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ORIGINAL RESEARCH

Quantitatively Assessed Emphysema Severity on HRCT Independently Predicts Coronary Artery Disease in COPD: A Retrospective Cohort Study

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Background: Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of coronary artery disease (CAD). However, the role of emphysema, which represents an important structural subtype of COPD, in the development of CAD remains insufficiently clarified. This study aimed to evaluate whether quantitatively assessed emphysema on high-resolution computed tomography (HRCT) independently predicts CAD in COPD patients.

Methods: This retrospective cohort study included 392 COPD patients with no prior history of CAD between 2015 and 2020. All participants underwent HRCT for automated emphysema quantification using 3D Slicer software. Emphysema extent was quantified as the percentage of low attenuation areas (LAA%) below −950 Hounsfield units, with severe emphysema defined as LAA% >16.95%. Logistic regression and restricted cubic spline (RCS) analysis were employed to assess the relationship between emphysema index and CAD, including subgroup and interaction analyses. The ability of the emphysema index to predict CAD was evaluated using receiver operating characteristic (ROC) curves.

Results: Severe emphysema was independently associated with a higher risk of CAD in COPD patients (OR = 2.08, 95% CI: 1.30–3.34; $p = 0.002$). This association remained robust even after adjusting for confounders (adjusted OR= 2.28, $p = 0.005$). RCS analysis indicates that the risk of CAD increases with the rise of the emphysema (p for nonlinearity =0.031). The area under the ROC curve for the predictive model was 0.81 (95% CI 0.77, 0.86). Additionally, patients with severe emphysema exhibited significantly more complex coronary lesions, reflected by higher SYNTAX scores (median 10.00 vs 16.29; $p = 0.013$).

Conclusion: Quantitative HRCT-based emphysema independently predicts CAD in COPD and demonstrates additive risk with traditional cardiovascular factors. Integrating emphysema quantification with clinical risk assessment improves CAD risk stratification in COPD patients.

Keywords: COPD, emphysema, coronary artery disease, SYNTAX scores

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Introduction

Chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) are two of the leading causes of morbidity and mortality worldwide.[1,2] Cardiovascular diseases, especially CAD, are among the most common and clinically significant comorbidities in COPD, worsening patient outcomes and increasing healthcare utilization.[3–5] A 2022 cohort study highlighted that COPD patients had a 25% higher risk of major cardiovascular events compared to non-COPD individuals,[6] while CAD alone was responsible for over one million deaths among COPD patients, representing the leading cause of premature mortality in this population.[7] Emphysema, a key pathological feature of COPD, is characterized by protease-mediated alveolar wall destruction, resulting in lung hyperinflation and loss of elasticity.[8,9] These changes can impair ventricular function and elevate pulmonary vascular resistance, increasing cardiovascular strain.[10] In addition, previous studies have provided mechanistic evidence supporting the link between

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emphysema and more frequent and complex CAD. First, a key pathway is chronic systemic inflammation, where activated macrophages and neutrophils in the lungs release cytokines and proteases, which contribute to atherosclerosis by inducing endothelial dysfunction, foam-cell formation, and plaque destabilization.[11] Second, hypoxemia and vascular remodeling further exacerbate cardiovascular risk. Alveolar destruction and air trapping lead to chronic hypoxia, reducing VEGFR2 expression and nitric oxide (NO) production, inducing endothelial apoptosis, and increasing vessel permeability.[12] These changes promote LDL-C infiltration and plaque vulnerability, thereby increasing cardiovascular risk.[13]

Previous studies have linked lung hyperinflation to CAD, and the associations between forced expiratory volume in one second (FEV_1), emphysema, and CAD are substantially attenuated after adjusting for hyperinflation, suggesting that the direct relationship between emphysema and CAD remains unclear and warrants further investigation.[14] From a symptomatic perspective, acute exacerbations of COPD (AECOPD) are also associated with increased cardiovascular risk, with both their severity and frequency linked to worse clinical outcomes.[15] According to the 2023 GOLD guidelines, patients in Group E—characterized by frequent exacerbations and greater symptom load—may be particularly vulnerable to CAD.[16] Furthermore, studies have confirmed that poorer lung function (lower FEV_1) was associated with higher SYNTAX scores (SS), indicating more severe and complex coronary lesions once CAD is present in advanced COPD.[17–19] These findings raise the possibility that emphysema may be associated with the complexity of CAD.

According to the 2025 GOLD guidelines, computed tomography (CT) is an effective tool for assessing the distribution and severity of emphysema and identifying individuals at increased risk for COPD.[20] It has been widely adopted in both COPD-related research and clinical practice. Emphysema is typically quantified by calculating the percentage of low attenuation areas (LAA), defined as the proportion of lung voxels with a density of ≤ –950 Hounsfield Units.[21] Quantitative lung density analysis is a valuable tool for COPD detection. In the NLST, a 1% emphysema threshold in individuals over 65 years old achieved sensitivities of around 65% (women) and around 75% (men), with specificities above 70% and 65%, respectively.[22] This quantitative metric shows strong correlation with pathological emphysema, airflow limitation, and increased risks of symptoms, exacerbations, disease progression, and mortality. These advances support the growing role of quantitative high-resolution computed tomography (HRCT) in identifying COPD patients at higher risk of comorbid conditions such as CAD.[22,23] Given that overlapping symptoms often delay CAD diagnosis in COPD patients,[24] identifying imaging-based predictors could improve early recognition and guide preventive strategies.

Therefore, this study aims to investigate the association between HRCT-based emphysema metrics and CAD, providing novel insights into the prevention and management of CAD in patients with COPD.

Materials and Methods

Study Population

This retrospective cohort study enrolled patients diagnosed with COPD (post-bronchodilator FEV1/FVC < 0.70) hospitalized at the **** between January 2015 and January 2020.

Inclusion Criteria

(1) Completion of chest HRCT, pulmonary function test, and transthoracic echocardiography during hospitalization; (2) availability of hospital visit records within five years in addition to the index admission.

Exclusion Criteria

(1) Interstitial lung disease; (2) pulmonary malignancies; (3) renal insufficiency (eGFR < 30 mL/min/1.73 m²); (4) pre-existing cardiovascular diseases. A total of 392 patients were ultimately included in the analysis (Figure 1).

