -0.242$, $p < 0.05$) correlated significantly and negatively with subjective sleep quality.

Discussion

The present study examined the association between sleep quality indices and HRV parameters. Global PSQI scores were found to be negatively correlated with RMSSD, pRR50, and HF. LF and LF/HF ratio were found to be positively correlated with global PSQI scores.[11]

The above findings indicate that the poorer the sleep quality, the less is the parasympathetic activity and the more is the sympathetic activity. This is consistent with the study by Cvejic et al. (2018), which found poor sleep was associated with reduced nocturnal parasympathetic activity in medical students.[14] Studies in other population groups also found that parasympathetic-related HRV indices were reduced with sleep problems.[12,15,16] In contrast, Guo et al. (2022), utilizing 24-hour

Table 1: Time domain parameters

SDRR (ms)	Standard deviation of the R-R intervals	Reflects total HRV
RMSSD (ms)	Root square of the mean of the sum of the squares of differences between adjacent RR intervals	With normal sinus rhythm reflects vagal activity
pRR50 (%)	Percentage of RR intervals >50 ms different from previous (RR)	With normal sinus rhythm reflects vagal activity

ms, milliseconds

Table 2: Frequency domain parameters

Frequency bands	*Frequency*		*Mediated by*
Low frequency (LF) n.u.	0.04–0.15 Hz	[LF/(TP-VLF), some calculate LF/(LF + HF)]	Reflect sympathetic activity
High frequency (HF) n.u.	0.15–0.4 Hz	[HF/(TP-VLF), some calculate HF/(LF + HF)]	Reflect parasympathetic activity
LF/HF ratio			Sympatho-vagal balance

n.u., normalized unit; TP, total power; VLF, very low frequency;

Table 3: Demographic characteristics of participants

Variables	
Gender (%)	Male 54 (64.28%), female 30 (35.71%)
Age (mean ± SD) in years	20.19 ± 1.36
BMI (mean ± SD) in kg/m^2	21.76 ± 1.86
Participants with good sleep (global score <5)	20 (23.81%)
Participants with poor sleep (global score >5)	64 (76.19%)

SD, standard deviation

Table 4: HRV parameters, mean global, and component PSQI scores

Variable		*Numbers (percentage, %)*	*Mean (SD)*
Sleep duration (hours)			1.39 (0.95)
	>7	16 (19.04)	
	6–7	31 (36.90)	
	5–6	25 (29.76)	
	<5	12 (14.28)	
Sleep disturbance			0.87 (0.33)
	Never	11 (13.09)	
	Once or twice	73 (86.90)	
Sleep latency (minutes)			1.32 (0.95)
	<15	19 (22.62)	
	16–30	29 (34.52)	
	31–60	26 (30.95)	
	>60	10 (11.90)	
Daytime dysfunction			1.46 (0.79)
	0	8 (9.52)	
	1–2	37 (44.04)	
	3–4	31 (36.90)	
	5–6	8 (9.52)	
Sleep efficiency (%)			0.36 (0.72)
	>85	63 (75.00)	
	75–84	15 (17.86)	
	65–74	3 (3.57)	
	<65	3 (3.57)	
Sleep quality			1.12 (0.70)
	Very good	13 (15.48)	
	Fairly good	51 (60.71)	
	Fairly bad	17 (20.23)	
	Very bad	3 (3.57)	
Use of sleep medication			0.02 (0.21)
	Not during the past	83 (98.80)	
	Once or twice a week	1 (1.19)	
PSQI global score			6.44 (2.62)
Time domain parameters			
SDRR (ms)			148.05 (18.46)
RMSSD (ms)			48.69 (18.43)
pRR50 (%)			26.72 (16.82)
Frequency domain parameters			
LF (n.u.)			44.44 (15.99)
HF (n.u.)			53.37 (14.87)
LF/HF			1.00 (0.72)

SD, standard deviation

HRV indicators in medical students, did not find a difference between groups of sleep quality.[8]

SDRR, RMSSD, and pRR50 were also found to be inversely correlated with subjective sleep quality. In addition, SDRR was inversely correlated with sleep efficiency and was significantly and positively correlated with daytime dysfunction. These findings suggest that higher values in parasympathetic indices (RMSSD and pRR50) are associated with very/fairly good sleep quality and higher sleep efficiency (% sleep, hours slept, and hours spent in bed after sleep onset). These findings are consistent with Sajjadieh et al. (2020), who found lower SDRR correlated with sleep quality indices (bad subjective sleep quality, poor sleep efficiency, very high daytime dysfunction).[17] A study by Cosgrave et al. (2020) found that poor sleepers with short sleep duration had significantly lower SDRR compared to good sleepers.[18]

Various studies have demonstrated that poor sleep can produce reduced parasympathetic activity and may affect the ability of ANS to inhibit sympathetic activity.[3,19,20] Dettoni et al. (2012) showed that mild sleep restriction for a few nights resulted in increased sympathetic activity.[3] A study by Bourdillon et al. (2021) found decreased parasympathetic and increased sympathetic activity in healthy adults with partial sleep deprivation.[21]

Although we did not measure stress levels in the participants, one major cause of poor sleep quality is the perception of stress. Cvejic et al. (2018) found that poor sleep was associated with psychological distress and reduced nocturnal HRV.[14] Hall et al. (2004) utilized a standard speech task paradigm to elicit stress before sleep and found decreased parasympathetic activity. These studies suggest that changes in HRV due to stress may be associated with poor sleep.[22]

In this study, the mean total PSQI score was 6.44 (SD = 2.62). This finding is consistent with the pooled mean total PSQI score of 6.1 (95% CI: 5.6–6.5) across 41 studies.[23] The PSQI subscale means suggest that sleep duration, sleep latency, daytime dysfunction, and subjective sleep quality contributed most to the PSQI global scores. These findings align with other studies (Brick et al. 2010, Ahrberg et al. 2012, Rao et al. 2020), which also highlighted that subjective sleep quality, sleep duration, sleep latency, sleep disturbance, and daytime dysfunction play a significant role in elevating the PSQI global scores in medical students.[2,23,24]

The present study found that 71% of participants were sleeping <7 hours per night on average, which is below the recommendation of at least 7 hours per night (National Sleep Foundation recommendation for young adults).[25] Academic pressure, poor sleep hygiene, staying away from home, academic year, low physical activity, and taking naps during the daytime were found to be associated with poor sleep in medical students.[2,20,26]

In order to keep up with their academic workloads, many students sacrifice sleep or delay sleep for immediately rewarding activities.[14,27] However, abstaining from sleep could potentially hinder their learning outcomes in the immediate future while also affecting their overall health and effectiveness as medical practitioners in the long run.[14,19,22]

Limitations

The current study had a few limitations. First, sleep was assessed through a self-reported questionnaire. Although the PSQI is a well-validated tool, it is still subjective

Table 5: Correlation among sleep parameters and HRV (n = 84)

	Sleep duration	*#Sleep disturbance*	*Sleep latency*	*Sleep daytime dysfunction*	*#Sleep efficiency*	*Sleep quality*	*#Sleep medication*	*Total PSQI*
SDRR	0.122	–0.020	–0.040	0.223*	–0.219*	–0.223*	–0.043	–0.087
RMSSD	0.079	0.055	–0.010	0.147	–0.165	–0.258*	–0.123	–0.227*
pRR50	0.045	0.033	–0.003	0.114	–0.161	–0.242*	–0.130	–0.288**
LF	–0.075	0.092	0.011	0.016	0.082	0.021	0.054	0.375**
HF	0.133	–0.124	–0.023	–0.038	–0.095	–0.031	–0.049	–0.358**
LF/HF (log)	–0.090	0.108	0.016	0.002	0.076	0.042	0.056	0.390**

**p-value < 0.01 (2-tailed); *p-value < 0.05 (2-tailed); #Spearman's rank-order correlation

in nature. This study was correlational in nature; hence, causal inferences cannot be determined. The cross-sectional design hinders tracking changes in sleep quality in medical students over time. Further studies with more thorough screening of individuals, including assessments of psychological health and sleep attitudes with objective sleep outcomes, are warranted.

Conclusion

This study found a significant correlation between poor sleep in medical students and altered HRV, indicating a potential imbalance in ANS activity. The prevalence of inadequate sleep and higher PSQI scores emphasizes the need for interventions to address sleep patterns among medical students, which is crucial for both academic performance and long-term well-being.

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ORIGINAL ARTICLE

Optimizing Management Beyond Triple Therapy in Stable Severe Chronic Obstructive Pulmonary Disease: Efficacy of Adjunctive Oral Doxophylline in a Randomized Controlled Trial

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition commonly managed with triple inhaler therapy comprising long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS). Despite optimal inhalation therapy, many patients continue to experience persistent symptoms. Doxophylline, a novel xanthine derivative, offers bronchodilator and anti-inflammatory benefits with a more favorable safety profile than traditional methylxanthines.

Objective: To assess the efficacy, safety, and tolerability of oral doxophylline in addition to triple inhaler therapy in patients with stable severe COPD.

Materials and methods: In this randomized controlled trial, 78 patients were allocated to group A (triple therapy + doxophylline 650 mg once daily) and group B (triple therapy alone). Assessment included the COPD assessment test (CAT score), C-reactive protein (CRP), spirometry parameters (FEV_1, FEV_1%, FEV_1/FVC), adverse events, and evaluations were performed on days 0 and 90.

Results: By day 90, group A showed greater improvement in CAT score (7.94 ± 4.17 vs 10.06 ± 3.99; $p = 0.033$) and CRP (12.2 ± 4.47 vs 15.33 ± 5.37 mg/L; $p = 0.01$). Spirometry gains were comparable: FEV_1 (0.97 ± 0.23 vs 0.96 ± 0.26 L/minute; $p = 0.872$), FEV_1% predicted (49.10 ± 8.73 vs 48.69 ± 9.72%; $p = 0.482$), and FEV_1/FVC% (54.09 ± 6.57 vs 52.89 ± 6.95%; $p = 0.397$). Mild adverse events including palpitations (14.29%), tremors (8.57%), and nausea (2.86%) were more frequent in group A but were generally tolerated.

Conclusion: Adjunctive oral doxophylline significantly improved symptom burden and systemic inflammation in patients with stable severe COPD without conferring additional spirometric benefits. Although mild adverse effects were observed, doxophylline was overall well tolerated and may represent a viable adjunctive option in selected COPD patients with persistent symptoms despite optimized inhaler therapy.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a lung condition characterized by persistent inflammation and irreversible airflow limitation, leading to breathing difficulties.[1] It affects 11.7% of the global population and is responsible for approximately 3 million deaths annually, particularly in individuals aged ≥40 years.[2] The pathogenesis of COPD involves both innate and adaptive immune responses, primarily TH1-mediated along with chronic inflammation, protease-antiprotease imbalance, and oxidative stress. These mechanisms contribute to structural damage in the airways and alveoli, influencing symptom severity, disease progression, and treatment responses.[3]

Chronic obstructive pulmonary disease symptoms such as dyspnea, cough, and fatigue are frequently underreported, making tools like COPD assessment test (CAT) and modified Medical Research Council (mMRC) essential for grading severity.[1,4] Diagnosis is confirmed by a postbronchodilator FEV_1/FVC ratio <0.7, although clinical signs may aid in settings without spirometry.[1,5] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 update introduced the ABCD classification to guide therapy based on symptoms and exacerbation risk,[6] while the 2023 revision redefined COPD as a progressive, heterogeneous condition and combined groups C and D into "group E" for frequent exacerbators.[7]

Triple inhaled therapy, including a long-acting β_2 agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS), is recommended for severe COPD, especially in patients with high eosinophil counts or frequent exacerbations. However, some patients remain symptomatic despite this regimen, necessitating additional therapeutic options.[7]

Doxophylline, a xanthine derivative with reduced A1 and A2 receptor affinity, offers bronchodilation with fewer cardiac and neurological adverse effects. Although beneficial in patients with COPD, its role in triple therapy remains underexplored. This study assessed the effectiveness, safety, and tolerability of adding oral doxophylline to triple inhaler therapy in stable severe COPD, per GOLD 2023 guidelines.[8]

Aim

To evaluate the effectiveness, safety, and tolerability of oral doxophylline added to triple drug therapy in patients with stable severe COPD.

Materials and Methods

Trial registration: CTRI/2024/08/071763 (registered on 1st August 2024).

Study Design and Setting

A prospective randomized controlled trial was conducted over 18 months in the Department of Respiratory Medicine, SRM Medical College, with ethics approval and informed consent. Adults aged 40–65 years with COPD (≥6 months) and postbronchodilator FEV_1 <50% were included. Patients with comorbid respiratory or major systemic illnesses, recent MI, or poor inhaler technique were excluded. Patients were followed up for 90 days.

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Sampling and Randomization

Consecutive sampling was performed during outpatient visits. Eligible patients were randomized into two groups using a computer-generated sequence to ensure allocation concealment.

Sample Size Justification

This study was designed as a pilot randomized controlled trial due to limited prior evidence on adjunctive doxophylline in stable severe COPD. A regular sample size calculation was not feasible because of the absence of robust prior effect size data for the primary outcomes (COPD assessment score and C-reactive protein). We aimed for 40 participants per group based on feasibility, recruitment pool over 18 months, and minimum sample size recommendations for pilot RCTs.

Intervention and Methods

Group A received oral doxophylline sustained release 650 mg once daily plus fixed triple inhaler therapy (formoterol 4.8 µg, glycopyrrolate 9 µg, budesonide 160 µg). Group B received triple therapy. Inhalers were administered *via* metered-dose or dry powder devices.

Outcome Measures

Assessments were conducted at baseline, 30, 60, and 90 days. The primary outcomes included changes in the CAT score, serum CRP levels, and spirometric indices (FEV_1 and FEV_1/FVC). Adverse drug reactions and tolerability were also monitored.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) v25.0. Statistical significance was set at $p < 0.05$.

Results

The baseline characteristics were comparable between the groups, with similar mean ages (56.41 ± 4.91 vs 55.28 ± 5.49 years) and male predominance (76.92 vs 79.49%). Cough with expectoration and shortness of breath were reported by 94.87 and 97.44% of the patients, respectively. Smoking history was noted in 74.36% of group A vs 76.92% of group B, with mean pack-years of 29.72 ± 7.86 and 25.73 ± 6.52. Most patients had a normal BMI (64.10 vs 69.23%), while 30.77 vs 28.21% were underweight, and 5.13 vs 2.56% were overweight. Mean hemoglobin was 12.18 ± 1.32 gm/dL (group A) vs 12.34 ± 1.20 gm/dL (group B), with WBC counts of 6717.41 ± 1492.85/mm^3 vs 6344.26 ± 1738.84/mm^3. Chest X-ray findings showed low flat diaphragm (79.49 vs 58.97%), tubular heart (38.46 vs 30.77%), prominent bronchovascular markings (33.33 vs 35.90%), and hyperinflation (46.15 vs 56.41%) (Table 1).

At baseline, GOLD stage distribution was similar between groups, with the severe stage in 31 (79.49%) patients in group A and 32 (82.05%) in group B, and very severe stage in 8 (20.51%) and 7 (17.95%) patients, respectively ($p = 0.774$). The mean CAT score on day 0 was comparable (20.74 ± 3.91 vs 22.23 ± 3.47; $p = 0.08$), but group A showed significantly lower CAT scores at follow-up: day 30 (14.49 ± 3.53 vs 16.49 ± 3.10; $p = 0.013$), day 60 (10.51 ± 4.71

Table 1: Baseline demographic and clinical characteristics

Parameter		*Group A (n = 39)*	*Group B (n = 39)*
Mean age (years) (mean ± SD)		56.41 ± 4.91	55.28 ± 5.49
Gender (male)		30 (76.92%)	31 (79.49%)
Cough with expectoration		37 (94.87%)	37 (94.87%)
Shortness of breath		38 (97.44%)	38 (97.44%)
Smoking history		29 (74.36%)	30 (76.92%)
Mean pack-years		29.72 ± 7.86	25.73 ± 6.52
BMI	Normal	25 (64.10%)	27 (69.23%)
	Underweight	12 (30.77%)	11 (28.21%)
	Overweight	2 (5.13%)	1 (2.56%)
Hematological parameters (mean ± SD)	Hemoglobin (gm/dL)	12.18 ± 1.32	12.34 ± 1.20
	WBC count (/mm^3)	6717.41 ± 1492.85	6344.26 ± 1738.84
Chest X-ray findings, *N* (%)	Low flat diaphragm	31 (79.49%)	23 (58.97%)
	Tubular heart	15 (38.46%)	12 (30.77%)
	Bronchovascular markings	13 (33.33%)	14 (35.90%)
	Hyperinflation	18 (46.15%)	22 (56.41%)

BMI, body mass index; WBC, white blood cell

Table 2: Comparison of GOLD staging: *n* (%), CAT scores, and CRP levels (mean ± SD)

Parameter		*Group A (n = 39)*	*Group B (n = 39)*	*p-value*
GOLD stage	Severe, *n* (%)	31 (79.49%)	32 (82.05%)	0.774
	Very severe, *n* (%)	8 (20.51%)	7 (17.95%)	
CAT score (mean ± SD)	Day 0	20.74 ± 3.91	22.23 ± 3.47	0.08
	Day 30	14.49 ± 3.53	16.49 ± 3.10	0.013
	Day 60	10.51 ± 4.71	12.69 ± 3.97	0.038
	Day 90	7.94 ± 4.17	10.06 ± 3.99	0.033
CRP level (mg/L) (mean ± SD)	Day 0	19.5 ± 6.43	17.11 ± 5.54	0.083
	Day 90	12.2 ± 4.47	15.33 ± 5.37	0.01

$p < 0.05$ significant; CAT, COPD assessment score; CRP-C, reactive protein

Table 3: Comparison of pulmonary function parameters up to 90 days: (mean ± SD)

Parameter	*Time point (days)*	*Group A (mean ± SD)*	*Group B (mean ± SD)*	*p-value*
FEV1 (L/minute)	0	0.77 ± 0.21	0.81 ± 0.23	0.382
	30	0.85 ± 0.20	0.87 ± 0.24	0.732
	60	0.92 ± 0.22	0.93 ± 0.25	0.912
	90	0.97 ± 0.23	0.96 ± 0.26	0.872
FEV1 (% predicted)	0	38.85 ± 8.57	40.74 ± 9.58	0.319
	30	43.64 ± 9.15	44.18 ± 10.01	0.783
	60	46.90 ± 8.67	47.79 ± 9.43	0.673
	90	49.10 ± 8.73	48.69 ± 9.72	0.482
FEV1/FVC (%)	0	46.51 ± 6.68	45.64 ± 7.13	0.544
	30	49.36 ± 6.45	48.38 ± 6.92	0.519
	60	52.36 ± 6.41	51.00 ± 6.79	0.348
	90	54.09 ± 6.57	52.89 ± 6.95	0.397

$p < 0.05$ significant; FEV1, forced expiratory volume in 1st second; FVC, forced vital capacity

Table 4: Comparison of hemodynamic parameters at baseline and day 90: (mean ± SD)

Parameter	*Time point (days)*	*Group A (mean ± SD)*	*Group B (mean ± SD)*	*p-value*
Pulse rate (beats/minute)	0	86.77 ± 5.88	87.51 ± 3.37	0.496
	90	85.23 ± 6.31	86.53 ± 3.25	0.283
Respiratory rate (/minute)	0	18.41 ± 1.57	18.62 ± 1.02	0.495
	90	18.34 ± 1.24	17.89 ± 0.75	0.067
Systolic BP (mm Hg)	0	120.26 ± 7.07	120.77 ± 7.03	0.749
	90	121.43 ± 6.92	118.33 ± 5.61	0.042
Diastolic BP (mm Hg)	0	78.97 ± 7.18	79.49 ± 7.24	0.754
	90	80.00 ± 7.28	75.28 ± 7.74	0.01

BP, blood pressure

vs 12.69 ± 3.97; $p = 0.038$), and day 90 (7.94 ± 4.17 vs 10.06 ± 3.99; $p = 0.033$), indicating better symptom control. Mean CRP levels were similar on day 0 (19.5 ± 6.43 vs 17.11 ± 5.54 mg/L; $p = 0.083$), but significantly lower in group A by day 90 (12.2 ± 4.47 vs 15.33 ± 5.37 mg/L; $p = 0.010$) (Table 2).

The mean FEV_1 (L/minute) was similar between groups A and B throughout the study: day 0 (0.77 ± 0.21 vs 0.81 ± 0.23; $p = 0.382$), day 30 (0.85 ± 0.20 vs 0.87 ± 0.24; $p = 0.732$), day 60 (0.92 ± 0.22 vs 0.93 ± 0.25; $p = 0.912$), and day 90 (0.97 ± 0.23 vs 0.96 ± 0.26; $p = 0.872$). FEV_1 (% predicted) was also comparable on day 0 (38.85 ± 8.57 vs 40.74 ± 9.58; $p = 0.319$), day 30 (43.64 ± 9.15 vs 44.18 ± 10.01; $p = 0.783$), day 60 (46.90 ± 8.67 vs 47.79 ± 9.43; $p = 0.673$), and day 90 (49.10 ± 8.73 vs 48.69 ± 9.72; $p = 0.482$). Similarly, FEV_1/FVC (%) showed no significant difference at baseline (46.51 ± 6.68 vs 45.64 ± 7.13; $p = 0.544$), day 30 (49.36 ± 6.45 vs 48.38 ± 6.92; $p = 0.519$), day 60 (52.36 ± 6.41 vs 51.00 ± 6.79; $p = 0.348$), and day 90 (54.09 ± 6.57 vs 52.89 ± 6.95; $p = 0.397$) (Table 3).

The mean pulse rate was comparable between groups A and B at baseline (86.77 ± 5.88 vs 87.51 ± 3.37; $p = 0.496$) and day 90 (85.23 ± 6.31 vs 86.53 ± 3.25; $p = 0.283$). Respiratory rate also showed no significant difference on day 0 (18.41 ± 1.57 vs 18.62 ± 1.02; $p = 0.495$) or day 90 (18.34 ± 1.24 vs 17.89 ± 0.75; $p = 0.067$). Systolic blood pressure was similar at baseline (120.26 ± 7.07 vs 120.77 ± 7.03; $p = 0.749$), but significantly lower in group B at day 90 (121.43 ± 6.92 vs 118.33 ± 5.61; $p = 0.042$). Diastolic pressure showed no difference at baseline (78.97 ± 7.18 vs 79.49 ± 7.24; $p = 0.754$), yet group B had a significantly lower value at day 90 (80.00 ± 7.28 vs 75.28 ± 7.74; $p = 0.010$) (Table 4).

No adverse effects were reported at the baseline in either group. By day 30, 94.29% of group A and 100% of group B remained free of side effects ($p = 0.233$), with palpitations and tremors observed in 1 patient (2.86%) in group A. At day 60, adverse effects were absent in 85.71% of group A and all of group B ($p = 0.025$); group A reported palpitations (5.71%), tremors (2.86%), and nausea/vomiting (5.71%). By day 90, only 74.29% in group A remained symptom-free compared to 100% in group B ($p = 0.0009$), with 14.29% reporting palpitations, 8.57% tremors, and 2.86% nausea/vomiting (Table 5).

Discussion

This randomized controlled trial evaluated the safety and efficacy of adding oral doxophylline to standard triple therapy in severe COPD, with both groups well matched at baseline to minimize confounding, consistent with findings from a previous study.[9]

Triple therapy combining corticosteroids, LABA, and muscarinic antagonists is standard in COPD management. Formoterol was selected for its potent bronchodilator and anti-inflammatory effects.[10] While major trials (IMPACT, TRIBUTE, ETHOS) confirm the efficacy of triple therapy,[11–13] evidence on the addition of doxophylline, a safer xanthine derivative than theophylline, remains limited.[10]

The doxophylline group experienced earlier and more sustained symptom relief, with significant reductions in CAT scores, indicating better control than triple therapy alone. This aligns with earlier studies showing improved symptom burden and quality of life with doxophylline, supporting its role as a valuable adjunct in COPD treatment.[10,14,15]

Spirometry showed significant improvements in FEV_1, FEV_1%, and FEV_1/FVC in both groups, with no notable intergroup differences, suggesting that lung function improved irrespective of doxophylline. These results are consistent with those of previous studies and major trials such as IMPACT, TRIBUTE, and ETHOS, which reported similar spirometric outcomes.[10–18]

Table 5: Adverse effects over time in both groups: *n* (%)

Time point (days)	*Adverse effect*	*Group A (n = 39)*	*Group B (n = 39)*	*p-value*
0	No adverse effects	39 (100%)	39 (100%)	NA
30	No adverse effects	33 (94.29%)	37 (100%)	0.233
	Palpitations	1 (2.86%)	0 (0%)	
	Tremors	1 (2.86%)	0 (0%)	
60	No adverse effects	30 (85.71%)	36 (100%)	0.025
	Palpitations	2 (5.71%)	0 (0%)	
	Tremors	1 (2.86%)	0 (0%)	
	Nausea and vomiting	2 (5.71%)	0 (0%)	
90	No adverse effects	26 (74.29%)	36 (100%)	0.0009
	Palpitations	5 (14.29%)	0 (0%)	
	Tremors	3 (8.57%)	0 (0%)	
	Nausea and vomiting	1 (2.86%)	0 (0%)	

A previous study in mild-to-moderate COPD (FEV_1 ≥50%) found doxophylline as effective as theophylline-etofylline, with fewer side effects. In contrast, our study in severe COPD (FEV_1 <50%) showed comparable spirometric improvements but greater symptom relief and better CAT scores with doxophylline, suggesting its added benefit in advanced disease.[16]

The FEV_1/FVC ratio improved in both groups during follow-up without significant intergroup differences, consistent with previous studies showing improvements in this parameter with doxophylline therapy.[10,14,15,17,18]

By day 90, the doxophylline group showed a significant reduction in CRP, indicating its anti-inflammatory effect and clinical benefit in COPD. In contrast, the control group showed no significant decrease in CRP levels. These findings align with prior evidence showing greater reduction in inflammatory markers with adjunctive therapies.[15,19]

A previous study also reported a significant CRP reduction with adjunctive therapy, supporting our finding of a greater CRP decline in the doxophylline group. This consistency highlights the potential of doxophylline to reduce systemic inflammation and improve COPD outcomes.[15]

Adverse effects such as palpitations, tremors, and gastrointestinal symptoms were more common in the doxophylline group but were mild and did not require discontinuation, likely due to its partial adenosine receptor activity.[10,14,16,18] Triple therapy alone was well tolerated in this study, although major trials such as IMPACT, TRIBUTE, and ETHOS have reported systemic and respiratory-related side effects even with triple therapy.[11–13]

Clinical Implications

In clinical practice, adjunctive doxophylline may be considered for patients with stable severe COPD who remain symptomatic despite optimal triple inhaler therapy, and in those with systemic inflammation (e.g., raised CRP) and no contraindications to xanthine derivatives. Its favorable safety profile compared to theophylline, along with once-daily dosing in its sustained release preparation, may aid adherence in selected patients. However, mild cardiovascular or gastrointestinal side effects should be monitored. Additionally, doxophylline may have a steroid-sparing role in individuals who are unable to tolerate high-dose inhaled corticosteroids, enabling maintenance of symptom control without escalation beyond medium ICS doses.

