

Short-time deep-inspiratory breath-hold perfusion SPECT/CT in pulmonary emphysema: perfusion defect extent, not CT-quantified emphysema extent, tracks major adverse events

Yoshimitsu Fukushima

fuku@nms.ac.jp

Nippon Medical School <https://orcid.org/0000-0001-6224-4914>

Teruhiko Hamana

Nippon Medical School

Kenji Yodogawa

Nippon Medical School

Takahiro Ando

Nippon Medical School

Yujiro Nakaoka

Nippon Medical School

Yoshimitsu Honda

Nippon Medical School

Satoshi Harashina

Nippon Medical School Hospital

Kyouji Asano

Nippon Medical School Hospital

Hiromitsu Hayashi

Nippon Medical School

Shinichiro Kumita

Nippon Medical School

Research Article

Keywords: Pulmonary emphysema, Perfusion imaging, Single-photon emission computed tomography, Breath holding, Prognosis

Posted Date: October 8th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11146157/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Abstract

Objective Computed tomography (CT) quantifies emphysema extent but not the accompanying perfusion loss. This study evaluated whether perfusion defect extent, the percent perfusion defect (%PPD) on short-time deep-inspiratory breath-hold (STDIBH) perfusion single-photon emission computed tomography/CT (SPECT/CT), is associated with major adverse events (MAE) in emphysema, and whether CT-quantified emphysema extent carries comparable information.

Methods Of 91 patients with emphysema who underwent STDIBH perfusion SPECT/CT, 74 were analyzed retrospectively. Perfusion defect volume as a percentage of CT lung volume defined %PPD, and emphysema extent was the percentage of low-attenuation area (%LAA) on the same CT. MAE comprised all-cause death, hospitalization for respiratory failure or acute exacerbation of chronic obstructive pulmonary disease, and new home oxygen therapy. The primary analysis was Cox regression adjusted for B-type natriuretic peptide and for combined pulmonary fibrosis and emphysema (CPFE), supplemented by clinical adjustment, penalized estimation, restricted cubic splines, and exploratory time-dependent areas under the curve (AUCs).

Results Over a median follow-up of 70.9 months, MAE occurred in 54 patients (73.0%). In the primary model, %PPD was associated with MAE (hazard ratio [HR] 1.1641 per 10%, 95% confidence interval [CI] 1.0437–1.2982, $P = 0.006$), and the estimate was similar after adjustment for age, sex, percent predicted forced expiratory volume in 1 s, and CPFE (HR 1.1651, 95% CI 1.0392–1.3063). Unadjusted %LAA was not significantly associated with MAE (HR 1.0080 per 1%, 95% CI 0.9884–1.0280, $P = 0.425$). The time-dependent AUC of %PPD exceeded that of %LAA at 36 months (difference 0.183, 95% CI 0.069–0.303) and 60 months (0.189, 0.044–0.338) but not clearly at 12 months (0.050, –0.069 to 0.164). Risk rose up to a %PPD of about 55% and no further (nonlinearity $P < 0.001$). The planar Meyer perfusion score discriminated MAE similarly to %PPD (binary AUC 0.813 vs 0.776, $P = 0.263$).

Conclusions In pulmonary emphysema, perfusion defect extent on STDIBH SPECT/CT, not CT-quantified emphysema extent, tracks major adverse events. Because STDIBH SPECT/CT measures the perfusion defect against the same CT that quantifies emphysema, one examination places the vascular and structural components of the disease on a common anatomical denominator.

Introduction

Pulmonary emphysema is characterized by irreversible alveolar wall destruction and distal airspace enlargement, leading to airflow limitation and impaired gas exchange [1]. It affects a substantial proportion of patients with chronic obstructive pulmonary disease (COPD), and the global prevalence of COPD has risen [2]. Emphysema severity on computed tomography (CT) predicts mortality independently of spirometric measures [3, 4], which has made CT-quantified emphysema extent a widely used imaging measure of disease severity.

Emphysema extent describes only part of the disease. Capillary destruction and endothelial dysfunction impair pulmonary perfusion [5, 6], and vascular dysfunction is associated with exercise intolerance, reduced quality of life, and exacerbations [7, 8]. Vascular injury may be both a consequence of parenchymal destruction and an independent driver of progression [9, 10]. CT-derived vascular parameters provide morphological surrogates [11] but do not measure blood flow.

Pulmonary perfusion scintigraphy with ^{99m}Tc -macroaggregated albumin (^{99m}Tc -MAA) is the established method for mapping pulmonary blood flow [12], and single-photon emission computed tomography/CT (SPECT/CT) adds three-dimensional quantification with anatomical correlation [13]. Conventional perfusion SPECT/CT, however, is acquired during tidal breathing, and incomplete lung inflation and respiratory motion can blur defects in emphysema. Suga et al. showed that deep-inspiratory breath-hold perfusion SPECT improves defect clarity in smokers' lungs [14] and, with SPECT/CT fusion, in pulmonary thromboembolism and emphysema [15, 16]. CT density-based attenuation correction further sharpens defect contrast [17]. Related approaches include respiratory-gated perfusion imaging [18], the ^{99m}Tc -Technegas stripe sign [19], and automated ventilation/perfusion quotient SPECT [20]. Perfusion SPECT/CT also predicts outcomes after lung volume reduction surgery [21], and ventilation/perfusion SPECT tracks symptoms, spirometry, and emphysema extent in COPD [22, 23]. The percent perfusion defect (%PPD) was introduced as a quantitative index of pulmonary circulatory impairment in chronic lung disease [24].