This study was exploratory in nature, and currently, no prior literature provides established incidence rates of CAD or corresponding odds ratios (ORs) specifically comparing mild versus severe emphysema in patients with COPD. Therefore, the sample size was determined based on the study design and the predefined observation period.[25] All eligible patients meeting the inclusion criteria between January 2015 and January 2020 were consecutively enrolled. To address concerns about sample adequacy, we performed a post-hoc power analysis. Based on the observed sample

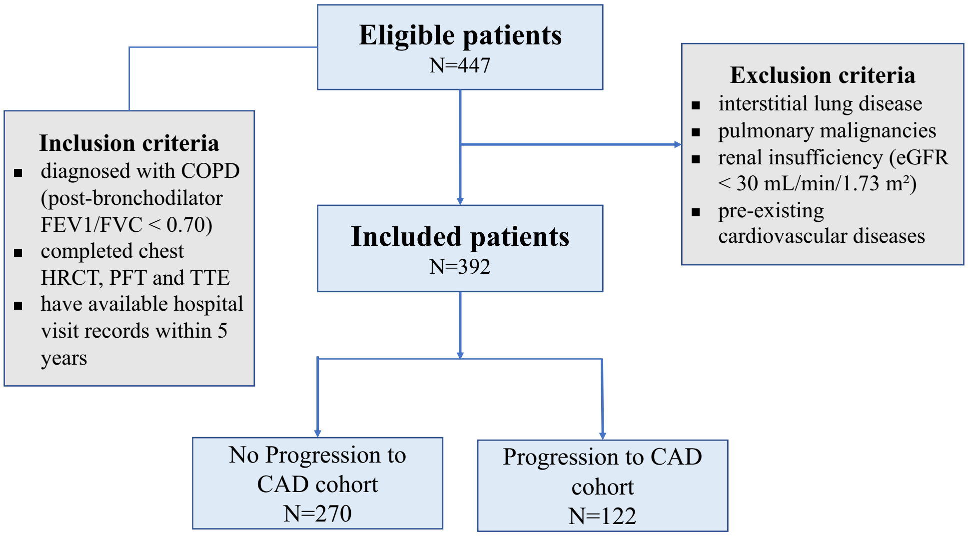


Figure 1 Flow-chart of study cohort.

Abbreviations: COPD, Chronic obstructive pulmonary disease; FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; HRCT, High-resolution computed tomography; PFT, Pulmonary function test; TTE, Transthoracic echocardiography; eGFR, Estimated glomerular filtration rate; CAD, Coronary artery disease.

distribution (143 patients with mild emphysema and 249 with severe emphysema) and corresponding CAD incidence rates (15.4% vs 40.2%), we estimated the statistical power of our study. Although there is no definitive literature on overall CAD prevalence in COPD populations, we conservatively assumed a baseline CAD rate of 20% in the mild emphysema group. Using an odds ratio of 2.28 for the severe emphysema group, the calculated power at a two-sided alpha level of 0.05 was approximately 99.4%. These findings indicate that our sample size was sufficiently powered to detect the observed association between emphysema severity and CAD risk.

Gathering of Information

Basic information collected: Demographic and clinical data including age, sex, body mass index (BMI), ABE classification, and comorbidities (hyperlipidemia, hypertension, diabetes mellitus, and smoking history) were collected from medical records by trained researchers. Anthropometric measurements such as weight and height were used to calculate BMI (kg/m²). Post-bronchodilator pulmonary function tests—including FEV1, FEV1 predicted %, FEV1/FVC ratio, MEF50, MEF25, and MMEF75/25—were performed during hospitalization to evaluate the degree of airflow limitation and the small airway dysfunction. Cardiac function was assessed using transthoracic echocardiography, with left ventricular ejection fraction (LVEF) calculated via the modified Simpson's method and pulmonary artery systolic pressure (PASP) estimated from peak tricuspid regurgitation velocity. Coronary artery calcification (CAC) was evaluated using chest HRCT with mediastinal window settings. In this study, the indication for invasive coronary angiography (ICA) was guided by clinical criteria aligned with the 2024 European Society of Cardiology (ESC) Guidelines.[26] Patients were referred for ICA if they exhibited persistent or severe symptoms refractory to anti-anginal therapy, demonstrated significant functional impairment attributable to angina or dyspnea, or showed high-risk features on non-invasive testing —such as suspected ≥50% stenosis of the left main coronary artery. The primary outcome was five-year progression of CAD, defined as either ≥50% coronary stenosis on coronary angiography (CAG) or the presence of significant coronary artery narrowing as indicated by coronary computed tomography angiography (CCTA), as assessed by certified cardiologists in accordance with standard diagnostic criteria.[27] To support outcome assessment, all cardiovascular-related medical records within five years prior to the index hospitalization—including CCTA and ICA—were comprehensively reviewed.

For patients who developed CAD, ICA documented lesion characteristics, including affected vessels, vessel occlusion, number of involved vessels, and revascularization procedures (PCI or Coronary artery bypass grafting [CABG]).

SYNTAX scores were calculated to assess lesion complexity. The observation period spanned from the date of initial hospital admission to a five-year follow-up.

The study protocol was approved by the Institutional Ethics Committee (First Affiliated Hospital of Wenzhou Medical University 2016NO.131), with waived informed consent.

Quantitative Assessment of Emphysema by HRCT

All participants underwent HRCT scans using one of the following scanners: LightSpeed Pro 16 Slice (GE, United States). Scans were performed at full inspiration in the supine position with the following parameters: detector collimation width of 64×0.6 mm or 128×0.6 mm; tube voltage of 120 kV; tube current of 40–80 mA; slice thicknesses of 1.25 mm or 2.00 mm; and reconstruction intervals of 1.25 mm or 2.00mm.

HRCT images were analyzed using 3D Slicer 5.0.3 (https://www.slicer.org) (Figure 2). The Lung CT Segmenter module automatically segmented the lungs into left lung, right lung, and trachea, with manual corrections applied as needed (Figure 2A). The Lung CT Analyzer V2.60 module then quantified lung tissue characteristics, including emphysema, inflated lung, infiltration, collapsed regions, and vessels, providing measurements in absolute volumes and percentages relative to total lung volume (Figure 2B). The extended results feature further calculated the proportion of each feature within the total lung volume.

