

Original article

Association of NT-proBNP Levels with Cardiopulmonary Dysfunction in Chronic Obstructive Pulmonary Disease

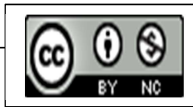
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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder with significant systemic consequences, particularly affecting cardiovascular function. Pulmonary hypertension and right ventricular dysfunction frequently complicate advanced COPD, adversely impacting prognosis. However, regional data on these cardiac sequelae, especially from South India, remain limited. To evaluate cardiovascular alterations across different severity grades of COPD patients using echocardiographic parameters and to establish correlations between pulmonary hypertension, right ventricular dysfunction, and disease severity. An observational cross-sectional study was conducted at Meenakshi Medical College Hospital & Research Institute, Tamil Nadu, enrolling 65 COPD patients aged over 40 years. Pulmonary function tests classified COPD severity based on GOLD criteria. Electrocardiographic and echocardiographic assessments were performed to detect signs of cor pulmonale and pulmonary hypertension. Associations between COPD severity and cardiovascular findings were analyzed statistically. Among 65 participants (mean age 59.4 ± 10.7 years; 89.2% male), moderate to severe COPD predominated (GOLD stages 2 and 3). Echocardiographic evidence of pulmonary hypertension was observed in 86.2% of cases, with moderate and severe grades accounting for 36.9% and 41.5%, respectively. Right ventricular dysfunction and elevated NT-proBNP levels were significantly associated with increasing COPD severity. A strong correlation was found between pulmonary hypertension severity and advancing GOLD stages ($\chi^2 = 14.65$, $p = 0.003$). Cardiovascular complications, particularly pulmonary hypertension and right ventricular dysfunction, are highly prevalent in COPD patients and strongly correlate with disease severity. Early echocardiographic screening is crucial for timely identification and management of cardiac involvement in COPD, especially in resource-limited settings.

Keywords: Chronic Obstructive Pulmonary Disease; Pulmonary Hypertension

Introduction

Chronic Obstructive Pulmonary Disease (COPD) stands as an important contributing factor to ongoing health issues and fatalities across the globe. It is marked by enduring respiratory symptoms and a gradual decline in airflow that typically worsens over time and cannot be completely reversed. The disease arises from a complex interaction of genetic factors and environmental influences, particularly tobacco smoke, air pollution both indoors and outdoors, workplace hazards, and, more recently acknowledged, early-life respiratory challenges [1]. The key features of COPD are rooted in inflammation, changes in the small airways, and damage to lung tissue, leading to emphysema. COPD continues to pose a significant challenge to public health worldwide. The 2023 Global Burden of Disease Study highlights that COPD ranks as the third leading cause of death, contributing to around 3.2 million fatalities

each year, which represents 6% of total global mortality. It is important to highlight that the prevalence of COPD is on the rise, driven by continued exposure to various risk factors, the swift pace of urbanization, an aging population, and the lingering effects of past smoking epidemics, especially in low- and middle-income countries [2-4]. While smoking continues to be the main risk factor in wealthier regions, in South Asia, particularly in India, exposure to biomass fuels, air pollution, and occupational dust plays a significant role in the development of COPD, particularly affecting women and those in rural areas. In addition to affecting lung function, COPD is increasingly understood as a condition that impacts the entire body, particularly influencing cardiovascular health. In advanced stages of COPD, factors such as chronic low oxygen levels, systemic inflammation, oxidative stress, and changes in the pulmonary blood vessels play a significant role in the onset of pulmonary hypertension (PH). Pulmonary hypertension in COPD primarily arises from hypoxic pulmonary vasoconstriction and the reduction of pulmonary vascular beds as a result of emphysema. When the pressures in the pulmonary artery increase, the right ventricle experiences greater afterload. This can result in changes such as hypertrophy, dilation, and ultimately, failure of the right ventricle, a condition known as cor pulmonale. Moreover, mechanical factors like hyperinflation can hinder the filling of the left ventricle, which can further exacerbate cardiovascular issues. Heart failure and arrhythmias stand out as significant cardiovascular issues that contribute to high rates of hospitalization and mortality in individuals with COPD [5-7]. Right ventricular dysfunction, diastolic dysfunction, and subtle myocardial impairments frequently go undetected until they reach advanced stages, even though they play a crucial role in influencing prognosis. Echocardiography is a non-invasive, accessible, and affordable tool that significantly contributes to the early detection and ongoing monitoring of heart issues in individuals with COPD. Recent guidelines highlight the significance of a holistic cardiopulmonary assessment in the thorough care of patients with COPD.