We developed a short-time deep-inspiratory breath-hold (STDIBH) technique that acquires perfusion SPECT/CT during 12 repeated 10-second breath-holds [25]. Short breath-holds are feasible for patients with advanced lung disease, and full inspiration aligns the SPECT with its co-registered CT. STDIBH %PPD was prognostic in pulmonary thromboembolism [25], but, to our knowledge, STDIBH perfusion SPECT/CT has not been applied to outcomes in emphysema. We therefore evaluated whether perfusion defect extent (%PPD) on STDIBH perfusion SPECT/CT is associated with major adverse events (MAE), and whether CT-quantified emphysema extent, the percentage of low-attenuation area (%LAA) on the same CT, carries comparable information. We also compared %PPD with the planar Meyer perfusion score, the conventional regional index of perfusion defects.

Materials and Methods

Study design and patients

This retrospective single-center observational study was conducted at Nippon Medical School Hospital. Consecutive patients with emphysema, diagnosed by pulmonologists on clinical and CT findings, who underwent STDIBH pulmonary perfusion SPECT/CT between May 2012 and March 2023 were identified ($n = 91$). Coexisting interstitial pneumonia, also diagnosed by pulmonologists on clinical and CT findings, constituted combined pulmonary fibrosis and emphysema (CPFE) [26]. Patients with pulmonary thromboembolism ($n = 9$) or malignancy ($n = 7$) were excluded. One further patient had insufficient follow-up data, leaving 74 patients (Fig. 1). Left and right ventricular ejection fractions and the tricuspid

regurgitation pressure gradient (TRPG) were measured by transthoracic echocardiography. A TRPG > 31 mmHg approximates the 2.8 m/s velocity threshold for at least an intermediate echocardiographic probability of pulmonary hypertension [27]. Online Resource 1 details pulmonary function and B-type natriuretic peptide (BNP) measurements.

The study was approved by the Central Ethics Committee of Nippon Medical School (approval number M-2026-544) and was performed in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived because of the retrospective design, and an opt-out approach was used under the Ethical Guidelines for Medical and Biological Research Involving Human Subjects in Japan.

STDIBH pulmonary perfusion SPECT/CT

Perfusion SPECT/CT was performed with a dual-head system (Symbia T2; Siemens Healthineers) and low-energy high-resolution collimators. Two divided doses of ^{99m}Tc -MAA were administered (185 MBq supine and 185 MBq prone; total 370 MBq), and SPECT acquisition began 10 minutes after the second dose. The STDIBH protocol used 12 repeated 10-second deep-inspiratory breath-hold acquisitions during 360° continuous detector rotation, with a 128 × 128 matrix and recovery intervals of approximately 10 seconds. At least 8 adequate acquisitions were required for composite reconstruction.

Low-dose CT for attenuation correction and anatomical correlation was acquired during a single deep-inspiratory breath-hold matched to the SPECT acquisition (tube voltage 110 kV, tube current–time product 10–40 mAs, slice thickness 5 mm). SPECT images were reconstructed with the Flash-3D iterative algorithm (Siemens Healthineers; 8 iterations, 6 subsets), incorporating CT-based attenuation correction, triple-energy-window scatter correction, and resolution recovery.

Image analysis

On the syngo workstation (Siemens Healthineers), %PPD was quantified with the semiautomated, threshold-based volumetric method described for STDIBH perfusion SPECT/CT [25]:

$$\text{\%PPD} = (\text{perfusion defect volume on SPECT} / \text{anatomical lung volume on CT}) \times 100$$

The perfusion defect volume comprised SPECT voxels with uptake below 31% of the maximum pulmonary uptake, a threshold calibrated so that the mean %PPD in control participants was 0% [25]. The anatomical lung volume was segmented from the co-registered CT between – 1024 and – 400 Hounsfield units (HU) so that emphysematous low-attenuation parenchyma remained in the denominator. A radiologic technologist and a board-certified diagnostic radiologist, both blinded to outcomes and clinical information, quantified %PPD in consensus.

For regional scoring, relative uptake in 6 zones of the planar perfusion images, acquired separately from SPECT in anterior, posterior, and both lateral views, was graded from 1.0 (normal) to 0 (absent), and the Meyer P-score (%) was calculated as the volume-weighted total deficiency [28] (Online Resource 1). The same method, applied to planar $^{81\text{m}}\text{Kr}$ gas ventilation scintigraphy performed when clinically indicated, gave the Meyer V-score. A second board-certified diagnostic radiologist, blinded to outcomes and clinical information, performed all Meyer scoring.

CT-quantified emphysema extent was expressed as %LAA, the percentage of lung voxels below -950 HU on the same low-dose CT. Two mismatch metrics were calculated: the perfusion-structure mismatch (%PPD - %LAA) and, in patients with ventilation imaging, the ventilation-perfusion mismatch (Meyer P-score - Meyer V-score). Positive values indicate perfusion impairment exceeding the structural or ventilation reference. The perfusion-structure mismatch, a fixed re-expression of a model containing both terms, was exploratory.

Outcomes

The primary endpoint was MAE-free survival, with MAE defined as the first of all-cause death, hospitalization for respiratory failure, hospitalization for acute exacerbation of COPD (AECOPD), or new home oxygen therapy (HOT). Patients already receiving HOT at baseline could reach only the other 3 components. Heart failure (HF) hospitalization, which is driven largely by cardiac comorbidity, was excluded from the primary composite and included in a 5-component composite for sensitivity analysis. Follow-up was open-ended from the SPECT/CT examination to the last clinical contact, without administrative censoring. Events were identified from admissions, notes, prescriptions, and high-resolution CT, and were independently adjudicated by a board-certified pulmonologist and a board-certified cardiologist, both blinded to %PPD, with disagreement resolved by consensus.

Statistical analysis

The study plan, including the variables to be collected, the outcome definitions, and the analyses, was fixed before data acquisition. All clinical, laboratory, imaging, and outcome variables were recorded from the outset of the study, and the analyses were performed after data collection closed. Continuous variables are summarized as mean $\pm$ standard deviation (SD) or median [interquartile range (IQR)], and categorical variables as number (percentage), with denominators shown where data were incomplete. Each analysis used complete cases.