Emphysema was quantified based on voxel density, with regions below −950 Hounsfield Units (HU) identified as low-attenuation areas. The total emphysema volume was determined by summing the volumes of all voxels meeting this threshold. The percentage of emphysema was determined by dividing the emphysema volume by the total lung volume and multiplying by 100.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 and R version 4.4.3, with two-tailed p-values <0.05 considered statistically significant. The normality of continuous variables was assessed using the Kolmogorov–Smirnov

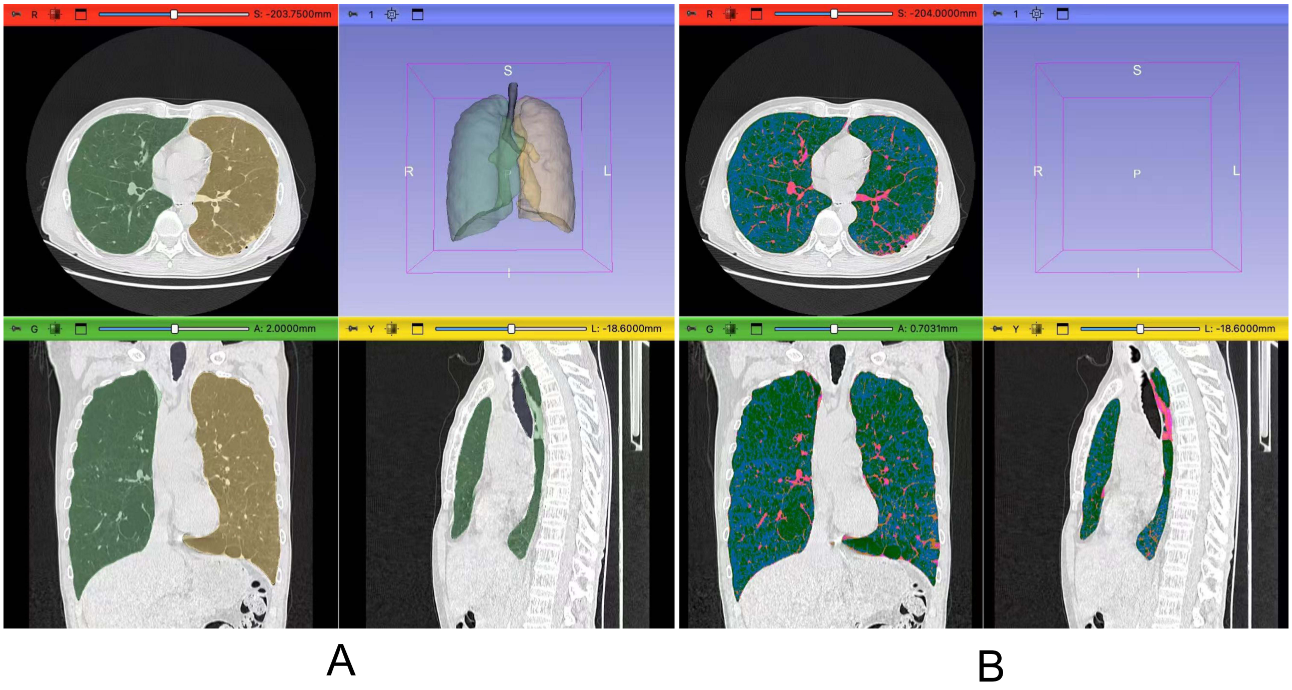


Figure 2 Quantitative Analysis of Lung Tissue Features Using 3D Slicer 5.0.3. (**A**) The Lung CT Segmenter module automatically segmented the lungs into left lung, right lung, and trachea. (**B**) The Lung CT Analyzer V2.60 module quantified lung tissue characteristics, including emphysema, inflated lung, infiltration, collapsed regions, and vessels.

Abbreviations: R, right; S, superior; P, posterior; L, left; I, inferior.

test. Normally distributed variables are expressed as mean ± standard deviation (SD), while non-normally distributed variables are presented as median with interquartile range (IQR). Categorical variables are reported as frequencies and percentages. Emphysema severity was classified into mild (emphysema% ≤ 16.95%) and severe (emphysema% > 16.95%) groups based on the optimal cut-off, with the mild group as the reference. Comparisons between continuous variables were made using the independent samples *t*-test or the Mann–Whitney *U*-test, and categorical variables were compared using the chi-square test.

The relationship between emphysema and CAD was assessed using both univariate and multivariate logistic regression models to compute odds ratios (ORs) with 95% confidence intervals (CIs). Three models were constructed: (1) unadjusted model; (2) adjusted for age and sex; (3) fully adjusted model, including comorbidities (hypertension, diabetes, hyperlipidemia) and covariates with $p < 0.1$ in univariate analysis (FEV1, LVEF ≥50%, PASP ≥50 mmHg, CAC, and ABE group). Restricted cubic splines (RCS) were used to examine the potential non-linear relationship between emphysema and CAD. Subgroup analyses were conducted to explore variations in the association across different patient subgroups. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC). Interaction effects between emphysema and selected covariates were assessed using the likelihood ratio test.

Results

Baseline Characteristics

Among the 392 COPD patients included, 143 (36.5%) had mild emphysema and 249 (63.5%) had severe emphysema. The baseline demographic and clinical characteristics are summarized in Table 1. While age distributions were balanced between cohorts (70.8±8.5 vs 70.8±8.3 years, $p = 0.938$), the severe emphysema group showed significantly greater

Table 1 Participant Characteristics

Variable	Mild Emphysema N=143	Severe Emphysema N=249	*P*
Demographics			
Age, years	70.76 ± 8.47	70.82 ± 8.32	0.938
Sex, male	115 (80.4)	225 (90.4)	0.008
BMI, kg/m^2	23.58 ± 3.67	21.64 ± 3.62	<0.001
ABE Group			0.188
A	17 (11.9)	19 (7.6)	
B	29 (20.3)	41 (16.5)	
E	97 (67.8)	189 (75.9)	
Comorbidities & Risk Factors			
Hyperlipidemia	25 (17.5)	36 (14.5)	0.470
Hypertension	69 (48.3)	115 (46.2)	0.753
Diabetes	31 (21.7)	37 (14.9)	0.097
Smoking	96 (67.1)	188 (75.5)	0.079
Pulmonary Function			
FEV1, L	0.99 (0.70–1.35)	0.88 (0.68–1.13)	0.021
FEV1 pred,%	44.10 (33.70–59.20)	37.60 (27.60–48.95)	<0.001
FEV1/FVC,%	55.32 ± 10.86	48.31 ± 10.63	<0.001
MEF50	0.52 (0.34–0.82)	0.40 (0.29–0.59)	<0.001
MEF50 pred,%	14.45 (9.85–22.60)	13.92 (7.93–17.08)	<0.001
MEF25	0.22 (0.15–0.31)	0.20 (0.15–0.25)	0.081
MEF25 pred,%	20.65 (14.75–29.98)	19.15 (13.60–25.75)	0.066
MMEF75/25	0.44 (0.29–0.70)	0.35 (0.26–0.50)	0.001
MMEF75/25 pred,%	15.80 (10.63–24.88)	12.90 (9.83–18.48)	0.002

(*Continued*)

Table 1 (Continued).

