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Original Research

Forced Expiratory Flow at 25%-75% Links COPD Physiology to Emphysema and Disease Severity in the SPIROMICS Cohort

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Abstract

Background: Forced expiratory volume in 1 second (FEV₁) is central to the diagnosis of chronic obstructive pulmonary disease (COPD) but is imprecise in classifying disease burden. We examined the potential of the maximal mid-expiratory flow rate (forced expiratory flow rate between 25% and 75% [FEF_{25%-75%}]) as an additional tool for characterizing pathophysiology in COPD.

Objective: To determine whether FEF_{25%-75%} helps predict clinical and radiographic abnormalities in COPD.

Study Design and Methods: The SubPopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS) enrolled a prospective cohort of 2978 nonsmokers and ever-smokers, with and without COPD, to identify phenotypes and intermediate markers of disease progression. We used baseline data from 2771 ever-smokers from the SPIROMICS cohort to identify associations between percent predicted FEF_{25%-75%} (%predFEF_{25%-75%}) and both clinical markers and computed tomography (CT) findings of smoking-related lung disease.

Results: Lower %predFEF_{25%-75%} was associated with more severe disease, manifested radiographically by increased functional small airways disease, emphysema (most notably with homogeneous distribution), CT-measured residual volume, total lung capacity (TLC), and airway wall thickness, and clinically by increased symptoms, decreased 6-minute walk distance, and increased bronchodilator responsiveness (BDR). A lower %predFEF_{25%-75%} remained significantly associated with increased emphysema, functional small airways disease, TLC, and BDR after adjustment for FEV₁ or forced vital capacity (FVC).

Interpretation: The %predFEF_{25%-75%} provides additional information about disease manifestation beyond FEV₁. These associations may reflect loss of elastic recoil and air trapping from emphysema and intrinsic small airways disease. Thus, %predFEF_{25%-75%} helps link the anatomic pathology and deranged physiology of COPD.

Abbreviations: forced expiratory volume in 1 second, **FEV₁**; forced expiratory flow rate between 25% and 75%, **FEF_{25%-75%}**; SubPopulations and Intermediate Outcome Measure In COPD, **SPIROMICS**; percent predicted FEF_{25%-75%}, **%predFEF_{25%-75%}**; computed tomography, **CT**; total lung capacity, **TLC**; bronchodilator responsiveness, **BDR**; forced vital capacity, **FVC**; National Institutes of Health, **NIH**; National Heart, Lung, and Blood Institute, **NHLBI**; residual volume, **RV**; parametric response mapping functional small airways disease, **PRM^{fSAD}**; square root of the wall area of a single hypothetical airway with internal diameter of 10mm, **Pi10**; modified Medical Research Council, **mMRC**; chronic bronchitis, **CB**; St George's Respiratory Questionnaire, **SGRQ**; COPD Assessment Test, **CAT**; 6-Minute Walk Distance, **6MWD**; pre-bronchodilator, **preBD**; post-bronchodilator, **postBD**; body mass index, **BMI**; BMI-airway Obstruction-Dyspnea-Exercise tolerance, **BODE**; emphysema, **emph**; emphysema as a continuous variable, **emph-C**; odds ratio, **OR**; confidence interval, **CI**; lower limit of normal, **LLN**

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This article has an online data supplement

Introduction

Chronic obstructive pulmonary disease (COPD) affects both large and small airways with most dysfunction occurring in airways <2mm in diameter.¹ Spirometry is used to diagnose airflow obstruction and grade severity in COPD, with emphasis on the forced expiratory volume in 1 second (FEV₁).² In the normal lung, FEV₁ reflects both passive and active lung and chest wall recoil, reflecting resistance through both large and small airways. However, in the obstructed lung, use of FEV₁ alone may underestimate the extent of small airway abnormality.^{1,3,4} Later parts of the exhalation curve, such as average forced expiratory flow rate between 25% and 75% (FEF_{25%-75%}) of the vital capacity, also referred to as maximum mid-expiratory flow rate are less effort-dependent and more representative of air movement through the small airways.⁵ FEF_{25%-75%} has been previously accepted as a measure of small airways function, and prior studies suggested it may be abnormal

in early or mild disease despite normal FEV₁, forced vital capacity (FVC) and FEV₁/FVC ratio.^{1,5,6} However, this parameter has been difficult to use clinically in the assessment of early disease at the level of the individual patient due to its high intra- and inter-user variability, and wide range of recommended normal values.⁷