Time to the first MAE was analyzed with Cox proportional-hazards regression. Entered as a continuous variable, %PPD was reported per 10% increase, with per-1%, per-SD, and per-IQR scaling. The primary model adjusted %PPD for BNP (per 100 pg/mL) and CPFE. An Akaike information criterion (AIC) best-subset search among candidates with univariable $P < 0.20$ other than %DLCO and pack-years, limited to models with at least 10 events per variable [29], selected these covariates and TRPG, which was

removed as nonsignificant. Hazard ratios (HRs) are reported with Wald 95% confidence intervals (CIs), and tied event times were handled with the Efron approximation.

Proportional hazards were assessed with rank-transformed Schoenfeld residual tests, and collinearity with variance inflation factors. The functional form of %PPD was examined with restricted cubic splines (3 knots at the 10th, 50th, and 90th percentiles, and 4 knots) and a log2 transformation, all compared by partial AIC [30].

Each of 16 clinical and imaging variables was entered with %PPD one at a time. When a covariate was missing, the unadjusted HR in the same patients was also estimated. In the 73 patients with complete data, %PPD was also entered in a clinical model containing age, sex, percent predicted forced expiratory volume in 1 s (%FEV1.0), and CPFE, with and without log2 BNP. Because the proportional-hazards test for sex gave $P < 0.05$ in the clinical model, both clinical models were also stratified by sex. The primary and unstratified clinical models were refitted with Firth penalization and profile-likelihood intervals [31] and with ridge penalization ($\lambda = 0.01, 0.1, \text{ and } 1.0$). Marker correlations used Spearman coefficients.

Sensitivity analyses replaced the primary endpoint with the 5-component composite, estimated the %PPD association separately in patients with and without CPFE, and tested the %PPD $\times$ CPFE interaction. Median follow-up was estimated by the reverse Kaplan-Meier method.

Discrimination of the primary model was summarized by the Harrell concordance index, corrected for optimism with 1000 bootstrap resamples, and calibration by the bootstrap-corrected slope [30]. The change in concordance when %PPD was added to reference models was reported with percentile bootstrap intervals. For descriptive display, patients were grouped at the Youden cutoff of %PPD for MAE from receiver operating characteristic (ROC) analysis, whose area under the curve (AUC) was reported with a bootstrap 95% CI. MAE-free survival was estimated by the Kaplan-Meier method, compared by the log-rank test, and summarized by the restricted mean survival time (RMST) to 60 months. In an exploratory analysis, %PPD was compared with %LAA, the Meyer P-score, and BNP by time-dependent AUCs at 12, 36, and 60 months, estimated with inverse probability of censoring weighting [32], with percentile bootstrap intervals for paired differences. Binary AUCs were compared by the DeLong method [33]. The mismatch metrics, the Meyer V-score, and the Youden cutoffs of the comparison markers were exploratory, and no cut point is proposed for clinical use.

All tests were 2-sided, and $P < 0.05$ was considered statistically significant. No adjustment was made for multiplicity, and P values and confidence intervals outside the primary analysis are interpreted descriptively. No formal power calculation was performed. Precision depends on the number of events rather than patients. With 54 events and 3 parameters, the primary model had 18 events per variable, above the conventional threshold of 10 [29], and a 2-sided test at $\alpha = 0.05$ had 80% power for an unadjusted HR of 1.4641 per SD of %PPD [34].

Analyses were performed in Python 3.12 with lifelines 0.30.3, scikit-learn 1.8.0, and SciPy 1.17.1. The estimates were independently re-derived in R 4.6.1 with survival 3.8.6 and coxphf 1.13.4. Claude

(Anthropic) and Codex (OpenAI) were used for language editing and manuscript formatting. No AI tool was used to generate, analyze, or interpret data or scientific content. All authors reviewed and approved the final content.

Results

Patient characteristics

Of 91 patients identified, 74 were analyzed (Fig. 1). Mean age was 69.5 ± 10.3 years, and 57 patients (77.0%) were male (Table 1). CPFE was present in 26 patients (35.1%), and HOT was in use at baseline in 34 patients (45.9%). Of the 68 patients with measurable TRPG, 39 (57.4%) had a TRPG > 31 mmHg. Median %PPD was 44.8% [IQR 31.7–68.9], median %LAA 5.9% [1.6–12.8], and median Meyer P-score 41.4% [28.1–61.1] (Table 2). The Meyer P-score correlated strongly with %PPD (Spearman $\rho = 0.944$), and %LAA, moderately ($\rho = 0.658$).

Table 1
Baseline characteristics of the study population

Variable	Total (n = 74)
Demographics	
Age (years)	69.5 ± 10.3
Male sex, n (%)	57 (77.0%)
BMI (kg/m ²)	22.3 ± 4.9
Smoking history	
Smoking status (current / former / never), n (%)	1 (1.4%) / 61 (82.4%) / 12 (16.2%)
Pack-years	43.0 [24.7–64.0]
Pulmonary function	
%VC (%) (n = 73)	81.4 [67.7–96.2]
%FEV1.0 (%) (n = 73)	85.0 [59.1–106.5]
FEV1.0/FVC (%) (n = 73)	73.6 [56.4–84.0]
%DLCO (%) (n = 55)	40.1 [26.6–61.8]
GOLD stage (1 / 2 / 3 / 4), n (%)	41 (55.4%) / 20 (27.0%) / 9 (12.2%) / 4 (5.4%)
Cardiac function	
LVEF (%) (n = 71)	71.0 [62.5–75.0]
RVEF (%) (n = 73)	39.0 [31.9–50.0]
TRPG (mmHg) (n = 68)	36.6 [23.9–52.0]
Heart rate (beats/min)	70.0 [63.0–79.0]
Laboratory data	
Data are mean ± SD, median [IQR], or n (%). LVEF, RVEF, and TRPG were measured by transthoracic echocardiography. TRPG > 31 mmHg approximates a tricuspid regurgitation velocity above 2.8 m/s, which indicates at least an intermediate echocardiographic probability of pulmonary hypertension. GOLD stage was assigned from pre-bronchodilator %FEV1.0 cut points regardless of FEV1.0/FVC, so the staging departs from the GOLD classification. The patient with a missing %FEV1.0 was recorded as stage 1. ACE, angiotensin-converting enzyme; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CPFE, combined pulmonary fibrosis and emphysema (emphysema with coexisting interstitial pneumonia); %DLCO, percent predicted diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; %FEV1.0, percent predicted forced expiratory volume in 1 s; FEV1.0/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HOT, home oxygen therapy; IQR, interquartile range; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; SaO₂, arterial oxygen saturation; SD, standard deviation; TRPG, tricuspid regurgitation pressure gradient; %VC, percent predicted vital capacity	