Variable	Mild Emphysema N=143	Severe Emphysema N=249	*P*
Cardiac Parameters			
LVEF ≥50%	58 (40.6)	75 (30.1)	0.046
PASP ≥50mmHg	15 (10.5)	30 (12.0)	0.743
CAC	71 (49.7)	137 (55.0)	0.305

Note: All continuous data are given as median (IQR), all categorical data as N (%).

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; MEF, maximum expiratory flow; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; CAC, coronary artery calcification; pred, predicted value; *P*, *P*-value; N, number of patients.

male prevalence (90.4% vs 80.4%; OR 2.25, 95% CI 1.24–4.08) and reduced adiposity (BMI 21.6±3.6 vs 23.6±3.7 kg/m², $p < 0.001$). The distribution of ABE groups did not differ significantly ($p = 0.188$), with group E predominating in both. Comorbidities such as hyperlipidemia, hypertension, diabetes, and smoking history were comparable between groups.

Pulmonary function was more impaired in the severe emphysema group, with significantly lower FEV_1 (0.88 vs 0.99 L, $p = 0.021$), FEV_1% predicted (37.60% vs 44.10%, $p < 0.001$), and FEV_1/FVC ratio (48.31% vs 55.32%, $p < 0.001$). Markers of small airway function, including MEF_{50}, MMEF75/25, and their predicted percentages, were also significantly reduced (all $p < 0.01$). Differences in MEF25 and MEF25% predicted did not reach statistical significance.

Regarding cardiac parameters, patients with severe emphysema were less likely to have preserved LVEF (≥50%) (30.1% vs 40.6%, $p = 0.046$). There were no significant differences in PASP (≥50 mmHg) or CAC between the groups.

Association of Emphysema Severity with CAD Risk

In the logistic regression analysis, the unadjusted model (Model 1) revealed that emphysema percentage (%) was significantly associated with an increased risk of CAD (OR = 1.03, 95% CI: 1.01–1.05; $p = 0.017$). After adjusting for age and sex (Model 2), the association was attenuated and became borderline significant (OR = 1.02; $p = 0.069$). In the fully adjusted model (Model 3), which additionally included covariates with $p < 0.1$ in the univariate analysis (Supplementary file 1), the association remained significant (OR = 1.03, 95% CI: 1.00–1.06; $p = 0.020$), suggesting that emphysema severity is independently associated with CAD in COPD patients. Additionally, severe emphysema (≥16.95%) was associated with more than a twofold higher risk of CAD (OR = 2.08, 95% CI: 1.30–3.34; $p = 0.002$). This association remained significant after adjusting for age and sex (OR = 1.93, 95% CI: 1.19–3.12; $p = 0.007$). The final model (Model 3) demonstrated that severe emphysema remained an independent risk factor for CAD (OR = 2.28, 95% CI: 1.29–4.03; $p = 0.005$). The final model (Model 3), using emphysema as a binary variable, is shown in Table 2. The OR of emphysema-related variables across the three models are summarized in Table 3.

Table 2 Multivariable Logistic Regression Analysis of Risk Factors Associated with Progression to CAD

	Odds Ratio	95% CI	*P*
Age	1.01	0.97–1.04	0.714
Sex, male	3.76	1.47–9.61	0.006*
ABE ref:A			<0.001***
B	3.07	1.16–8.14	0.024*
E	0.80	0.33–1.93	0.622
FEV1, L	1.32	0.70–2.49	0.397
Hyperlipidemia	3.01	1.54–5.91	0.001*

(*Continued*)

Table 2 (Continued).

	Odds Ratio	95% CI	*P*
Hypertension	1.65	0.98–2.78	0.060
Diabetes	0.94	0.48–1.84	0.855
LVEF ≥50%	0.46	0.26–0.80	0.007*
PASP ≥50mmHg	0.76	0.32–1.81	0.536
CAC	4.65	2.66–8.15	<0.001***
Severe Emphysema (≥16.95%)	2.28	1.29–4.03	0.005*

Note: *P<0.05, ***P<0.001.

Abbreviations: FEV1, forced expiratory volume in one second; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; CAC, coronary artery calcification; *P*, *P*-value; CI, confidence interval; ref:A, reference group A.

Table 3 Association Between Emphysema Severity and the Presence of CAD

	Model 1		Model 2		Model 3	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Emphysema,%	1.03 (1.01–1.05)	0.017	1.02 (1.00–1.04)	0.069	1.03 (1.00–1.06)	0.020
Severe Emphysema (≥16.95%)	2.08 (1.30–3.34)	0.002	1.93 (1.19–3.12)	0.007	2.28 (1.29–4.03)	0.005

Notes: Adjusted covariates: Model 1: unadjusted; Model 2: adjusted by age, sex; Model 3: Model 2 + comorbidities (hypertension, diabetes, hyperlipidemia) + covariates with $p < 0.1$ in univariate analysis (FEV1, LVEF≥50%, PASP ≥50 mmHg, CAC, ABE group).

Abbreviations: OR, odds ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; CAC, coronary artery calcium; *P*, *P*-value.

Restricted Cubic Spline and Subgroup Analyses of the Emphysema–CAD Association

To further assess the potential nonlinear association between emphysema (%) and the risk of CAD, we applied a RCS regression model (Figure 3). The overall association was statistically significant (Chi-square = 6.95, $p = 0.031$), indicating that emphysema (%) is significantly associated with CAD risk. However, the test for nonlinearity was not significant (Chi-square = 1.66, $p = 0.199$), suggesting that the relationship is more likely to be linear rather than nonlinear across the range of emphysema (%).

In the subgroup analyses, the association between emphysema severity and the risk of CAD remained broadly consistent across most subgroups (Figure 4). No significant interactions were detected (all $p > 0.05$).