Conclusion

Adding doxophylline to triple therapy in stable severe COPD improved symptom control and reduced CRP levels, with similar spirometric gains to triple therapy alone. Although mild adverse effects such as palpitations and tremors were more frequent, doxophylline was well tolerated and did not affect exacerbation rates. It shows promise as an adjunct in severe COPD; however, long-term studies are needed to confirm its safety and efficacy.

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ORIGINAL ARTICLE

Community-based Estimates of the Prevalence of Hepatitis B and C Infections and their Correlates in Two Districts of West Bengal, India

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Abstract

Objectives: This study was conceptualized to estimate the prevalence and correlates of hepatitis B and C infections among the adult population of West Bengal and review the progress made so far toward the stated goal of controlling these infections in the state.

Materials and methods: A population-based cross-sectional study was conducted during February 2023 to April 2024 in two districts of the state in adults. Participants were recruited from subdistrict clusters using the population-proportion-to-size sampling method. Sociodemographic information, along with laboratory parameters of hepatitis B and C infections, was collected from individuals.

Results: Information from 22,320 individuals revealed that the prevalence of hepatitis B and C infections was 0.47 and 0.02%, respectively. Hepatitis B infection was higher in males (0.5%) and daily laborers (0.8%). In the population, 80.2% was considered susceptible to hepatitis B infection. A significant association of hepatitis B infection was found with a history of dialysis (AOR 21.1), multiple sex partners (AOR 7.3), and a family history of jaundice (AOR 3.4).

Conclusion: Prevalences of hepatitis B and C were lower than earlier estimates done in 2015–2016. A higher proportion of susceptible individuals among young adults remains a point of concern. As the prevalence is low among adults, West Bengal should focus on the triple elimination of mother-to-child transmission (EMTCT) of human immunodeficiency virus (HIV), syphilis, and hepatitis B virus (HBV) to progress further toward the elimination of hepatitis B.

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Background

Inflammation of liver tissue from diverse viral infections leads to viral hepatitis. The clinical spectrum varies from asymptomatic, apparently healthy individuals to patients with fulminant hepatitis, eventually leading to death.[1] The five common hepatitis viruses have dissimilarities in terms of structural and functional properties; however, affinity for liver cells is the common feature, which led to classifying them as hepatitis viruses, with alphabetic nomenclature as hepatitis A, B, C, D, and E viruses. Viral hepatitis is also the leading preventable cause of two debilitating conditions, liver cirrhosis and hepatic malignancy, across the globe. A considerable proportion of individuals infected with hepatitis B and C can eventually succumb to either condition. Early detection and prompt treatment of the estimated 354 million people living with hepatitis B or C still remain a major public health challenge.[2] The burden of viral hepatitis infections is higher than that of human immunodeficiency virus (HIV) infection, with 1.34 million deaths from the disease, comparable with that of tuberculosis. The number of people with chronic hepatitis B and C infections is estimated to be 254 and 50 million, respectively, in 2022. About 1.2 million new hepatitis B and 1 million hepatitis C infections occur every year. Approximately 1.34 million people die every year from these infections, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).[3,4]

Community-based estimates indicate prevalence of chronic hepatitis B virus (HBV) in India varies between 1.2 and 2.4%.[5] It differs over geographical distribution, with the highest prevalence in Arunachal Pradesh and Andaman and Nicobar Islands. Seroprevalence study embedded in National Family Health Survey (NFHS)-4, conducted in 2015–2016, revealed 0.95% prevalence of hepatitis B and 0.32% prevalence of hepatitis C infection in the country. Prevalence of hepatitis C is higher in six states compared to others.[6] To estimate the prevalence, the leftover dried blood spots (DBS) collected under the NFHS-4 during 2015–2016 were tested for serological biomarkers of hepatitis B and C.[7,8]

There is a paucity of studies that provide prevalence among the general population of the state in the recent past. Estimates for hepatitis B (2.97%) and C (0.87%) prevalences date back to 2003–2005[9,10] and later to 2015–2016, when estimates were found to be 1.26 and 0.16%, respectively.[11]

Besides, data for infected, immune, and susceptible individuals with hepatitis B are needed for better insight in planning strategies for National Viral Hepatitis Control Program (NVHCP). To understand the current disease burden in the community and validate the progress toward elimination targets in the state of West Bengal, a study was conceptualized. Under the aegis of the State Viral Hepatitis Management Unit, NVHCP, West Bengal, this seroprevalence study among the adult population in the state was conducted.

Objective

To find out the prevalence of hepatitis B and C among the adult population of selected districts of West Bengal.

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Materials and Methods

It was a community-based cross-sectional study conducted during February 2023 to April 2024. Required data were collected during April to December 2023. There are 28 health districts in West Bengal. District-wise percentage of hepatitis B surface antigen (HBsAg) positives found during screening under NVHCP routine activities during 2022 were collected from the State Viral Hepatitis Management Unit, NVHCP, West Bengal. With the help of this data, all these districts and health districts were divided into two groups—high- and low-burden districts. Districts/health districts with higher positivity rate than the mean were considered high burden, and the rest were low burden. One district from each group was selected by lottery method. Murshidabad and Malda districts were finally identified for data collection.

Study population was the adult population of West Bengal. People aged ≥18 years and residents of Murshidabad and Malda districts were included as study participants. The required sample sizes for estimating prevalence of hepatitis B and C were calculated as 5,400 males and 5,400 females for each district. The underlying assumptions behind calculation of the sample sizes are: (1) $p = 0.12$, (2) 95% confidence interval, (3) relative precision of 0.08. Prevalence of hepatitis C among the adult population was used as the key indicator (p) for calculating sample sizes as it is lower than hepatitis B prevalence in the state. The factsheet data on prevalence of hepatitis B and C among the adult population in the state, estimated by NFHS-4, were considered for the calculation.[7] Total target sample size became 21,600 (10,800 from Murshidabad and 10,800 from Malda). Considering 5% of total blood samples will be discarded due to quality issues, the final target of sample collection was 22,738. There are a total of 41 blocks in these two districts (26 in Murshidabad and 15 in Malda). Out of all subcenters (SCs), 20% were selected from each block. Population proportion to size (PPS) sampling method was applied for selection of SCs and calculation of target sample for each SC in each district.

A schedule was prepared for the participants' data collection, which included sociodemographic details, history of related risk behaviors, and blood sample test results. A digital version of the schedule was also prepared in Google Spreadsheet for digital data entry. With the help of the State NVHCP Branch and District Health Administration, a sample collection team, including one medical technician (laboratory) [MT (Lab.)], one data entry operator (DEO), and three village-level health workers [auxiliary nurse midwife (ANM) and accredited social health activist (ASHA)] was constituted at each Block Primary Health Center. This team was utilized for sample collection, filling of the schedule, and digital data entry in Google Spreadsheet for the selected SCs of their block. Every SC was provided a date by the Block Health Authority to organize a camp for sample collection. Extensive information, education, and communication (IEC) was done by field-level workers (ANM and ASHA) in their catchment area regarding this camp. Persons who attended the camp and were eligible as per inclusion/exclusion criteria for sample collection were included consecutively until the targeted sample number was reached. Five blood tests were done utilizing existing testing facilities available under the NVHCP, among which two tests were whole blood finger-prick tests—HBsAg and anti-HCV Ab. Three tests were ELISA tests—anti-HBs Ab, anti-HBc IgM Ab, and anti-HBc total Ab. Both whole blood finger-prick tests were done on the spot. For ELISA tests, 5 mL venous blood was collected and sent to the nearest government hospital where ELISA testing facilities were available. A standard operating protocol (SoP) was prepared for data recording, sample collection, transportation, testing, and recording of test results in Google Spreadsheet. All stakeholders were trained adequately before the start of sample collection.

Each blood sample collected during the survey was tested for five distinct biomarkers, viz., HBsAg, antibody against surface antigen, antibodies (IgM and total) against hepatitis B core antigen, and hepatitis C antigen. Among the above, antigen HBs and antibody anti-HCV were performed with qualitative rapid diagnostic test kits (Biolab Diagnostics and Medsource Ozone Biomedicals, respectively). The remaining three investigations, that is, antibodies anti-HBs (quantitative), anti-HBc IgM (quantitative), and anti-HBc total (qualitative), were performed on ELISA format (Dia.Pro Diagnostic Bioprobes Srl). Around 5 mL of venous blood was collected from each participant in EDTA tubes (BD) for specimen volume adequacy for the analyses and repeat test wherever necessary. A unique ID was assigned to each participant for identification and tracking of the blood sample. After completion of on-spot two tests and data collection, the block-level data collection team entered the collected data into Google Sheets along with their unique ID. In the meantime, collected blood samples were sent to the identified ELISA testing facility for remaining laboratory tests. Once the ELISA test results were available, the concerned laboratory entered the test result of a participant into Google Sheets as per the unique ID.

All the collected data in Google Sheets were finally reentered into MS Excel version 19 (Microsoft Corporation, USA) and analyzed using SPSS version 23 (IBM Corporation, USA). Continuous variables were summarized by mean, standard deviation, median, and interquartile range, whereas categorical variables were tabulated using proportions. Categorical variables were analyzed by Chi-square or Fisher's exact test. Potential predictors of acquiring hepatitis B infection were investigated using multivariate binary logistic regression (forward LR) model. A 95% confidence interval with statistical significance at the 5% level was considered. The adjusted OR (AOR) for each risk factor was estimated by adjustments for age, sex, occupation, history of jaundice, family history of jaundice, hepatitis B adult vaccination status, and history of blood transfusion, dialysis, multiple sex partners, unsafe circumcision, and tattoo/piercing. Ethical clearance was obtained from the Institute of Health and Family Welfare, Kolkata.

Results

A total of 22,780 samples were collected. Among them, 460 samples were discarded. Finally, data from 22,320 samples were eligible for analysis. Among them, 11,330 and 10,990 samples were from Murshidabad and Malda districts, respectively. The median age of the participants was 37 years (IQR 24). Age distribution among female and male participants was comparable, as shown in Figure 1.

The number of female and male respondents were 12,013 (53.8%) and 10,307 (46.2%), respectively. Among the female participants, the majority were housewives (40.6%), followed by agricultural workers (15%) and daily laborers (14.2%). Prevalence of hepatitis B and C among the participants was 0.47 and 0.02%, respectively. Prevalence of hepatitis B was slightly higher in Murshidabad (0.56%) than in Malda (0.45%) district, whereas prevalence of hepatitis C was similar in both districts (0.02%). Table 1 shows prevalence of hepatitis B among various sociodemographic and risk behavior groups and their association. No HBsAg-positive case was found among persons who inject drugs (PWID) and AIDS patients. Family history of jaundice, history of blood transfusion, dialysis, and multiple sex partners was associated with hepatitis B infection. The only risk factor found to be

associated with hepatitis C was persons who inject drugs (PWID) (Table 1).

For interpretation of hepatitis B serology result, CDC classification was followed.[12] Participants were grouped into categories according to this classification. Among all the participants, the majority (80.17%) were susceptible to hepatitis B infection, followed by resolved infection (4.26%), immune from receipt of prior vaccination (4.02%), chronic infection (0.36%), and acute infection (0.12%). Results of the remaining 11.07% of samples could not be categorized into the above groups (i.e., occult infection/only core antibody positive/equivocal result/interpretation unclear) (Table 2).

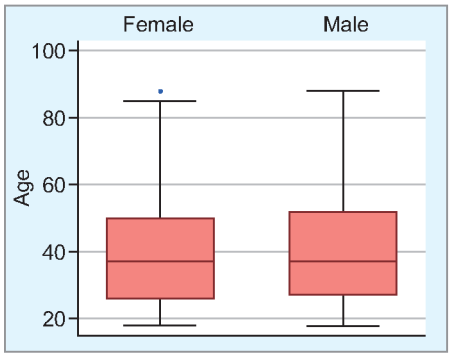

Fig. 1: Sex-wise age distribution of the study participants

Multivariate binary logistic regression (Forward LR method) was applied to find out the determinants of hepatitis B infection (adjusted for variables). Family history of jaundice [AOR (CI): 3.4 (2.1–5.5)], history of dialysis [AOR (CI): 21.1 (2.5–177.6)], and history of multiple sex partners [AOR (CI): 7.3 (1.7–31)] were associated with a significantly higher chance of having hepatitis B infection.

Discussion

There are variations in prevalences of hepatitis B and C infections in studies reported from India. In the current study, prevalence of hepatitis B and C among adults of West Bengal were found to be 0.47 and 0.02%, respectively. This is lower than the findings of NFHS-4 and other studies in India.[5,11,13–16] Viral Hepatitis Services, in accordance with NVHCP guidelines, were envisaged for West Bengal in late 2018 and operationalized in 2019. Since its commencement in the state, the services have rapidly been expanding, aiming toward the elimination targets by 2030 set by the program. State-specific prevalence estimation studies conducted previously show prevalence of hepatitis B as 2.97% and C as 0.87% among the general population two decades ago.[9,10] NFHS-4 shows prevalence of hepatitis B as 1.26% and C as 0.16% in

Table 1: Prevalence of hepatitis B among various sociodemographic and risk behavior groups (n = 22,320)

Variables	*Response*	*HBsAg reactive (%)*	*p-value*
Age	<25 years	20 (0.4)	0.121
	26–37 years	31 (0.5)	
	38–49 years	31 (0.7)	
	>49 years	24 (0.4)	
Sex	Female	50 (0.4)	0.173
	Male	56 (0.5)	
Occupation	Housewife	37 (0.4)	0.128
	Agricultural worker	17 (0.5)	
	Daily laborer	25 (0.8)	
	Service	6 (0.6)	
	Student	3 (0.2)	
	Businessman	3 (0.3)	
	Healthcare worker	2 (0.3)	
	Others	13 (0.5)	
Past history of jaundice	Yes	6 (0.8)	0.157
	No	100 (0.5)	
Family history of jaundice	Yes	20 (1.4)	<0.01*
	No	86 (0.4)	
Hepatitis B adult vaccination status	Vaccinated	1 (0.3)	0.552
	Not vaccinated	91 (0.5)	
	Don't know	14 (0.4)	
History of blood transfusion	Yes	5 (1.3)	0.041*
	No	101 (0.5)	
History of dialysis	Yes	1 (11.1)	0.042*
	No	105 (0.5)	
History of multiple sex partner	Yes	2 (4.3)	0.02*
	No	104 (0.5)	
History of unsafe circumcision (n_1 = 10,307)	Yes	13 (0.7)	1.04
	No	43 (0.5)	
History of tattoo/piercing	Yes	11 (0.3)	0.27
	No	95 (0.5)	

* Significant at $p < 0.05$, 95% CI

Table 2: Distribution of participants according to serological status and their place of residence, age, sex, and occupation (n = 22,320)

Variables	*Response*	*Susceptible (%)*	*Resolved infection (%)*	*Immune from receipt of prior vaccination (%)*	*Infected (%)**
District	Murshidabad	9,676 (85.4)	298 (2.6)	403 (3.6)	64 (0.5)
	Malda	8,218 (74.8)	654 (6)	494 (4.5)	42 (0.4)
Age	≤25 years	4,134 (82.2)	175 (3.5)	260 (5.2)	20 (0.4)
	26–37 years	5,080 (81.7)	242 (3.9)	233 (3.7)	31 (0.5)
	38–49 years	3,676 (79.3)	195 (4.2)	199 (4.3)	31 (0.7)
	≥50 years	5,004 (77.7)	340 (5.3)	205 (3.2)	24 (0.3)
Sex	Female	9,752 (81.2)	503 (4.2)	470 (3.9)	50 (0.4)
	Male	8,142 (79)	449 (4.4)	427 (4.1)	56 (0.5)
Occupation	Housewife	7,440 (82.2)	392 (4.3)	263 (2.9)	37 (0.4)
	Agricultural worker	2,699 (80.7)	129 (3.9)	92 (2.8)	17 (0.5)
	Daily laborer	2,429 (76.7)	195 (6.2)	130 (4.1)	25 (0.8)
	Service	769 (76.7)	31 (3.1)	89 (8.9)	6 (0.6)
	Student	1,084 (82.9)	21 (1.6)	96 (7.3)	3 (0.2)
	Businessman	977 (82.7)	33 (2.8)	41 (3.5)	3 (0.3)
	Healthcare worker	509 (74.7)	33 (4.8)	59 (8.7)	2 (0.3)
	Others	1,987 (76.9)	118 (4.6)	127 (4.9)	13 (0.5)

*Includes both acute and chronic infection

2015–2016.[11] The results of this study show a substantial decline in the magnitude of hepatitis B and C infections in the state. This trend is indicative of successful program implementation in the state. Improvement of screening coverage, decentralization of viral hepatitis centers across the state, availability of drugs free of cost, and change in healthcare-seeking behavior of people may have influenced the downward trend in prevalence.

Prevalence of hepatitis B was higher among the older age-group and male population. Similar findings were reported by multiple studies in India and other countries.[9,14,15,17–20] The majority of the male population was working as daily laborers and agricultural workers. Migration is very common among these populations. Daily laborers from Murshidabad and Malda commonly migrate to various states of India for jobs. A large portion of agricultural workers in these two districts also migrate to other districts of West Bengal during farming seasons for work. Therefore, risk behaviors would expectedly be more common among them and may be the cause of higher prevalence. Prevalence of hepatitis B was found to be highest among daily laborers, which corroborates the aforesaid explanation. A study conducted in northeast China also reported a higher chance of HBV infection among labourers.[20] These migratory laborers are mostly middle age-group males. This may be the reason for higher prevalence of hepatitis B in the 26–49 years age-group.

Hepatitis B prevalence was much lower among the people who have received adult vaccination. Healthcare workers are usually vulnerable to acquiring hepatitis B infection.[15,16] In this study, prevalence was lower among healthcare workers than other occupational groups. Under the NVHCP of India, healthcare workers are entitled to receive the full course of hepatitis B adult vaccination. This may be the reason for the lower prevalence among healthcare workers. Though the majority (92.7%) of them had not received any hepatitis B vaccination, the serological status showed 74.7% of them were still susceptible to hepatitis B infection. This indicates the vaccination coverage among healthcare workers was poor. The State NVHCP branch must gear up the vaccination activities at the earliest.

Prevalence of hepatitis B was higher among those people who had previously suffered from jaundice or whose family member had suffered from jaundice. Multivariate logistic regression showed chances of hepatitis B infection were higher among the people whose family member had already suffered from jaundice. Multiple studies conducted in various countries reported a similar finding. This may be due to the transmission dynamics of the disease, as it is well-established that horizontal household transmission plays a significant role in hepatitis B.[16,20–23] This finding indicates that housewives are vulnerable to hepatitis B if their spouse had risk behaviors. Even in this study, prevalence among housewives was the same as the general population, though the history of risk behaviors was not very common among them.

Hepatitis B infection was associated with a history of blood transfusion, dialysis, and multiple sex partners. Prevalence was much higher among them with respect to the whole study population. In the multivariate logistic regression model, a person who had undergone dialysis and had a history of multiple sex partners had a higher chance of acquiring hepatitis B infection. Similar findings are well documented in multiple studies worldwide.[22–26]

Majority of the participants (80.17%) were found to be susceptible to hepatitis B infection. The proportion of susceptible populations was higher among young adults compared to the older generation. People with resolved infection were more among older people. The higher proportion of susceptible population among younger age-groups needs more evaluation. In India, hepatitis B vaccination among under-5 children was introduced in 2002 under the Universal Immunization Program (UIP).[26] In West Bengal, hepatitis B vaccination for under-5 children was introduced in 2009 with a 3-dose schedule. The birth dose of hepatitis B was added later to the schedule in 2011 (source: Reproductive and Child Health Branch, Department of Health and Family Welfare, Government of West Bengal). Therefore, the younger population included in this study might not have received any hepatitis B vaccine during childhood, leading to a higher proportion of susceptible individuals among them. Further studies are suggested to find out the factors associated with higher susceptibility among younger people.

According to the serological results, 0.36 and 0.12% of the participants were suffering from chronic and acute hepatitis B infection, respectively. The decrease in prevalence over time is an indicator that the program is on the right track to eliminate the disease. Between 2016 and 2030, all WHO Member States are committed to reducing new hepatitis infections by 90% and deaths by 65%.[27] However, approximately 90% of infants infected with HBV perinatally have a chance of developing chronic infection.[28] Achieving the elimination of mother-to-child transmission (EMTCT) of hepatitis B is now a global health priority.[29,30] As per this guidance, the impact target for validation of EMTCT of HBV is HBsAg prevalence of ≤0.1% in the ≤5-year-old birth cohort.[31] Therefore, a study to estimate seroprevalence of hepatitis B among under-5 children of West Bengal is suggested. The State should also focus on the Triple EMTCT of HIV, Syphilis, and HBV to expedite the process of achieving elimination of the disease.

Only four (0.018%) study participants were found to be hepatitis C positive. One of them had a history of injecting drugs (PWID), which is one of the risk factors for hepatitis C.[4,10] Prevalence of hepatitis C has decreased drastically in West Bengal over the period. Promotion of safe injection practices and tracking of high-risk groups through targeted intervention (TI) under WBSAPCS have played a major role in limiting the spread of the disease. Strengthening coordination among departments like blood safety and maternal and child health has been prioritized by NVHCP from its inception. Promotion of harm reduction programs, safer medical practices, and blood safety interventions may have also contributed to this trend.

State representative data to assess the disease burden in West Bengal for hepatitis B and C were required to assist in optimal planning for prevention and management of viral hepatitis. This is one of its kind studies in the country, conducted among the general population, involving such a large sample, to find out seroprevalence of hepatitis B and C in a state. All the participants who were found to be hepatitis B or C positive during the study were linked with the nearest Viral Hepatitis Treatment Centre for further management.

This study was subjected to a few limitations. History of symptoms, disease, vaccination, and risk behaviors were based on personal interviews and were not verified by any documents. Chances of social desirability bias do exist, as participants sometimes opt for socially acceptable responses to questions related to risk behaviors to avoid stigma. Infection could have occurred at any time since birth, possibly preceding the risk factors evaluated. Cross-sectional design precludes risk estimates and causal association in exact terms. Chances of selection bias are present, as the individuals who attended medical camps were included in the study. Despite these limitations, as the first study to report statewide prevalence of hepatitis B and C infection in West Bengal, these findings are important for understanding the public health burden of these infections in the state.

Conclusion

The state of West Bengal, India, has a low seroprevalence for hepatitis B and C infections on a global scale; it is lower than the country average. However, given its large population, the burden of HBV infection in the state is still considerable. Family history of jaundice, history of blood transfusion, dialysis, and multiple sex partners were identified as associated with hepatitis B. Focus should be given to curbing risk behaviors among migrant laborers. Adherence to existing vaccination programs, including birth dose vaccinations, and promotion of adult vaccination could help to reduce the spread of infections further. Strengthening tracking of PWID and promotion of safe injection practices could also help to limit the transmission of hepatitis C infection. The state of West Bengal should also focus on Triple EMTCT of HIV, Syphilis, and HBV to progress further toward elimination of hepatitis B.

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ORIGINAL ARTICLE

Evaluating the Real-world Effectiveness and Safety of Formoterol Fumarate and Fluticasone Propionate Combination in Asthma: A Prospective, Multicenter Study

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Abstract

Background: India bears a significant burden of asthma, and asthma in India is characterized by high mortality rates. Poor adherence to treatment guidelines is observed. Several inhaled corticosteroid (ICS) with long-acting beta (β) 2 agonist (LABA) combinations are commercially marketed in India, formoterol fumarate–fluticasone propionate being one of them. Real-world Indian studies on fluticasone-formoterol from India are scarce. This study aims to evaluate the effectiveness and safety of formoterol fumarate (6 µg) and fluticasone propionate (250 µg) administered through a dry powder inhaler (DPI) or metered-dose inhaler (MDI) in Indian asthma patients.

Materials and methods: This 24-week prospective, multicenter study (CTRI/2023/08/056250) evaluated Formoflo 250 (formoterol fumarate 6 µg with fluticasone propionate 250 µg) transcaps (DPI), and Formoflo 250 transhaler (MDI) in adults aged 18–65 years. The primary endpoint was the mean change in trough forced expiratory volume in 1 second (FEV1) at week-24. Secondary endpoints included changes in trough forced vital capacity (FVC), asthma control test (ACT), and asthma quality of life questionnaire (AQLQ) scores. Safety was assessed through adverse events (AEs) and asthma exacerbations, with appropriate statistical analyses conducted on the modified intention-to-treat (mITT) population.

Results: A total of 503 patients were enrolled, with 495 included in the mITT analysis and all 503 in the safety analysis. At week-24, a mean increase of 312.2 ± 121.1 mL was observed in trough FEV1, while trough FVC improved by 279.3 ± 147.3 mL ($p < 0.0001$). The mean ACT score increased by 11.6 ± 3.7 ($p < 0.0001$), while the mean AQLQ score improved by 2.5 ± 1.2 ($p < 0.0001$) at week-24. Adverse events were reported in 7.0% of patients, primarily mild, with no serious AEs or fatalities. The findings were consistent across both Formoflo DPI and MDI formulations.