In COPD, different processes contribute to increased airflow resistance. Small airways disease leads to airway narrowing, while increased intrathoracic pressure during forced exhalation contributes to dynamic collapse of small bronchioles, leading to air trapping. This is exaggerated in emphysema due to loss of the parenchymal elastic recoil and alveolar tethering that normally keep these airways open.^{1,8-13} Air trapping and hyperinflation contribute to decreased ventilatory efficiency and the sensation of dyspnea.^{10,11}

Beyond the extensive evaluation of early disease, studies of FEF_{25%-75%} and its relationship to clinical or radiographic characteristics of disease severity have been limited. A major goal of this study is to explore the link between structure and function in COPD as we relate FEF_{25%-75%}, a physiological measure, to anatomical evidence of airway and parenchymal abnormality by computed tomography (CT) imaging, and to clinical parameters of disease severity, including symptoms, functional capacity, and bronchodilator responsiveness. We hypothesize that there is an inverse relationship between FEF_{25%-75%} and measures of disease severity, and that FEF_{25%-75%} adds additional insight beyond FEV₁ into the pathophysiology of COPD.

Methods

Participants

This study was conducted as part of the SubPopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS). SPIROMICS enrolled a prospective cohort of 2978 nonsmokers and ever-smokers, with and without COPD over a range of severity, to identify new COPD subgroups and intermediate markers of disease progression. Participants in 4 different groups were recruited to SPIROMICS: (1) never-smokers, (2) smokers without airflow obstruction, (3) mild/moderate COPD, and (4) severe/very severe COPD. The design of this study was approved by the institutional review boards of all participating institutions and has been described previously.¹⁴

All participants in SPIROMICS gave written consent.

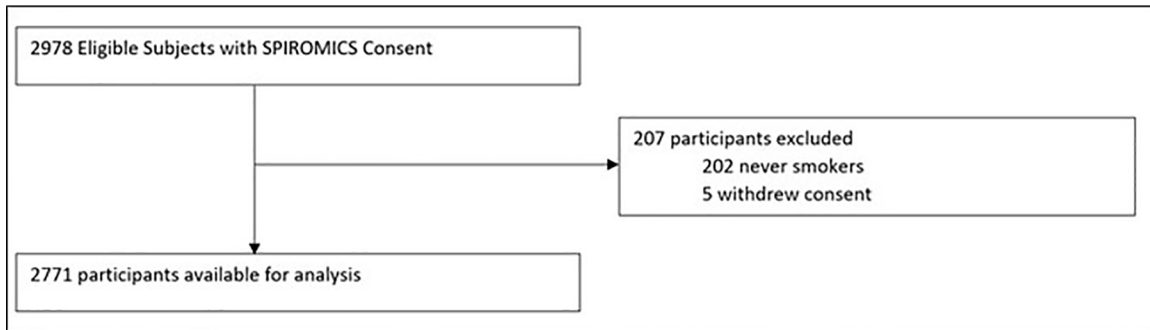
Our study included data from the baseline visit of current or former smokers, with or without COPD, from the SPIROMICS cohort (n=2771). Never smokers and those who had withdrawn consent were excluded from our analysis. See Figure 1 for the analysis profile.

Definitions and Testing Parameters

Pulmonary function testing in SPIROMICS was performed based on 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines^{15,16} with reference values for lower limit of normal and percent predicted based on the Third National Health and Nutrition Examination Survey.¹⁷ In this analysis, COPD was defined as a post-bronchodilator ratio of FEV₁/FVC less than 0.70 with severity based on previously established post-bronchodilator cutoffs for FEV₁.^{15,16} FEF_{25%-75%} is defined as the average forced expiratory flow rate at 25%-75% of the vital capacity^{5,15-17} and is expressed herein as a percentage of the predicted value (%predFEF_{25%-75%}). Other spirometry-based measurements are also represented as percent predicted values (%predFEV₁ and %predFVC). Bronchodilator responsiveness is defined as an increase in FEV₁ or FVC of ≥ 200 mL and $\geq 12\%$ relative to pre-bronchodilator values, based on the ATS definition.^{2,16}