Predictive Value of Emphysema for CAD in COPD Patients

Figure 5 presents the ROC curves for all three models. Model 1, which included only the emphysema index, achieved an AUC of 0.58 (95% CI: 0.53–0.63; $p = 0.002$), indicating a modest ability to discriminate between patients with and without CAD. Upon adjusting for age and sex in Model 2, the AUC increased to 0.65 (95% CI: 0.59–0.71; $p < 0.001$). Model 3, which incorporated a broader set of clinical covariates, demonstrated the highest predictive accuracy, with an AUC of 0.81 (95% CI: 0.77–0.86; $p < 0.001$). This substantial increase underscores the significant predictive value of emphysema, particularly when considered alongside other clinical factors, enhancing its utility in identifying CAD risk among COPD patients.

Association of Emphysema with CAD Complexity and Intervention

Among the 122 patients who developed CAD within 5 years, no significant associations were observed between emphysema severity and the involvement of the four major coronary arteries or the presence of total occlusion in the three primary coronary arteries. Involvement of the left anterior descending artery (LAD) was more frequent in the severe emphysema group compared to the non-severe group (87.3% vs 66.7%), approaching but not reaching statistical significance ($p = 0.098$). However, severe emphysema was significantly associated with a higher rate of PCI (68.2% vs 33.3%, $p = 0.037$) and a higher SYNTAX score (median: 16.29 vs 10.00, $p = 0.013$), indicating more complex CAD in this group (Table 4).

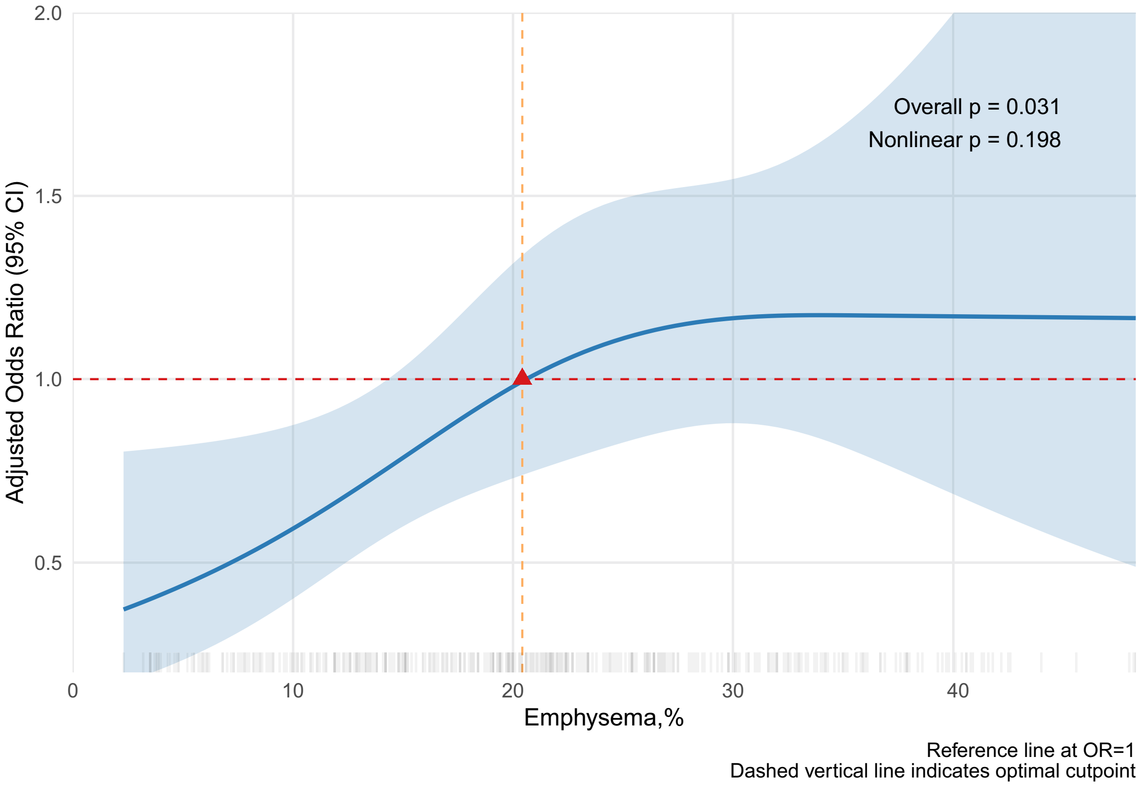
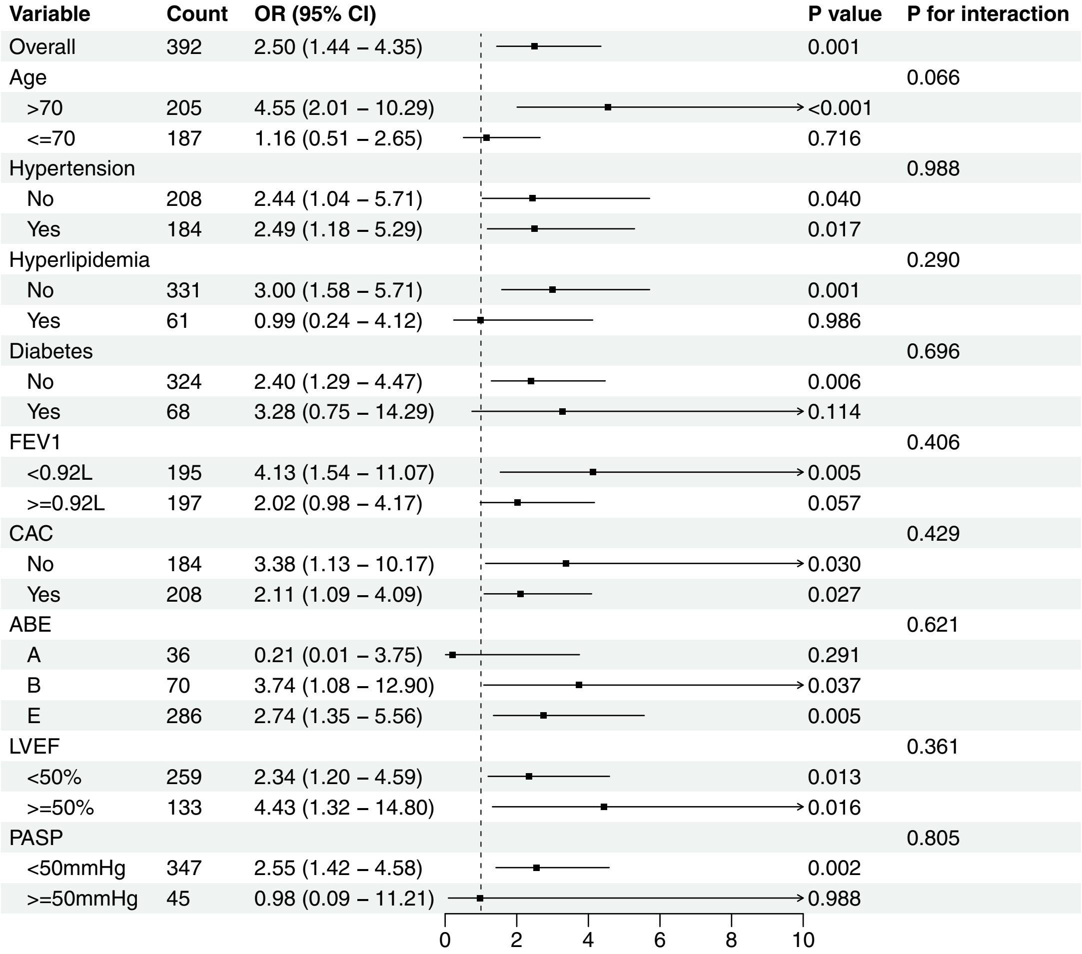