Conclusion: The combination of formoterol fumarate and fluticasone propionate significantly improved lung function, asthma control, and quality of life, demonstrating marked effectiveness and safety with both DPI and MDI in Indian asthma patients.

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Introduction

Asthma is a chronic inflammatory condition of the airways, marked by repeated occurrences of wheezing, shortness of breath, chest constriction, and coughing. These symptoms are typically provoked by exposure to allergens, environmental irritants, or respiratory tract infections.[1] Globally, asthma is a significant public health concern, affecting more than 262 million people annually and causing an estimated 455,000 deaths each year.[2] Asthma ranks as the second most prevalent chronic respiratory disorder globally, with an estimated prevalence of 3.33%.[3] The global burden of disease (GBD) 2019 report highlights India as a major contributor to the global asthma burden, accounting for approximately 34.3 million cases, or 13.09% of the worldwide total. Notably, asthma-related mortality in India is reported to be threefold higher than the global average, with disability-adjusted life years (DALYs) exceeding twice the global figures for asthma.[4–6] The SWORD study showed a huge treatment gap, with 34.8% of patients with poor control and 26.8% of those hospitalized not receiving any treatment. Additionally, only 48.9% of patients underwent spirometry, contributing to increased mortality, DALYs, and a substantial overall healthcare burden.[6] This elevated mortality rate is an offshoot of multiple contributing factors, including the progressive decline in air quality, inadequate public awareness, the persistence of myths and social stigma surrounding asthma, underdiagnosis and misdiagnosis by healthcare professionals, suboptimal prescription and utilization of inhalation therapies, and poor compliance with established evidence-based management guidelines.[5]

Asthma management remains suboptimal on a global scale, with particularly significant challenges observed in developing countries such as India.[7] The treatment options available for asthma are broad, encompassing diverse pharmacological classes such as short-acting β-agonists (SABAs), long-acting β-agonists (LABAs), inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), and combination therapies.[8] These treatment strategies are tailored to improve symptoms, reduce exacerbations, and enhance the overall quality of life for patients with asthma.

For patients with asthma, except those with the mildest severity, the recommended standard treatment involves a combination of an ICS and a LABA. Currently approved ICS/LABA inhalers for asthma management, including fluticasone propionate–salmeterol, fluticasone furoate–vilanterol, beclomethasone–formoterol, fluticasone

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propionate–formoterol, mometasone–indacaterol, budesonide–formoterol, and mometasone–formoterol, are well-established for their effectiveness in achieving optimal control when administered once or twice daily.[9–11] Fluticasone propionate combined with formoterol fumarate is an approved ICS/LABA therapy, now available in several countries across Europe and Asia, including India, providing an effective option for asthma management.[12] The 2024 GINA (Global Initiative for Asthma) guidelines also recommend ICS/LABA combination therapy, such as fluticasone and formoterol, as the mainstay of asthma treatment to achieve optimal disease control.[13] Fluticasone propionate, a potent ICS, exerts its effects in asthma management by inhibiting multiple inflammatory pathways, reducing the production of inflammatory mediators, and decreasing airway hyper-responsiveness and swelling.[14] Clinical studies have shown that their relative potency is highest for fluticasone propionate, followed by budesonide, beclomethasone dipropionate, triamcinolone acetonide, and flunisolide.[14,15] Its safety and efficacy are well-documented, and it is approved for use as monotherapy treatment or in combination with LABAs in patients aged above 4 years.[14,16,17] Formoterol fumarate, a LABA, rapidly activates β-2 adrenergic receptors within 1–3 minutes, leading to smooth muscle relaxation and sustained bronchodilation, comparable to short-acting β-agonists such as salbutamol but with a longer duration of action.[18–20] This rapid onset of bronchodilation, comparable to that of SABAs (within approximately 3 minutes), coupled with a prolonged effect lasting up to 12 hours, differentiates formoterol among LABAs and ensures its efficacy in asthma control for 12 years and older patients.[18,21] The fluticasone and formoterol combination effectively targets both airway inflammation and bronchoconstriction, providing a comprehensive approach to asthma management. Its robust efficacy and favorable safety profile, demonstrated in extensive randomized controlled trials, highlight its clinical importance in treating asthma.[22–25]

Despite extensive international research, data on the effectiveness of this combination as a first-line treatment in asthma patients, both globally and in Indian real-world clinical practice, remain limited, particularly over the last 6–8 years. To address this gap, AFFIRM (Asthma management with Formoterol and Fluticasone In a Real-world post-Marketing study), a prospective, multicenter, real-world evidence study, was designed to assess the effectiveness and safety of formoterol fumarate (6 µg) and fluticasone propionate (250 µg) delivered through either dry powder inhaler (DPI) or metered-dose inhaler (MDI) in asthma patient. This is the first real-world study from India to evaluate the change in trough FEV_1 (from baseline) as a primary endpoint in asthmatics with formoterol fumarate and fluticasone propionate combination therapy.

Materials and Methods

Study Design

This prospective, multicenter, real-world clinical study was conducted over 24 weeks at five centers in India and is registered with the Clinical Trials Registry of India (CTRI) under the identifier CTRI/2023/08/056250. The study adhered to the ethical principles of the current Declaration of Helsinki and good clinical practice (GCP) guidelines by the International Council for Harmonization (ICH), and local regulatory requirements. Following approval from the Institutional Ethics Committees of all participating centers and after obtaining written informed consent from each patient, the study was conducted over the period from August 2023 to July 2024.

Study Patients

The study included adult patients aged 18–65 years, of either gender, with mild to moderate asthma. Mild asthma was characterized by a predicted forced expiratory volume in 1 second (FEV_1) of 80% or greater, with a normal FEV_1 to forced vital capacity (FEV_1/FVC) ratio, whereas moderate asthma was defined as a predicted FEV_1 between 60% and less than 80%, with a possible reduction in the FEV_1/FVC ratio of up to 5%. Furthermore, eligible patients had not received any regular controller medication in the last 12 weeks and demonstrated bronchodilator reversibility, defined as an increase in FEV_1 of at least 12% and 200 mL following salbutamol inhalation, along with a prebronchodilator FEV_1 between 60 and 85% of the predicted normal value at screening. Additionally, patients were also needed to have an asthma control test (ACT) score of 15 or less at screening and to provide informed consent in writing, agreeing to adhere to all study protocol requirements.

Patients were excluded if they had known hypersensitivity to any β2-agonist, sympathomimetic drug, or corticosteroid (inhaled, intranasal, or systemic), a history of life-threatening asthma in the past 5 years, or an asthma exacerbation requiring systemic corticosteroids or hospitalization within 6 months prior to screening. Those diagnosed with COVID-19 within 3 months or a bacterial or viral respiratory tract infection within 4 weeks before screening were also excluded. The exclusion criteria further included patients with any chronic respiratory disease other than asthma, clinical evidence of oropharyngeal candidiasis, clinically significant uncontrolled systemic diseases, hepatic or renal dysfunction, current or recent smokers, alcohol or drug abuse history, or participation in another clinical trial within 3 months before screening. Women who were pregnant, breastfeeding, or not willing to use reliable contraceptive methods were excluded from the study.

Medication Regimen and Administration

Patients enrolled in the study received a fixed-dose combination (FDC) therapy comprising formoterol fumarate (6 µg) and fluticasone propionate (250 µg), delivered either via a DPI as Formoflo 250 transcaps or through an MDI as Formoflo 250 transhaler. The appropriate formulation was determined by the investigator, considering the preferences of the patient, compatibility, and their ability to effectively use either a DPI or MDI. Patients prescribed Formoflo 250 transcaps (DPI) were instructed to inhale one transcap twice daily (morning and evening) using the Lupihaler device. Those using Formoflo 250 transhaler (MDI) were directed to administer one puff twice daily (morning and evening) via an MDI with transpacer V, according to the approved package insert. All patients were provided with detailed instructions on the proper technique for using both DPI and MDI formulations to ensure correct administration of the medication. Administration of the medication was to be performed immediately after recording the FEV_1 reading.

Data Collection

In this prospective study, patients were followed up with three scheduled visits conducted across a 6-month period to systematically collect data. At visit 1 (day 0), patients provided informed consent and were screened for eligibility based on inclusion and exclusion criteria, with demographic data, medical history, vital signs, and clinical examination results recorded. Female patients of childbearing potential underwent a urine pregnancy test, and a blood sample was collected for laboratory investigations. Spirometry was conducted to confirm bronchodilator reversibility (an increase in FEV_1 of at least 12% and 200 mL postsalbutamol inhalation), along with ACT and asthma quality of life questionnaire (AQLQ) scores were documented. Eligible patients were enrolled and prescribed formoterol fumarate and fluticasone propionate FDC via DPI or MDI in doses as mentioned above, along with rescue medication (salbutamol MDI), based on the investigator's discretion.

At visit 2 (month 3 ± 14 days), reassessments included vital signs, clinical examination, recording of any adverse events (AEs), asthma exacerbations, along with updates to ACT and AQLQ scores. The global impression of change (GIC) in the disease condition was recorded by patients. At visit 3 (month 6 ± 14 days), final evaluations encompassed all previous assessments, including spirometry, laboratory tests, and recording of AEs or asthma exacerbations, along with final patient-reported and investigator-assessed global evaluations of the disease and treatment efficacy. Unscheduled visits were allowed throughout the study for managing AEs or other clinical conditions, and any protocol deviations, such as visits outside the permitted window, missed or incomplete procedures, or evaluations, were recorded as they occurred.

Efficacy Assessment

The primary efficacy endpoint of the study was the evaluation of the change in predose (trough) FEV_1 from baseline to week 24 (visit 3). Trough FEV_1 was measured using spirometry before the administration of the study drugs' morning dose, with baseline values (visit 1) compared to those obtained at the end of week 24 (visit 3). Secondary endpoints assessed changes from baseline in trough FVC at the end of week 24, as well as changes in the ACT score and the AQLQ score at the end of week 12 and week 24. Trough FVC was measured similarly to trough FEV_1. ACT scores, which have been validated in numerous studies for evaluating asthma control, were calculated at baseline and at each subsequent visit, using a five-item questionnaire that scored responses from 5 to 25 (higher scores indicating better control).[26–28] AQLQ scores, widely used in clinical studies to assess asthma-related quality of life, were also evaluated at baseline and each follow-up visit, with patients responding to 32 questions across four domains, scored on a 7-point scale (higher scores indicating less impairment).[29,30] Additionally, global assessments included the GIC in disease condition, recorded by patients at week 12 and week 24, on a 7-point scale. Furthermore, global assessment of efficacy was conducted by the investigator at week 24, based on the ACT score, using a 4-point scale to categorize efficacy as "Excellent" (ACT score > 20), "Good" (ACT score 16–20), "Fair" (improvement from baseline with ACT score ≤ 15), or "Poor" (no improvement or a decrease in ACT score compared to baseline).

Safety Assessment

The safety of the study drugs was evaluated by monitoring all AEs and serious adverse events (SAEs) reported throughout the clinical study. Hematological and biochemical laboratory investigations were performed at screening and at the end of treatment to detect any clinically significant abnormalities, which were recorded as AEs if observed. All abnormalities identified during physical examinations, including vital signs, and any AEs observed or volunteered by the patients, regardless of their suspected causal relationship to the study drug, were documented. Asthma exacerbations, defined as acute or subacute worsening episodes with a progressive increase in symptoms and a decline in expiratory flow, were closely monitored throughout the study. These exacerbations were categorized as nonsevere, severe, or life-threatening, based on clinical presentation and the required level of care, as specified in the clinical study protocol. All exacerbations occurring after the administration of the study medication were documented to ensure a comprehensive safety assessment.

Statistical Analysis

All data from the study were accurately managed using an EDC platform. The data collected was then used to perform statistical analyses. Efficacy parameters were analyzed for the modified intention-to-treat (mITT) population, which included all enrolled patients who completed the specified postenrollment visits (visit 2 or visit 3), regardless of major protocol deviations. The per-protocol (PP) analysis, excluding patients with significant protocol deviations, yielded conclusions consistent with those observed in the mITT analysis, indicating no substantial impact on overall study outcomes. Therefore, the mITT analysis results, which more closely reflect real-world scenarios, are presented in this manuscript. In contrast, safety parameters were evaluated for all patients who gave informed consent in writing and received a minimum of one dose of the investigational drug.

Descriptive statistics were employed to summarize baseline demographic and clinical characteristics. This includes such information as age, gender, height, weight, body mass index, asthma severity, the percentage of patients who demonstrate reversibility, the percentage of patients who are prescribed medication, the type of medication prescribed, and any coexisting medical conditions that may be present. Continuous variables were expressed as mean ± standard deviation (SD) along with their corresponding 95% confidence intervals (CIs). Categorical variables were described using frequencies and proportions (*n*, %) with associated 95% CIs, unless otherwise specified.

To assess efficacy, the paired *t*-test was utilized to determine the mean differences in trough FEV_1 and FVC values between baseline and follow-up visits, given that the data followed a normal distribution. Additionally, mean changes in the ACT and AQLQ scores from baseline to subsequent visits were assessed using Dunnett's multiple comparisons test, while the overall mean change across different time points was determined using a mixed-model Analysis of Variance (ANOVA). The GIC in disease condition, as reported by patients at week 12 and at the end of the study (week 24), and the global assessment of efficacy by the investigator at the end of the study (week 24) were analyzed using descriptive statistics.

Safety assessments were conducted through descriptive statistics, including frequency and percentage distributions, to provide a thorough evaluation of safety parameters. Statistical analyses were carried out using GraphPad Prism software (version 8.4.3) along with a licensed version of Microsoft Excel 2010.

Results

Patient Demographics

A total of 503 patients were enrolled in the study, with eight patients lost to follow-up after visit 2. The remaining patients completed the study as per protocol. Fifteen major protocol deviations were identified, leading to the inclusion of 480 patients in the PP analysis, 495 patients in the mITT efficacy analysis, along with all 503 patients in the safety analysis. For this manuscript, the mITT population was considered for efficacy analysis, as it provides comprehensive assessment of the study outcomes (Fig. 1).

Out of the 503 patients enrolled in the study, 236 (46.9%) were within the age group of 18–40 years, 217 (43.1%) were aged between 40–60 years, and 50 (9.9%) were above 60 years. A total of 272 patients (54.1%) were prescribed Formoflo DPI, while 231 patients (45.9%) received Formoflo MDI. Among the participants, 43.1% were female and 56.9% were male. The detailed distribution of patients receiving Formoflo via DPI or MDI is provided in Table 1. The enrolled patients had a mean height of 165.3 ± 8.2 cm, a mean weight of 64.8 ± 12.4 kg, and a mean BMI of 23.7 ± 4.4 kg/m^2. Asthma severity was categorized as mild in 41.0% patients, moderate in 58.8% and severe in 0.2%. Reversibility after bronchodilator administration was observed in 97.6% of patients, with a slightly higher rate in the Formoflo MDI group (99.1%) compared to the Formoflo DPI group (96.3%). Table 1 presents

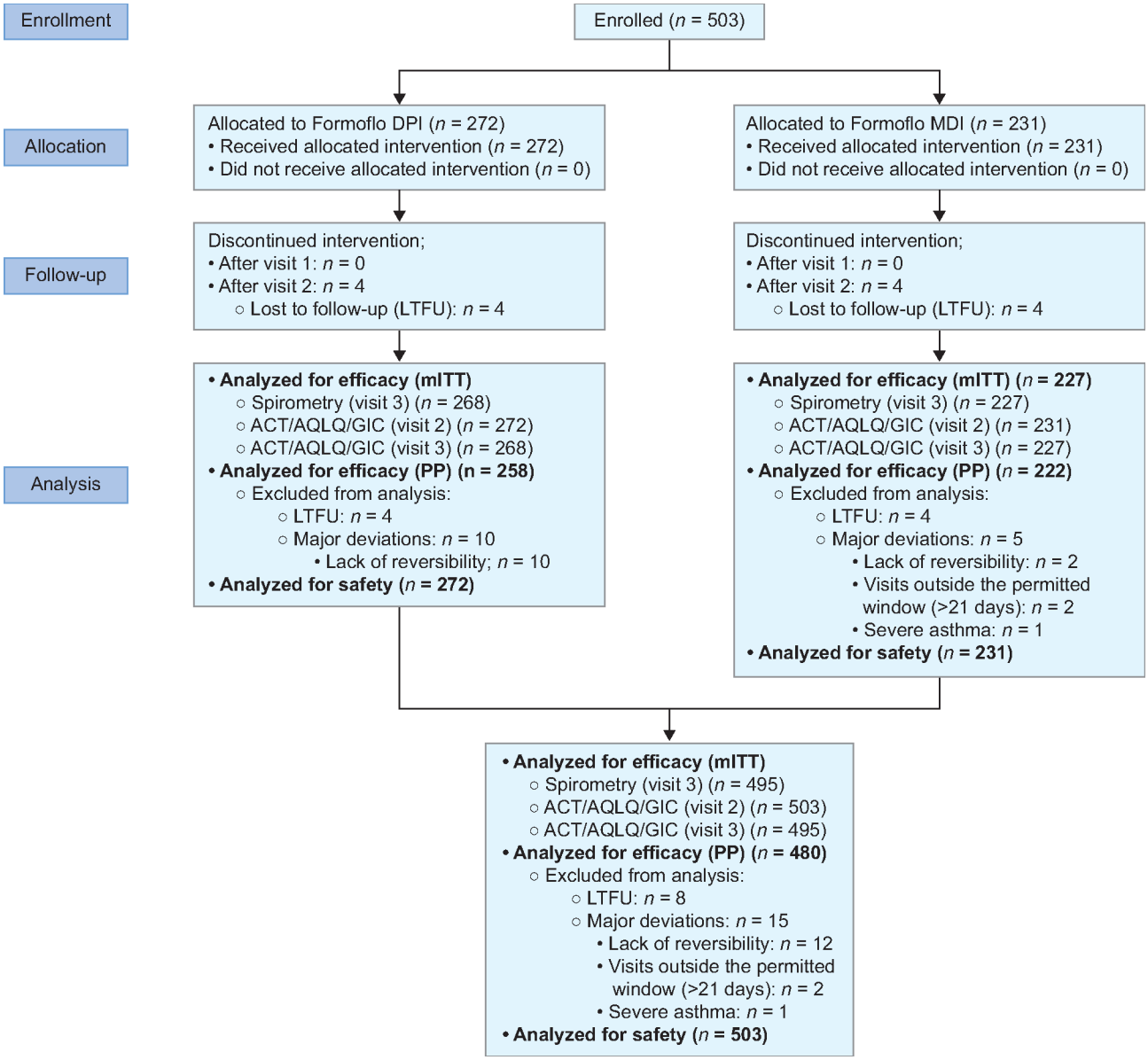


Fig. 1: Patient enrollment and progression through the study

the demographic profile and baseline clinical characteristics of the enrolled patients.

Primary Efficacy Endpoint

Trough FEV1

The primary endpoint was defined as the change from baseline in trough FEV_1 at week 24. The mean difference in trough FEV_1 at week 24 for the study participants (n = 495) was 312.2 ± 121.1 mL (95% CI: 301.5, 322.9) from baseline, demonstrating statistical significance ($p < 0.0001$). Similarly, the mean change in trough FEV1 at week 24 was 326.2 ± 135.3 mL (95% CI: 310.0, 342.5) for patients receiving Formoflo DPI and 295.7 ± 99.6 mL (95% CI: 282.7, 308.7) for those receiving Formoflo MDI, both demonstrating statistically significant improvements ($p < 0.0001$). These findings indicate consistent and significant lung function improvements with both Formoflo DPI and MDI, as outlined in Table 2.

Secondary Efficacy Endpoints

Trough FVC

One of the key secondary endpoints was the change in trough FVC at week 24 from baseline. The mean change in trough FVC for study patients (N = 495) at week 24 was 279.3 ± 147.3 mL (95% CI: 266.3, 292.3), which was statistically significant compared to baseline ($p < 0.0001$). In subgroup analyses, patients receiving Formoflo DPI had a mean change of 288.1 ± 160.8 mL (95% CI: 268.8, 307.5), while those receiving Formoflo MDI showed a mean change of 268.9 ± 129.2 mL (95% CI: 252.0, 285.8), both achieving statistically significant lung function improvements ($p < 0.0001$), as shown in Table 3.

ACT Score

The results of the change from baseline in ACT score at week 12 and at the end of the study (week 24) are presented in Table 4. The mean change in ACT score at week 12 was 8.5 ± 5.3 (95% CI: 8.0, 9.0), and at week 24, it was 11.6 ± 3.7 (95% CI: 11.2, 11.9), both of which were statistically significant ($p < 0.0001$), as compared to baseline. In patients receiving Formoflo DPI, the mean difference in ACT score from baseline to week 12 was 9.4 ± 4.8 (95% CI: 8.9, 10.0), and to week 24, it was 12.2 ± 3.8 (95% CI: 11.7, 12.7). For those receiving Formoflo MDI, the mean change was 7.4 ± 5.7 (95% CI: 6.6, 8.1) at week 12 and 10.8 ± 3.5 (95% CI: 10.4, 11.3) at week 24, both showing statistically significant improvements ($p < 0.0001$). Baseline data showed that an ACT score ≤15 was observed in 100% of patients,

Table 1: Demographic and baseline characteristics of the study population

Parameters		*Total (N = 503)*	*Formoflo DPI (N = 272)*	*Formoflo MDI (N = 231)*
Age (years)#	18–40	236 (46.9%)	151 (55.5%)	85 (36.8%)
	40–60	217 (43.1%)	97 (35.7%)	120 (51.9%)
	>60	50 (9.9%)	24 (8.8%)	26 (11.3%)
Gender#	Male	286 (56.9%)	145 (53.3%)	141 (61.0%)
	Female	217 (43.1%)	127 (46.7%)	90 (39.0%)
Height (cm)*		165.3 ± 8.2 (164.6–166)	165.3 ± 6.6 (164.5–166.1)	165.2 ± 9.8 (163.9–166.5)
Weight (kg)*		64.8 ± 12.4 (63.7–65.8)	62.5 ± 10.9 (61.2–63.8)	67.4 ± 13.4 (65.7–69.2)
Body mass index (kg/m^2)*		23.7 ± 4.4 (23.4–24.1)	22.9 ± 4.0 (22.4–23.4)	24.8 ± 4.7 (24.1–25.4)
Severity of asthma#	Mild	206 (41.0%)	89 (32.7%)	117 (50.6%)
	Moderate	296 (58.8%)	183 (67.3%)	113 (48.9%)
	Severe	1 (0.2%)	0 (0%)	1 (0.4%)
Patients showing reversibility#	Yes	491 (97.6%)	262 (96.3%)	229 (99.1%)
	No	12 (2.4%)	10 (3.7%)	2 (0.9%)
Comorbidities# (*N* = 227)	Gastroesophageal reflux disease (GERD)	106 (21.1%)	55 (20.2%)	51 (22.1%)
	Allergic rhinitis	40 (8.0%)	26 (9.6%)	14 (6.1%)
	Sinusitis	36 (7.2%)	19 (7.0%)	17 (7.4%)
	Ischemic heart disease (IHD)	15 (3.0%)	14 (5.1%)	1 (0.4%)
	Others [hypertension, diabetes mellitus (DM), deviated nasal septum (DNS)]	30 (6.0%)	12 (4.4%)	18 (7.8%)
Concomitant medications# (*N* = 227)	Respiratory medications (antiallergic and mucolytic agents)	135 (26.8%)	79 (29.0%)	56 (24.2%)
	Gastroprotective agents [proton pump inhibitors (PPI)]	48 (9.5%)	22 (8.1%)	26 (11.3%)
	Cardiovascular agents (antihypertensive, antiplatelet, and statins)	31 (6.2%)	20 (7.4%)	11 (4.8%)
	Antidiabetic medications (hypoglycemic agents)	13 (2.6%)	5 (1.8%)	8 (3.5%)

*Data presented as mean ± SD (95% CI); #Data presented as *n* (%)

Table 2: Mean change in trough FEV_1 from baseline to the end of week 24

Population	*Parameter*	*Values (mL)*	*Change as compared to baseline (mL)*	*p-value#*
Total (*N* = 495)	Trough FEV_1* (baseline)	1993.0 ± 423.6 (1955.6–2030.4)	NA	< 0.0001
	Trough FEV_1* (week 24)	2305.2 ± 441.3 (2266.2–2344.2)	312.2 ± 121.1 (301.5–322.9)	
Formoflo DPI (*N* = 268)	Trough FEV_1* (baseline)	2027.6 ± 393.2 (1980.3–2074.9)	NA	< 0.0001
	Trough FEV_1* (week 24)	2353.8 ± 416.0 (2303.8–2403.9)	326.2 ± 135.3 (310.0–342.5)	
Formoflo MDI (*N* = 227)	Trough FEV_1* (baseline)	1952.2 ± 454.3 (1892.7–2011.6)	NA	< 0.0001
	Trough FEV_1* (week 24)	2247.8 ± 463.9 (2187.1–2308.5)	295.7 ± 99.6 (282.7–308.7)	

*Data presented as mean ± SD (95% CI); #*p*—as compared to baseline (based on paired *t*-test)

reflecting poor asthma control in both the DPI and MDI groups. Week 12 results indicated significant improvements, with an ACT score ≥20 achieved by 55.2% of DPI patients and 43.2% of MDI patients. An ACT score of 16–19 was recorded in 15.7% of DPI patients and 17.6% of MDI patients, while an ACT score ≤15 was observed in 29.1% of DPI patients and 39.2% of MDI patients. Further improvements were reported at week 24, with an ACT score ≥20 achieved by 80.2% of DPI patients and 86.3% of MDI patients. An ACT score of 16–19 was recorded in 13.8% of DPI patients and 8.4% of MDI patients, while an ACT score ≤15 was observed in 6.0% of DPI patients and 5.3% of MDI patients, demonstrating significant asthma control in both groups.