In SPIROMICS, baseline visit CT imaging was performed at both maximum inspiration (total lung capacity [TLC]) and full exhalation (residual volume [RV]) with co-registration of images allowing for voxel matching using a previously published protocol.¹⁴ Emphysema was defined as the percentage of voxels below -950 HU at full inspiration (TLC), with the cutoff for disease presence based on age-predicted norms.¹⁸⁻²¹ Parametric response mapping functional small airways disease (PRMfSAD), a previously recognized measure of small airways disease on imaging,^{22,23} was measured as the percentage of total voxels ≤ -856 HU at full expiration (RV) and > -950 HU at full inspiration (TLC), representing nonemphysematous air trapping. RV and TLC were estimated using CT-derived imaging parameters at full exhalation and full inspiration respectively.¹⁴ Airway wall thickness was measured using the square-root of the wall area of a single hypothetical airway with an internal diameter of 10 mm (Pi10).^{9,19-29}

Figure 1. Study Analysis Profile



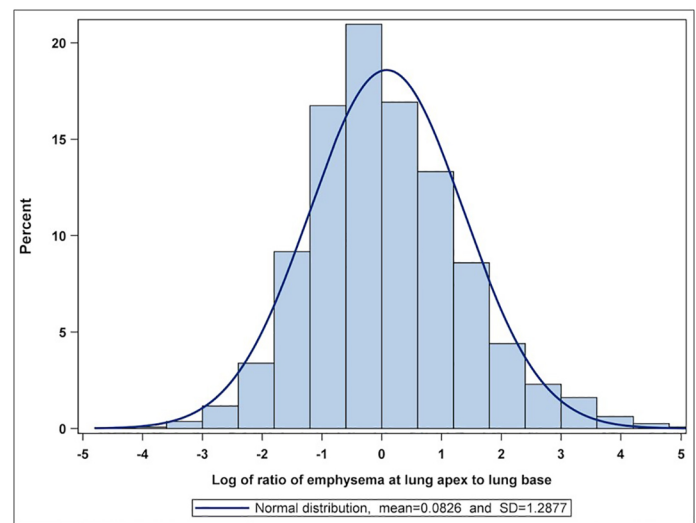
Statistical Analysis

We fit logistic regression models to evaluate %predFEF_{25%-75%} as the independent variable relative to the following dichotomous variables at baseline: modified Medical Research Council (mMRC) dyspnea scores (converted to a dichotomous variable by grouping mMRC scores 0–1 to indicate no clinically relevant dyspnea and mMRC scores 2–4 to indicate clinically relevant dyspnea), chronic bronchitis (CB) as determined by the St George’s Respiratory Questionnaire (SGRQ), bronchodilator responsiveness (BDR) and presence of emphysema on CT. BDR represents a change in either FEV₁ or FVC based on the above ATS definition.

We fit linear regression models to evaluate %predFEF_{25%-75%} as the independent variable relative to the following dependent continuous variables at baseline: COPD assessment test (CAT) score, 6-minute walk distance (6MWD), extent of emphysema on CT represented by a continuous variable, PRM^{fSAD}, SGRQ scores, and CT-derived parameters including RV, TLC, RV/TLC ratio, and airway thickness (Pi10).

Our preliminary analysis of %predFEF_{25%-75%} and emphysema as a categorical variable suggested that emphysema distribution (homogeneous versus heterogeneous) may influence the association. We, therefore, performed a secondary analysis to evaluate this further. We plotted the distribution of emphysema as the log of the ratio of emphysema at the lung apex to the lung base (Figure 2). Based on this population distribution and to account for the clinical importance of apical versus Basilar emphysema for advanced management of COPD,³⁰ we developed a definition of homogeneous disease as the absolute value of the log of the ratio within 1 standard deviation (1.3) of the mean. Those with the log of the ratio outside this distribution