Variable	Total (n = 74)
Demographics	
BNP (pg/mL)	229.8 [59.8–609.8]
SaO ₂ (%)	91.4 [85.7–95.5]
Creatinine (mg/dL)	0.8 [0.6–1.2]
eGFR (mL/min/1.73 m ²)	70.0 [42.7–88.6]
Comorbidities, n (%)	
Coronary artery disease	8 (10.8%)
Hypertension	33 (44.6%)
Dyslipidemia	20 (27.0%)
Diabetes mellitus	17 (23.0%)
CKD (eGFR < 60 mL/min/1.73 m ²)	29 (39.2%)
TRPG > 31 mmHg (n = 68)	39 (57.4%)
Atrial fibrillation	12 (16.2%)
Coexisting interstitial pneumonia (CPFE)	26 (35.1%)
Treatment, n (%)	
Calcium-channel blocker	26 (35.1%)
Angiotensin II receptor blocker	16 (21.6%)
ACE inhibitor	8 (10.8%)
Spironolactone	10 (13.5%)
Beta-blocker	12 (16.2%)
Statin	18 (24.3%)
Data are mean ± SD, median [IQR], or n (%). LVEF, RVEF, and TRPG were measured by transthoracic echocardiography. TRPG > 31 mmHg approximates a tricuspid regurgitation velocity above 2.8 m/s, which indicates at least an intermediate echocardiographic probability of pulmonary hypertension. GOLD stage was assigned from pre-bronchodilator %FEV1.0 cut points regardless of FEV1.0/FVC, so the staging departs from the GOLD classification. The patient with a missing %FEV1.0 was recorded as stage 1. ACE, angiotensin-converting enzyme; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CPFE, combined pulmonary fibrosis and emphysema (emphysema with coexisting interstitial pneumonia); %DLCO, percent predicted diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; %FEV1.0, percent predicted forced expiratory volume in 1 s; FEV1.0/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HOT, home oxygen therapy; IQR, interquartile range; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; SaO₂, arterial oxygen saturation; SD, standard deviation; TRPG, tricuspid regurgitation pressure gradient; %VC, percent predicted vital capacity	

Variable	Total (n = 74)
Demographics	
HOT use at baseline	34 (45.9%)
Data are mean $\pm$ SD, median [IQR], or n (%). LVEF, RVEF, and TRPG were measured by transthoracic echocardiography. TRPG > 31 mmHg approximates a tricuspid regurgitation velocity above 2.8 m/s, which indicates at least an intermediate echocardiographic probability of pulmonary hypertension. GOLD stage was assigned from pre-bronchodilator %FEV1.0 cut points regardless of FEV1.0/FVC, so the staging departs from the GOLD classification. The patient with a missing %FEV1.0 was recorded as stage 1. ACE, angiotensin-converting enzyme; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CPFE, combined pulmonary fibrosis and emphysema (emphysema with coexisting interstitial pneumonia); %DLCO, percent predicted diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; %FEV1.0, percent predicted forced expiratory volume in 1 s; FEV1.0/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HOT, home oxygen therapy; IQR, interquartile range; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; SaO₂, arterial oxygen saturation; SD, standard deviation; TRPG, tricuspid regurgitation pressure gradient; %VC, percent predicted vital capacity	

Table 2
Imaging parameters and outcomes

Variable	Total (n = 74)
Imaging: STDIBH perfusion SPECT/CT	
%PPD (%)	44.8 [31.7–68.9]
Imaging: planar scintigraphy	
Meyer P-score (%)	41.4 [28.1–61.1]
Meyer V-score (%) (n = 46)	17.2 [8.8–28.5]
Imaging: quantitative CT	
%LAA (%)	5.9 [1.6–12.8]
Imaging: mismatch metrics	
%PPD – %LAA (%)	36.9 [26.0–48.4]
Meyer P – V mismatch (%) (n = 46)	26.6 [7.7–36.7]
Follow-up	
Follow-up, months (reverse Kaplan-Meier)	70.9 [45.9–125.1]
Period of SPECT/CT examinations	May 2012 to March 2023
Events, n (%)	
MAE	54 (73.0%)
All-cause death	37 (50.0%)
Respiratory failure hospitalization	37 (50.0%)
AECOPD hospitalization	28 (37.8%)
New HOT introduction	10 (13.5%)
HF hospitalization (sensitivity analysis only)	19 (25.7%)
Data are median [IQR] or n (%). MAE is the first of all-cause death, respiratory failure hospitalization, AECOPD hospitalization, or new HOT introduction. The indented rows count patients with that event at any time during follow-up. Patients could have more than one component event, so the counts do not sum to the MAE count. New HOT introduction was possible only in the 40 patients not receiving HOT at baseline (10 of 40). HF hospitalization enters only the 5-component sensitivity composite. The Meyer P- and V-scores are volume-weighted deficiency scores derived from the planar perfusion and ventilation images. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HF, heart failure; HOT, home oxygen therapy; IQR, interquartile range; %LAA, percentage of low-attenuation area; MAE, major adverse events; %PPD, percent perfusion defect; SPECT/CT, single-photon emission computed tomography/computed tomography; STDIBH, short-time deep-inspiratory breath-hold	

Over a median follow-up of 70.9 months (IQR 45.9–125.1), MAE occurred in 54 patients (73.0%). At any time during follow-up, all-cause death occurred in 37 patients (50.0%), respiratory failure hospitalization in 37 (50.0%), AECOPD hospitalization in 28 (37.8%), and new HOT in 10 (13.5%; all among the 40 patients not receiving HOT at baseline; Table 2).