Figure 3 Dose–Response Relationship between Emphysema and the Risk of CAD Using Restricted Cubic Spline Analysis. Adjusted OR for CAD according to emphysema (%) using restricted cubic spline analysis. The blue line represents adjusted ORs, and the shaded area indicates the 95% confidence interval. A logistic regression model was fitted, adjusting for age, sex, FEV1, diabetes, hypertension, hyperlipidemia, LVEF, PASP, CAC, and ABE classification. The dashed horizontal line represents the reference OR = 1.0, while the red arrow and vertical dashed line indicate the turning point, suggesting a potential threshold for increased risk.

Discussion

In this study, we evaluated whether CT-quantified emphysema could independently predict the presence and complexity of CAD in patients with COPD. Our key findings were as follows: (1) Emphysema extent, measured as the percentage of low-attenuation lung on HRCT, was significantly associated with CAD, even after adjusting for age, sex, and other conventional risk factors. (2) Using a data-driven cutoff (≥16.95%) to define severe emphysema, we found that patients with severe emphysema had a markedly higher likelihood of CAD compared to those with milder disease. (3) Severe emphysema was also associated with more complex CAD, as indicated by higher SYNTAX scores and a greater need for PCI procedures.

Our findings support substantial evidence that emphysematous COPD is associated with increased atherosclerotic progression. COPD patients have approximately twice the risk of cardiovascular comorbidities compared to non-COPD individuals.[28] A meta-analysis further reported a 2–5-fold increase in ischemic heart disease (IHD) risk among those with COPD.[29] Consistently, several angiographic studies have demonstrated more severe CAD in COPD patients, with lower FEV_1 correlating with more complex CAD,[30] and a linear relationship between advanced COPD and higher SYNTAX scores.[31] Our findings extend these observations by using imaging-based emphysema quantification rather than airflow metrics. However, the link between emphysema and CAD has not been consistent across studies. In large population cohorts, CT-measured emphysema did not independently predict CAC.[32,33] For instance, Barr et al found that while airflow obstruction (FEV1/FVC) was associated with CAC, quantitative emphysema on CT was not.[33] Similarly, the MESA Lung Study showed no correlation between emphysema on cardiac CT and CAC scores.[32] These differences may reflect study design and endpoints: CAC is a marker of calcific plaque burden in asymptomatic individuals, while our study focused on angiographically significant CAD in symptomatic patients. It is possible that emphysema may have a stronger association with non-calcified vulnerable plaques or the overall complexity of atherosclerosis compared to



Variable	Count	OR (95% CI)	P value	P for interaction
Overall	392	2.50 (1.44 – 4.35)	0.001	
Age				0.066
>70	205	4.55 (2.01 – 10.29)	<0.001	
<=70	187	1.16 (0.51 – 2.65)	0.716	
Hypertension				0.988
No	208	2.44 (1.04 – 5.71)	0.040	
Yes	184	2.49 (1.18 – 5.29)	0.017	
Hyperlipidemia				0.290
No	331	3.00 (1.58 – 5.71)	0.001	
Yes	61	0.99 (0.24 – 4.12)	0.986	
Diabetes				0.696
No	324	2.40 (1.29 – 4.47)	0.006	
Yes	68	3.28 (0.75 – 14.29)	0.114	
FEV1				0.406
<0.92L	195	4.13 (1.54 – 11.07)	0.005	
>=0.92L	197	2.02 (0.98 – 4.17)	0.057	
CAC				0.429
No	184	3.38 (1.13 – 10.17)	0.030	
Yes	208	2.11 (1.09 – 4.09)	0.027	
ABE				0.621
A	36	0.21 (0.01 – 3.75)	0.291	
B	70	3.74 (1.08 – 12.90)	0.037	
E	286	2.74 (1.35 – 5.56)	0.005	
LVEF				0.361
<50%	259	2.34 (1.20 – 4.59)	0.013	
>=50%	133	4.43 (1.32 – 14.80)	0.016	
PASP				0.805
<50mmHg	347	2.55 (1.42 – 4.58)	0.002	
>=50mmHg	45	0.98 (0.09 – 11.21)	0.988	

Figure 4 Logistic Regression Subgroup Analysis of Emphysema as a Risk Factor for CAD. The primary outcome was five-year progression of CAD, defined as either ≥50% coronary stenosis on coronary angiography (CAG) or the presence of significant coronary artery narrowing as indicated by coronary computed tomography angiography (CCTA), as assessed by certified cardiologists in accordance with standard diagnostic criteria. Arrows on the confidence interval bars indicate that the upper or lower boundary of the confidence interval is off the scale.

calcification alone.[34] In support of the emphysema-CAD link, other imaging studies have shown a higher prevalence of significant CAD in emphysematous patients.[35] Moreover, emphysema severity has been associated with higher arterial stiffness[36] and increased cardiovascular mortality,[37] indicating systemic vascular consequences.