Figure 2. Log of Ratio of Emphysema at Lung Apex to Lung Base



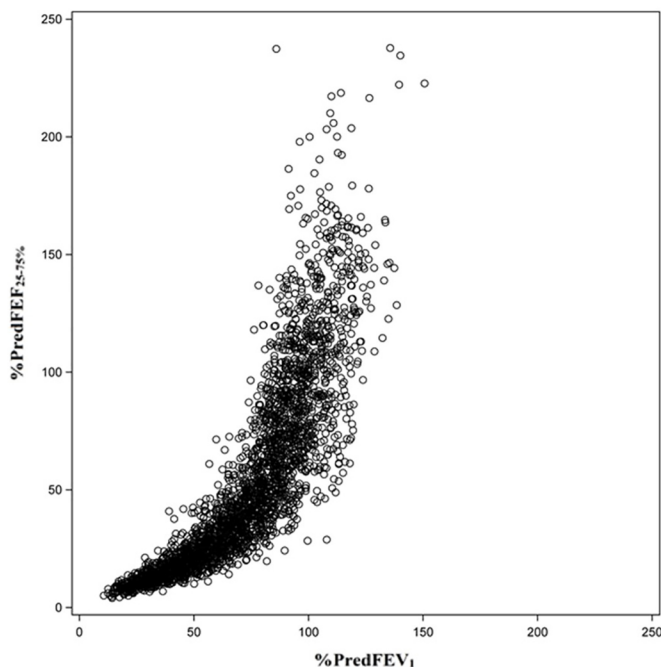
were considered to have heterogeneous disease that was either apical predominant (>1.3) or basilar predominant (<-1.3). We then evaluated the effect of emphysema distribution by adding an indicator of homogeneous versus heterogeneous distribution as a categorical interaction variable to the logistic regression model of %predFEF_{25%-75%} and emphysema as a dichotomous variable.

Both pre-bronchodilator (preBD) and post-bronchodilator (postBD) values were studied. Given the similarity between our findings, we present the postBD analyses. PreBD analyses are presented in e-Table S1 in the online supplement. All analyses were evaluated per 10 percentage point reduction in %predFEF_{25%-75%} and were adjusted for smoking pack-year history. Since predicted values already account for age and sex-related differences, our data also account for these confounders.

During analysis, we noticed many of our linear models were strongly influenced by the addition of %predFEV₁. To determine the collinearity between %predFEF_{25%-75%} and %predFEV₁, we plotted the correlation between the values for the entire SPIROMICS cohort at baseline and found a nonlinear relationship (Figure 3). To account for this nonlinear relationship, and to ensure our findings were not due to disease severity reflected by FEV₁, all analyses were adjusted for %predFEV₁ and the square of %predFEV₁. The results of our original post-bronchodilator linear model are included in the e-Table S2 in the online supplement.

As a measure of mid-expiratory flow rate, %predFEF_{25%-75%} may be highly affected by FVC. To confirm our findings were not attributable to the FVC, we separately adjusted select associations (emphysema, BDR, PRMfSAD, and TLC) for %predFVC and its square instead of %predFEV₁ (online supplement, e-Table S3).

Figure 3. Correlation Between Percent Predicted Forced Expiratory Flow at 25% to 75% and Percent Predicted Forced Expiratory Volume in 1 Second for the Entire SPIROMICS Cohort



%predFEF_{25%-75%}=percent predicted of forced expiratory flow at 25% to 75%;
%predFEV₁=percent predicted of forced expiratory volume in 1 second

Analyses were conducted using SAS v 9.4 (SAS Inc., Cary, North Carolina). Two-sided *p*-values <0.05 were considered statistically significant.

Results

The baseline characteristics of our study cohort are presented in Table 1. Those with obstruction tended to be older, more symptomatic, and included a lower percentage of women than those without overt obstruction.

The relationships between %predFEF_{25%-75%} and parameters of disease severity are presented in Table 2, with select relationships (based on categorical variables) shown in Figure 4. Odds ratios and beta estimates are all expressed per 10 percentage point change in %predFEF_{25%-75%}. Due to similarities in findings using pre- and post-bronchodilator values, only post-BD analyses are represented here unless otherwise stated. Pre-BD analyses are available in e-Table S1 in the online supplement.

Imaging Parameters of Smoking-Related Lung Disease

A lower %predFEF_{25%-75%} was associated with increased odds of having emphysema on CT scan (odds ratio [OR] 1.663, 95% confidence interval [CI] [1.593, 1.736], *p*<0.0001), as well as increased extent of emphysema (analyzed as a continuous variable) (estimate 1.318, 95% CI [1.237, 1.398], *p*<0.0001). To understand the contribution of distribution of disease to this relationship, we included distribution of emphysema as an interaction variable in the categorical analysis. A lower %predFEF_{25%-75%} was more strongly associated with a homogeneous distribution of emphysema versus a heterogeneous distribution (homogeneous OR 1.755, 95% CI [1.661, 1.853], versus heterogeneous OR 1.483, 95% CI [1.383, 1.591], *p*=0.0002).