Nonetheless, there is still a lack of region-specific data, especially from South India, that explores cardiovascular changes across the spectrum of COPD severity through echocardiographic measures. Given the significant impact of COPD and the distinct exposure patterns in this area, it is crucial to explore the cardiovascular effects to facilitate prompt intervention. This study seeks to thoroughly evaluate how common and severe pulmonary hypertension, right ventricular dysfunction, and associated cardiac changes are in patients with COPD, while also examining the relationship between these findings and spirometric staging [8-10]. These insights play a crucial role in enhancing comprehensive care and achieving better clinical outcomes for individuals with COPD. This study seeks to thoroughly explore the cardiovascular changes in patients with COPD through the use of echocardiography, especially considering the limited regional data available. Our aim is to clarify how common and severe pulmonary hypertension, right ventricular dysfunction, and associated heart changes are throughout the different stages of COPD. This study aims to deepen our clinical understanding and refine management strategies for COPD patients who are at risk of cardiovascular complications by establishing these important associations.

Materials and Methods

Study Design, Ethics and Setting

This study, which took place over a span of 20 months from February 2016 to September 2017, was carried out at the Department of Tuberculosis and Respiratory Medicine at Meenakshi Medical College Hospital and Research Institute in Enathur, Kanchipuram, Tamil Nadu, India. The main goal was to evaluate the clinical, spirometric, electrocardiographic, and echocardiographic characteristics of patients who have been diagnosed with COPD. The Institutional Ethics Committee reviewed and approved the study protocol before it began (21/MMCHRI/2015(A)). The study involving human participants was carried out following the ethical standards set by the relevant institutional and national research committees, as well as the principles outlined in the 1964 Helsinki declaration and its subsequent amendments (World Medical Association, 2013). All participants provided written informed consent in their native language, following a thorough explanation of the study's objectives and procedures.

Study Population

The study included patients aged 40 and older, whether they were previously diagnosed or newly identified cases of COPD, who were visiting the outpatient and inpatient departments. The diagnosis of COPD was established through spirometry, following the guidelines outlined by the Global Initiative for Chronic Obstructive Lung Disease [3]. Individuals who had a history of pulmonary tuberculosis complications, ischemic heart disease, congenital or acquired valvular heart disease, bronchial asthma, or interstitial lung disease were not included in the study. Moreover, individuals who were either unwilling or unable to give their consent were not included in the study.

Demographic assessment

Detailed demographic and clinical information through a framed for the initial evaluation, we gathered detailed information about the smoking history measured in pack-years, exposure to biomass fuels, and occupational exposure to dust and chemicals. We also noted symptoms such as cough, sputum production, dyspnea, wheezing, and chest pain, along with any history of exacerbations, previous hospitalizations, and related comorbidities. A comprehensive general and systemic physical examination was conducted, paying special attention to the respiratory and cardiovascular systems [10-13].

Pulmonary Function Testing

Pulmonary function tests were conducted utilizing a KoKo Legend spirometer (nSpire Health, USA) in compliance with the guidelines set forth by the American Thoracic Society/European Respiratory Society (ATS/ERS) [8]. Measurements were conducted for parameters such as Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV₁), and the FEV₁/FVC ratio. Post-bronchodilator spirometric values were employed for the diagnosis and classification of COPD. Patients were classified into four stages based on post-bronchodilator FEV₁ values: mild (FEV₁ ≥80% predicted), moderate (50% ≤ FEV₁ <80% predicted), severe (30% ≤ FEV₁ <50% predicted), and very severe (FEV₁ <30% predicted), in accordance with GOLD recommendations [11-14].

ECG and Echocardiographic Evaluation

A standard 12-lead electrocardiogram (ECG) was conducted for all patients to evaluate cardiac rhythm and identify any indications of cor pulmonale. Specific electrocardiographic abnormalities, including P-pulmonale (P-wave amplitude exceeding 2.5 mm in lead II), right axis deviation (QRS axis greater than +90°), right bundle branch block (RBBB), and patterns indicative of right ventricular strain (such as S1Q3T3 or S1S2S3 patterns), were systematically assessed. Electrocardiograms were assessed independently by two qualified physicians to reduce observer variability, adhering to the standard interpretation criteria outlined in Fraser and Paré's Diagnosis of Diseases of the Chest [5,15-16].