Perfusion defect extent and MAE

Higher %PPD was associated with MAE on univariable analysis (HR 1.0147 per 1%, 95% CI 1.0040–1.0254, $P = 0.007$) and in the primary model with BNP and CPFE (HR 1.0153 per 1%, 95% CI 1.0043–1.0264, $P = 0.006$; Table 3). This corresponds to an HR of 1.1641 (1.0437–1.2982) per 10% and 1.4153 (1.1029–1.8164) per SD of 22.9%. Schoenfeld residual tests did not indicate nonproportional hazards (Table 3), and the maximum variance inflation factor was 1.030. The Firth-penalized HR per 10% was 1.1643 (1.0445–1.2984). Ridge penalization attenuated the estimate with its direction preserved (1.1619, 1.1452, and 1.0719 at $\lambda = 0.01, 0.1$, and 1.0 ; Table S1).

Table 3
Selected Cox regression results for associations with MAE

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Primary model covariates						
%PPD (per 1%)	1.0147	1.0040–1.0254	0.007	1.0153	1.0043–1.0264	0.006
BNP (per 100 pg/mL)	1.0218	1.0099–1.0339	< 0.001	1.0219	1.0099–1.0340	< 0.001
CPFE	2.3739	1.3272–4.2461	0.004	2.4153	1.3418–4.3475	0.003
Selected clinical variables						
TRPG (per mmHg) (n = 68)	1.0275	1.0121–1.0431	< 0.001	—	—	—
TRPG > 31 mmHg (n = 68)	1.9159	1.0793–3.4013	0.026	—	—	—
Atrial fibrillation	0.3639	0.1551–0.8539	0.020	—	—	—
%DLCO (per 1%) (n = 55)	0.9786	0.9633–0.9943	0.007	—	—	—
RVEF (per 1%) (n = 73)	0.9769	0.9550–0.9993	0.044	—	—	—
HOT use at baseline	2.0676	1.1936–3.5816	0.010	—	—	—
FEV1.0/FVC (per 1%) (n = 73)	1.0073	0.9938–1.0209	0.291	—	—	—

Imaging metrics

The multivariable model is the primary model (74 patients, 54 events), with a partial AIC of 364.92 and a concordance index of 0.702 (bootstrap optimism-corrected 0.692). No Schoenfeld residual test indicated nonproportional hazards (smallest $P = 0.473$). A dash marks a variable not in the multivariable model. The multivariable %PPD HR corresponds to 1.1641 per 10% and 1.7604 per IQR. TRPG > 31 mmHg approximates a tricuspid regurgitation velocity above 2.8 m/s, which indicates at least an intermediate echocardiographic probability of pulmonary hypertension. The atrial fibrillation estimate is clinically implausible and is not interpreted as protective. The mismatch metrics and the Meyer V-score are exploratory. AIC, Akaike information criterion; BNP, B-type natriuretic peptide; CI, confidence interval; CPFE, combined pulmonary fibrosis and emphysema (emphysema with coexisting interstitial pneumonia); %DLCO, percent predicted diffusing capacity for carbon monoxide; FEV1.0/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; HOT, home oxygen therapy; HR, hazard ratio; IQR, interquartile range; %LAA, percentage of low-attenuation area; MAE, major adverse events; %PPD, percent perfusion defect; RVEF, right ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient

Variable	Univariable			Multivariable		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Primary model covariates						
Meyer P-score (per 1%)	1.0188	1.0062–1.0315	0.003	—	—	—
Meyer V-score (per 1%) (n = 46)	1.0257	1.0030–1.0490	0.026	—	—	—
%LAA (per 1%)	1.0080	0.9884–1.0280	0.425	—	—	—
%PPD – %LAA (per 1%)	1.0215	1.0077–1.0355	0.002	—	—	—
Meyer P – V mismatch (per 1%) (n = 46)	1.0283	1.0078–1.0493	0.007	—	—	—
The multivariable model is the primary model (74 patients, 54 events), with a partial AIC of 364.92 and a concordance index of 0.702 (bootstrap optimism-corrected 0.692). No Schoenfeld residual test indicated nonproportional hazards (smallest <i>P</i> = 0.473). A dash marks a variable not in the multivariable model. The multivariable %PPD HR corresponds to 1.1641 per 10% and 1.7604 per IQR. TRPG > 31 mmHg approximates a tricuspid regurgitation velocity above 2.8 m/s, which indicates at least an intermediate echocardiographic probability of pulmonary hypertension. The atrial fibrillation estimate is clinically implausible and is not interpreted as protective. The mismatch metrics and the Meyer V-score are exploratory. AIC, Akaike information criterion; BNP, B-type natriuretic peptide; CI, confidence interval; CPFE, combined pulmonary fibrosis and emphysema (emphysema with coexisting interstitial pneumonia); %DLCO, percent predicted diffusing capacity for carbon monoxide; FEV1.0/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; HOT, home oxygen therapy; HR, hazard ratio; IQR, interquartile range; %LAA, percentage of low-attenuation area; MAE, major adverse events; %PPD, percent perfusion defect; RVEF, right ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient						