A lower %predFEF_{25%-75%} was also significantly associated with increased functional small airways disease (PRMfSAD) on CT imaging (estimate 2.273, 95% CI [2.154, 2.392], *p*<0.0001).

Regarding CT-measured lung volumes, a lower %predFEF_{25%-75%} was significantly associated with a higher TLC (estimate 75.054, 95% CI [63.184, 86.924], *p*<0.0001) and RV (estimate 146.206, 95% CI [137.365, 155.048], *p*<0.0001) resulting in a very small, but significant, inverse relationship with the RV/TLC

Table 1. Participant Demographics at Baseline Visit

All Participants (n = 2771)			
Variables at Baseline Visit	Smokers Without COPD (n=941)	Mild-Moderate COPD (n=1205)	Severe/Very Severe COPD (n=625)
Age (years)	60.3 (9.7)	65.5 (8.2)	64.3 (7.8)
Male	448 (48%)	701 (58%)	349 (56%)
BMI (kg/m ²)	29.0 (5.1)	27.9 (5.2)	26.3 (5.4)
BODE Index			
0–3	908 (96%)	1091 (91%)	215 (34%)
4–10	14 (1.5%)	66 (5%)	344 (55%)
BODE score unavailable	19 (2%)	48 (4%)	66 (11%)
Smoking Status			
Current Smoker	475 (50%)	458 (38%)	159 (25%)
Smoking History (pack years)	42.7 (24.3)	52.9 (29.6)	52.2 (23.1)
FEV₁			
Value (L)	2.77 (0.71)	2.12 (0.66)	1.00 (0.34)
Percent (%) predicted	96.8 (13.6)	74.0 (15.7)	35.4 (9.9)
FEF_{25%-75%}			
Value (L)	2.64 (0.99)	0.99 (0.48)	0.36 (0.17)
Percent (%) predicted	103.6 (33.1)	41.2 (16.5)	15.0 (6.3)
FVC			
Value (L)	3.59 (0.91)	3.66 (1.00)	2.74 (0.89)
Percent (%) Predicted	96.6 (12.9)	96.6 (16.5)	72.8 (17.1)
Chronic Bronchitis Symptoms	160 (17%)	280 (23%)	155 (25%)
CAT Score	11.5 (8.2)	13.8 (7.8)	18.6 (7.5)
SGRQ Score	24.8 (19.3)	32.5 (19.1)	48.2 (16.9)
Inhaler Use			
Bronchodilators	223 (24%)	660 (55%)	548 (88%)
Inhaled Steroids	111 (12%)	430 (36%)	426 (68%)

Data are presented as mean (standard deviation) or n

COPD=chronic obstructive pulmonary disease; BMI=body mass index; BODE=BMI-airway Obstruction-Dyspnea-Exercise tolerance; FEV₁=forced expiratory volume in 1 second; FEF_{25%-75%}=maximum mid-expiratory flow rate; FVC=forced vital capacity; CAT=COPD Assessment Test, SGRQ=St George's Respiratory Questionnaire

(estimate 0.020, 95% CI [0.019, 0.021], $p<0.0001$).

A lower %predFEF_{25%-75%} was also weakly, but significantly, associated with increased airway thickness as measured by Pi10 (estimate 0.002, 95% CI [0.001, 0.002], $p<0.0001$).

Symptoms, Functional Capacity, and Bronchodilator Response

%PredFEF_{25%-75%} was significantly and inversely associated with symptoms and directly associated with functional capacity. In analyses unadjusted for %predFEV₁, lower %predFEF_{25%-75%} was significantly associated with the increased presence of dyspnea as indicated by higher mMRC dyspnea scores (OR 1.237, 95% CI [1.201, 1.275] $p<0.0001$), increased presence of chronic bronchitis symptoms (OR 1.065, 95% CI [1.040, 1.092], $p<0.0001$), higher CAT scores (estimate 0.647, 95% CI [0.574, 0.720], $p<0.0001$), higher SGRQ scores (estimate 2.086, 95% CI [1.910, 2.263], $p<0.0001$) and a decreased 6MWD (estimate -6.724, 95% CI [-7.810, -5.639], $p<0.0001$) at the baseline visit. A lower %predFEF_{25%-75%} was also associated with significantly higher odds of having a BDR at the baseline visit (OR 1.347, 95% CI [1.308, 1.387], $p<0.0001$).