AQLQ Score

At week 12, the mean increase in AQLQ score was 1.6 ± 1.2 (95% CI: 1.5, 1.7), which further improved to 2.5 ± 1.2 (95% CI: 2.4, 2.6) by week 24, both demonstrating statistical significance compared to baseline ($p < 0.0001$). In patients receiving Formoflo DPI, the mean AQLQ score improvement was 1.8 ± 1.2(95% CI: 1.6, 1.9) at week 12 and 2.6 ± 1.2 (95% CI: 2.5, 2.8) at week 24, both of which were statistically significant. Similarly, for patients treated with Formoflo MDI, the mean changes were 1.5 ± 1.1 (95% CI: 1.3, 1.6) at week 12 and 2.3 ± 1.2 (95% CI: 2.2, 2.5) at week 24, also demonstrating statistical significance ($p < 0.0001$). The results for these changes in AQLQ score are provided in Table 5.

Table 3: Mean change in trough FVC from baseline to the end of week 24

Population	*Parameter*	*Values*	*Change as compared to baseline*	*p-value#*
Total (*N* = 495)	Trough FVC* (baseline)	2495.6 ± 531.4 (2448.7–2542.5)	NA	< 0.0001
	Trough FVC* (week 24)	2774.9 ± 533.4 (2727.8–2822.0)	279.3 ± 147.3 (266.3–292.3)	
Formoflo DPI (*N* = 268)	Trough FVC* (baseline)	2469.2 ± 504.5 (2408.5–2529.9)	NA	< 0.0001
	Trough FVC* (week 24)	2757.3 ± 521.3 (2694.6–2820.0)	288.1 ± 160.8 (268.8–307.5)	
Formoflo MDI (*N* = 227)	Trough FVC* (baseline)	2531.2 ± 558.4 (2458.1–2604.2)	NA	< 0.0001
	Trough FVC* (week 24)	2800.1 ± 543.2 (2729.1–2871.1)	268.9 ± 129.2 (252.0–285.8)	

*Data presented as mean ± SD (95% CI); #*p*–as compared to baseline (based on paired *t*-test)

Table 4: Mean change from baseline in ACT score at week 12 and at the end of week 24

Populations	*Parameter*	*Values*	*Change as compared to baseline*	*p-value**
Total	ACT score (baseline) (*N* = 503)	10.3 ± 2.5 (10.1–10.6)	NA	NA
	ACT score (week 12) (*N* = 503)	18.8 ± 4.7 (18.4–19.2)	8.5 ± 5.3 (8.0–9.0)	< 0.0001
	ACT score (week 24) (*N* = 495)	21.9 ± 3.2 (21.6–22.2)	11.6 ± 3.7 (11.2–11.9)	< 0.0001
	p-value (ANOVA)^	< 0.0001	NA	NA
Formoflo DPI	ACT score (baseline) (*N* = 272)	9.8 ± 2.3 (9.6–10.1)	NA	NA
	ACT score (week 12) (*N* = 272)	19.3 ± 4.7 (18.7–19.8)	9.4 ± 4.8 (8.9–10.0)	< 0.0001
	ACT score (week 24) (*N* = 268)	22.0 ± 3.6 (21.6–22.4)	12.2 ± 3.8 (11.7–12.7)	< 0.0001
	p-value (ANOVA)^	< 0.0001	NA	NA
Formoflo MDI	ACT score (baseline) (*N* = 231)	10.9 ± 2.6 (10.6–11.2)	NA	NA
	ACT score (week 12) (*N* = 231)	18.3 ± 4.5 (17.7–18.9)	7.4 ± 5.7 (6.6–8.1)	< 0.0001
	ACT score (week 24) (*N* = 227)	21.8 ± 2.7 (21.4–22.1)	10.8 ± 3.5 (10.4–11.3)	< 0.0001
	p-value (ANOVA)^	< 0.0001	NA	NA

^*p*-value based on mixed model ANOVA; **p*—as compared to baseline (based on Dunnett's multiple comparisons test)

Table 5: Mean change from baseline in AQLQ score at week 12 and at the end of week 24

Populations	*Parameter*	*Values*	*Change as compared to baseline*	*p-value**
Total	AQLQ score (baseline) (*N* = 503)	3.5 ± 1.0 (3.4–3.6)	NA	NA
	AQLQ score (week 12) (*N* = 503)	5.1 ± 1.2 (5.0–5.2)	1.6 ± 1.2 (1.5–1.7)	< 0.0001
	AQLQ score (week 24) (*N* = 495)	5.9 ± 1.0 (5.8–6.0)	2.5 ± 1.2 (2.4–2.6)	< 0.0001
	p-value (ANOVA)^	< 0.0001	NA	NA
Formoflo DPI	AQLQ score (baseline) (*N* = 272)	3.5 ± 0.9 (3.4–3.6)	NA	NA
	AQLQ score (week 12) (*N* = 272)	5.2 ± 1.5 (5.1–5.4)	1.8 ± 1.2 (1.6–1.9)	< 0.0001
	AQLQ score (week 24) (*N* = 268)	6.1 ± 1.2 (5.9–6.2)	2.6 ± 1.2 (2.5–2.8)	< 0.0001
	p-value (ANOVA)^	< 0.0001	NA	NA
Formoflo MDI	AQLQ score (baseline) (*N* = 231)	3.5 ± 1.0 (3.3–3.6)	NA	NA
	AQLQ score (week 12) (*N* = 231)	4.9 ± 0.8 (4.8–5.0)	1.5 ± 1.1 (1.3–1.6)	< 0.0001
	AQLQ score (week 24) (*N* = 227)	5.8 ± 0.8 (5.7–5.9)	2.3 ± 1.2 (2.2–2.5)	< 0.0001
	p-value (ANOVA)^	< 0.0001	NA	NA

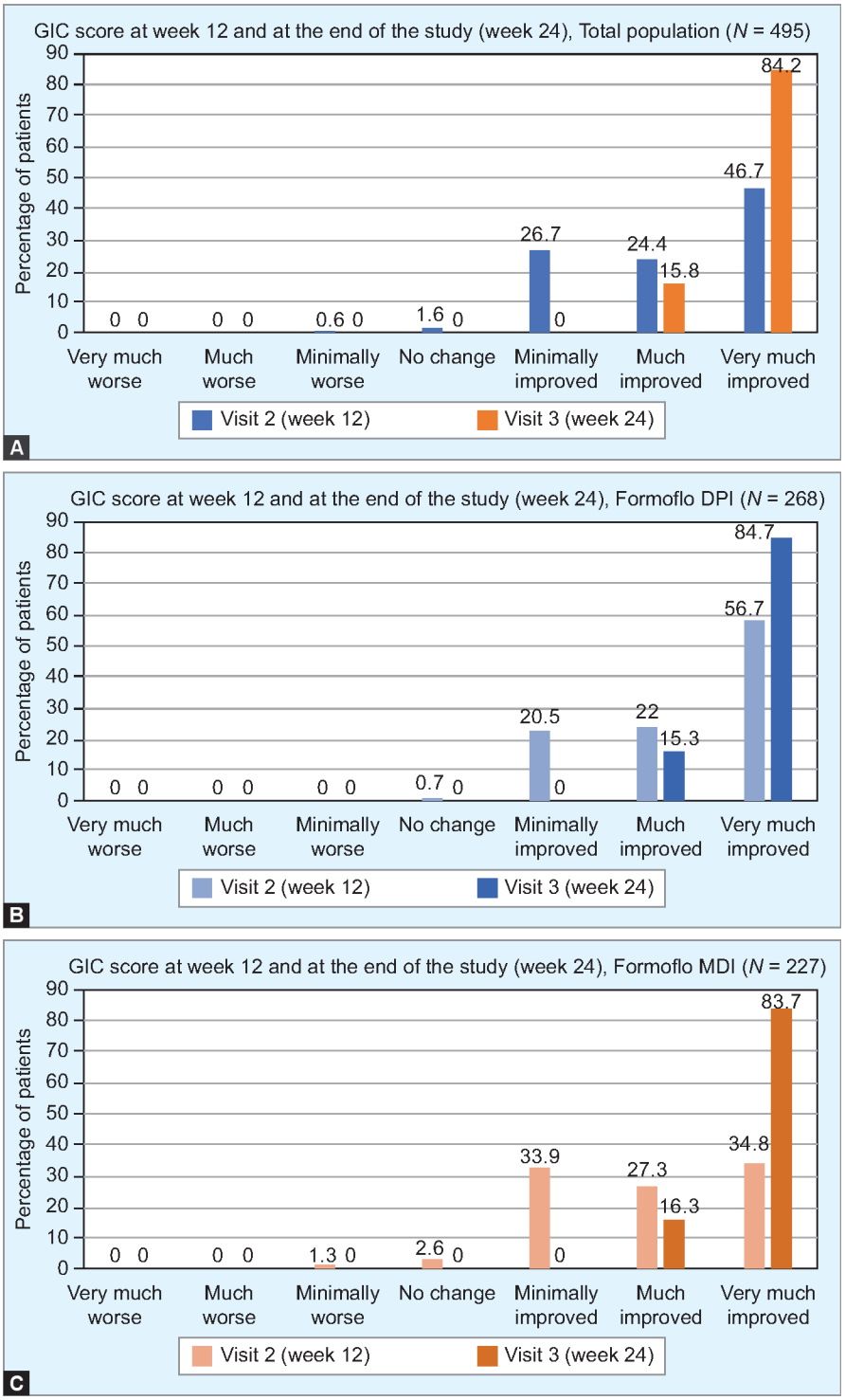
^*p*-value based on mixed model ANOVA; **p*—as compared to baseline (based on Dunnett's multiple comparisons test)

GIC Score Reported by Patients

The GIC score at week 12 and at the end of the study (week 24) from baseline is depicted in Figure 2A. The GIC scores from the total population of 495 patients indicated that at the end of week 12, 0.6% of patients reported "minimal worsening", 1.6% reported "no change", 26.7% reported "minimal improvement", 24.4% reported "much improvement", and 46.7% reported "very much improvement". At the end of week 24, 15.8% of patients reported "much improvement", and 84.2% reported "very much improvement".

The results for patients receiving Formoflo DPI, as depicted in Figure 2B, showed that 0.7% of patients reported "no change", 20.5% experienced "minimal improvement", 22.0% were "much improved", and 56.7% were "very much improved" by the end of week 12. At the end of week 24, 15.3% reported being "much improved", and 84.7% reported being "very much improved". Similarly, for patients receiving Formoflo MDI (Fig. 2C), 1.3% reported "minimal worsening", 2.6% reported "no change", 33.9% experienced "minimal improvement", 27.3% were "much improved", and 34.8% were "very much improved" at week 12, while at the end of week 24, 16.3% reported being "much improved", and 83.7% reported being "very much improved". The GIC analysis indicates that both Formoflo DPI and Formoflo MDI resulted in marked improvement at the end of week 24, with the majority of patients reporting being "very much improved".

At the end of the study (week 24), the physician's global assessment of efficacy showed that, out of 495 patients (Fig. 3A), 388 (78.4%) were rated as having "excellent" control (ACT score > 20), 79 (16.0%) as "good" (ACT score 16–20), and 28 (5.7%) as "fair" (improvement with an ACT score ≤ 15), with no patients rated as "poor" (0%). For the Formoflo DPI group (n = 268; Fig. 3B), physicians rated 203 patients (75.7%) as "excellent," 49 (18.3%) as "good," and 16 (6.0%) as "fair." In the Formoflo MDI group (n = 227; Fig. 3C), 185 patients (81.5%) were rated as "excellent," 30 (13.2%) as "good," and 12 (5.3%) as "fair." Both groups showed high efficacy, with a nearly equivalent proportion of "excellent" control reported between the Formoflo MDI and DPI groups.



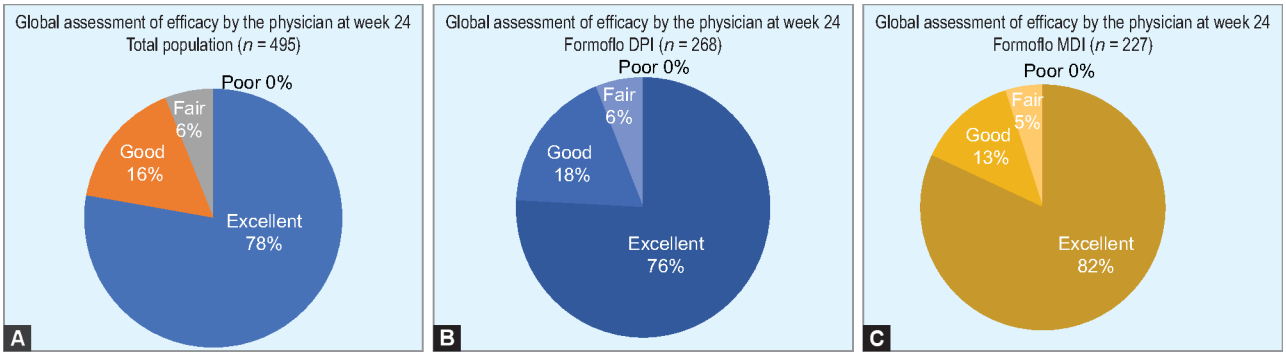
Figs 2A to C: (A) GIC score at week 12 and 24 (end of study)—total population (N = 495); (B) GIC score at week 12 and 24 (end of study)—Formoflo DPI (N = 268); (C) GIC score at week 12 and 24 (end of study)—Formoflo MDI (N = 227)

Safety Evaluation

Figure 4 provides a listing of all AEs reported during the study. A total of 35 AEs were recorded in 35 patients (7.0% of the study population). Of these, 33 were mild (grade I) in severity, while two were of moderate severity. Additionally, two nonsevere exacerbations were observed in patients of the Formoflo MDI group, both of which were determined to be unrelated to the study drug and resolved completely. All other AEs resolved completely, with or without the need for treatment. There were no fatalities during the study, and no patients exhibited any clinically significant alterations in vital signs, systemic examinations, or laboratory parameters throughout the entire study. Furthermore, no pneumonia cases or SAEs were reported during the study period.

Discussion

Asthma contributes to 27.9% of DALYs within the Indian population, with an associated mortality rate of 13.2 per thousand deaths



Figs 3A to C: (A) Global assessment of efficacy by the physician at week 24 (total population, *N* = 495); (B) global assessment of efficacy by the physician at week 24 (Formoflo DPI, *N* = 268); (C) global assessment of efficacy by the physician at week 24 (Formoflo MDI, *N* = 227)

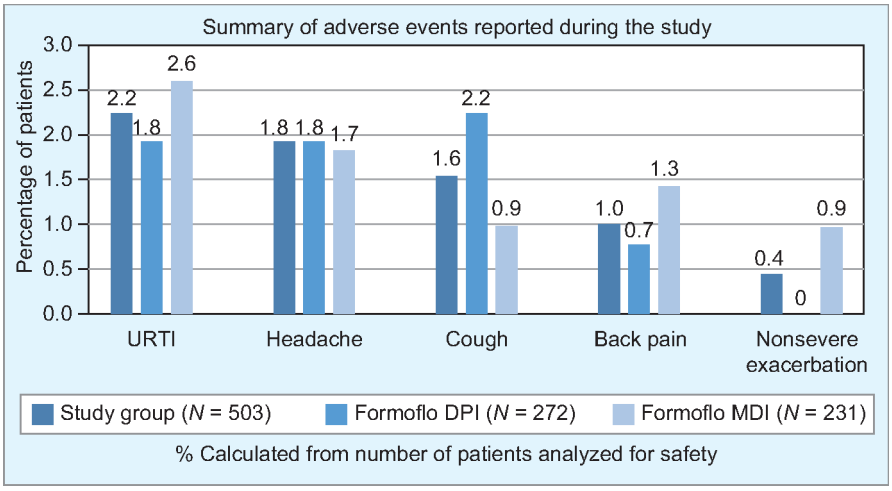


Fig. 4: Summary of adverse events reported during the study

in the country.[4,31] The SWORD survey further highlights suboptimal asthma management in India, with only 53.8% of patients using inhalers, while the rest of the patients relied on oral medications or remained untreated. Among inhaler users, 41.7% received ICS. Although treatment guidelines are available, only 41.3% of patients with poorly controlled asthma and 52.9% of those with a history of hospitalization receive appropriate therapy, highlighting a persistent gap in asthma management.[6] These highlight the need for modification and optimization of asthma treatment strategies in India to improve patient outcomes. While various international studies have examined formoterol fumarate and fluticasone propionate combination, comprehensive data on its use as a first-line therapy in Indian asthma patients remains limited. This real-world evidence study, AFFIRM, evaluated the effectiveness and safety of formoterol fumarate (6 µg) and fluticasone propionate (250 µg) combination, administered through DPI or MDI, in patients with asthma.

The 2024 GINA guidelines (Global Initiative for Asthma) represent a significant advancement in asthma management, emphasizing the need for control-based treatment strategies across various levels of disease severity. The recommendation to use a combination of ICS and LABA, reflects a strategy aimed at addressing both symptom control and long-term risk mitigation across all severity levels of asthma. In asthma management across all treatment steps, the use of ICS-formoterol as both maintenance and reliever therapy is recommended due to its proven efficacy in lowering hospitalization rates and improving patients' quality of life. Given the persistently high burden of asthma-related morbidity and mortality in India, the incorporation of evidence-based, guideline-recommended therapies is crucial for enhancing clinical outcomes in affected patients.[7,13] A recent study by Salvi et al. revealed that India utilizes less than 10% of the required ICS for its estimated 34.2 million asthma patients, contributing to high asthma mortality rates, and emphasized that improving ICS usage could reduce asthma-related deaths by 50%.[32] Thus, implementing the ICS-LABA combination (fluticasone and formoterol) could significantly improve asthma management in India by enhancing symptom control, reducing exacerbations, and potentially lowering asthma-related mortality.

Numerous studies have demonstrated improved lung function with the utilization of the formoterol/fluticasone combination in asthma management.[33–35] Rattu et al. conducted a randomized, open-label, prospective, parallel-group study to assess the effectiveness of two inhalation therapies in 80 bronchial asthma patients over 8 weeks. Group A was treated with formoterol and fluticasone (6/125 µg) twice daily, while group B received salmeterol and fluticasone (50/125 µg) twice daily. In group A, a significant increase in FEV_1 was observed, from 1.34 ± 0.11 to 1.50 ± 0.12 L ($p < 0.001$), along with an improvement in FVC from 2.39 ± 0.15 to 2.48 ± 0.19 L ($p < 0.001$). Similarly, group B demonstrated a significant rise in FEV_1 from 1.36 ± 0.12 to 1.48 ± 0.13 L ($p < 0.001$) and FVC from 2.40 ± 0.15 to 2.49 ± 0.16 L ($p < 0.001$).[36] The current study results align with these findings, further supporting the effectiveness of the formoterol fumarate and fluticasone propionate combination in enhancing lung function in asthma patients.

The combination of formoterol fumarate and fluticasone propionate has been evaluated in several other studies, demonstrating significant enhancement in asthma control and improving the quality of life of asthma patients.[37,38] Ghoshal et al. conducted an observational clinical study of 24-week in persistent asthma patients showed a mean ACT™ score improvement from 14.9 ± 3.26 at baseline to 21.6 ± 2.75, with 80.7% of patients achieving ACT™ score ≥20 by the end of the clinical study (week 24). The findings of the current study are consistent with these results, further supporting the effectiveness of formoterol fumarate and fluticasone propionate combination in enhancing asthma control. This study also highlighted a favorable safety profile for fluticasone/formoterol, reporting AEs in 6.7% of patients, none fatal, and a single nondrug-related SAE. The current study

results align with these findings, confirming a better safety profile with 7.0% mild, fully resolved AEs, no SAEs or fatalities, and no clinical significant changes in laboratory parameters or vital signs, which further support the tolerability of the combination of formoterol fumarate and fluticasone propionate.[39] Further supporting these findings, a 12-month observational study by Backer et al. conducted an evaluation of asthma outpatients who were treated with the fluticasone/formoterol combination therapy as per approved clinical indications. Among the 2116 patients, 83.3% maintained a stable dosage, with 4.8% on a low dose (50/5 µg, two puffs BD), 48.0% on a medium dose (125/5 µg, two puffs BD), and 30.6% on a high dose (250/10 µg, two puffs BD). The mean ACT™ score, which assesses asthma control, increased from 16.3 (4.8) at baseline to 20.4 (4.3) by the end of the study. The percentage of patients attaining well-controlled asthma, defined as an ACT™ score of ≥ 20, rose from 29.4 to 67.4%. Improvements in lung function were noted as well, with the mean FEV_1 increasing from 2.58 to 2.72 L and the mean FVC from 3.32 to 3.43L. The mean AQLQ score improved from 4.7 (1.2) to 5.6 (1.1).[35] The current study further supports the efficacy of the formoterol fumarate and fluticasone propionate combination in improving asthma control and pulmonary function, aligning with previously reported findings.

The findings of the current study demonstrate a strong alignment between patient-reported GIC, with 84.2% of patients reporting "very much improved", and the physician's global assessment of efficacy, with 78.4% of patients achieving "excellent" control, highlighting the significant clinical effectiveness of the treatment at the end of the study (week 24). In addition, DPIs were identified as a preferred alternative to MDIs, possibly due to their ease of use, eliminating the need for inhalation-actuation coordination, and their lack of chlorofluorocarbon propellants, along with potential cost-effectiveness advantages.[40–42] The study further demonstrated that the DPI formulation produced a marginally greater improvement in efficacy outcomes compared to MDI; however, both formulations were equally effective and safe, aligning with findings from previous studies in real-world settings. Formoterol fluticasone combination has been evaluated with other ICS/LABA combinations in asthma in systematic reviews and reviews, which have placed the combination of formoterol fluticasone as an upfront option.[43,44] This combination has also been shown to have a very low tuberculosis risk.[45]

The study's multicentric, real-world design provided useful insights into the effectiveness and safety of the FDC of formoterol fumarate and fluticasone propionate in a diverse cohort of Indian asthma patients, demonstrating significant improvements in pulmonary function, asthma control, and quality of patients' life over a 24-week period while adhering to stringent ethical standards. It offers crucial real-world evidence for Indian pulmonologists, addressing longstanding data gaps in asthma management specific to Indian patients. By bridging these gaps with region-specific findings, the study supports evidence-based, guideline-aligned therapies to optimize asthma outcomes and reduce the disease burden in India. However, the open-label study design may introduce potential bias in patient behavior and adherence due to the lack of blinding between DPI and MDI treatment types, despite the use of spirometry measures to minimize such bias. Additionally, the exclusion of severe asthma patients limits the applicability of these findings to populations with more severe disease, especially in the context of management of chronic asthma. Therefore, further studies including severe asthma patients are necessary to fully evaluate the long-term effectiveness and safety of the FDC of formoterol fumarate and fluticasone propionate, especially under more severe clinical conditions.

Conclusion

The AFFIRM study is the first real-world Indian study to evaluate change in trough FEV1 (from baseline) as a primary endpoint in asthmatics with FDC therapy of formoterol fumarate and fluticasone propionate. The findings of this study indicate that the FDC of formoterol fumarate and fluticasone propionate, administered via DPI or MDI, significantly improves lung functions, asthma control, and health-related quality of life in Indian patients with asthma, demonstrating a safety profile consistent with existing international literature. The findings are in favor of using formoterol fluticasone combinations as an effective first-line therapy in Indian asthma patients.

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REVIEW ARTICLE

Hemophilia: Reducing Treatment Burden with Pen Devices

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Abstract

Hemophilia is a coagulation disorder caused by deficient or absent clotting factors. It is a chronic disease that starts from birth and requires lifelong intravenous administration of antihemophilic factors. Healthcare professionals (HCPs), patients living with hemophilia, and their caregivers have reported concerns regarding the challenges associated with the intravenous route and the deterioration in their quality of life (QoL) due to the frequently repeated infusions necessary to maintain the desired levels of clotting factors. Patients with hemophilia and their caregivers have often voiced their need for easier methods of treatment administration, similar to the way insulin is delivered subcutaneously using a pen. Subcutaneous injection using a pen device is a known way to improve treatment compliance and adherence in patients with chronic diseases. The recent introduction of pen devices for hemophilia treatment administration is expected to reduce the administration burden and improve QoL. The narrative review presents the advantages of pen devices and patient and caregiver attitudes toward these newly introduced pen devices in hemophilia.

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Introduction

Hemophilia is a rare inherited chronic disease (coagulation disorder) characterized by deficiency, reduced activity, or complete absence of clotting factors.[1–3] Hemophilia A (factor VIII deficiency) is more common than hemophilia B (factor IX deficiency), accounting for 80–85% of global hemophilia cases.[1,2] Hemophilia A is underdiagnosed in India.[2] According to a 2019 Indian Council of Medical Research report, there were approximately 80,000–1,00,000 cases of severe hemophilia in India, but only 19,000 cases had been registered with the Hemophilia Federation India.[4] Most patients in India (61.96%) present with hemophilia between 0 and 18 years.[5] Further, the majority (63.29%) had severe hemophilia, and another 22.78% had moderate hemophilia.[5]

Patients with hemophilia have an increased tendency for spontaneous and prolonged bleeding into joints, muscles, and other internal organs, thereby causing damage and pain.[1,6] In pediatric patients with hemophilia, these complications impact their education, play, and outdoor activities.[7] In adult patients with hemophilia, these complications restrict and compromise mobility, daily living, caring for children, and career options.[7] Thus, hemophilia significantly burdens patients, caregivers, and healthcare systems due to high morbidity and poor health-related quality of life (HRQoL), also demonstrated by the large HAEMOcare study conducted in developing nations, including India.[8]

Since deficient or absent clotting factors cause hemophilia, replenishing clotting factors is the absolute lifelong treatment for hemophilia.[1] The World Federation of Hemophilia (WFH) recommends prophylactic administration of antihemophilic factors as the standard of care for hemophilia.[1,2] However, in resource-limited countries like India, episodic (on-demand) clotting factor administration is a more practiced approach.[2,3,9]

Prophylactic treatment improves HRQoL and treatment costs by decreasing bleeding episodes, reducing hospitalizations and emergency department visits, reducing complications like joint damage and pain, and leading a more fulfilling life.[1,2] However, these treatment advantages are limited by the need for frequent and repeated parenteral administrations necessary to maintain the desired levels of clotting factors.[1,7,10,11]

A chronic disease like hemophilia, requiring repeated treatment administration and monitoring, possesses a massive treatment burden.[10] Therefore, a patient-centric approach in a chronic disease aims to relieve the treatment burden and help the affected individuals feel as disease-free as possible and not appear as "patients" to others.[12] Hence, the treatment paradigm of hemophilia is continuously innovating to reduce the treatment administration burden and improve the HRQoL of patients and caregivers. Introducing therapeutics that can be delivered subcutaneously with injector pen devices is a step toward reducing the administration burden.