Across the 16 single-covariate models, the HR per 10% increase in %PPD ranged from 1.1063 to 1.2672 (Table S2; 15 shown in Fig. 2). The CI included 1 after adjustment for percent predicted diffusing capacity for carbon monoxide (%DLCO; %PPD HR 1.1157, 95% CI 0.9807–1.2694), atrial fibrillation (1.1063, 0.9847–1.2428), or baseline HOT use (1.1156, 0.9952–1.2506). In the 55 patients with %DLCO, the unadjusted HR was 1.1599 (1.0256–1.3117). The HR increased after adjustment for %FEV1.0, the ratio of FEV1.0 to forced vital capacity (FEV1.0/FVC), Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, or %LAA, but the estimates for these covariates ran counter to the expected direction. In the clinical model with age, sex, %FEV1.0, and CPFE, the %PPD HR was 1.1651 (1.0392–1.3063, *P* = 0.009), and, with log2 BNP added, it was 1.1887 (1.0566–1.3372, *P* = 0.004). The latter model had 8.8 events per variable, and its Firth-penalized HR was 1.1858 (1.0557–1.3339). Stratified by sex, these 2 models gave 1.1767 (1.0459–1.3238, *P* = 0.007) and 1.1871 (1.0536–1.3376, *P* = 0.005), respectively.

Functional form and sensitivity analyses

The 3-knot restricted cubic spline did not support a linear log-hazard for %PPD, either unadjusted or adjusted for BNP and CPFE (nonlinearity $P < 0.001$ for both; Fig. 3), and the 4-knot spline agreed (Table S3). Risk rose steeply up to a %PPD of about 55% and no further. Partial AIC favored the 3-knot spline over the log2 and linear forms. Per doubling of %PPD, the adjusted HR was 1.7221 (1.2171–2.4368).

With the 5-component endpoint (56 events), the HR per 10% in the primary model was 1.1186 (1.0055–1.2444, $P = 0.039$). The unadjusted HR per 10% was 1.1369 (0.9928–1.3019, $P = 0.064$) in the 48 patients without CPFE and 1.1994 (1.0056–1.4306, $P = 0.043$) in the 26 patients with CPFE, and the %PPD $\times$ CPFE interaction was not significant ($P = 0.672$; Table S4).

Discrimination and survival

Bootstrap validation of the primary model gave an optimism-corrected concordance index of 0.692 and, in a second run, a corrected calibration slope of 0.921 (Table S5). Adding %PPD to BNP and CPFE raised the apparent concordance by 0.045 (95% CI – 0.013 to 0.124; Table S6). The AUC of %PPD for MAE was 0.776 (95% CI 0.639–0.898), and the Youden cutoff of 34.2% had a sensitivity of 81.5% and a specificity of 75.0% (Fig. 4; Table S7). Median MAE-free survival was 11.3 months in the 49 patients with %PPD $\geq$ 34.2% and 80.6 months in the 25 patients below the cutoff (log-rank $P < 0.001$; Fig. 5). MAE-free survival at 60 months was 17.3% and 69.6%, respectively, and the RMST to 60 months was 31.7 months (95% CI 21.9–40.6) longer in the lower-%PPD group.

Perfusion defect extent versus CT-quantified emphysema extent

Unlike %PPD, %LAA was not significantly associated with MAE (HR 1.0080 per 1%, 0.9884–1.0280, $P = 0.425$; Table S8). Its binary AUC was 0.662 (0.510–0.801), and the AUC difference of 0.113 (– 0.013 to 0.240, $P = 0.080$) in favor of %PPD was not significant. The time-dependent AUCs of %PPD were 0.705, 0.754, and 0.713 at 12, 36, and 60 months, against 0.655, 0.571, and 0.524 for %LAA. The paired differences were 0.050 (– 0.069 to 0.164), 0.183 (0.069–0.303), and 0.189 (0.044–0.338) (Table S9).

Planar Meyer scoring and mismatch metrics

The Meyer P-score was associated with MAE (HR 1.0188 per 1%, 1.0062–1.0315, $P = 0.003$). Its AUC was 0.813 (0.694–0.928; Fig. S1), and the AUC difference (%PPD minus Meyer P-score) of – 0.037 (– 0.102 to 0.028, $P = 0.263$) was not significant. At every horizon, the interval of the paired time-dependent AUC difference included 0 (Table S9).

The %PPD – %LAA mismatch was associated with MAE (HR 1.0215 per 1%, 1.0077–1.0355, $P = 0.002$), and its Youden split separated MAE-free survival (RMST difference 32.2 months, 22.5–40.2; Table S7; Fig. S2d). In the 46 patients with ventilation imaging, the Meyer V-score and the Meyer P – V mismatch were associated with MAE on univariable analysis (Table 3).

Representative cases

Two patients illustrate small and large perfusion–structure mismatches (Fig. 6). A 58-year-old man with %LAA of 16.0% and %PPD of 20.7% remained free of MAE for 76 months. A 65-year-old man with %LAA of 39.0% and %PPD of 81.0% was hospitalized for AECOPD at 9.6 months and died at 43.6 months.

Discussion

STDIBH perfusion SPECT/CT showed that perfusion defect extent, not CT-quantified emphysema extent, tracks major adverse events in pulmonary emphysema. After adjustment for BNP and CPFE, and for age, sex, and airflow limitation, %PPD remained associated with MAE, whereas unadjusted %LAA on the same CT showed no detectable association. This is, to our knowledge, the first application of STDIBH perfusion SPECT/CT to outcomes in emphysema.

Perfusion defect extent versus emphysema extent

The contrast between perfusion defect extent and emphysema extent rests on the association and on exploratory time-dependent discrimination at 36 and 60 months. The binary AUC comparison, which ignores unequal follow-up, was not significant. Endothelial injury and remodeling may drive pulmonary vascular disease in COPD rather than passively follow parenchymal destruction [9, 10, 35]. Lung microvascular alterations may themselves drive emphysema [36], and restoring pulmonary endothelial cells reverses emphysematous changes in experimental models [37]. Perfusion can therefore fail in parenchyma that CT scores as mildly emphysematous. CT surrogates such as pulmonary arterial enlargement and small-vessel area predict exacerbations [7] and reflect severity [11]. They remain morphological, whereas %PPD measures perfusion directly.