Transthoracic echocardiography was conducted utilizing a Philips HD11XE system, adhering to established imaging protocols. The evaluation concentrated on the dimensions and functionality of the right ventricle, the measurements of the left ventricle, the motion of the interventricular septum, and the pressures within the pulmonary artery. The estimation of pulmonary artery systolic pressure (PASP) was conducted through the peak tricuspid regurgitation velocity measured by continuous-wave Doppler imaging, utilizing the modified Bernoulli equation, expressed as $PASP = 4(V_r)^2 + RAP$ (Right Atrial Pressure). The estimation of RAP was conducted by evaluating the size and collapsibility index of the inferior vena cava, following established guidelines (Lang et al., 2015). Pulmonary hypertension (PH) is categorized into three levels: mild, characterized by a pulmonary artery systolic pressure (PASP) of 30–40 mmHg; moderate, with a PASP of 41–60 mmHg; and severe, indicated by a PASP exceeding 60 mmHg. The assessment of right ventricular systolic function was conducted through the measurement of the tricuspid annular plane systolic excursion (TAPSE), with values below 17 mm signifying dysfunction (Rudski et al., 2010). Furthermore, the assessment of left ventricular diastolic dysfunction was conducted through Doppler measurements of mitral inflow velocities, specifically the E/A ratio, alongside tissue Doppler imaging to determine the E/e' ratio [16-18].

Six-Minute Walk Test (6MWT)

The six-minute walk test (6MWT) was performed to evaluate exercise tolerance, adhering to the guidelines established by the American Thoracic Society (ATS, 2002). Participants were directed to traverse a standardized 30-meter flat corridor for a duration of six minutes, during which the distance covered was meticulously documented. The assessment of pre- and post-exercise heart rate, oxygen saturation (SpO₂), dyspnea, and fatigue was conducted utilizing the modified Borg scale. The biochemical analysis encompassed the assessment of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, aimed at evaluating cardiac stress and dysfunction. Blood samples were obtained in EDTA tubes and subsequently analyzed utilizing chemiluminescent immunoassay methodologies. A NT-proBNP level exceeding 125 pg/mL is regarded as indicative of cardiac involvement, as established in prior research by Januzzi et al., 2006 [16].

Statistical Analysis

The data were entered and subsequently analyzed utilizing MS Excel software, version 2021. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were represented as percentages. The analysis of associations among categorical variables was conducted utilizing the Chi-square test. A p-value of less than 0.05 is regarded as statistically significant.

Results

A total of 65 patients diagnosed with COPD were included in the study cohort. The average age of the cohort was 59.4 years, with a standard deviation of 10.7 years, and a significant male predominance, accounting for 89.2% of the participants. Regarding exposure history, it was observed that 43.1% of the participants were current smokers, whereas 47.7% were classified as ex-smokers. The exposure to biomass fuel was recorded in 9.2% of the participants, underscoring the role of environmental factors as a potential contributor to the development of disease. All patients exhibited clinical symptoms, with a prevalence of chronic cough reported by 100% of the cohort. Sputum production and exertional dyspnea exhibited a significant prevalence, with both being reported by 93.8% of the cohort, as illustrated in Table 1. Wheezing was observed in 35.4% of the patients, whereas chest pain was reported as a less prevalent symptom, occurring in 6.2% of individuals.

Table 1: Demographic, Clinical Profile, and Risk Factors of COPD Patients			
Parameter	Category	Frequency (n)	Percentage (%)
Age Distribution	40–50 years	22	33.8%
	51–60 years	18	27.7%
	61–70 years	16	24.6%
	71–80 years	7	10.8%
	81–90 years	2	3.1%
Gender	Male	58	89.2%
	Female	7	10.8%
Smoking Status	Current smoker	28	43.1%
	Ex-smoker	31	47.7%
	Biomass exposure	6	9.2%
Common Symptoms	Cough	65	100%
	Sputum production	61	93.8%
	Shortness of breath	61	93.8%
	Wheeze	23	35.4%
	Chest pain	4	6.2%
Chest X-ray Findings	Bilateral Emphysema	52	80.0%
	Normal	13	20.0%
Demographic characteristics, clinical profiles, and risk factors among COPD patients (n = 65), including age distribution, gender, smoking status, symptomatology, and radiographic findings.			