Pen devices have been the preferred method for self-administering repeated subcutaneous injections of biologics in diabetes, rheumatology, and growth hormone deficiency.[13–16] The recent introduction of pen devices for hemophilia treatment administration is expected to reduce the administration burden and improve HRQoL. The narrative review presents the advantages of pen devices, and patient and caregiver attitudes toward these newly introduced pen devices in hemophilia.

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Hemophilia: Burden of Intravenous Administration

Hemophilia treatments are generally delivered intravenously. The intravenous route of administration has several drawbacks, as outlined in Box 1. Earlier, hemophilia treatments could only be administered in hospitals or clinics.[10] With access to better technology, home infusions have become a reality. However, home infusions are also cumbersome and time-consuming, need people with phlebotomy skills, have venous access issues, and can be painful.[10] Patients with hemophilia may permanently stop prophylactic treatment due to the burden of intravenous infusions.[10] Therefore, intravenous infusions impact treatment adherence and efficacy in hemophilia.[1,3,10,17–19]

Healthcare professionals (HCPs) treating patients with hemophilia identified several treatment administration burden issues in their patients, such as the ability to insert the needle correctly, find good venous access, carry out the infusion steps, and prepare and administer the treatment.[10] The HCPs felt that infusions had an emotional impact on patients because they feared they would lose the venous access or that it might become infected, and they also questioned their ability to self-infuse. For patients who did not have good venous access, there was an additional burden of getting a port or a peripherally inserted central line.[10] These burdens were further enhanced due to the need for repeated and frequent infusions.[10]

People with hemophilia and their caregivers have repeatedly expressed that they experience several challenges (economic, physical, educational, and technical) with these intravenous treatments that impact their QoL.[7,10,20] The patients with hemophilia identified several challenges with the infusion treatments, including packaging, storage/refrigeration of medications, and reconstitution.[7,10] Traveling for treatment, treatment time, treatment schedules and frequency, interference with daily life, pain, skin scarring, and emotional trauma were other concerns of patients with hemophilia and their caregivers.[7,10,11]

People with hemophilia and their caregivers voiced the need for treatments with longer-lasting effects and treatments that could be delivered through an alternative or easier method.[7,20]

Box 1: Drawbacks of intravenous factor concentrates[1,3,10,17–20]

- Coordination of treatment schedules with hospital/clinic staff
- Complicated home infusion scenarios
- Skilled or trained individual's availability for frequent intravenous infusions
- Challenges with venous access
- Considerable time commitment
- Portability
- Injection pain
- Poor treatment adherence
- Reduced quality of life (QoL)
- Emotional impact & fear of stigma

Exploring the Subcutaneous Route for Hemophilia Treatment

Self-management is an important strategy in any chronic disease, known to improve patient HRQoL and adherence to treatment. For patients with chronic diseases such as hemophilia and diabetes that require parenteral treatment administration, self-reliance and compliance can be achieved by improving convenience and ease of treatment administration.

Administering parenteral drugs through a subcutaneous route is a strategy toward self-reliance for treatment administration. The subcutaneous route of administration has been successfully deployed to deliver other biologics (e.g., insulin and growth hormone) and has several benefits over the intravenous route.[2,3,17,19] The subcutaneous route allows self-administration with a much smaller needle size, reduces treatment burden and injection pain, and improves convenience and treatment adherence.[2,3,17,19]

This has been amply demonstrated in diabetes, where patients on insulin therapy self-administer insulin subcutaneously. Many patients with type 2 diabetes (T2D) mellitus also face an insulin injection burden during the T2D disease trajectory due to progressive beta-cell failure.[21] Insulin injection is the only way to replenish complete insulin deficiency for patients with type 1 diabetes (T1D) mellitus.[21,22] Since T1D starts in childhood, just like hemophilia, the treatment administration burden starts early in the life of the patient with T1D and the caregiver.[22]

A recent survey conducted in the US and the UK showed that patients with hemophilia and their caregivers significantly preferred the subcutaneous route over intravenous administration.[23] The challenges with administering hemophilia treatment through the intravenous route were overcome by developing nonfactor products, such as emicizumab and anti tissue factor pathway inhibitors (anti-TFPI), that could be administered through a subcutaneous route.[2,3,17,19,24]

Subcutaneous Administration through Injector Pen Devices

Despite the advantages of subcutaneous drug administration over the intravenous route, traditional ways of injecting medication subcutaneously require vials and syringes. However, patients and caregivers face many challenges while using vials and syringes, such as a cumbersome and time-consuming process (Box 2).[17,21] This impacts treatment adherence, psychosocial well-being, and overall HRQoL.[17]

Ready-to-use prefilled syringes (PFS), auto injectors, and other pen devices overcame the disadvantages of syringes and vials.[26] These devices conferred many advantages for patients and their caregivers, including dose accuracy, improved HRQoL, and others, as shown in Box 3.[1,17,26]

The journey of ready-to-use devices began with the introduction of PFS in the subcutaneous administration landscape.[26] However, PFS use was limited by many manufacturing and other challenges, including compatibility between the drug formulation and the material of the syringe and the rubber stopper; the inability to maintain drug functionality throughout its

Box 2: Disadvantages of administering subcutaneous injections with vials and syringes[17,21,25]

- Cumbersome packaging and storage
- Need for reconstitution
- Possibility of contamination during reconstitution
- Drawing erroneous dosing
- Medication wastage
- Time-consuming as several steps are required for preparing the injection

Box 3: Advantages of pen devices over traditional subcutaneous administration using vials and syringes[1,16,17,21,23,25–28]

- Ready-to-use injection device
- Dose accuracy and better therapeutic efficacy
- Less medication wastage
- Long-term cost-effectiveness
- More flexibility
- More discreet and easily portable
- Quicker to use
- Ease of use and easier administration
- Better patient acceptability and compliance
- Fewer resources (single pen over vials and syringes)
- Reduce needle phobia and injection anxiety
- More socially acceptable

shelf life; and the incompatibility between the formulation's viscosity and the requisite syringe-needle configuration, etc.[26] Further, patients need to manage the force with which they inject the formulation.[26]

Since the introduction of the insulin pen in 1985, using pen devices has been an acceptable practice for subcutaneous self-administration.[12,21] The continuous innovation of pens using a patient-centric approach has revolutionized the HRQoL of patients with chronic diseases and their caregivers.[12,21] These innovations prevented medication wastage by introducing features such as dose dialing and allowing half-unit dose increments.[21] Features such as touch buttons, color-coded cartridge holders, dose magnification windows, audible click with each unit dialed, and prominent dose arrows and labels improved convenience and ease of use for patients of all age-groups.[21,27] Pens were adapted for pediatric patients by creating colorful, discreet designs, memory function, and the ability to inject with reduced force.[21,29] The advent of connected pens and "smart pens" further eased dose calculations, dialing, reminders, and monitoring.[21]

Further patient-reported outcomes show that patients feel more confident in their ability to self-administer the drug with pens, as they find pens "more stable" and "easier to handle" than syringes.[27] Patients perceived pen devices as more socially acceptable and felt that pens allowed better disease (diabetes) self-management than vials and syringes.[27]

Advantages of Pen Devices in Hemophilia: Clinical Evidence

A patient experience study showed that several patients with hemophilia desired a mode of administration similar to an insulin pen.[7]

A recent US and UK survey reported that patients with hemophilia preferred a prefilled pen over vials and syringes.[23] Another recent large utility study conducted in the UK, Canada, and the US showed that people living with hemophilia in these countries assigned a lot of importance to the injection device.[1] Patients with hemophilia and their caregivers reported a significant utility gain with monthly subcutaneous injections with a prefilled pen device vs subcutaneous injections with a syringe and IV infusions.[1] Using less time-consuming and easy-to-use pen devices was expected to improve HRQoL significantly.[1]

Using pen injection devices in hemophilia is a breakthrough that is likely to revolutionize the treatment landscape. No pen devices are available for subcutaneous administration of non factor products like emicizumab. However, pens and microneedle devices have been recommended for precise dosing and reducing drug wastage of emicizumab.[25] Precise dosing is necessary for therapeutic efficacy. Currently, concizumab pen injector are available only for subcutaneous anti-TFPI administration.

Concizumab Pen Device in Hemophilia A or B

Concizumab is a once-daily novel anti-TFPI monoclonal antibody that can be subcutaneously delivered once daily using a prefilled, multidose pen-injector for prophylactic prevention or reduction of bleeding episodes in patients with hemophilia A or B with or without inhibitors.[17,30] Analysis of landmark trials (Explorer 4,[31] Explorer 5,[31] Explorer 7,[32,33] and Explorer 8[34]) demonstrates that subcutaneous concizumab prophylaxis improves HRQoL and reduces treatment burden. The injection is approved in hemophilia A or B patients with inhibitors and shows similar benefits in the ongoing Explorer 8 study in hemophilia A or B patients without inhibitors.[30,33]

The concizumab pen-injector has an easy-to-use mechanism to set the precise dose and is an adapted version of the FlexTouch insulin pen, which demonstrates dosing accuracy (ISO 11608–1 certified) across a wide dose range (10–400–800 µL).[17,30,35] The pen-injector has disposable, single-use small (4 mm long) and thin [32 gauge (G): 0.23/0.25 mm] needles.[17,30] The 4 mm pen needle is the shortest and requires low thumb force, making it more comfortable and easier to use.[21] Pens with 4 mm and 32G needles are the gold standard.[36] They reduce needle pain, restrict the needle to subcutaneous space only, prevent injection from entering muscles, and are also suitable for pediatric patients and those with needle phobia.[21,27,36] Smaller needle size facilitates almost painless drug delivery in everyday life settings.[37]

Patients have reported ease of use, precise dosing, and satisfaction with the concizumab pen-injector. A recent study demonstrated that 98% of the patients using emicizumab or any other factor replacement therapy could independently administer concizumab at their first attempt with an average injection time of 1 minute 21 seconds.[17] In this study, the adult patients had been on treatment for an average of 25 years, and patients cared by caregivers and adolescents had been on treatment for an average of 12 years. The pen-injector was assessed as "easy" or "very easy" to learn and use by 97% of adults and 96% of adolescent participants; 99% found the pen-injector easy to prepare for use; 98% found it "easy" or "very easy to use"; 88% of participants on factor replacement therapies and 82% of participants on emicizumab preferred the concizumab pen injector over their current injection method.[17]

Further, 95% of the participants reported that the pen-injector was easily portable and could be used outside the home; 97% were "very confident" or "extremely confident" that they could correctly use the pen-injector; 84% were "fully confident" that the correct dose was delivered, and 12.5% were "somewhat confident." All the adults and caregivers reported that medication preparation and injection time with the pen-injector was "quick" or "very quick."[17]

Marstacimab Pen Device in Hemophilia A or B

Marstacimab-hncq is a prophylactic anti-TFPI administered subcutaneously with a single-dose prefilled syringe or single-dose auto-injector pen once weekly to prevent or reduce bleeding episodes in adults and adolescents with hemophilia A or B without inhibitors.[38] The phase 3 BASIS study (NCT03938792) demonstrated a significant decrease in annual bleeding rates (ABRs) with marstacimab subcutaneous injection compared to routine prophylaxis with factor products ($p = 0.0376$), and the results were consistent across all hemophilia types and age subgroups.[39] The improvement in HRQoL with marstacimab was non inferior to that achieved *via* routine prophylaxis.[39]

Early results from an ongoing study reported a delivery system success rate of 99.2% by patients and caregivers who administered weekly marstacimab flat-dose using a prefilled auto-injector pen for ≤6 consecutive weeks.[29] Participants had completed the phase 3 BASIS study and had either severe hemophilia A (factor VIII <1%) or moderate to severe hemophilia B (factor IX ≤2%) with or without inhibitors. All the participants could inject the full marstacimab dose with the auto-injector prefilled pen, except one participant at week 2, and all participants reported ease of use.[29] No pen-related adverse event was reported by any patient or caregiver except one incorrect dosing.[30–39]

Future Insights

There is an unmet need to reduce the treatment administration burden in hemophilia. Targeting the subcutaneous route and developing pen devices are expected to reduce the treatment administration burden. The experience with pen devices in hemophilia can be further enhanced by improving injection rates,

customizing injection speed and duration, and developing connected devices to provide injection logs and reminders or real-time stepwise instructions.[16,40]

However, the designs and features of future pen devices in hemophilia should address the requirements and expectations of the end users (patients and caregivers) of all educational and age backgrounds.[12,41] Well-designed questionnaires, surveys, and product prototype testing should be conducted with end users.[12,27,41] Improved patient-centric hemophilia pen devices will likely improve treatment adherence, therapeutic efficacy, and HRQoL.

Conclusion

The subcutaneous route and pen devices are slowly revolutionizing the treatment administration landscape in hemophilia. The review highlights early results demonstrating patient and caregiver acceptance, preference, ease of use, and satisfaction with pen devices over traditional subcutaneous or intravenous hemophilia treatment administration methods.

Ethics Compliance

This is a narrative review and hence does not require EC approval.

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All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

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REVIEW ARTICLE

Expanding the Diagnostic Horizon in COPD: Insights from GOLD 2025 on Early Detection and Comprehensive Assessment

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Abstract

The 2025 update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines redefines the chronic obstructive pulmonary disease (COPD) diagnostic framework by recognizing earlier-stage conditions like "pre-COPD" and "PRISm" (preserved ratio impaired spirometry). This new approach captures patients who display early symptoms or structural changes in the lungs but do not yet meet traditional COPD criteria, marking a shift toward early detection and personalized management. By broadening the diagnostic criteria and promoting advanced imaging and biomarker use, GOLD 2025 offers pulmonologists a more precise, individualized approach to assessing COPD. This article examines the implications of these diagnostic updates for clinical practice, emphasizing the importance of proactive intervention to improve outcomes, slow disease progression, and tailor treatment to the unique profiles of at-risk patients. By embracing diverse pathophysiological profiles, the new GOLD framework underscores the necessity for comprehensive diagnostic tools, including imaging and biomarker analyses, to redefine COPD as a preventable and manageable condition.

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Introduction

Chronic obstructive pulmonary disease (COPD) has traditionally been understood and diagnosed through a narrow focus on irreversible airflow limitation, assessed by spirometric measurements of the forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio. However, this approach often delays diagnosis until significant lung damage has occurred, missing critical opportunities for early intervention. The 2025 update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines represents a paradigm shift by expanding the diagnostic framework to recognize earlier stages of COPD, including the conditions termed "pre-COPD" and "PRISm" (preserved ratio impaired spirometry). These categories capture individuals who may show early symptoms or structural lung changes without meeting the full diagnostic criteria for COPD, thus addressing a broader spectrum of patients at various stages of disease risk.

This expanded framework acknowledges the heterogeneous nature of COPD, where factors like environmental exposures, genetic predispositions, and early lung abnormalities contribute to disease progression long before classic symptoms manifest. By integrating advanced imaging, biomarkers, and a refined understanding of the disease continuum, GOLD 2025 enables clinicians to adopt a proactive approach to COPD management, focusing on early identification and personalized treatment strategies. This article explores the impact of these diagnostic advancements, detailing how they facilitate more effective screening, monitoring, and intervention in COPD care.

Expanded Copd Diagnostic Framework

The 2025 update to the GOLD guidelines redefines the diagnostic framework for COPD by broadening the criteria to recognize earlier stages of the disease. This change addresses gaps in the previous understanding, which focused primarily on diagnosing COPD at more advanced stages, characterized by irreversible airflow limitation. In the past, COPD diagnosis was heavily reliant on the presence of airflow obstruction, measured through spirometry by a postbronchodilator FEV_1/FVC ratio <0.7. However, GOLD 2025 now introduces terms such as "pre-COPD" and "PRISm" to better capture a spectrum of patients who show signs of early disease or are at increased risk of progression but may not yet meet the traditional spirometric criteria for COPD.

Pre-COPD: Identifying Early Indicators

"Pre-COPD" is a new category for individuals who may present with respiratory symptoms (e.g., cough, wheezing, or dyspnea) or structural lung changes (such as emphysema or small airway disease visible through imaging) despite having normal spirometry values. This term allows clinicians to identify patients in whom early structural and functional lung changes are occurring. Recognizing pre-COPD is particularly valuable as it opens the door to early therapeutic interventions that could potentially slow disease progression, reduce symptom burden, and improve overall outcomes.[1,2]

PRISm: Preserved Ratio Impaired Spirometry

The GOLD 2025 also introduces the concept of "PRISm." This category encompasses individuals with a normal FEV_1/FVC ratio (≥0.7) but a reduced FEV_1, indicating impaired lung function without full obstruction. Patients in the PRISm category may have various underlying lung changes that predispose them to developing COPD over time. Research has shown that PRISm patients are at an increased risk of future lung function decline and progression to COPD, particularly if they exhibit symptoms or comorbidities.[3,4]

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Implications for Early Intervention and Prevention

By broadening the diagnostic framework, GOLD 2025 aims to address COPD as a disease with a progressive trajectory that may begin long before traditional diagnostic criteria are met. This expanded view recognizes that multiple factors, including environmental exposures, genetic predispositions, and early-life influences, contribute to COPD risk and progression. Consequently, this redefined approach promotes a shift toward proactive screening and management strategies, particularly for individuals with known risk factors, such as smokers or those with frequent environmental pollutant exposure. Early diagnosis in these cases allows for timely implementation of preventive and therapeutic measures, such as smoking cessation, environmental risk reduction, and, in some cases, pharmacologic intervention.

Incorporating Diverse Pathophysiological Profiles

The updated GOLD guidelines underscore the importance of acknowledging COPD as a heterogeneous disease with varying phenotypes and progression patterns. Patients categorized under pre-COPD and PRISm may exhibit diverse pathophysiological features, including emphysema, airway inflammation, or structural remodeling, that differ significantly from the classic COPD phenotype. This broader understanding encourages clinicians to use a more individualized approach in assessing, monitoring, and treating patients based on their specific disease profile, rather than relying solely on airflow limitation as the defining criterion for COPD.[5,6]

Reinforcing the Need for New Diagnostic Tools and Biomarkers

The new diagnostic categories also highlight the need for more advanced diagnostic tools, such as imaging and biomarkers, to identify early structural changes in the lungs. GOLD 2025 advocates for the integration of such tools alongside traditional spirometry to gain a more comprehensive view of lung health and detect early changes indicative of potential COPD progression. Advanced imaging techniques, such as computed tomography (CT) scans, can reveal subclinical emphysema or small airway disease, while emerging biomarkers could offer insights into the inflammatory and genetic factors driving early disease.[7,8]

Summary

The redefined diagnostic framework in GOLD 2025 acknowledges COPD as a disease continuum that includes early-stage conditions, such as pre-COPD and PRISm, that are detectable before full obstruction develops. This shift toward recognizing at-risk and early-stage patients marks a significant evolution in COPD management. It underscores the importance of a proactive, personalized approach to COPD diagnosis and treatment, aiming to intervene earlier in the disease course to potentially improve long-term outcomes.

Revised Pharmacological Strategies

The 2025 GOLD report introduces updated pharmacological strategies for managing COPD, reflecting an increasing emphasis on personalized medicine and targeting specific inflammatory pathways. These updates incorporate new therapeutic agents, such as ensifentrine and dupilumab, which provide treatment options for patients with specific inflammatory profiles or those who do not respond adequately to traditional bronchodilators and anti-inflammatory agents. The addition of these agents signifies a shift toward understanding COPD not merely as a single disease but as a complex spectrum with varying pathophysiological drivers.

Introduction of Ensifentrine: a Dual-mechanism Therapy

Ensifentrine is a novel phosphodiesterase 3 and 4 (PDE3 and PDE4) inhibitor that operates through a unique dual-action mechanism, combining bronchodilation with anti-inflammatory effects. The PDE3 inhibition primarily facilitates smooth muscle relaxation, resulting in bronchodilation, while PDE4 inhibition reduces inflammation in the airways. Ensifentrine's ability to simultaneously address two key aspects of COPD pathology—airway constriction and inflammation—makes it particularly valuable for patients who have had suboptimal responses to traditional therapies like long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS).[9]

This dual approach is especially relevant for COPD patients with chronic airway inflammation that persists despite standard treatment, as it provides a targeted anti-inflammatory effect without the potential corticosteroid-related side effects. Clinical trials have shown that ensifentrine can reduce exacerbation rates, improve lung function, and enhance symptom control, offering an effective option for individuals with frequent exacerbations or those who have difficulty achieving control with existing bronchodilators.[10]

Dupilumab: Targeting Type 2 Inflammation in COPD

Dupilumab is a monoclonal antibody that targets the interleukin-4 receptor alpha (IL-4Rα), effectively inhibiting the signaling pathways of IL-4 and IL-13, which are central to type 2 inflammation. Type 2 inflammation, characterized by elevated eosinophils and specific cytokine profiles, is increasingly recognized in a subset of COPD patients. This inflammatory phenotype often presents with overlapping asthma-like features, including airway hyper-responsiveness and mucus hypersecretion.

The GOLD 2025 incorporates dupilumab as an option for COPD patients with evidence of type 2 inflammation, particularly those with elevated blood eosinophil levels, who may derive limited benefit from conventional bronchodilators and ICS alone. By targeting the IL-4 and IL-13 pathways, dupilumab addresses the root cause of type 2 inflammation, leading to significant reductions in exacerbation rates and improvements in lung function and quality of life. Dupilumab's ability to reduce exacerbations makes it a valuable choice for patients with frequent hospitalizations or deteriorating lung function despite optimized treatment.[11]

Refinement of Inhaled Therapy Recommendations

The GOLD 2025 also refines the recommendations for the use of inhaled therapies, including bronchodilators and corticosteroids, emphasizing a patient-centered approach. The report updates the guidelines for the combined use of LABA, LAMA, and ICS based on disease severity, symptom burden, and exacerbation history. For instance, patients with high symptom burden and frequent exacerbations are recommended to start or escalate to triple therapy (LABA + LAMA + ICS) to achieve optimal control. For others, ICS withdrawal may be advised, particularly in patients with lower blood eosinophil counts who have a higher risk of pneumonia when on ICS therapy. GOLD 2025 provides updated guidance on how to safely taper and discontinue ICS in these patients to minimize adverse effects.

Additionally, the guidelines outline the importance of adjusting treatment based on patient-reported outcomes and spirometric data, ensuring that therapy aligns with the patient's evolving needs. The updated pharmacological strategy encourages pulmonologists to continuously reassess the effectiveness of treatment and make adjustments to ensure optimal benefit and minimal adverse effects.

Incorporation of Biomarkers for Personalized Therapy

The GOLD 2025 report promotes the use of blood eosinophil counts as a biomarker to guide treatment choices, particularly regarding ICS and biologic therapies like dupilumab. Patients with elevated eosinophil counts are more likely to benefit from anti-inflammatory treatments targeting type 2 inflammation, as this biomarker reflects an underlying inflammatory process that corticosteroids or biologics can address. This biomarker-driven approach reduces the risk of overtreatment, aligning therapy with individual inflammatory profiles and making personalized treatment accessible and clinically relevant.[12]

Biomarkers are not only helpful for selecting appropriate therapies but also valuable for ongoing treatment monitoring. For instance, a rise in eosinophil levels may prompt the initiation of ICS or a biologic agent, while a decrease may indicate an opportunity to reduce or discontinue ICS, thereby reducing the potential for side effects.

Strengthening Nonpharmacological Support with Pharmacotherapy

The GOLD 2025 also emphasizes the role of pharmacotherapy in complementing nonpharmacological interventions, such as pulmonary rehabilitation (PR), smoking cessation, and lifestyle modifications. The integration of pharmacological and nonpharmacological approaches helps to improve patient outcomes by addressing both the physiological and lifestyle factors contributing to disease progression and exacerbation risk. For example, patients who successfully quit smoking or adhere to rehabilitation programs may require lower doses or fewer medications over time, underscoring the importance of a comprehensive COPD management strategy.[13]

Summary

The revised pharmacological strategies in GOLD 2025 reflect a more nuanced, patient-centered approach to COPD management. By incorporating innovative therapies like ensifentrine and dupilumab and by embracing biomarker-driven decisions, these guidelines empower clinicians to tailor treatment to each patient's specific inflammatory profile and symptom burden. This evolution in treatment strategy not only broadens the options available to manage COPD but also enhances the quality of care through more precise and individualized therapeutic interventions.

Focus on Multimorbidity Management

The 2025 GOLD report places a heightened emphasis on the management of multimorbidity in COPD, recognizing the complex interplay between COPD and various comorbid conditions that significantly influence patient outcomes. Multimorbid conditions, particularly cardiovascular diseases (CVD), pulmonary hypertension (PH), metabolic disorders, and other systemic complications, contribute to the overall burden of COPD, impacting exacerbation frequency, hospitalizations, and mortality. The GOLD 2025 report introduces a comprehensive framework to help clinicians address these overlapping conditions effectively, moving toward a treatable-traits approach that encourages tailored, patient-specific management.[14–16]

Cardiovascular Diseases and COPD

Cardiovascular diseases are among the most prevalent and impactful comorbidities in COPD, contributing to increased mortality and morbidity. COPD patients commonly experience heart failure, ischemic heart disease, arrhythmias, and hypertension, often due to shared risk factors like smoking and systemic inflammation. The GOLD 2025 report underscores the need for integrated management strategies that address both respiratory and cardiovascular health to mitigate the risk of cardiovascular events, such as heart attacks or strokes, which are particularly high in COPD patients with exacerbations.