Influence of %PredFEV₁

We next explored the relationship between %predicted FEF_{25%-75%} and %predFEV₁ to determine whether the above relationships between %predFEF_{25%-75%} and disease characteristics were simply a reflection of overall lung function decline as measured by FEV₁. Figure 3 shows the correlation between %predFEF_{25%-75%} and %predFEV₁ for the whole SPIROMICS cohort. As expected, we found a strong correlation between %predFEF_{25%-75%} and %predFEV₁, especially when disease is more severe. There was greater spread between values for %predFEF_{25%-75%} and %predFEV₁ when disease was less severe, especially when values of %predFEV₁ were in the normal range. We then adjusted all associations for %predFEV₁ (Table 2; categorical variables represented in Figure 4). Select associations (categorical emphysema, bronchodilator response, PRM^fSD, and TLC) were adjusted separately for %predFVC.

The association between %predFEF_{25%-75%} and emphysema as a categorical variable remained significant after adjustment for either %predFEV₁ (adjusted OR 1.740, 95% CI [1.607, 1.883], $p<0.0001$; Table 2 and Figure 4) or %predFVC (adjusted OR 1.761, 95% CI [1.674, 1.853], $p<0.0001$; e-Table S3 in the online supplement). In the analysis of emphysema as a continuous variable, this effect was tempered by the adjustment for %predFEV₁, but remained significant (estimate 0.580, 95% CI [0.449, 0.711], $p<0.0001$). The relationship between %predFEF_{25%-75%} and emphysema

Table 2. Post-bronchodilator Analysis of Percent Predicted Forced Expiratory Flow at 25% to 75% and Clinical Parameters

Variable	Unadjusted for %predFEV ₁ ^a		Adjusted for %predFEV ₁ ^b		
	OR (95% CI)	P value	OR (95% CI)	P value	
Categorical	Emph	1.663 (1.593, 1.736)	<0.0001	1.740 (1.607, 1.883)	<0.0001
	BDR (FVC or FEV ₁)	1.347 (1.308, 1.387)	<0.0001	1.392 (1.312, 1.477)	<0.0001
	mMRC	1.237 (1.201, 1.275)	<0.0001	0.965 (0.916, 1.017)	0.188
	CB	1.065 (1.040, 1.092)	<0.0001	1.009 (0.962, 1.059)	0.701
Variable	Estimate (95% CI)	P value	Estimate (95% CI)	P value	
Continuous	PRM ^{fSAD}	2.273 (2.154, 2.392)	<0.0001	1.533 (1.323, 1.743)	<0.0001
	Emph-C	1.318 (1.237, 1.398)	<0.0001	0.580 (0.449, 0.711)	<0.0001
	TLC	75.054 (63.184, 86.924)	<0.0001	124.611 (102.344, 146.879)	<0.0001
	RV	146.206 (137.365, 155.048)	<0.0001	81.965 (67.215, 96.716)	<0.0001
	RV/TLC	0.020 (0.019, 0.021)	<0.0001	0.005 (0.003, 0.007)	<0.0001
	Pi10	0.002 (0.001, 0.002)	<0.0001	-0.0046 (-0.006, -0.003)	<0.0001
	CAT	0.647 (0.574, 0.720)	<0.0001	0.034 (-0.106, 0.173)	0.637
	6MWD	-6.724 (-7.810, -5.639)	<0.0001	-0.150 (-2.198, 1.897)	0.886
	SGRQ score	2.086 (1.910, 2.263)	<0.0001	0.064 (-0.262, 0.389)	0.702