Radiological assessment via chest X-rays demonstrated that 80% of the patients exhibited bilateral emphysematous alterations, signifying advanced structural damage to the lungs, while 20% presented with no notable radiographic abnormalities. The majority of the cohort was classified into moderate and severe stages of airflow limitation based on pulmonary function tests (PFTs) in accordance with the GOLD criteria. In particular, 40% of patients were classified as being in GOLD stage 2 (moderate), 32.3% in GOLD stage 3 (severe), and 15.4% in GOLD stage 4 (very severe). A total of 12.3% of the subjects exhibited mild obstruction, classified as GOLD stage 1. The findings from the PFT results underscored the prevalence of notable airflow limitation within the cohort of study participants.

Electrocardiographic (ECG) analysis revealed that 55.4% of the patients demonstrated alterations indicative of cor pulmonale. Of the subjects examined, 26.2% exhibited isolated P-pulmonale patterns, whereas 21.5% presented with P-pulmonale in conjunction with right axis deviation (RAD). A smaller subset, comprising 7.7%, demonstrated the triad of P-pulmonale, right axis deviation (RAD), and right bundle branch block (RBBB), whereas 9.2% exhibited a clockwise rotation of the cardiac axis. Normal electrocardiogram findings were identified in 35.4% of the patients (Table 2).

Table 2: Severity Classification Based on GOLD Staging, PFT, ECG, and ECHO Findings			
Clinical Assessment	Category	Frequency (n)	Percentage (%)
COPD Severity (GOLD)	Mild (GOLD 1)	8	12.3%
	Moderate (GOLD 2)	26	40.0%
	Severe (GOLD 3)	21	32.3%
	Very Severe (GOLD 4)	10	15.4%
PFT Severity	Mild Obstruction	8	12.3%
	Moderate Obstruction	26	40.0%
	Severe Obstruction	21	32.3%
	Very Severe Obstruction	10	15.4%
ECG Findings	P-pulmonale only	17	26.2%
	P-pulmonale + RAD	14	21.5%
	P-pulmonale + RAD + RBBB	5	7.7%
	Clockwise rotation	6	9.2%
	Normal ECG	23	35.4%
ECHO Findings	Normal Echo	9	13.8%
	Mild Pulmonary Hypertension	5	7.7%
	Moderate Pulmonary Hypertension	24	36.9%
	Severe Pulmonary Hypertension	27	41.5%

The echocardiographic evaluation demonstrated notable cardiac involvement in patients with COPD. Pulmonary hypertension (PAH) was observed in 86.2% of the cases analyzed. Among the subjects examined, moderate pulmonary arterial hypertension (PAH) was observed in 36.9% of the patients, whereas severe PAH was identified in 41.5% of the cohort. A mere 13.8% of the subjects presented with a normal echocardiogram, while 7.7% demonstrated mild pulmonary arterial hypertension (PAH). The analysis revealed a statistically significant association between the severity of COPD and the extent of pulmonary hypertension, as indicated by chi-square analysis ($\chi^2 = 14.65$, $p = 0.003$). Individuals exhibiting advanced stages of COPD demonstrated an increased prevalence and severity of pulmonary hypertension. Among the cohort classified with mild COPD, 87.5% exhibited a normal echocardiogram, whereas a minority of 12.5% presented with mild pulmonary arterial hypertension (PAH). In the cohort of moderate cases, it was observed that 53.8% progressed to moderate pulmonary arterial hypertension (PAH), while 30.8% exhibited severe PAH. In cases of severe COPD, a progressive pattern was observed, with 57.1% of patients exhibiting severe Pulmonary Arterial Hypertension (PAH). Notably, within the cohort of patients classified as having very severe COPD, 70% presented with severe pulmonary hypertension, while the remaining 30% exhibited moderate pulmonary arterial hypertension (Table 3).