The report highlights evidence showing that managing cardiovascular risk factors—including blood pressure control, lipid management, and anticoagulation where indicated—can reduce exacerbation frequency and improve survival in COPD patients. Additionally, the use of beta-blockers, previously controversial in COPD, is now encouraged in patients with coexisting cardiovascular conditions, as studies have shown they can be safely used without worsening respiratory function.[17]

Pulmonary Hypertension and the PH-COPD Phenotype

Pulmonary hypertension is a recognized complication of COPD, particularly in advanced cases, where chronic hypoxemia and vascular remodeling contribute to increased pulmonary artery pressures. GOLD 2025 identifies PH-COPD as a specific phenotype, emphasizing that this group of patients has distinct management needs and often poorer prognosis. For these patients, targeted management strategies—such as long-term oxygen therapy (LTOT) and careful monitoring of right heart function—are essential to prevent further deterioration.[18]

The GOLD report introduces "treatable traits" specific to PH-COPD, guiding clinicians in selecting appropriate interventions based on individual patient characteristics. This may include therapies that improve oxygenation, reduce pulmonary pressures, and support right ventricular function. By addressing PH directly, these tailored treatments can alleviate symptoms, reduce hospitalizations, and improve quality of life in patients with this complex comorbidity.

Dysbiosis and Its Role in COPD Progression

The 2025 report introduces a new section on dysbiosis, the disruption of the normal microbial balance within the body, particularly within the lungs and gut. Emerging evidence suggests that dysbiosis may exacerbate systemic inflammation, contributing to disease progression and worsening outcomes in COPD. The GOLD 2025 framework advocates for further exploration of microbiome-targeted interventions, such as probiotics, prebiotics, and possibly microbiome-based therapies, which could help restore a healthier microbial environment and reduce inflammation.

Understanding and addressing dysbiosis in COPD management is a step toward a more holistic approach to treatment, recognizing that the microbial ecosystem within the body can significantly impact respiratory health. By acknowledging dysbiosis as a modifiable trait, GOLD 2025 opens new avenues for research and potential therapeutic interventions aimed at stabilizing the COPD disease course through microbiome modulation.[19]

Impact of Climate Change on COPD

The GOLD 2025 takes a pioneering approach by incorporating climate change and environmental factors into the COPD management framework, acknowledging that rising air pollution and extreme weather events pose significant health risks for COPD patients. Poor air quality, particularly high levels of particulate matter (PM), is strongly associated with an increase in COPD exacerbations, while temperature extremes can exacerbate symptoms and increase mortality rates. The report encourages pulmonologists to incorporate environmental considerations into patient care, advising patients on strategies to minimize exposure to pollutants and manage symptoms during extreme weather conditions.

This section reflects a forward-thinking approach to COPD care, recognizing that environmental health is closely tied to respiratory health. By addressing climate-related impacts on COPD, GOLD 2025 encourages preventive strategies, such as advising patients on indoor air quality improvement and reinforcing the importance of vaccinations to protect against respiratory infections that may be more prevalent during extreme weather events.[20]

Metabolic and Systemic Comorbidities

Metabolic disorders, including diabetes, obesity, and osteoporosis, are also recognized as significant comorbidities in COPD, affecting disease progression and patient outcomes. These conditions can lead to increased inflammation, reduced physical activity, and impaired lung function. GOLD 2025 recommends an integrative approach to managing metabolic conditions alongside COPD, encouraging weight management, dietary modifications, and exercise to improve overall health and reduce the systemic burden of the disease.

Additionally, osteoporosis is particularly prevalent in COPD patients, especially those on long-term corticosteroids, due to their increased risk of bone density loss. GOLD 2025 advises routine screening for osteoporosis in COPD patients and recommends preventive measures, such as calcium and vitamin D supplementation, along with consideration of pharmacologic treatment when needed.[21]

Treatable Traits Approach in Multimorbidity Management

A central theme in GOLD 2025's approach to multimorbidity is the "treatable traits" concept, which advocates identifying and targeting specific modifiable traits in each patient. For example, a COPD patient with both CVD and PH may have traits related to systemic inflammation, right heart strain, and reduced physical endurance. Addressing these traits individually allows for a more holistic, tailored approach that aligns with each patient's unique needs, improving both respiratory and systemic outcomes.

This treatable traits model enables clinicians to move away from a one-size-fits-all approach and instead design integrative treatment plans based on the totality of each patient's health profile. This framework not only allows for more effective COPD management but also promotes collaboration between pulmonologists, cardiologists, and other specialists, ensuring a coordinated approach to complex cases with multiple comorbidities.[22,23]

Summary

The GOLD 2025 report's focus on multimorbidity management represents a paradigm shift in COPD care. By recognizing the intricate links between COPD and various comorbid conditions and encouraging a treatable traits approach, GOLD 2025 promotes a holistic, patient-centered management strategy. This comprehensive framework equips clinicians to address COPD as part of a broader health context, targeting the unique needs of patients and ultimately improving quality of life and long-term outcomes in this complex population.

Advanced Nonpharmacological Interventions

The 2025 GOLD report highlights the critical role of advanced nonpharmacological interventions in COPD management, especially in light of pandemic-related challenges and the growing need for accessible, flexible care models. Recognizing that effective COPD treatment requires a comprehensive approach beyond pharmacotherapy, the GOLD 2025 guidelines expand on the importance of PR, self-management education, and telehealth to enhance patient outcomes, improve adherence, and increase access to care.

Pulmonary Rehabilitation as a Cornerstone of Nonpharmacological COPD Management

Pulmonary rehabilitation remains a cornerstone of COPD management due to its well-documented benefits, which include reduced symptoms, improved exercise tolerance, and enhanced quality of life. PR programs typically involve a multidisciplinary approach with components such as exercise training, education, nutritional support, and psychosocial care. GOLD 2025 continues to emphasize that all COPD patients with moderate to severe disease, particularly those with a history of exacerbations, should be encouraged to participate in PR.

The guidelines note that PR not only improves physical function but also decreases the risk of future exacerbations and hospitalizations. By enhancing the patient's ability to perform daily activities and cope with breathlessness, PR serves as a nonpharmacological strategy that has a lasting impact on COPD progression and patient well-being. GOLD 2025 also highlights the importance of individualized PR programs that can be tailored to meet each patient's specific needs, maximizing engagement and benefit.[24]

Telehealth and Virtual Rehabilitation: Expanding Access and Adaptability

One of the significant advancements in GOLD 2025 is its endorsement of telehealth and virtual rehabilitation as viable and effective alternatives to in-person care. The pandemic underscored the importance of remote care models, which ensure continuity of care even during times of restricted access to healthcare facilities. Virtual rehabilitation includes remote delivery of exercise training, education, and self-management support through online platforms, video conferencing, and wearable technology.

Telehealth allows healthcare providers to monitor patients' symptoms, progress, and adherence to exercise programs from a distance. Virtual PR has been shown to offer comparable benefits to traditional in-person programs, improving exercise capacity, reducing symptom severity, and maintaining quality of life. This model also offers additional advantages by eliminating geographical barriers, reducing the burden of travel, and making care accessible to patients who may face mobility or transportation challenges. Virtual PR programs are particularly valuable for rural populations and underserved communities, where access to PR facilities may be limited.

Self-management Education: Empowering Patients in COPD Care

Self-management education is another essential component of nonpharmacological COPD interventions, equipping patients with the knowledge and skills to manage their condition effectively. GOLD 2025 underscores the value of patient education in promoting adherence to treatment, recognizing exacerbation symptoms, and implementing appropriate self-care practices, such as breathing exercises and energy conservation techniques.

Self-management programs are designed to improve patients' ability to make informed decisions, manage symptoms, and avoid triggers. Such programs have been shown to decrease hospital admissions, improve health-related quality of life, and enhance patient confidence in managing their condition. Telehealth platforms can enhance self-management education by providing access to educational resources, symptom trackers, and communication tools that enable patients to engage with their healthcare providers as needed.

Incorporating Digital Health Tools and Remote Monitoring

The GOLD 2025 highlights the potential of digital health tools and wearable technology in the remote management of COPD. Remote monitoring devices can track key health metrics, such as oxygen saturation, heart rate, and physical activity levels, allowing for continuous, real-time monitoring. By analyzing this data, clinicians can detect early signs of exacerbation, monitor adherence to exercise regimens, and adjust care plans based on the patient's current health status.

Digital tools, including mobile apps and online platforms, enable patients to log symptoms, receive automated reminders for medication adherence, and access health education materials. GOLD 2025 supports the integration of these tools to enhance patient engagement and adherence while providing healthcare professionals with valuable insights into the patient's day-to-day experience with COPD.[25]

Physical Activity and Exercise Training: Essential Components of Rehabilitation

Physical activity and structured exercise training are crucial components of PR and are strongly encouraged in the GOLD 2025 guidelines. Regular physical activity is linked to improved cardiorespiratory fitness, reduced symptoms, and a lower risk of exacerbations. GOLD 2025 advocates for integrating exercise training into both in-person and virtual PR programs, encouraging patients to maintain an active lifestyle despite the limitations posed by COPD.

Exercise training can be tailored to each patient's capability and gradually increased as they build endurance and strength. For remote or virtual settings, telehealth platforms provide exercise videos, tutorials, and support from healthcare providers to ensure patients can perform exercises safely at home. Physical activity is not only a treatment modality but also a preventive strategy, helping to slow disease progression and improve resilience against COPD exacerbations.

Psychosocial Support in Pulmonary Rehabilitation

The psychosocial aspect of COPD care, including mental health support, is a growing focus in GOLD 2025. Patients with COPD frequently experience anxiety and depression, which can worsen symptoms, reduce quality of life, and affect treatment adherence. GOLD 2025 encourages the integration of mental health support within PR programs, whether through counseling, peer support groups, or telecounseling sessions.

Providing access to psychosocial resources as part of nonpharmacological care is particularly valuable in a virtual format, where patients may feel more comfortable engaging in counseling from home. By addressing the psychological impact of COPD, clinicians can support overall well-being and help patients manage the emotional burden of their disease.

Summary

The GOLD 2025's advanced nonpharmacological interventions reflect an expanded, patient-centered approach to COPD care. By emphasizing PR, telehealth, self-management education, and the use of digital health tools, GOLD 2025 promotes accessible, flexible, and effective treatment options that enhance patient engagement and adherence. The integration of virtual rehabilitation models and remote monitoring technologies offers innovative pathways for delivering high-quality COPD care, particularly for patients who face barriers to in-person services. Through these comprehensive, multidisciplinary strategies, GOLD 2025 provides a robust framework for improving outcomes, quality of life, and overall health in COPD patients.

Updated Vaccination

The GOLD 2025 report places a renewed emphasis on vaccination as a preventive measure in COPD management, recognizing the heightened susceptibility of COPD patients to respiratory infections, which can lead to exacerbations, hospitalizations, and even mortality. By aligning with the latest CDC guidelines, GOLD 2025 aims to improve protection against common respiratory pathogens, specifically through updated recommendations for influenza, pneumococcal, and respiratory syncytial virus (RSV) vaccines. These revised guidelines underscore the importance of vaccinations in reducing the disease burden and stabilizing patient health by preventing acute respiratory infections that often worsen COPD symptoms.[26]

Influenza Vaccination: Annual Immunization as a Critical Preventive Measure

Influenza poses a significant threat to COPD patients, who are more likely to experience severe illness, complications, and exacerbations if infected. GOLD 2025 reaffirms the importance of annual influenza vaccination for all individuals with COPD, emphasizing that vaccination reduces the risk of influenza-related morbidity and mortality.

Influenza vaccines are typically updated yearly to match circulating virus strains, making annual vaccination necessary for effective protection. GOLD 2025 advises healthcare providers to encourage their COPD patients to receive the vaccine each year before the flu season starts, usually in the fall. Notably, patients should be informed of the availability of high-dose or adjuvanted influenza vaccines, which may provide enhanced protection for older adults and those with weakened immune systems, who are at higher risk of complications.[27]

Pneumococcal Vaccination: Preventing Bacterial Pneumonia and Associated Complications

Pneumococcal infections are a common cause of bacterial pneumonia, which can be particularly severe in individuals with COPD. GOLD 2025 emphasizes the critical role of pneumococcal vaccination in preventing these infections, recommending both pneumococcal conjugate and polysaccharide vaccines to maximize protection.

The CDC currently recommends two types of pneumococcal vaccines for adults with COPD:

- PCV20 (20-valent pneumococcal conjugate vaccine): This vaccine provides broad coverage against pneumococcal strains and is recommended as a single dose.
- PPSV23 (23-valent pneumococcal polysaccharide vaccine): This vaccine offers extended protection against additional pneumococcal strains not covered by the conjugate vaccine.

The GOLD 2025 recommends that COPD patients who have not previously received any pneumococcal vaccine should receive the PCV20 vaccine alone or as a series with the PPSV23 if indicated, following CDC's age- and risk-specific guidelines. For patients with a history of pneumococcal vaccination, providers should assess the timing and type of previous doses to determine the need for additional doses. These recommendations are particularly important for patients with severe COPD and older adults, who are at an increased risk of pneumococcal infections.[28,29]

Respiratory Syncytial Virus Vaccination: New Recommendations for COPD Patients

For the first time, GOLD 2025 includes recommendations for the RSV vaccine, reflecting the availability of new vaccines for adults and the recognition of RSV as a

significant respiratory pathogen in older adults and those with chronic lung disease. RSV can cause severe lower respiratory tract infections in COPD patients, leading to exacerbations and complications.

Recent advances have led to the development of effective RSV vaccines specifically targeting adults aged 60 and older, a population that includes many COPD patients. GOLD 2025 recommends that COPD patients within this age-group receive the RSV vaccine to reduce the risk of severe RSV infection and associated respiratory complications. As RSV vaccines are a new addition to adult vaccination schedules, healthcare providers are encouraged to discuss the benefits and availability of the RSV vaccine with their COPD patients, particularly those with advanced disease or frequent exacerbations.[30]

Integrated Vaccination Strategy for COPD Patients

The GOLD 2025 promotes a coordinated approach to vaccinations, advising healthcare providers to use routine visits as opportunities to assess patients' vaccination status and ensure they are up to date with all recommended immunizations. The report underscores that vaccinations are a key component of COPD preventive care, helping to reduce the frequency and severity of respiratory infections, which in turn minimizes exacerbation risk, hospital admissions, and overall healthcare costs.

By incorporating a proactive, integrated vaccination strategy, healthcare providers can help maintain stability in COPD patients and improve their quality of life. This preventive approach is particularly relevant for COPD patients with comorbidities or those at high risk of severe infection, as even minor respiratory infections can have substantial impacts on disease progression and long-term outcomes.

Future Directions: Continuous Monitoring and Updates in Vaccination Recommendations

The GOLD 2025 acknowledges that the landscape of infectious diseases and vaccines is continually evolving, and vaccination recommendations may be updated as new data and vaccines become available. The report encourages ongoing research and surveillance of vaccine efficacy and safety, particularly among COPD patients, who may have unique immune responses to vaccines. This commitment to evidence-based updates ensures that vaccination strategies remain aligned with the latest scientific developments, offering the most effective protection for COPD patients against emerging respiratory threats.

Summary

The updated vaccination recommendations in GOLD 2025 emphasize a proactive stance on infection prevention in COPD through influenza, pneumococcal, and RSV vaccinations. These guidelines aim to provide comprehensive protection against common respiratory infections, thereby reducing exacerbations and supporting better long-term disease management. By aligning with CDC guidelines and introducing RSV vaccination, GOLD 2025 strengthens the role of immunization in COPD care, equipping healthcare providers to better safeguard their patients against infection-related complications.

Impact of Climate Change

The 2025 GOLD report marks a significant step forward by addressing the impact of climate change on COPD for the first time. This new focus reflects an evolving understanding of COPD as not only a disease of the airways but also one profoundly affected by environmental factors beyond traditional risk factors like smoking. Climate change, with its influence on air quality, temperature extremes, and pollutant exposure, poses direct and indirect threats to respiratory health, particularly for COPD patients who are more vulnerable to fluctuations in environmental conditions. By recognizing the links between climate change and COPD, GOLD 2025 encourages pulmonologists and healthcare providers to adopt a broader perspective on COPD management, integrating awareness of environmental determinants into patient care.

Air Pollution: A Major Driver of COPD Exacerbations

One of the most pressing environmental risks associated with climate change is air pollution, which has been extensively linked to increased COPD exacerbations and accelerated lung function decline. Air pollutants such as $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) can penetrate the respiratory tract, leading to inflammation, oxidative stress, and exacerbation of respiratory symptoms. COPD patients are especially susceptible to air pollution because of their already compromised lung function and heightened inflammatory response.

The GOLD 2025 emphasizes that COPD patients should minimize exposure to high levels of air pollution, which are increasingly common in urban areas and during specific times of the year when climate conditions exacerbate pollution levels. The report encourages healthcare providers to educate patients about air quality indices (AQI) and suggest practical strategies, such as avoiding outdoor activities during peak pollution times, using air purifiers indoors, and wearing protective masks on high-pollution days to reduce exposure.[31]

Temperature Extremes and Respiratory Health in COPD

Climate change has led to more frequent and severe temperature extremes, including both heatwaves and cold spells. These extremes pose significant health risks for COPD patients, as both high and low temperatures can exacerbate respiratory symptoms and increase the risk of hospitalization. Hot weather can cause dehydration and exacerbate breathlessness, while cold weather can lead to bronchoconstriction, airway inflammation, and a heightened risk of respiratory infections.

The GOLD 2025 underscores the importance of temperature management for COPD patients, especially during extreme weather events. Recommendations include staying hydrated, maintaining indoor air quality, using humidifiers in winter, and ensuring that patients have access to air conditioning or heating as needed. The guidelines also advise patients to monitor local weather forecasts and take preventive measures to avoid unnecessary exposure to extreme temperatures, which can help prevent symptom exacerbation and maintain stability in COPD management.

Wildfires and Other Climate-related Disasters: A Growing Concern for COPD Patients

Wildfires, increasingly common due to climate change, pose severe health risks, especially for COPD patients who are sensitive to smoke and PM. Smoke from wildfires can travel long distances, impacting air quality in areas far from the actual fire location. Exposure to wildfire smoke can cause a sharp increase in respiratory symptoms, trigger exacerbations, and lead to acute respiratory distress in vulnerable populations, including those with COPD.

The GOLD 2025 recommends that COPD patients in wildfire-prone regions stay informed about air quality alerts and take measures to protect themselves during fire events. This may include staying indoors, using HEPA filters, and keeping windows closed. For healthcare providers, the guidelines suggest

incorporating preparedness for climate-related events into patient education, helping COPD patients plan for emergencies and minimize smoke exposure during wildfire events.[32]

Environmental and Social Inequalities in COPD Care

Climate change disproportionately impacts individuals in lower socioeconomic brackets who may have limited access to healthcare, live in high-pollution areas, or lack resources for air conditioning or heating during temperature extremes. GOLD 2025 highlights the role of environmental and social inequalities in COPD care, acknowledging that some patients may face greater challenges in protecting themselves from environmental triggers due to financial or geographic constraints.

The report encourages healthcare providers to consider these disparities when developing COPD management plans, offering guidance on low-cost strategies to reduce environmental exposure and improve respiratory health. This could include education on monitoring AQI, using simple household interventions to improve air quality, and providing resources for patients with limited means to manage their environment.

COPD and the Role of Climate-related Respiratory Infections

Climate change is also associated with the spread of respiratory infections, such as influenza and RSV, which can be particularly harmful to COPD patients. Warmer temperatures and humidity changes influence the distribution and seasonality of pathogens, potentially leading to more frequent or severe outbreaks. GOLD 2025 emphasizes the need for vaccinations and preventive measures to protect COPD patients from infections that could exacerbate their condition during climate-related changes in infectious disease patterns.

Vaccinations against influenza, pneumococcus, and RSV are highlighted as essential preventive steps, and healthcare providers are encouraged to stay vigilant about emerging infectious risks linked to climate change. By aligning infection prevention strategies with environmental health considerations, GOLD 2025 seeks to protect COPD patients from the dual threat of infection and climate-related respiratory challenges.

Integrating Climate Awareness into COPD Management

The GOLD 2025 promotes the integration of climate awareness into routine COPD care, encouraging pulmonologists and healthcare providers to proactively consider environmental triggers in patient assessments. This approach includes discussing the impacts of air quality, temperature extremes, and other climate-related factors during patient visits, helping individuals with COPD make informed choices to reduce environmental risks. For instance, providers can recommend digital tools or apps that offer real-time air quality and weather updates, enabling patients to make lifestyle adjustments that minimize exposure to environmental stressors.

Additionally, the guidelines advocate for a collaborative approach that involves public health initiatives and policy measures to reduce air pollution and mitigate the health impacts of climate change. The involvement of policymakers, public health agencies, and community organizations is essential to create a supportive infrastructure that safeguards vulnerable populations, including COPD patients, from environmental risks associated with climate change.[33]

Summary

The inclusion of climate change in the GOLD 2025 report marks a forward-thinking approach to COPD management, recognizing that environmental factors play a crucial role in disease progression and symptom exacerbation. By addressing air pollution, temperature extremes, wildfires, and infectious disease risks, GOLD 2025 offers comprehensive guidance for managing COPD in an increasingly unpredictable climate. This expanded framework empowers healthcare providers to incorporate climate-related considerations into patient care, enhancing protection against environmental threats and promoting resilience in COPD patients. Through proactive strategies and patient education, GOLD 2025 seeks to improve long-term outcomes for individuals with COPD in the face of climate challenges.

Enhanced Spirometric Criteria and Imaging Utilization

The GOLD 2025 report introduces important updates to spirometry standards and imaging guidelines aimed at enhancing the precision and reliability of COPD diagnosis, monitoring, and treatment. These enhancements reflect a commitment to providing pulmonologists with detailed, evidence-based tools that support a more nuanced understanding of disease severity, progression, and structural changes in the lungs over time. The updated guidelines on spirometry and imaging align with GOLD's overarching goal of refining COPD management through early diagnosis and individualized care.

Refined Spirometric Standards: Pre- and Postbronchodilator Testing

Spirometry remains a fundamental tool for diagnosing and assessing the severity of COPD, primarily by measuring the FEV_1 and the FVC. GOLD 2025 elaborates on spirometric criteria with updated pre- and postbronchodilator testing standards, particularly in Table 1, which provides guidance on measuring and interpreting changes in lung function after bronchodilator administration. This distinction between pre- and postbronchodilator measurements helps in distinguishing COPD from other respiratory conditions, such as asthma, by assessing the reversibility of airway obstruction.

The revised spirometry criteria emphasize the importance of accurately measuring the FEV_1/FVC ratio to confirm nonreversible airflow limitation, which is the hallmark of COPD. The postbronchodilator FEV_1/FVC ratio remains the gold standard diagnostic criterion, with a value <0.7 confirming COPD. However, the guidelines now provide additional context for identifying patients at risk who may not yet meet this threshold but still exhibit symptoms or structural changes associated with COPD. This shift allows for more inclusive monitoring of individuals who may be in early stages or at risk of progression to full COPD.[34]

Introduction of "Lower Limit of Normal" and Z-scores

The GOLD 2025 encourages the use of the "lower limit of normal" (LLN) and z-scores alongside the fixed FEV_1/FVC ratio for interpreting spirometric results. While the fixed ratio of 0.7 is widely used, it can sometimes lead to misclassification, especially in older adults who may have reduced lung elasticity, resulting in lower FEV_1/FVC ratios even without COPD. Conversely, younger individuals with COPD may have ratios >0.7 due to the natural variability in lung function across ages and body sizes.

The LLN and z-scores address these issues by accounting for individual variations, providing a more precise reference for diagnosing airflow limitation based on age, sex, height, and ethnicity. The LLN represents the fifth percentile of a healthy population, meaning that values below this threshold suggest abnormal lung function. Incorporating these additional metrics helps pulmonologists avoid both under- and overdiagnosis, improving the accuracy of COPD diagnosis and the ability to track disease progression across different patient populations.[35]

Table 1: Key updates in spirometry standards and imaging utilization in GOLD 2025

Aspect	*GOLD 2025 update*	*Clinical implication*
Spirometry standards	Emphasizes both pre- and postbronchodilator testing to assess reversibility of airflow obstruction	Helps distinguish COPD from asthma and identify COPD patients with nonreversible airflow limitation
FEV_1/FVC ratio	Reaffirms postbronchodilator FEV_1/FVC <0.7 as the primary diagnostic criterion for COPD	Standardizes COPD diagnosis based on irreversible airflow limitation
LLN	Encourages use of LLN and z-scores to adjust for individual variations in age, sex, height, and ethnicity	Reduces misclassification, especially in older adults and younger individuals with atypical lung function
Imaging utilization	Expands use of CT imaging for assessing lung structure, including emphysema and small airway disease	Complements spirometry by detecting structural changes, especially in early or atypical cases of COPD
Quantitative imaging	Supports adoption of quantitative imaging (e.g., lung density, airway wall thickness) and AI-based analysis	Provides standardized, objective measurements that enhance accuracy and enable early detection of structural changes
Disease severity and progression	Stratifies COPD severity based on imaging findings such as emphysema extent and air trapping	Assists in tailored treatment planning and timely adjustments to management based on progression risk
Combined assessment approach	Advocates for integrated use of spirometry and imaging for comprehensive COPD assessment	Facilitates a holistic view of COPD, supporting early diagnosis, accurate staging, and a personalized treatment plan

Expanded Role of Imaging in COPD Management

The GOLD 2025 places an increased emphasis on imaging, particularly chest CT scans, as a complementary tool to spirometry for assessing lung structure and diagnosing COPD-related abnormalities, such as emphysema and small airway disease. While spirometry remains the primary diagnostic tool, imaging provides valuable insights into structural changes that spirometry alone cannot capture, enabling a more comprehensive assessment of the disease.