What STDIBH adds to planar scoring

The planar Meyer P-score discriminated MAE similarly to %PPD, and the 2 were almost collinear. The prognostic information therefore lies in the perfusion defect itself rather than in the tomographic format. STDIBH adds the form of the measurement, expressing the defect as a volume fraction of the anatomical lung on a co-registered CT that is acquired at full inspiration and also yields %LAA [14–17, 25]. The Meyer score, in contrast, rests on visual grading of 6 zones on planar images.

Shape of the association

Because the association was not linear, the HR per 10% summarizes an average gradient across the observed range. The early rise in risk fits the wide Kaplan-Meier separation at 34.2%. That cutoff, however, was derived in the same data and describes the cohort, not a clinical threshold.

Robustness of the association

The association weakened when %DLCO, atrial fibrillation, or baseline HOT use entered the model. In the 55 patients with %DLCO, the adjusted HR fell below the unadjusted value, so adjustment, not sample size alone, contributed. Both %DLCO and perfusion depend on the pulmonary capillary bed and may carry shared information. Baseline HOT marks disease severity and precludes the new-HOT component. The

protective estimate for atrial fibrillation is clinically implausible. The rise in the HR after adjustment for %FEV1.0, FEV1.0/FVC, GOLD stage, or %LAA reflects suppression between correlated measures, not added robustness. Excluding HF hospitalization, which reflects cardiac comorbidity [38], kept the endpoint predominantly respiratory. Adding it attenuated but did not remove the association.

Clinical implications

Quantifying %PPD may identify patients with emphysema whose pulmonary circulation is severely impaired and who might warrant closer follow-up, pulmonary hypertension screening, or rehabilitation. Exacerbation history, which predicts further events [39], was not available for adjustment. Adding %PPD to BNP and CPFE did not significantly improve concordance. A prospective multicenter study of incremental discrimination over exacerbation history and BNP would test whether %PPD refines risk assessment.

Limitations

This retrospective single-center study included only patients referred for perfusion imaging, limiting generalizability. The primary model was selected by AIC in the same data, so its estimates and the optimism-corrected concordance may remain optimistic. Values of %DLCO were missing in 19 patients, not necessarily at random. Measured on 5-mm low-dose attenuation-correction CT, %LAA may underestimate emphysema relative to thin-section CT, and the narrow %LAA distribution (IQR 1.6–12.8%) limits power. The null %LAA result is not evidence of no association, and the 2 HRs were not formally compared. The association was not significant in the 48 patients without CPFE, so it is not established in emphysema alone. Even on univariable analysis, the airflow covariates were not significant and ran counter to the expected direction (Table S8). Both %PPD and the Meyer P-score are relative to each patient's maximum uptake and cannot register uniformly reduced perfusion. Meyer scoring was performed by 1 observer, and %PPD quantification by 2 observers in consensus. Interobserver agreement was therefore not assessed. No tidal-breathing comparator was acquired. External validation is required before %PPD informs care.

Conclusions

In pulmonary emphysema, perfusion defect extent on STDIBH SPECT/CT, not CT-quantified emphysema extent, tracks major adverse events. Because STDIBH SPECT/CT measures the perfusion defect against the same CT that quantifies emphysema, one examination places the vascular and structural components of the disease on a common anatomical denominator.

Declarations

Acknowledgments

The authors thank the physicians in the Department of Pulmonology, who cared for and followed the patients, and the SPECT/CT technologists in the Department of Radiology, who assisted with imaging.

Conflict of interest

No potential conflicts of interest were disclosed.

Funding

This study received no external funding.

Authors' contributions

TH: Conceptualization; Methodology; Formal analysis; Investigation; Data curation; Visualization; Writing – original draft; Writing – review & editing. YF: Conceptualization; Methodology; Formal analysis; Investigation; Data curation; Visualization; Supervision; Writing – original draft; Writing – review & editing. KY: Investigation; Validation; Writing – review & editing. TA: Investigation; Validation; Writing – review & editing. YN: Investigation; Data curation; Writing – review & editing. YH: Investigation; Data curation; Writing – review & editing. SH: Investigation; Resources; Writing – review & editing. KA: Investigation; Resources; Writing – review & editing. HH: Investigation; Methodology; Writing – review & editing. SK: Resources; Supervision; Writing – review & editing.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am J Respir Crit Care Med*. 2023;207:819–37.
2. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health*. 2015;5:020415.
3. Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, et al. CT scan findings of emphysema predict mortality in COPD. *Chest*. 2010;138:635–40.
4. Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, et al. Mortality by level of emphysema and airway wall thickness. *Am J Respir Crit Care Med*. 2013;187:602–8.
5. Barberà JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21:892–905.
6. Voelkel NF, Gomez-Arroyo J, Mizuno S. COPD/emphysema: The vascular story. *Pulm Circ*. 2011;1:320–6.

7. Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamary AJ, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med*. 2012;367:913–21.
8. Estépar RS, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, Ross JC, et al. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. *Am J Respir Crit Care Med*. 2013;188:231–9.
9. Blanco I, Torres-Castro R, Barberà JA. Pulmonary vascular disease in chronic lung diseases: cause or comorbidity? *Curr Opin Pulm Med*. 2024;30:437–43.
10. Barr RG. The epidemiology of vascular dysfunction relating to chronic obstructive pulmonary disease and emphysema. *Proc Am Thorac Soc*. 2011;8:522–7.
11. Matsuoka S, Washko GR, Dransfield MT, Yamashiro T, San Jose Estepar R, Diaz A, et al. Quantitative CT measurement of cross-sectional area of small pulmonary vessel in COPD: correlations with emphysema and airflow limitation. *Acad Radiol*. 2010;17:93–9.
12. Bajc M, Schümichen C, Grüning T, Lindqvist A, Le Roux PY, Alatri A, et al. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. *Eur J Nucl Med Mol Imaging*. 2019;46:2429–51.
13. Roach PJ, Schembri GP, Bailey DL. V/Q scanning using SPECT and SPECT/CT. *J Nucl Med*. 2013;54:1588–96.
14. Suga K, Yasuhiko K, Iwanaga H, Hayashi N, Yamashita T, Matsunaga N. Enhanced perfusion defect clarity and inhomogeneity in smokers' lungs with deep-inspiratory breath-hold perfusion SPECT images. *Nucl Med Commun*. 2005;26:801–7.
15. Suga K, Kawakami Y, Iwanaga H, Tokuda O, Matsunaga N. Automated breath-hold perfusion SPECT/CT fusion images of the lungs. *AJR Am J Roentgenol*. 2007;189:455–63.
16. Suga K, Kawakami Y, Iwanaga H, Hayashi N, Seto A, Matsunaga N. Assessment of anatomic relation between pulmonary perfusion and morphology in pulmonary emphysema with breath-hold SPECT-CT fusion images. *Ann Nucl Med*. 2008;22:339–47.
17. Suga K, Okada M, Kunihiro M, Iwanaga H, Matsunaga N. Clinical significance of CT density-based, non-uniform photon attenuation correction of deep-inspiratory breath-hold perfusion SPECT. *Ann Nucl Med*. 2011;25:289–98.
18. Kawakami Y, Suga K, Zaki M, Iwanaga H, Yamashita T, Hayashi N, et al. Semi-quantitation of pulmonary perfusion heterogeneity on respiratory-gated inspiratory and expiratory perfusion SPECT in patients with pulmonary emphysema. *Ann Nucl Med*. 2007;21:577–84.
19. Suga K, Kawakami Y, Iwanaga H, Tokuda O, Matsunaga N. A stripe sign on 99mTc-TechneGas SPECT in pulmonary emphysema. *Nucl Med Commun*. 2008;29:553–61.
20. Suga K, Kawakami Y, Koike H, Iwanaga H, Tokuda O, Okada M, et al. Lung ventilation-perfusion imbalance in pulmonary emphysema: assessment with automated V/Q quotient SPECT. *Ann Nucl Med*. 2010;24:269–77.
21. Takenaka D, Ohno Y, Koyama H, Nogami M, Onishi Y, Matsumoto K, et al. Co-registered perfusion SPECT/CT: utility for prediction of improved postoperative outcome in lung volume reduction

- surgery candidates. *Eur J Radiol.* 2010;74:465–72.
22. Jögi J, Ekberg M, Jonson B, Bozovic G, Bajc M. Ventilation/perfusion SPECT in chronic obstructive pulmonary disease: an evaluation by reference to symptoms, spirometric lung function and emphysema, as assessed with HRCT. *Eur J Nucl Med Mol Imaging.* 2011;38:1344–52.
 23. Bajc M, Chen Y, Wang J, Li XY, Shen WM, Wang CZ, et al. Identifying the heterogeneity of COPD by V/P SPECT: a new tool for improving the diagnosis of parenchymal defects and grading the severity of small airways disease. *Int J Chron Obstruct Pulmon Dis.* 2017;12:1579–87.
 24. Atsumi K, Fukushima Y, Tanaka Y, Nishima S, Tanaka T, Seike M, et al. Novel evaluation of pulmonary hypertension associated with chronic lung disease using perfusion SPECT/CT: A pilot study. *Pulm Circ.* 2024;14:e12423.
 25. Fukushima Y, Yodogawa K, Ando T, Honda Y, Hayashi H, Kumita S. Prognostic Value of Short-Time Deep-Inspiratory Breath-Hold Pulmonary Perfusion SPECT/CT for Patients with Pulmonary Thromboembolism. *Ann Nucl Cardiol.* 2026. 10.17996/anc.25-00013.
 26. Cottin V, Selman M, Inoue Y, Wong AW, Corte TJ, Flaherty KR, et al. Syndrome of Combined Pulmonary Fibrosis and Emphysema: An Official ATS/ERS/JRS/ALAT Research Statement. *Am J Respir Crit Care Med.* 2022;206:e7–41.
 27. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;43:3618–731.
 28. Meyer G, Collignon MA, Guinet F, Jeffrey AA, Barritault L, Sors H. Comparison of perfusion lung scanning and angiography in the estimation of vascular obstruction in acute pulmonary embolism. *Eur J Nucl Med.* 1990;17:315–9.
 29. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol.* 1995;48:1503–10.
 30. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996;15:361–87.
 31. Heinze G, Schemper M. A solution to the problem of monotone likelihood in Cox regression. *Biometrics.* 2001;57:114–9.
 32. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med.* 2013;32:5381–97.
 33. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44:837 – 45.
 34. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. *Control Clin Trials.* 2000;21:552–60.

35. Polverino F, Celli BR, Owen CA. COPD as an endothelial disorder: endothelial injury linking lesions in the lungs and other organs? (2017 Grover Conference Series). *Pulm Circ*. 2018;8:2045894018758528.
36. Weissmann N. Chronic Obstructive Pulmonary Disease and Pulmonary Vascular Disease. A Comorbidity? *Ann Am Thorac Soc*. 2018;15(Suppl 4):S278–81.
37. Hisata S, Racanelli AC, Kermani P, Schreiner R, Houghton S, Palikuqi B, et al. Reversal of emphysema by restoration of pulmonary endothelial cells. *J Exp Med*. 2021;218:e20200938.
38. Alter P, Lucke T, Watz H, Andreas S, Kahnert K, Trudzinski FC, et al. Cardiovascular predictors of mortality and exacerbations in patients with COPD. *Sci Rep*. 2022;12:21882.
39. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363:1128–38.