Potential Mechanisms Linking Emphysema to CAD

Several mechanisms may explain why severe emphysema predisposes to more frequent and complex CAD. First, chronic systemic inflammation, a hallmark of COPD, intensifies with disease progression.[38] Activated macrophages and neutrophils in emphysematous lungs release cytokines (eg IL-6, TNFα) and proteases (eg MMP-2/9), which enter the circulation and promote atherogenesis by inducing endothelial dysfunction, foam-cell formation, and plaque destabilization.[39,40] This inflammatory milieu also reduces nitric oxide (NO) bioavailability, impairing vasodilation and accelerating atherosclerosis.[41] Moreover, concurrent elastin and collagen degradation in pulmonary and vascular tissues suggests shared proteolytic mechanisms linking emphysema with arterial stiffening and atherosclerosis.[42–44]

Second, hypoxemia and vascular remodeling further contribute. Alveolar destruction and air trapping reduce gas exchange, causing chronic hypoxia. This downregulates VEGFR2 expression, triggering endothelial apoptosis and vascular remodeling.[12,45] These changes compromise endothelial integrity and NO production, facilitating LDL-C and immune cell infiltration and increasing plaque vulnerability.[13,46] Capillary rarefaction and reduced myocardial perfusion further exacerbate coronary ischemia.[47] Hypoxia induces inflammation, oxidative stress, and upregulation of endothelial

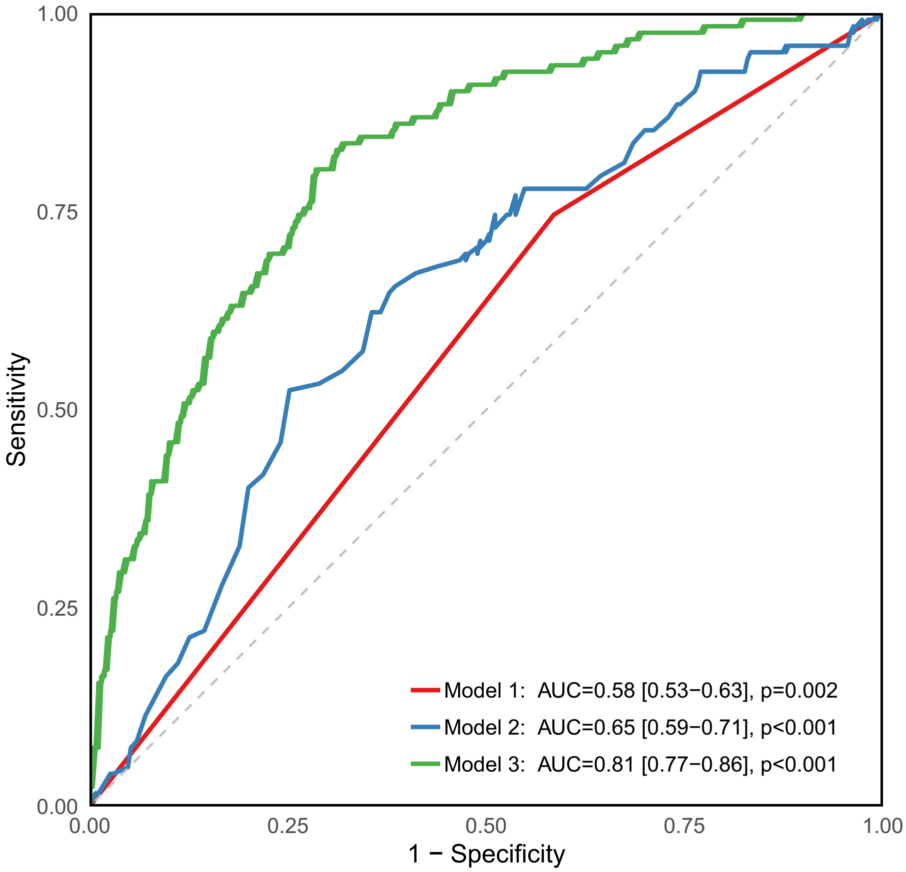


Figure 5 ROC Curves of Three Logistic Regression Models for Predicting CAD. Adjusted covariates: Model 1: unadjusted; Model 2: adjusted by age, sex; Model 3: Model 2 + comorbidities (hypertension, diabetes, hyperlipidemia) + covariates with $p < 0.1$ in univariate analysis (FEV1, LVEF≥50%, PASP ≥50 mmHg, CAC, ABE group).

adhesion molecules, all promoting atherosclerosis progression.[39,48] It further drives pulmonary hypertension via HIF-mediated pathways, exacerbating coronary dysfunction.[48] Additionally, hyperinflation and dynamic respiratory pressures may impair cardiac filling and left ventricular diastolic dysfunction, further limiting myocardial ischemia.[12,49–51]

Third, the presence of protective factors in individuals with mild emphysema may help explain the lower incidence of CAD compared to those with severe disease. Recent studies have suggested that anti-inflammatory mediators, such as

Table 4 Comparison of CAD-Related Outcomes Between Mild and Severe Emphysema Groups

Variable	**Mild Emphysema N = 22**	**Severe Emphysema N = 100**	***P***
Affected Vessels			
LCA	7 (77.8)	72 (87.8)	0.399
LAD	6 (66.7)	69 (87.3)	0.098
LCX	4 (50.0)	38 (48.7)	0.945
RCA	5 (55.6)	53 (65.4)	0.557
Occluded Vessel			
LAD occlusion	0 (0.0)	18 (16.1)	0.170
LCX occlusion	2 (20.0)	8 (7.1)	0.156
RCA occlusion	1 (10.0)	16 (14.3)	0.708

(*Continued*)

Table 4 (Continued).

Variable	**Mild Emphysema** **N = 22**	**Severe Emphysema** **N = 100**	***P***
Number of Affected Vessels	2 (1–3)	2 (0.5–3)	0.924
Treatment			
PCI	3 (33.3)	58 (68.2)	0.037
CABG	1 (11.1)	4 (4.7)	0.416
SYNTAX score	10.00 (5.00–12.00)	16.29 (11.00–21.00)	0.013

Note: All continuous data are given as median (IQR), all categorical data as N (%).
Abbreviations: CAD, coronary artery disease; LCA, left coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; PCI, Percutaneous coronary intervention; CABG, coronary artery bypass grafting; *P*, *P*-value; N, number of patients.