Computed tomography imaging can reveal areas of emphysema, airway wall thickening, air trapping, and other structural lung changes associated with COPD. These structural findings are particularly valuable for identifying patients with "pre-COPD" or "PRISm" phenotypes, where early lung changes occur before traditional spirometric criteria indicate COPD. GOLD 2025 recommends using imaging to assess the extent of emphysema and monitor disease progression, especially in patients with persistent symptoms or at high risk of progression. These insights allow for tailored treatment planning, including early intervention strategies that may slow or prevent disease progression.[36]

Assessing Disease Severity and Progression through Imaging

Imaging plays a crucial role in assessing disease severity and progression, particularly in advanced cases of COPD. GOLD 2025 provides guidance on how to utilize imaging findings to stratify disease severity based on the extent of emphysema, air trapping, and other structural abnormalities. This stratification can help clinicians determine the most appropriate interventions, from pharmacological treatments to nonpharmacological options like PR.

By monitoring changes in lung structure over time, imaging enables clinicians to assess the effectiveness of treatments and identify rapid disease progression, allowing for timely adjustments to the management plan. For instance, a significant increase in emphysema detected through CT imaging may indicate the need for more aggressive treatment, while stable imaging results could support a conservative approach focused on maintenance and preventive care.

Advancements in Quantitative Imaging and Artificial Intelligence Integration

The GOLD 2025 guidelines acknowledge the growing role of quantitative imaging techniques, such as automated CT analysis and artificial intelligence (AI) tools, in COPD assessment. Quantitative imaging uses software algorithms to measure lung density, airway wall thickness, and emphysema extent, providing standardized, objective data that enhances the accuracy of disease assessment. AI-driven tools can assist in analyzing complex imaging data, identifying subtle structural changes that may not be easily visible to the human eye.

These advancements in imaging technology support more precise and consistent measurements, enabling clinicians to detect early structural changes and evaluate treatment effects with greater objectivity. GOLD 2025 encourages the adoption of these technologies, particularly in research and specialist settings, as they become more widely available and accessible. By incorporating quantitative imaging and AI analysis, clinicians can gain deeper insights into each patient's unique COPD profile, facilitating a more personalized approach to care.

Combining Spirometry and Imaging for a Comprehensive COPD Assessment

The GOLD 2025 emphasizes the complementary roles of spirometry and imaging, advocating for an integrated approach that uses both tools to provide a full picture of lung function and structure. While spirometry is effective for diagnosing airflow limitation and monitoring functional decline, imaging offers critical insights into structural abnormalities and can reveal early changes that spirometry might miss.

For example, a patient with mild airflow limitation on spirometry but significant emphysema visible on imaging may benefit from closer monitoring and targeted interventions to address disease progression. Conversely, patients with normal imaging but abnormal spirometry results may represent different COPD phenotypes, potentially guiding different therapeutic approaches. This combined approach enables a more comprehensive assessment, supporting early diagnosis, accurate staging, and tailored management strategies based on both functional and structural data.[37]

Table 1 captures the essence of the updated spirometry and imaging standards in GOLD 2025, emphasizing how these refinements aim to improve diagnostic precision and enable a more personalized approach to COPD management.

Summary

The enhanced spirometric criteria and imaging guidelines in GOLD 2025 offer pulmonologists refined tools to accurately diagnose, stage, and monitor COPD. By incorporating LLN and z-scores, emphasizing pre- and postbronchodilator testing, and expanding imaging utilization, these updates provide a more nuanced framework for understanding COPD as a heterogeneous and progressive disease. The integration of quantitative imaging and AI further supports a personalized approach, enabling clinicians

to identify early structural changes, tailor interventions, and optimize long-term outcomes for COPD patients.

Conclusion

The GOLD 2025 update introduces a transformative approach to COPD diagnosis, moving beyond the traditional criteria of irreversible airflow limitation to encompass early disease stages like pre-COPD and PRISm. This broadened framework, supported by advanced diagnostic tools such as imaging and biomarkers, equips clinicians with enhanced capabilities for detecting early lung changes and assessing disease risk before significant damage occurs. By emphasizing early intervention, personalized management, and the diversity of COPD phenotypes, GOLD 2025 sets the foundation for a more effective and individualized COPD care model. As pulmonologists integrate these new guidelines into clinical practice, the potential to slow disease progression, reduce symptom burden, and improve long-term patient outcomes becomes increasingly achievable. This proactive stance redefines COPD not as an inevitable consequence of aging and exposure but as a manageable and potentially preventable condition, marking a critical advancement in the field of pulmonary medicine.

Take-home messages from GOLD 2025 COPD guidelines updates:

- Expanded diagnostic scope: GOLD 2025 introduces earlier-stage diagnostic categories, "pre-COPD" and "PRISm," allowing clinicians to identify and manage patients at risk of COPD progression before significant airflow limitation occurs.
- Proactive intervention: Recognizing early symptoms and structural lung changes enables timely intervention, which can potentially slow disease progression, reduce exacerbations, and improve long-term outcomes.
- Personalized management: GOLD 2025 emphasizes individualized care by tailoring interventions based on each patient's unique COPD phenotype and pathophysiological profile, rather than relying solely on airflow limitation as the defining criterion.
- Role of imaging and biomarkers: Advanced diagnostic tools, such as CT imaging and biomarkers, are integrated into COPD assessment, providing detailed insights into lung structure and inflammatory profiles that support early diagnosis and monitoring.
- Spirometric innovations: The updated spirometry standards in GOLD 2025 encourage the use of the LLN and z-scores alongside traditional FEV_1/FVC ratios, enhancing diagnostic accuracy and reducing misclassification.
- Importance of treatable traits: The guidelines promote a treatable-traits approach, targeting modifiable risk factors and comorbid conditions for a holistic management strategy that addresses both respiratory and systemic health in COPD.
- New pharmacological options: New therapeutic agents, such as ensifentrine and dupilumab, offer targeted treatment for COPD patients with specific inflammatory profiles, broadening options for those unresponsive to conventional therapies.
- Nonpharmacological interventions: GOLD 2025 supports telehealth and virtual rehabilitation, ensuring continued access to PR, self-management education, and remote monitoring for patients facing barriers to in-person care.
- Climate change and environmental awareness: GOLD 2025 recognizes the impact of environmental factors, such as air pollution and temperature extremes, on COPD severity, urging providers to incorporate environmental risk-reduction strategies into patient education.
- Prevention focused on vaccination: Updated vaccination recommendations for influenza, pneumococcus, and RSV protect COPD patients from infections that exacerbate symptoms, highlighting the importance of preventive care in disease management.

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REVIEW ARTICLE

A Review of the Efficacy of Nanodrug Delivery Systems: Is It Worth the Hype?

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Abstract

Nanodrug delivery systems are gradually becoming the current "talk of the town" due to their efficiency in treating different diseases in a more advanced manner when compared to conventional drug-delivery systems. It is well known that drugs can be given through various routes of administration, such as the popular oral, subcutaneous, and intravenous routes. It is quite surprising that formulating these same drugs as nanoparticles (NPs) and administering them to the patient could produce better results. Different studies have shown the effects of nanodrug delivery systems in targeting cancer cells, ameliorating pulmonary arterial hypertension, and providing improved treatments for ophthalmic conditions such as glaucoma. In most studies, nanodrug delivery systems have been shown to exhibit targeted action at the desired site or organ, low toxicity, and fewer systemic side effects. These new insights can provide an enhanced understanding of the benefits of NP formulations of drugs, as well as open up new pathways for future creative techniques in addressing emerging medical conditions. Furthermore, these formulations generally consist of polymer- or liposome-based or coated NPs, as they are easily biodegradable, meaning they have a higher ability to disintegrate and, at the same time, are not harmful to living tissues, thereby displaying greater compatibility. New connections can be established through the utilization of NPs in the treatment of emerging diseases worldwide. Data from these studies could provide a foundation for groundbreaking and innovative strategies in coping with or fighting even the recent COVID-19 pandemic.

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Introduction

Whenever a patient is admitted to a hospital and diagnosed with any sort of disease or disorder, familiar or unfamiliar, the physician tends to start the patient on a regimen consisting of different medications. The patient is expected to follow unique schedules for each of the prescribed drugs, some taken *quaque die* or *bis in die*, meaning once or twice daily, respectively. Generally, these drugs can also be differentiated according to their route of administration, with a few injected intravenously and the majority given orally in the form of tablets. Pharmacokinetically, the pathway of any drug can be explained by the four critical processes of absorption, distribution, metabolism, and excretion.

The active components of the drug reach the systemic circulation and are distributed to various tissues of the body, including the specific dysfunctional tissues or organs. This conventional method of drug delivery has many drawbacks, however, such as causing severe adverse effects, allowing only a small dose of the drug to reach the proper site of action, and the fact that some drugs can easily be degraded by gastrointestinal (GI) secretions. Hence, researchers have already taken up the challenge of creating or modifying existing drugs in a new form that can be more beneficial to patients, such as the emergence of nanodrug delivery systems.

Nanoparticles (NPs) are tiny substances not visible to the human eye and are sized at the nanoscale, that is, under 100 nm.[1] NPs are not simple in their composition and consist of three distinct layers: (1) the surface layer, operationalized with a range of small molecules, metal ions, surfactants, and polymers; (2) the shell layer, chemically different from the core, permitting absorbance of the drug onto its surface; and (3) the core, constituting the inner material and representing the central portion of the NP.[2] Thus, these NPs possess significant physical and chemical properties that enable them to participate in the innovative combination of nanotechnology and medicine. Due to their ultrafine size, NPs are easily taken up by the target organ, helping them to permeate and retain inside the tissues while producing minimal side effects.[3] In addition, the use of nanodrug delivery systems can improve the safety and effectiveness of therapeutic agents, lowering toxicity and preventing possible difficulties such as low water solubility and poor bioavailability.[3]

Potential Therapeutic Applications of Nanoparticles

Targeting Cancer Cells

Cancer is one of the leading causes of death worldwide, and more people are being affected by carcinogenic substances as the years pass. Cancer is a condition in which cells act abnormally and start proliferating at a rate beyond the usual borders, forming masses of cancer cells called tumors that can eventually spread to different parts of the body. Chemotherapy and radiation are currently the treatments available to slow down the progression of cancer in a patient. Although chemotherapy destroys the rapidly dividing cells in an attempt to eliminate cancer and prolong a person's life, it also kills the surrounding healthy cells, weakening the person's immune system and exhibiting serious side effects such as hair loss, GI disturbances, and others. On that account, it is crucial to specifically target the cancer cells or tumors without affecting the normal function of healthy tissues. This is the point where nanodrug delivery systems/nanocarriers come into play, as they are highly selective in releasing the loaded anticancer agent at a high concentration along with a reduced systemic distribution.[4] pH-responsive nanocarriers, especially, react to the acidic environment of the tumor, exposing a larger surface area to the drug.[5]

The design of the nanocarriers helps researchers achieve these optimal characteristics. In a recent study,

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nanocomposites containing iron oxide (Fe_3O_4) NPs embedded in chitosan (CS) polymer and coated with reduced graphene oxide (rGO) were invented.[4] In this design, graphene oxide (GO) acts as a surfactant to stabilize hydrophobic molecules, but due to its low solubility, it has been coated with the polymer CS.[6] The use of CS NPs has favored the development of nanodrug delivery systems since it is a natural, biodegradable polymer with enhanced bioavailability properties. Likewise, CS has an excellent ability to inhibit tumor cells, with an improved drug-loading capacity, and in the acidic environment of a tumor site can distribute the drug molecule to a larger extent.[4] In addition to CS, other polymers can form a spherical structure with a hydrophilic shell and a hydrophobic inner layer, enabling the storage of compounds with low water solubility in the heart of the mice.[6] The anticancer drug primarily used in this fabrication was doxorubicin (DOX), and Fe_3O_4 acted as a magnetic agent. While investigating the field emission-scanning electron microscopy (FE-SEM) images, it was found that the interactions between the rGO and Fe_3O_4 allowed for systematic drug loading, with a maximum of 95% of DOX molecules loaded onto the nanocomposite and released on the active surface.[4] A nanocarrier of nanoscale graphene oxide (NGO) and polyethylene glycol (PEG) helped release DOX in a parallel fashion due to the feeble hydrogen bonding.[7] In another study conducted to investigate the effects of anticancer auraptene (AUR)-NPs, the AUR-loaded penta-block and tri-block NP also displayed a sustained and controlled release of the drug, inhibiting the HT-29 colon cancer cells' growth rate.[6]

This proves that a high amount and concentration of a drug can be loaded onto the nanocarrier or NP, ensuring that more of it can reach the targeted site of action. The multidrug resistance effect that cells tend to exhibit can be prevented when cancer cells are treated with polymeric NPs containing drugs, since DOX-loaded rGO/Fe_3O_4/CS/folic acid (FA) nanocomposite was transported *via* the receptor-mediated endocytosis mechanism, being more easily absorbed.[4] Furthermore, the magnetic aspects involved in nanocarriers open the door for the active transport of drug molecules, concentrating on the tumor region.[8] Toxicity studies of the zebrafish suggested no toxic effects or abnormalities of the nanocomposite.[4]

Nanoeye Drop Formulations

Administration of eye drops may look like a simple task—the person tilts their head back and pulls their lower eyelid to form a pouch, then squeezes the bottle so that one or two drops fall into the pouch. But does that guarantee that those eye drops will be absorbed properly into the eye? Well, the answer is no, because even when applied correctly and completely, most of the liquid is drained by the nasolacrimal duct, having very poor bioavailability. Also, the compounds in eye drops lose their penetrating power due to the presence of the cornea, a structure at the surface of the eye, which prevents hydrophilic or bigger-sized materials from entering the eye.[9] NP drug delivery systems show promising results in this aspect as well, providing new applications for future ophthalmic treatments.

Dynamic light scattering (DLS) measurements of the trimethyl-lock (TML) prodrug NPs in aqueous media showed a maximum transmittance of 20% at an 800 nm wavelength. When compared to Azopt (glaucoma eye drops available commercially), the transmittance of TML prodrug NPs was higher by a hundredfold, since the maximum transmittance of Azopt was only 0.2%.[9]

When examining the hydrolysis rate of the nanoeye drops in the harvested aqueous humor of rats, the TML prodrug NPs were spontaneously hydrolyzed and released some of the brinzolamide, and upon further testing with the eyes of Sprague Dawley (SD) rats, produced the expected ocular hypotensive effects.[9] Again, NPs in eye drops penetrate the cornea with ease due to their minute size and "water-fearing" nature, leading to a decrease in intraocular pressure (IOP).[10] Additionally, the histological sections of the rat cornea were assessed for any toxicity after the administration of TML prodrug nanoeye drops, and no damage occurred in the tissues.[9] According to the evidence established in this study, it can be inferred that if Azopt and TML prodrug nanoeye drops were placed on a balance, TML prodrug nanoeye drops would weigh more because of their superior merits and high efficiency in treating glaucoma.

Attenuation of Pulmonary Artery Hypertension

Pulmonary artery hypertension (PAH) is a progressive condition identified by high blood pressure in the pulmonary artery along with increased pulmonary vascular resistance. If left untreated, it can lead to right ventricular failure and eventually death.[3] Even in improving lung disorders like PAH, NPs and nanodrug delivery systems have initiated a massive impact since their manipulation can aid in targeting a specific drug to the lungs. Intravenous prostacyclin or epoprostenol are generally the pharmacological treatments to improve the PAH condition, but it is inconvenient and, as previously mentioned, causes serious adverse effects.[3] ONO1301, a synthetic molecule, exhibits prostacyclin activity for a long duration and is also an inhibitor of thromboxane synthase, so if created in the form of nanospheres—ONONS—it can provide benefits in treating patients with PAH.[3] Results of the conducted experiment depicted that treatment with ONO1301/ONONS increased hepatocyte growth factor (HGF) levels in the supernatant, suppressing the proliferation of pulmonary smooth muscle cells (PASMCs) and decreasing the levels of inflammatory markers like transforming growth factor-beta (TGF-β), interleukin-1 beta (IL-1β), and IL-6.[3] HGF levels have also been correlated with the inhibition of inflammation in the lungs of PAH rats, alleviating the intensity of PAH.[11] Particularly focusing on the tissue distribution of these nanospheres, it is clear that there was a significant accumulation of ONONS in the lungs of the PAH rat, without any drastic changes in the other organs between the normal and PAH rats.[3]

In a similar study on PAH, a different nanoformulation containing an iron-based metal-organic framework (MOF), nano MIL-89, loaded with sildenafil, was tested to check the way it improves the condition.[12] The nano MIL-89 readily absorbed >90% of the sildenafil during loading, and within the first 60 minutes, sildenafil began to work on the mouse aorta, causing vasodilation and relaxing the vessels.[12] Once again, NPs have demonstrated their efficiency in affecting only the necessary organ, not any of the surrounding tissues or organs. Subsequently, a greater quantity of the drug can be loaded onto the NP, making it easier to release the drug over longer periods.

Bridging Connections to the Recent Pandemic

The world is still suffering from the deadly coronavirus, or COVID-19, which all of a sudden froze day-to-day lives and forced everyone to adapt to new ways of living, like wearing face masks, maintaining social distancing, quarantining, implementing lockdowns, and, not to forget, conducting online classes. The innovative strategies in formulating drug-loaded NPs can help in some way in recovering from this pandemic. COVID-19 is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which infects different parts of the respiratory system, mainly the lungs, and spreads from the mucous membranes of the upper and lower respiratory tract to other cells of the body, generating a sequence of immune responses.[13] Drugs that could

treat COVID-19 have to be able to target the main protease, M^{pro}, which plays an important role in mediating viral replication and transcription.[14] The ideology is that if it's possible to alter any of these drugs that could be potentially used in the treatment of COVID-19 in the future in the form of NPs, then the drugs will specifically concentrate and focus on the lungs and the respiratory tract. Thus, when a patient appears to have early symptoms of COVID-19 and is dealing with the initial stage of infection, these NP formulations will have the ability to improve their condition and prevent the worsening of their symptoms. Nevertheless, the process will be time-consuming and expensive, with several preclinical (*in vitro* and *in vivo* studies) and clinical trials before confirming its use in treating the disease.

Potential Drawbacks of Nanodrug Delivery Systems

Although the minute size of NPs allows them to enter the cells and tissues to provide targeted action easily, the same size can become a problem if the necessary precautions are not taken when formulating them. NPs are so small, and, due to this reason, they can lead to difficulties in inhalation and can irritate or even damage the lungs.[15] Therefore, the researchers should be careful while preparing the drug–NP combinations. Moreover, the steps involved in producing nanodrug delivery systems can be costly and require a lot of time to formulate unique compositions.

Conclusion

Utilizing NPs in the medical field as carriers for different drugs has contributed new knowledge to build future opportunities in treating emerging diseases. Therefore, nanodrug delivery systems are indeed worth the hype. The therapeutic goals that nanodrug delivery systems could achieve sound optimistic but still have some room for improvement. Reassuring, through multiple studies, that these NPs do not cause any toxicity and systemic side effects is a key element to progress any step further. Nanotechnology in medicine and pharmacy has an excellent scope, and its prospects seem to be high in the upcoming years.

Statement of Originality

We hereby declare that this submission is entirely our own work, in our own words, and that all sources used in researching it are fully acknowledged, and all quotations properly identified. The work has not been published or submitted elsewhere and is completely original.

Author Contributions

Daisy P Pugazhenthi came up with the idea and topic of interest and wrote the first draft. Ramya A and Dheenadhayalan Murugavel revised the draft and made the necessary corrections. Karthickeyan Krishnan and Shanmugasundaram Palani made further suggestions and approved the final draft of the article.

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UPDATE ARTICLE

Clinician's Health?

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Abstract

Usually, people are under stress because of their own health issues, but clinicians are under stress because of others' (patients') health, and for them, they put their own health at stake. Here, by clinician, we mean every specialty of healthcare professionals (HCPs), physicians and surgeons.

Clinicians are precious and their health is equally important. Unfortunately, most of the clinicians are not in good health because of the challenging and demanding needs of the profession, such as reading a lot while dealing with difficult cases and competition to cope with others. Most of the clinicians have a false belief that they are doing well, so they will not get any problem, or they themselves will take care of their health, and another very important fact is that most of them have little faith in their own colleagues, and this bitter truth must be accepted.

Doctors need their own clinicians because despite their medical knowledge, they face a unique set of challenges such as exposure to high-stress, long working hours, altered sleep due to shift duties and irregular eating habits and non-nutritious diet, less time for self-care, and imbalance between family, professional and social life as well as stigma around mental health and treatment are sufficient to neglect their own health. They must have a sensitive physician to manage their health, like their patients, as family members of the doctors do not know whom to contact in case of emergency or the doctor's ill health.

Doctors are not immune to health issues such as mental health, physical strain, burnout or infectious diseases, and various chronic diseases. Having their own doctor helps ensure they receive the unbiased healthcare they need, allowing them to continue caring for others effectively.

Doctors play an essential role in maintaining the health of society, yet their own health is often compromised due to the stress of the demanding profession. Chronic conditions such as obesity, diabetes, hypertension (HT), coronary artery disease (CAD), thyroid disorders, and cancer are highly prevalent among HCPs, and the reasons are long working hours, sleep deprivation, emotional strain, and lack of time for self-care. By prioritizing regular health check-ups, stress management, physical activity, and a healthy working environment, and a balance between social, familial, and professional life, doctors can improve their own health.

The key takeaway is adopting a holistic approach to doctors' well-being, which includes physical, mental, and emotional support, combining individual responsibility with institutional backing. Doctors should be empowered with the tools, resources, and cultural support they need to prioritize their own health to make society healthy.

Large-scale surveys are required to find out the exact prevalence of various acute and chronic conditions among HCPs and how they are tackling them.

Note: By clinician, we mean every specialty of doctors (HCPs), physicians, and surgeons. Terms such as physician, clinicians, doctors, and HCPs are used synonymously in this write-up.

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Introduction

Clinicians are precious and their health is important; usually, people are under stress because of their own health, but clinicians are under stress because of patients' health. Here, by 'clinician,' we mean doctors of every specialty. Unfortunately, many of the clinicians are not in good health because of the challenging profession, the demanding needs of academics to cope in a competitive world, and less time to think about their own health. It is observed that clinicians neglect their health due to lack of time, stress, sedentary lifestyle, finances, and higher socioeconomic status.[1] Clinicians are also human beings and need psychological satisfaction just like patients for their health, but unfortunately, time, familial and social responsibilities come in between. There are no data representing the actual clinician's health compared to nonclinicians, and whatever data available from small studies do not represent the actual picture; no data are available for how many clinicians consult other clinicians regularly for their own health.

Discussion

Clinicians are a creamy layer of society, and their health is important, as they work under stress, often dealing with life-threatening situations, long working hours, a huge number of patients, administrative tasks, lack of autonomy in institutions, and emotional trauma, which are important reasons for stress that make them susceptible to various health issues.

Clinicians, despite their expertise in healthcare, are often the worst patients in terms of adherence to treatment, follow-ups, routine preventive screening, and consultation with a clinician. "Medical student syndrome" is a condition where medical students, while studying a disease, convinced that they have the symptoms of that illness, without a real medical diagnosis. "Doctor syndrome" is not a recognized medical term, but refers to medical students or those with a lot of medical knowledge, who are overly concerned about their own health.[2]

Clinicians usually suppress their symptoms because they always project themselves as "healers" and not the "sufferer." The Medscape-2021 national physician burnout, depression, and suicide report revealed 42% of physicians burned out, 24% feel depressed, and higher rates of suicidal ideation in demanding specialties.[3]

Clinicians' ill health is due to less frequent medical advice for their own health, either because they feel they can manage themselves, or because of fear of being perceived as weak, or they do not have faith in colleagues, or social and financial reasons, or a combination of many of these reasons. This self-reliance can lead to untreated or undertreated medical conditions and worse long-term outcomes. An important fact is that stressed residents made more mistakes than their nonstressed peers, which may lead to medical negligence, aggression, and, in due course of time, many lawsuits, which may further increase their mental stress.[4]

About 40% of clinicians experience burnout, which may result in insomnia, anxiety, and depression.[5]

Clinicians often struggle to prioritize preventive healthcare for themselves, despite being aware of its importance again, because of the demanding profession, lack of time for personal care, regular exercise, healthy eating, and other self-care practices.[6]

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Clinicians, particularly in emergency departments, intensive care units, and infectious disease specialties, are exposed to a wide range of infections, making them more susceptible to serious and resistant infections.[7]

We have discussed mental health at length because mental ill health leads to chronic stress, which is contributing to many chronic conditions, such as obesity, diabetes mellitus (DM), hypertension (HT), and coronary artery disease (CAD). Doctors are often seen as the epitome of health, entrusted with diagnosing, treating, and guiding patients for a healthy life; at the same time, they themselves are at heightened risk of these chronic conditions.

Twenty percent of healthcare professionals (HCPs) had obesity, 53% had DM, and 24% had HT in a study conducted among 490 government doctors in Gujarat, India.[8]

Prevalence of DM among doctors and nurses was 25.4 and 5.6%, respectively; while HT was 29.4 and 13.7%, overweight was 36.5 and 12.9%; and obesity was 15.1 and 3.2% among nurses, and the factors responsible are almost similar stress, sedentary lifestyle, irregular eating habits, and high sugar intake, urban-based doctors and high-stress specialties.[9]

Hypertension affects around 30–40% of doctors worldwide. Prabhakaran et al. investigated the 26.7% HT and risk factors, which include age, body mass index (BMI), family history of HT, and physical inactivity. Urban areas and higher socioeconomic status were also associated with increased prevalence.[10]

Coronary artery disease affects 5–10% of doctors across the globe, and cardiologists and surgeons are at higher risk; the factors responsible are similar, plus smoking.[11,12]

Although clinicians may arguably be healthier than others due to their medical expertise, little is known about the actual health of clinicians compared to the general population. National Health Interview Survey found that obesity, DM, and HT were lower in HCPs compared to the general population, but still considerably higher.[13]

Incidence and prevalence of various chronic diseases, such as DM, HT, CAD, and obesity, are different in different study populations. A study in Singapore's large hospital assessed the modifiable cardiovascular risk factors among clinicians and nonclinicians, revealing that nonclinicians had a higher prevalence of obesity, systolic blood pressure, and DM compared to clinicians. Another study in Gaza found that 65% of clinicians were either overweight or obese; type 2 DM and HT have a higher prevalence.[14,15]

Worldwide, 15–20% of female HCPs suffer from thyroid issues; it is known that thyroid disorders, especially subclinical hypothyroidism, are eight to ten times more common in females, and major contributing factors are exposure to radiation among the radiologist, orthopedic surgeon, and interventional cardiologist; work stress, smoking, and pollution-induced inflammation.[16]

About 5–8% of doctors have some form of cancer, more so in high-risk specialties such as oncology and radiology, orthopedic surgeons, and interventional cardiologists, because of high exposure to radiation and carcinogens. The overall incidence of cancer was 27% lower in the clinicians than in the nonclinicians.[17]

What Clinicians Should Do?