Table 3: Cross-tabulation of COPD Severity vs Echocardiographic Changes				
COPD Severity	Normal Echo (n, %)	Mild PAH (n, %)	Moderate PAH (n, %)	Severe PAH (n, %)
Mild	7 (87.5%)	1 (12.5%)	0 (0%)	0 (0%)
Moderate	2 (7.7%)	2 (7.7%)	14 (53.8%)	8 (30.8%)
Severe	0 (0%)	2 (9.5%)	7 (33.3%)	12 (57.1%)
Very Severe	0 (0%)	0 (0%)	3 (30%)	7 (70%)
Total	9 (13.8%)	5 (7.7%)	24 (36.9%)	27 (41.5%)
Chi-square value = 14.65; p-value = 0.003 , indicating a significant association between increasing COPD severity and development of pulmonary hypertension.				

Right ventricular (RV) dysfunction, evaluated through echocardiographic methods, demonstrated a significant correlation with the severity of COPD. In individuals diagnosed with mild COPD, classified as GOLD stage 1, all subjects exhibited normal right ventricular function. In the cohort of moderate cases classified as GOLD stage 2, it was observed that 75% exhibited normal right ventricular (RV) function, while 17.9% presented with mild dysfunction, and 7.1% demonstrated moderate to severe dysfunction. In the context of advancing COPD severity

classified as GOLD stage 3, it was observed that 52.6% of patients maintained normal right ventricular (RV) function. Conversely, 26.3% demonstrated mild dysfunction, while 21.1% exhibited moderate to severe dysfunction, as detailed in Table 4. In the cohort classified as having very severe COPD, specifically those at GOLD stage 4, it was observed that merely 20% exhibited normal right ventricular (RV) function. Conversely, 30% presented with mild dysfunction, while a significant 50% displayed moderate to severe impairment of RV function. These findings underscore the substantial influence of advancing pulmonary pathology on cardiac performance.

Table 4. Right Ventricular (RV) Dysfunction in Relation to COPD Severity			
COPD Severity (GOLD Stage)	RV Normal Function	RV Mild Dysfunction	RV Moderate to Severe Dysfunction
Stage 1 (Mild)	4 (100%)	0 (0%)	0 (0%)
Stage 2 (Moderate)	21 (75%)	5 (17.9%)	2 (7.1%)
Stage 3 (Severe)	10 (52.6%)	5 (26.3%)	4 (21.1%)
Stage 4 (Very Severe)	2 (20%)	3 (30%)	5 (50%)

The functional status, evaluated through the six-minute walk test (6MWT), exhibited a progressive decline in correlation with the increasing severity of COPD. The average distance achieved in the 6-Minute Walk Test (6MWT) among patients with mild COPD was recorded at 420 ± 58 meters. Individuals diagnosed with moderate COPD exhibited an average walking distance of 368 ± 74 meters, whereas those classified with severe disease attained a distance of 310 ± 65 meters. The most significant reduction was observed in the very severe group, which demonstrated an average walking distance of only 240 ± 54 meters. The observed progressive decline in exercise tolerance is indicative of the escalating burden associated with the disease.

Levels of NT-proBNP were assessed as biochemical markers indicative of cardiac dysfunction. None of the patients diagnosed with mild chronic obstructive pulmonary disease exhibited elevated levels of NT-proBNP. In the cohort studied, it was observed that 21.4% of patients exhibiting moderate disease presented with elevated NT-proBNP levels. This proportion significantly increased to 63.2% in patients classified with severe disease, and further escalated to 90% among individuals diagnosed with very severe COPD. The observed trend indicates a robust correlation among the progression of COPD severity, increased NT-proBNP levels, and the onset of substantial right heart strain and failure (Table 5).

Table 5. Six-Minute Walk Test (6MWT) and NT-proBNP Levels across COPD Stages		
COPD Severity (GOLD Stage)	Mean 6MWT Distance (meters)	NT-proBNP Elevated Cases (%)
Stage 1 (Mild)	420 ± 58	0 (0%)
Stage 2 (Moderate)	368 ± 74	6 (21.4%)
Stage 3 (Severe)	310 ± 65	12 (63.2%)
Stage 4 (Very Severe)	240 ± 54	9 (90%)

This study findings demonstrate that increasing severity of COPD is associated with progressive pulmonary hypertension, right ventricular dysfunction, reduced functional capacity, and elevated biochemical markers of cardiac stress. These results emphasize the systemic impact of COPD beyond the pulmonary system and highlight the importance of comprehensive cardiovascular evaluation in these patients.