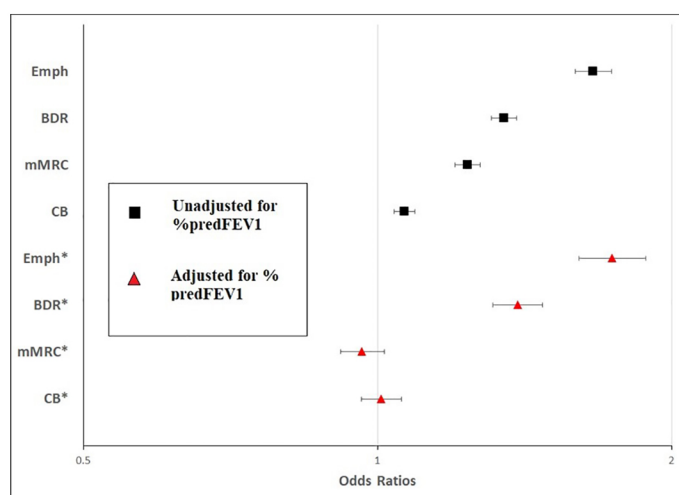
^aAdjusted for smoking pack year history.

^bAdjustment includes percent predicted FEV₁ (%predFEV₁).

Bold type indicates a result that retains significance and relationship integrity after adjustment for %predFEV₁. Values are presented per 10% reduction in %predFEF_{25%-75%}.

%predFEV₁=percent predicted of forced expiratory volume in 1 second; OR=odds ratio; CI=confidence interval; Emph=emphysema (binary variable below $-950HU$); BDR=bronchodilator response; FVC=forced vital capacity; FEV₁=forced expiratory volume in 1 second; mMRC=modified Medical Research Council score (Binary variable grouped as MRC score 0–1 for no clinically significant dyspnea and 2–4 for significant dyspnea); CB=chronic bronchitis; PRM^{fSAD}=parametric response mapping functional small airways disease; Emph-C=emphysema as a continuous variable; TLC=total lung capacity; RV=residual volume; Pi10=airway thickness relative to reference airway of 10mm; CAT=COPD Assessment Test score, 6MWD=6-minute walk distance; SGRQ=St George's Respiratory Questionnaire dyspnea score

Figure 4. Relationship Between Percent Predicted Forced Expiratory Flow at 25% to 75% and Parameters of Disease Severity



Emph=emphysema; BDR=bronchodilator responsiveness; mMRC=modified Medical Research Council; CB=chronic bronchitis; %predFEF_{25%-75%}=percent predicted of forced expiratory flow at 25% to 75%; %predFEV₁=percent predicted of forced expiratory volume in 1 second

distribution (homogeneous versus heterogeneous) remained following adjustment for %predFEV₁, with homogeneous distribution remaining more strongly associated than heterogeneous disease (adjusted homogeneous OR 1.809, 95% CI [1.660, 1.971] versus adjusted heterogeneous OR 1.590, 95% CI [1.447, 1.748], $p=0.0026$).

The relationship between %predFEF_{25%-75%} and PRM^{fSAD} persisted when adjusted for %predFEV₁ (adjusted estimate 1.533, 95% CI [1.323, 1.743], $p<0.0001$), as did the relationship with TLC (adjusted estimate 124.611, 95% CI [102.344, 146.879], $p<0.0001$) and with RV (adjusted estimate 81.965, 95% CI [67, 32.095], $p<0.0001$). When adjusted for %predFVC, both PRM^{fSAD} and TLC remained significant (adjusted PRM^{fSAD} estimate 2.151, 95% CI [2.022, 2.279], $p<0.0001$; adjusted TLC estimate 95.612, 95% CI [82.905, 108.319], $p<0.0001$) (e-Table S3 in the online supplement).

The relationship between %predFEF_{25%-75%} and BDR was retained after adjustment for %predFEV₁ (adjusted OR 1.392, 95% CI [1.312,

1.477], $p < 0.0001$; Table 2 and Figure 4) as well as %predFVC (adjusted OR 1.397, 95% CI [1.351, 1.444], $p < 0.0001$); (e-Table S3 in the online supplement).

Conversely, the relationships between %predFEF_{25%-75%} and respiratory symptoms, including functional capacity, were no longer significant following adjustment for %predFEV₁, suggesting %predFEF_{25%-75%} contributes similar, but not additional, information beyond %predFEV₁ in predicting symptoms of COPD. The addition of %predFEV₁ to the model for Pi10 negated the relationship. Further inquiry revealed this was a result of the strength of the effect of %predFEV₁. No further conclusions could be made from this association in this setting.