- Clinicians must have a clinician who can screen them at regular intervals, just like mediclaim policy premiums, and this must be mandatory and known to family members.
- Clinicians must prioritize their own health by organizing working hours, regular breaks, delegating tasks, and rebalancing their professional, family, and social lives.
- Regular health check-ups should be a habit. Though clinicians are health experts, early detection of chronic illnesses can help manage them more effectively and prevent long-term complications.
- Doctors should practice stress management techniques such as meditation, yoga, or deep-breathing exercises as a stress reliever.
- Incorporating physical activity into daily routines is essential, such as short walks during breaks, stretching, or engaging in exercise during free time.
- Nutritious and healthy eating, avoiding the temptation for junk food, or skipping meals during hectic hours.
- Clinicians should overcome the stigma associated with their problems and consult their professional colleagues.

Conclusion

- The medical profession is inherently stressful. The pressure to care for patients, combined with the emotional toll of dealing with life-threatening medical conditions, high workload, and long working hours with minimal breaks and busy schedules, leads to mental stress, making it difficult to prioritize their own health and develop many chronic conditions, such as HT, CAD, and DM.
- Clinicians play an important role in maintaining the health of society, but their own health is often compromised due to the demanding professional needs, altered sleep due to shift duties, irregular and non-nutritious diet, and imbalance between family, professional, and social life.
- Clinicians usually present themselves as "healers" and not the "sufferer," and the prevalent stigma that "clinicians do not fall sick" prevents them from seeking treatment.
- Lack of time, financial reasons, and social inhibitions (like waiting for their turn to consult a consultant, lying in the ward with patients), and negligence are the main reasons to neglect their health.
- Large-scale surveys are required to find out the exact prevalence of various acute and chronic conditions and long-term complications among clinicians and nonclinicians.
- Clinicians, despite their medical knowledge, must have a clinician who must be known to family members, as family members of the clinician do not know whom to consult in case of emergency for clinician's ill health.
- Clinicians are not immune to health problems, and having their own clinician helps ensure the unbiased health care they need, allowing them to continue caring for others (patients) effectively.

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POINT OF VIEW

The Weight of the Matter in Diabetes Care

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Abstract

The weight of the matter in diabetes care challenges the traditional glucose-centric model of diabetes management and argues for a paradigm shift toward prioritizing weight—specifically fat reduction—as the central lever in achieving metabolic health. Drawing insights from landmark trials such as SURMOUNT and Diabetes Remission Clinical Trial (DiRECT), as well as real-world Indian experience with agents like oral semaglutide, the article emphasizes that visceral adiposity is a root cause driving insulin resistance, beta-cell dysfunction, and multiorgan complications. Addressing weight early can lead to improved glycemic control, cardiorenal protection, and even disease remission—outcomes that far exceed glucose lowering alone. In the Indian context, where the "thin–fat" phenotype and central obesity present unique challenges, this weight-first approach demands culturally sensitive strategies and redefined success metrics beyond body mass index (BMI) or hemoglobin A1c (HbA1c). With the advent of incretin-based therapies, clinicians now have the tools to treat upstream rather than manage symptoms downstream. The piece calls for a unified therapeutic strategy that targets excess adiposity to deliver both glycemic and vascular legacy benefits—reframing weight not merely as a number but as a powerful determinant of risk, response, and recovery.

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The Weight of the Matter in Diabetes Care: Prioritizing What Truly Matters

At a recent national diabetes conference, a thought-provoking debate took place on a pressing question: what should be the main focus in managing diabetes—glucose, weight, or vascular protection? The discussion featured leading experts from across the country, and the final consensus—both from the panel and the audience—favored weight as the most crucial factor.

This piece builds on those arguments, aiming to reflect the clinical reality many of us face. It suggests that by giving timely attention to weight management—especially fat reduction—we may not only achieve better sugar control but also improve long-term heart, kidney, and liver health.

From Glucose Numbers to Fat Loss: A Shift in Thinking

For years, diabetes control meant managing sugar levels—hemoglobin A1c (HbA1c), fasting, and postmeal glucose. That approach still matters, but it no longer tells the full story. Increasingly, we are learning that excess fat—especially around the liver and pancreas—is what drives insulin resistance and disease progression. The underlying issues go beyond sugar to include adiposity, low-grade inflammation, and early beta-cell stress.[1] This change in understanding has been reinforced by newer evidence. The SURMOUNT-1 and SURMOUNT-2 trials, which studied tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) dual agonist, showed that people with obesity—even without diabetes—experienced up to 22.5% weight loss and marked health improvements. More strikingly, among those with prediabetes, over 95% returned to normal glucose levels, suggesting that remission is possible if weight is addressed early.[2]

This is not about choosing one number over another. It is about facing the real cause and treating it before complications take root.

Why Weight Wins: The Clinical Cascade

Glucose Control

Losing 10–15% of body weight can set off a positive chain reaction.[2] It reduces liver glucose production, improves insulin sensitivity, and helps restore beta-cell function. In early diabetes, this shift may work as well as—or sometimes better than—starting medication. In the SURMOUNT-1 trial, participants who lost ≥15% of their weight showed meaningful HbA1c improvements, even if they were not diabetic to begin with.

Cardiorenal Benefits

Obesity is no longer just a background risk factor—it is a direct contributor to heart and kidney disease.[2] Medications like tirzepatide, which help with weight loss, also lower inflammation, improve blood vessel health, and protect multiple organs. This broader benefit makes them more than just glucose-lowering agents.

Remission is Realistic

Several studies now suggest that with enough weight loss, diabetes remission is possible—especially in the first few years after diagnosis.[3] In SURMOUNT-1, over 95% of people with prediabetes returned to normal glucose levels. Results from calorie restriction trials like Diabetes Remission Clinical Trial (DiRECT) and real-world programs like the Indian Diabetes Prevention and Remission Program with Calorie Restriction (I-DAPA CR) support this idea: targeting weight early may help reverse the disease altogether.

"Weight is the lever. When you shift it, everything downstream—glucose, kidneys, heart, liver—aligns."

The time has come to move away from chasing sugar numbers alone. A weight-first approach addresses the root so the rest can follow.

Weight as the Common Denominator

When we look at the triad—glucose, weight, and vascular protection—it is clear that weight sits at the root.[4] Glycemia often shows up late in the course of metabolic dysfunction, while adiposity, especially visceral fat, is an early and active driver of the disease process. Addressing weight early can lead to wide-ranging benefits: better insulin action, preserved beta-cell function, and improvements in blood pressure, lipid levels, and inflammatory markers. It helps us tackle several problems at once—without treating them in isolation.

Glycemic legacy produced by conventional hypoglycemic agents or vascular legacy produced by antihypertensives can be achieved by agents like glucagon-like peptide-1 receptor agonist (GLP-1RAs)

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or GIP/GLP-1 dual agonism, which target body weight, especially visceral/ectopic adiposity, over and beyond reduction in subcutaneous adiposity, thus reducing the ongoing inflammation and endothelial damage.

In everyday clinical practice, weight tends to be the first domino. Once we manage it well, sugar control and vascular health often improve alongside. This does not mean glucose or cardiovascular care takes a backseat, but it does suggest that weight may be the one thread that ties them all together.

Put simply, weight is not just another number; it is the multiplier.

Beyond Glucose: Reframing the Indian Weight Narrative

In India, the challenge is not just about how much weight is gained; it is also about where and how fat is stored.[4] Many patients appear lean on the outside but carry high levels of visceral fat and develop insulin resistance early. This "thin–fat" phenotype calls for a shift in thinking, one that moves beyond conventional body mass index (BMI) cutoffs and embraces more culturally and biologically relevant measures. Medications like tirzepatide show promise, but alongside pharmacological tools, personalized lifestyle strategies—such as bite counting, mindful eating, meal sequencing, and early satiety cues—can play a major role, especially when rooted in Indian habits and food patterns.

Doctors may need to help patients redefine success, not just in terms of blood sugar levels, but in terms of sustainable fat loss that delivers long-term health gains. The revised Indian guidelines on obesity now highlight that central adiposity in Asian Indians carries a higher metabolic risk, even at lower BMIs. This calls for early, tailored interventions that go beyond generic targets and speak to the patient's unique risk profile.

Real-world Echoes: Oral Semaglutide in Indian Practice

This shift toward weight-first strategies is not just theoretical; it is being reflected in real-world Indian practice as well.[5] Our clinical experience with oral semaglutide mirrors outcomes seen in the PIONEER study series, demonstrating both meaningful glycemic control and sustained weight loss. Among Indian patients with early diabetes or metabolic syndrome, these effects are translating into tangible clinical gains. Oral agents with weight benefits may soon play a more prominent role in practical remission strategies, complementing newer GLP-1 receptor agonists and dual incretin therapies.

Final Word: The Weight of the Matter in Diabetes Care

This shift in thinking is more than academic—it reflects the lived reality of clinicians managing a complex and progressive disease. It reminds us that while sugar levels deserve attention, weight remains the upstream lever. Though microvascular complications are linked to the duration of dysglycemia, the macrovascular clock starts ticking even before diabetes is diagnosed. This means we must act upstream—targeting excess adiposity early to prevent both micro- and macrovascular damage downstream.

Rather than addressing each cardiometabolic complication in isolation, targeting weight—particularly visceral and ectopic adiposity—offers a unified therapeutic pathway. Agents such as GLP-1 receptor agonists and dual GIP/GLP-1 agonists do not just lower glucose or blood pressure—they address the root metabolic disturbance. In doing so, they replicate the glycemic legacy of older hypoglycemics and the vascular legacy of antihypertensives—but by acting earlier and deeper through anti-inflammatory and endothelial-restorative pathways.

Diabetes care must evolve from symptomatic control to root-cause targeting. We now have the evidence, the tools, and the clinical insight to shift gears.

Because in the end, weight does not just measure mass—it predicts risk, reveals opportunity, and signals a chance at reversal. By acting on it early, we may finally tip the balance—not just toward control but toward long-term healing and remission.

In diabetes, chasing sugar may win the battle, but losing weight wins the war.

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Unicuspid Aortic Valve Stenosis in a Child

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A 15-year-old male presented with a history of dyspnea for the last 1 year. Dyspnea progressed gradually, and he deteriorated to New York Heart Association (NYHA) class III for the last 3 months. History of paroxysmal nocturnal dyspnea (PND) was present for the last 1 month. He also had a history of dizziness during playing. His electrocardiogram (ECG) showed left ventricular hypertrophy with strain. His echocardiography showed the presence of unicuspid aortic valve (UAV) in parasternal short axis view, with typical teardrop appearance in systole (Fig. 1). The valve was unicommissural (Fig. 2). The peak gradient across the valve was 71 mm Hg, and the mean gradient was 46 mm Hg (Fig. 3). Left ventricular ejection fraction was 19.4%.

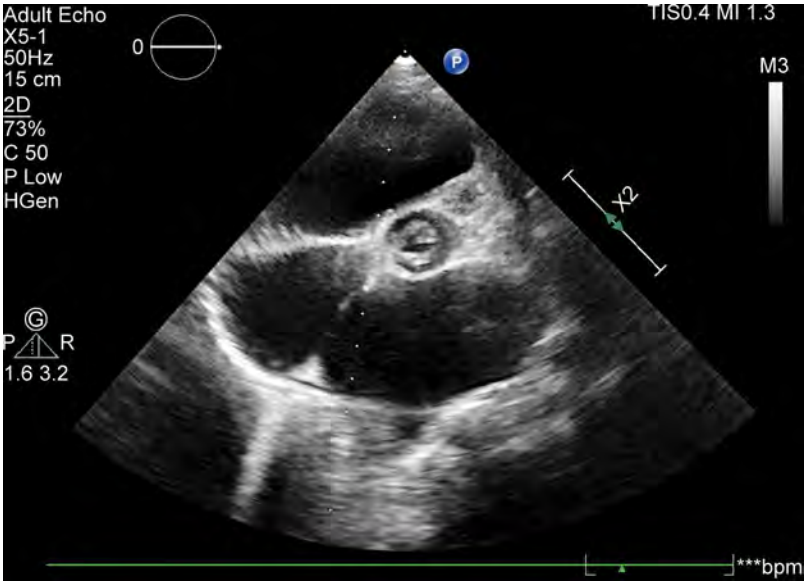

Fig. 1: Parasternal short axis view showing UAV in systole

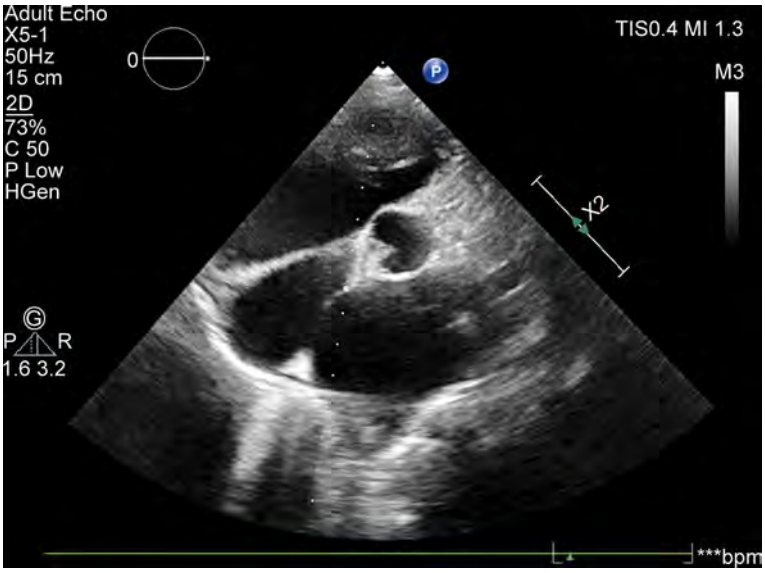

Fig. 2: Parasternal short axis view in diastole showing unicommissural unicuspid valve

The aortic valve normally has three cusps. Bicuspid aortic valve is the most common anomaly found in the aortic valve. UAV is a form of anomaly that is very rare and is found only in around 0.02% patients with aortic stenosis when echocardiography is used to find the prevalence and around 5% of patients when surgical series are seen.[1] On the basis of number of commissures, it is of two forms: Unicuspid unicommissural (UUAV), when one commissure is present, and when no commissure is present, it is called unicuspid acommissural (UAAV).[2] However, since many patients are asymptomatic, the true incidence in population is not known and may be much more than seen on echocardiography or at surgery.[3] UAAV form presents early in life, whereas UUAV has relatively late presentation. So, if seen in adults, it is almost always of UUAV variety.[4] Collins et al.[5] have shown that decreased number of cusps in the aortic valve cause more pathological changes in cusps as well as in aorta. Patients with UAV may present with pure aortic stenosis, pure aortic regurgitation, but more commonly with mixed lesion (aortic stenosis with aortic regurgitation).[6] Our patient had pure aortic stenosis and was of UUAV type.

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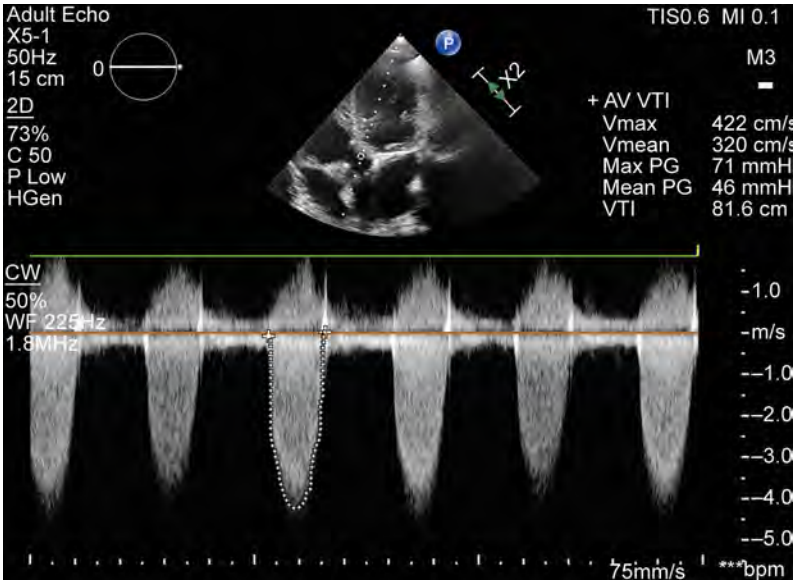

Fig. 3: Continuous wave Doppler showing gradients across the valve, suggesting severe aortic stenosis

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Letter to the Editor regarding "Ventilator-associated Pneumonia: A Prospective Observational Study"

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Respected Sir/Madam,

We read with considerable interest the article titled "Ventilator-associated Pneumonia: A Prospective Observational Study" by Natarajan et al., published in the May 2025 issue of JAPI.[1] We commend the authors for addressing a highly relevant and underexplored topic in the Indian critical care setting. The prospective design, adherence to standard diagnostic criteria, and detailed microbiological analysis make this study a valuable contribution to the literature on healthcare-associated infections, particularly in resource-limited environments.

The study effectively highlights the incidence and high mortality associated with ventilator-associated pneumonia (VAP), and its findings reinforce the need for strict implementation of infection control protocols and VAP prevention bundles in intensive care units (ICUs). The inclusion of local antimicrobial resistance data, especially the high prevalence of extensively drug-resistant (XDR) organisms, provides critical insights for empirical antibiotic stewardship.

However, we would like to respectfully highlight a few limitations that, if addressed in future studies, could further enhance the impact and generalizability of the findings:

- The authors have defined VAP clinically and on the basis of radiographic changes, as per standard practice. However, in some cases, radiographic infiltrates can be nonspecific, particularly in ICU settings. Therefore, including adjunct diagnostic tools such as procalcitonin levels and Clinical Pulmonary Infection Score (CPIS) would have reduced the false positives and thus enhanced the diagnostic accuracy.
- Several other clinically important and modifiable risk factors were not evaluated, including emergency intubation, intrahospital transport, subglottic suctioning, patient positioning (semi-recumbent), and maintenance of endotracheal cuff pressure. Omitting these factors limits the completeness of risk factor analysis, leaving out variables that could have important preventive implications. The authors have reported a VAP-associated mortality rate of 50%, but the absence of inclusion of illness severity scores like APACHE II or SOFA makes it difficult to tell whether the deaths were due to VAP alone or due to any underlying critical illness (like sepsis, multiorgan failure, or primary disease process).[2] Without a score, it is difficult to assess the baseline health status of the patient. Differences in mortality can be due to underlying illness severity rather than VAP. Inclusion of such illness severity scores would have helped to adjust for confounding variables and thus to quantify VAP-attributable mortality better.
- The study reported a 50% mortality rate among patients with VAP. It did not distinguish between deaths directly attributable to VAP and those due to other causes (e.g., sepsis, multiorgan failure, or primary disease process). This affects the validity of the mortality findings. Without attributing mortality specifically to VAP, the impact of VAP on outcomes remains unclear.
- The study included 138 patients, with 30 developing VAP. Although the sample size was statistically calculated, it may have been too small to detect associations between VAP and less common or weaker risk factors. Some nonsignificant findings [e.g., use of proton pump inhibitors (PPIs), prior antibiotic use] could be due to type II error (false negative), limiting the robustness of risk factor analysis.
- Patients were followed during their ICU stay only. There was no follow-up after ICU discharge to assess the long-term outcomes of VAP survivors (e.g., lung function, readmission, quality of life). VAP may have lasting effects after ICU discharge, and without follow-up, the true burden of disease is underestimated.[3]
- The authors have mentioned the usage of the VAP prevention bundle, but detailed documentation of adherence to individual bundle components, like daily sedation vacation, head-end of bed elevation, oral care of intubated patients, etc., has not been mentioned. Mentioning individual bundle components would have provided insight into the gaps in implementation, which could have been a reason for the high incidence of mortality.
- The study has identified factors like age >55 years, chronic lung disease, and prolonged ventilation as significant risk factors. However, other known contributors, like emergency intubation, suboptimal endotracheal cuff pressures, and transport within the hospital, were not analyzed. Inclusion of the above factors could have provided a more elaborate risk profile.
- The high rates of extended-spectrum beta-lactamase (ESBL) (100%), XDR (66.7%), and multidrug-resistant (MDR) (13.3%) among isolates call for routine surveillance of local antibiograms, restriction of broad-spectrum empiric antibiotics, and following of ICU-specific antibiotic stewardship protocols. It would have been helpful if the authors had commented on the antibiotic usage in their ICU, particularly regarding empirical antibiotic choices and deescalation practices.

In conclusion, the study lays the groundwork for future research.

This study elaborates the increasing burden of VAP and MDR organisms in Indian ICUs. The findings underscore the urgent need for stringent infection control practices, protocol-based weaning, and focused stewardship programs.

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Transforming Medical Education to Meet India's Healthcare Demands

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India's rapidly growing population necessitates an urgent overhaul of our

medical education system to strengthen both primary healthcare services and specialized medical care. The latest data shows that India's doctor-population ratio has improved to 1:811,[1] surpassing the World Health Organization (WHO)-recommended standard of 1:1000.[2,3] However, the distribution remains highly uneven, with a severe shortage of general physicians and essential specialists in rural and semi-urban areas. While government initiatives have increased MBBS seats to 1.18 lakh, producing more doctors, the current postgraduate (PG) system remains fragmented and does not adequately cater to the country's healthcare priorities.[1]

A Reformed Postgraduate Medical Education Structure

To address India's healthcare demands effectively, the PG medical education system needs a fundamental restructuring to balance the production of basic doctors and specialist physicians/surgeons. The goal should be to ensure that all doctors receive a strong foundation in general medicine or surgery before advancing to subspecialty training.[4]

Broad-based Specialty Training in Medicine and Surgery

After MBBS, PG training should be streamlined into two broad specializations:

- MD (internal medicine or pediatrics).
- MS (general surgery, gynecology, or orthopedics).

This training should include:

- Two years of intensive clinical training, focusing on the management of common and complex medical and surgical conditions.
- One year of mandatory senior residency, allowing for supervised hands-on experience to develop expertise.
- For those interested in academic careers, an additional 1-year research component (thesis work) should be introduced. Doctors completing this track should be designated as academic MD/MS, making them eligible for teaching roles in MBBS and MD/MS programs.

Revised Superspecialty Training Model

- Only academic MD/MS graduates should be eligible to apply for superspecialty training.
- Selection should be based on a NEET superspecialty (NEET SS) eligibility examination, followed by 2 additional years of structured subspecialty training, including thesis and research work.
- Candidates interested in becoming PG medical teachers should undergo 1 additional year of advanced research training, ensuring expertise in both bedside and benchside medicine.

Superspecialty fields should include:

- Medical specialties: Cardiology, endocrinology, nephrology, oncology, dermatology, gastroenterology, pulmonology, psychiatry, radiology, clinical pharmacology, anesthesia, and critical care, etc.
- Surgical specialties: Cardiothoracic and vascular surgery (CTVS) surgery, plastic surgery, pediatric surgery, etc.
- Diagnostic specialties: Pathology, microbiology (which should require an initial MD in medicine or pediatrics qualification before further specialization).

Restructuring Nonclinical Specialties for Better Integration

Instead of separate MD programs for anatomy, physiology, pharmacology, pathology, microbiology, and forensic medicine, these disciplines should be taught by academic MD/MS graduates with an additional 2-year focused training in their respective fields:

- MD medicine (academic) should cover medical physiology, medical biochemistry, medical pharmacology, and medical microbiology in the MBBS curriculum.
- MS surgery (academic) should cover surgical anatomy and forensic medicine in the MBBS curriculum.

This ensures that only clinically trained doctors lead medical education, strengthening the bedside-to-benchside approach in medical science.[5]

Proposed Pathway for Medical Education in India

- NEET UG → MBBS (with professional examinations).
- NEXT exam → MD or MS (medicine/pediatrics/surgery/gynecology/orthopedics)—2 years.
- Those opting for academic MD/MS complete an additional 1-year research component.
- NEET SS → subspecialty training (2 years) + optional 1-year PG teaching training for those wanting to become medical faculty.
- Pathology/microbiology aspirants must complete an MD in medicine or pediatrics before specialization.

Emphasizing a Skill-driven MBBS Curriculum

- Skill-based training should be the primary focus of MBBS education, ensuring that graduates can effectively manage 90% of common ailments before advancing to PG training.
- The MBBS curriculum should be shortened and streamlined to focus on essential clinical skills, primary healthcare delivery, and emergency medicine.
- Academic MD/MS specialists should teach MBBS students, while subspecialty-trained faculty should oversee advanced PG training.

Call for Holistic Reform in Medical Education

The future of India's healthcare system depends on how effectively we train our doctors—both at the primary care level and in specialized disciplines. The proposed restructuring of medical education and PG training ensures that we produce more skilled general physicians while also maintaining a robust pipeline of specialist and superspecialist doctors.

We urge medical educationists, policymakers, and healthcare leaders to holistically address this pressing issue by implementing a structured, competency-driven framework that aligns medical education with the country's real healthcare needs. By prioritizing clinical skill development, standardizing PG pathways, and ensuring the right balance of generalists and specialists, we can build a more effective and accessible healthcare system. A comprehensive national policy on medical education reform is the need of the hour, and we call upon all stakeholders

to engage in meaningful dialogue and take decisive action toward this transformation.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, the author used ChatGPT (OpenAI) to assist in refining language and improving readability. After utilizing this tool, the author thoroughly reviewed and edited the content to ensure accuracy, coherence, and alignment with the intended arguments, taking full responsibility for the final version of the publication.

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