TNF-related apoptosis-inducing ligand (TRAIL), may have protective effects against emphysema.[52] Circulating TRAIL levels are typically preserved in smokers with mild emphysema but significantly reduced in those with advanced disease, particularly among those with concurrent CAC. Furthermore, reduced TRAIL levels have been independently associated with increased mortality in smokers, particularly in those with coexisting emphysema and coronary artery calcification.[53] In addition, another study demonstrated that decreased TRAIL levels, along with elevated concentrations of its receptor TRAIL-R2, are associated with higher all-cause mortality in patients with cardiovascular disease.[54] Moreover, better functional status may serve as another protective factor. The ECLIPSE study found that worsening dyspnea and reduced exercise capacity are strongly linked to CAD in COPD patients, suggesting that preserved physical capacity in mild emphysema may reduce cardiovascular risk.[55] Together, these findings highlight that both biochemical and physiological factors may confer relative protection against CAD in patients with mild emphysema, whereas their loss in more advanced stages may contribute to increased cardiovascular vulnerability.

Fourth, shared risk factors and accelerated aging provide a backdrop. Smoking is a common etiologic factor for both, and although adjusted for in our analysis, residual confounding cannot be excluded.[56,57] COPD is increasingly recognized as a disease of accelerated aging, characterized by telomere shortening and oxidative stress. In emphysema, senescent parenchymal cells perpetuate inflammation and tissue damage.[58] While the role of oxidative stress in atherosclerosis remains debated, it is increasingly implicated in vascular injury among COPD patients.[59] Furthermore, emphysema-induced alveolar loss and elevated pulmonary pressures may impair diffusing capacity and reduce LVEF, leading to chronic hypoxemia and increased cardiovascular strain.[60]

Finally, our multivariate regression analysis revealed a significantly higher OR in Group E of the ABE classification. Persistent respiratory symptoms and systemic inflammation in this group likely promote atherogenesis. This is supported by evidence showing that GOLD E patients have double the cardiovascular hospitalization rates compared to A0 patients.[15] A 2022 study also found that greater respiratory symptom burden predicts higher CVD incidence and mortality in middle-aged populations,[61] while Australian data confirm increased mortality risk in symptomatic elderly patients.[62] Collectively, findings underscore the progressive cardiovascular risk associated with worsening respiratory symptoms across populations.

Clinical Relevance of Emphysema-Associated CAD Pathogenesis

These findings underscore the need for heightened cardiovascular vigilance in COPD patients with radiographic evidence of emphysema—particularly those with frequent respiratory symptoms or a history of $\geq$ 2 annual hospitalizations for exacerbations. First, the presence of emphysema on lung imaging should prompt comprehensive cardiovascular risk assessment. For instance, a chest CT showing $\geq$ 16.95% emphysema may warrant cardiology referral, intensified risk-factor modification (eg, lipid-lowering agents, antihypertensive therapy, smoking cessation), and potentially noninvasive screening for coronary artery disease. In the NLST cohort, incidental emphysema detected during lung cancer screening was independently associated with increased cardiovascular mortality.[63] Incorporating quantitative emphysema metrics into risk stratification models may enhance prediction accuracy; patients with severe emphysema might benefit from coronary artery imaging—such as CT angiography or calcium scoring. Second, raising clinical awareness is crucial. Although current guidelines increasingly recommend aggressive cardiovascular risk management in COPD patients, adherence in routine practice remains suboptimal. Early identification of high-risk individuals enables timely interventions, including Long-Term Oxygen Therapy (LTOT), which may alleviate hypoxemia and mitigate cardiovascular complications. Collectively, these insights support the integration of pulmonary imaging findings into multidisciplinary cardiovascular care strategies for COPD patients.

Strengths and Limitations

This study leveraged comprehensive imaging data to explore the interplay between pulmonary and cardiovascular disease, which represents a key strength. Quantitative HRCT enabled objective and reproducible assessment of emphysema burden. The inclusion of both continuous and dichotomous emphysema variables enhanced the robustness and interpretability of the results. Moreover, adjustment for a broad range of clinical confounders increases confidence that the observed association is not solely attributable to shared risk factors. Clinically, the use of angiographically confirmed CAD as the outcome provides a hard endpoint that directly reflects disease burden and patient morbidity.[64]

However, this study has several limitations. The retrospective design prevents causal inferences and may introduce selection bias since only patients receiving both HRCT and coronary evaluation were included. Residual confounding from unmeasured factors (eg, physical activity, smoking history) may persist despite adjustments. Technical variations in CT scanning and lack of longitudinal cardiac event data further constrain our findings. The single-center design and limited sample size also affect generalizability. Despite these caveats, the observed associations are strong and biologically plausible, and they complement external evidence linking emphysema to cardiovascular risk.

Conclusion

This study evaluated the association between emphysema severity and CAD in COPD patients, demonstrating that more severe emphysema is an independent risk factor for CAD progression. Additionally, patients with severe emphysema exhibited significantly more complex coronary lesions. These findings underscore the importance of incorporating emphysema severity into cardiovascular risk assessment and management strategies for COPD patients, highlighting its potential clinical predictive value. The emphysema threshold identified in this study ($\geq$16.95% LAA-950) may serve as a practical imaging biomarker for early cardiovascular risk stratification in COPD patients, enabling timely evaluation and intervention. However, as this threshold was derived from a single-center retrospective cohort, its clinical implementation requires further validation in external, prospective, and multicenter studies.

Abbreviations

COPD, Chronic obstructive pulmonary disease; CAD, Coronary artery disease; HRCT, High-resolution computed tomography; AECOPD, Acute exacerbations of COPD; OR, Odds ratio; CI, Confidence interval; FEV1, Forced Expiratory Volume in One Second; FVC, Forced vital capacity; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; AUC, Area Under the Curve; eGFR, Estimated glomerular filtration rate; CAC, Coronary artery calcification; LVEF, Left ventricular ejection fraction; PASP, Pulmonary artery systolic pressure; ICA, Invasive coronary angiography; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass graft surgery; CAG, Coronary angiography; CCTA, Coronary computed tomography angiography; HU, Hounsfield units; SD, Standard deviation; IQR, Median with interquartile range; IHD, Ischemic heart disease; VIFs, Variance inflation factors; VEGFR2, Vascular endothelial growth factor receptor II; HIFs, Hypoxia-inducible factors; LTOT, Long-term oxygen therapy; NO, Nitric oxide; IL-6, Interleukin-6; BMI, Body mass index.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. As it did not involve the collection or disclosure of any personally identifiable information, the requirement for informed consent was waived. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, Zhejiang Province (Approval No. KY2023-R084).

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Disclosure

The authors declare that they have no competing interests.

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