Discussion

COPD is a heterogeneous condition, with great variation in anatomical derangement, clinical symptoms and long-term outcomes. While most studies focus on FEV₁ as a marker of disease severity, this parameter is clearly limited in its ability to represent the variety seen in COPD patients. FEF_{25%-75%} remains an understudied and undervalued spirometric tool that can help bridge this gap. Past studies of FEF_{25%-75%} have focused extensively on its use as a predictor of early small airways disease.^{1,5,7,9} The present study offers the clinician new insight into the interaction between distal pathologic changes, as captured by CT scan, and physiologic changes in spirometry, beyond those represented by the FEV₁.

Our analysis supports a strong relationship between a lower %predFEF_{25%-75%}, homogeneous emphysema, and hyperinflation by TLC, independent of the %predFEV₁. These relationships likely reflect loss of elastic recoil and alveolar tethering attributable to emphysema, resulting in airflow limitation at the level of the small airway. Individuals with homogeneous emphysema are known to have more severe dynamic hyperinflation, decreased exercise tolerance, and more severe clinical outcomes compared to those with heterogeneous disease.^{8,13} The %predFEF_{25%-75%} is, therefore, a powerful resource for improving our knowledge and understanding of the underlying mechanisms that produce clinical disease and provides information beyond that provided by %predFEV₁.

While the %predFEF_{25%-75%} is also associated with significantly worse symptoms in our cohort, it does not provide additional information beyond that captured by

the %predFEV₁.

Clinical outcomes and symptoms in COPD are influenced by multiple factors, including bronchodilator response. Although COPD is defined as airflow obstruction that is not fully reversible with a bronchodilator, individuals with COPD can respond symptomatically to inhalers in the absence of spirometric change.^{10,11,31} Prior studies suggest that small airways disease and bronchodilator response may be associated, and that participants who are older, female, and have more severe disease show less bronchodilator response.^{12,32} The pathophysiology behind this association is not well understood. Bronchodilators are thought to improve symptoms by decreasing lung hyperinflation.^{10,11,31} Our findings of an inverse association between %predFEF_{25%-75%} and BDR support the idea that bronchodilators may decrease air trapping in peripheral airways, mitigating the effect of loss of elastic recoil from emphysema.

Our study has several strengths. SPIROMICS is a large cohort of well-characterized participants across a wide range of disease severity. Rigorous protocols are implemented to confirm the quality, validity, and reproducibility of spirometry, and imaging is performed and analyzed using state-of-the-art technology and image processing techniques. These protocols may not be available to all clinical practices and represent both a strength and a limitation for extrapolation to general clinical practice. A particular strength in our analysis lies in our assessment of the effect of multiple confounding parameters, allowing for a more detailed analysis of FEF_{25%-75%} in COPD.

Limitations of this study include the broad limitations of SPIROMICS data and specific limitations inherent to our analysis. The definition of COPD remains controversial.³³ This analysis uses the cutoff of post-bronchodilator FEV₁/FVC < 0.70 , cited by the Global Initiative for Chronic Obstructive Lung Disease³⁴ and often used in large databases, but which may underestimate COPD in the younger population while overestimating prevalence in the elderly.³⁵ In clinical practice, physicians are encouraged to use the lower limit of normal (LLN), which represents the 5th percentile of a normal distribution,² although a cutoff of 0.70 may be more indicative of clinically relevant disease.³⁶ While LLN data are available in SPIROMICS, a cutoff of 0.70 for the FEV₁/FVC was used to improve comparability with past studies. Measurement of %predFEF_{25%-75%} has

inherent limitations as well. Although the repeatability for a single participant was high in the SPIROMICS cohort,³⁷ our assessment of the correlation between %predFEF_{25%-75%} and %predFEV₁ in the full cohort shows a distinct, nonlinear relationship with high variability. There is especially marked variability of %predFEF_{25%-75%} values when FEV₁ values are $\geq 80\%$ predicted. With several FEF_{25%-75%} values well above 100% predicted, this finding suggests the utility of the current predictive equations for %predFEF_{25%-75%} may be limited.

Our analysis of %predFEF_{25%-75%} provides new insight into the relationship between structure and function in COPD. A lower %predFEF_{25%-75%} is strongly associated with more severe COPD in multiple domains, providing new understanding of the contributing pathophysiologic and anatomic abnormalities that lead to clinical outcomes in COPD.

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Data Availability: Information about how to access SPIROMICS data is available at www.spiromics.org.

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Declaration of Interest

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