Discussion

This cross-sectional study offers valuable insights into the burden of cardiovascular alterations in patients diagnosed with COPD in South India, emphasizing the strong association between the severity of the disease and the development of pulmonary hypertension (PH) and right ventricular (RV) dysfunction. The study population predominantly consisted of male patients, exhibiting a mean age of 59.4 years, which aligns with demographic patterns identified in similar research conducted in India and other low- and middle-income countries [15-18]. Smoking remains the predominant risk factor; nonetheless, considerable biomass exposure in a specific subset of patients highlights the environmental factors distinctive to South Asia, as observed by He et al. 2020 [19]. Pulmonary hypertension was identified in 86.2% of patients with COPD via echocardiographic assessment, revealing a clear stepwise increase in severity corresponding to the progression of GOLD stages. This finding is consistent with previous research conducted by Xie et al. 2025 [8] and Yao et al. 2021 [20], which demonstrated that pulmonary vascular remodeling exacerbates as airflow limitation advances. The prevalence of severe pulmonary hypertension

observed in this study, quantified at 41.5%, surpasses the rates reported in Western cohorts. This discrepancy suggests the potential influence of regional or environmental factors, including heightened chronic hypoxemia or impediments in access to healthcare services. Right ventricular dysfunction demonstrated a progressively correlated association with the severity of COPD. In individuals diagnosed with mild COPD, all cases exhibited preserved right ventricular function; conversely, moderate to severe dysfunction was increasingly prevalent at GOLD stages 3 and 4. The trends observed align with the results reported by Hilde et al. (2013), which demonstrated a notable reduction in right ventricular contractile performance in reaction to increased pulmonary pressures and heightened hypoxic pulmonary vasoconstriction. Right ventricular dysfunction is often observed prior to the development of overt clinical cor pulmonale, underscoring the importance of early echocardiographic monitoring in populations with COPD who are at risk.

The methodology employed, particularly the use of Doppler echocardiography for estimating pulmonary artery systolic pressure (PASP) and assessing right ventricular function, aligns with current standard recommendations by Rudski et al., 2010; Hiramatsu et al., 2021[6, 9]. Echocardiography serves as a non-invasive and accessible technique for cardiac evaluation; however, it is essential to acknowledge its limitations, including operator dependency and potential inaccuracies in the estimation of pulmonary pressures, particularly in instances of suboptimal acoustic windows, as highlighted by Su et al. 2023 [15]. The exclusion of patients with pre-existing cardiac disease significantly improved the internal validity of the findings by minimizing potential confounding factors. The elevation of serum NT-proBNP levels observed in patients with severe COPD provides additional evidence for the presence of subclinical myocardial stress and dysfunction, corroborating findings from studies by Su et al. 2023 [15] and Januzzi et al., 2006 [16]. The evaluation of NT-proBNP functions as a supplementary objective biochemical marker that enhances echocardiographic assessments; nevertheless, constraints in resources may limit its regular implementation in low-income settings.

This research differentiates itself from existing literature by emphasizing a particular regional context and integrating comprehensive pulmonary function evaluations, electrocardiogram analysis, echocardiographic assessments, and biomarker measurements. However, the study is limited by a relatively small sample size and a single-center design, which may constrain the generalizability of the findings. Furthermore, the cross-sectional design of the study constrains the capacity to infer causal relationships concerning the temporal evolution of cardiovascular alterations. Longitudinal studies incorporating right heart catheterization, acknowledged as the definitive standard for the diagnosis of pulmonary hypertension, would offer further validation for these findings.

Conclusion

This research underscores the significant prevalence of cardiovascular complications, specifically pulmonary hypertension and right ventricular dysfunction, in COPD patients in South India, demonstrating a strong correlation with the severity of the disease. Echocardiographic screening has been shown to be crucial in detecting subclinical cardiac changes, even in moderate stages of COPD. The timely identification of cardiovascular involvement is crucial for enhancing management strategies, improving prognostic outcomes, and decreasing morbidity and mortality linked to COPD. Further investigations involving larger, multi-center cohorts and longitudinal follow-up are necessary to enhance the understanding of the natural history of cardiopulmonary interactions in COPD, as well as to improve screening and therapeutic protocols that are adapted to regional requirements.

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