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Ratio of FEV_1/Slow Vital Capacity of < 0.7 Is Associated With Clinical, Functional, and Radiologic Features of Obstructive Lung Disease in Smokers With Preserved Lung Function

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BACKGROUND: Mild expiratory flow limitation may not be recognized using traditional spirometric criteria based on the ratio of FEV_1/FVC.

RESEARCH QUESTION: Does slow vital capacity (SVC) instead of FVC increase the sensitivity of spirometry to identify patients with early or mild obstructive lung disease?

STUDY DESIGN AND METHODS: We included 854 current and former smokers from the Subpopulations and Intermediate Outcome Measures in COPD Study cohort with a postbronchodilator FEV_1/FVC $\geq$ 0.7 and FEV_1 % predicted of $\geq$ 80% at enrollment. We compared baseline characteristics, chest CT scan features, exacerbations, and progression to COPD (postbronchodilator FEV_1/FVC, < 0.7) during the follow-up period between 734 participants with postbronchodilator FEV_1/SVC of $\geq$ 0.7 and 120 with postbronchodilator FEV_1/SVC < 0.7 at the enrollment. We performed multivariate linear and logistic regression models and negative binomial and interval-censored proportion hazards regression models adjusted for demographics and smoking exposure to examine the association of FEV_1/SVC < 0.7 with those characteristics and outcomes.

RESULTS: Participants with FEV_1/SVC < 0.7 were older and had lower FEV_1 and more emphysema than those with FEV_1/SVC $\geq$ 0.7. In adjusted analysis, individuals with postbronchodilator FEV_1/SVC < 0.7 showed a greater percentage of emphysema by 0.45% (95% CI, 0.09%-0.82%), percentage of gas trapping by 2.52% (95% CI, 0.59%-4.44%), and percentage of functional small airways disease based on parametric response mapping by 2.78% (95% CI, 0.72%-4.83%) at baseline than those with FEV_1/SVC $\geq$ 0.7. During a median follow-up time of 1,500 days, an FEV_1/SVC < 0.7 was not associated with total exacerbations (incident rate ratio [IRR], 1.61; 95% CI, 0.97-2.64), but was associated with severe exacerbations (IRR, 2.60; 95% CI, 1.04-4.89). An FEV_1/SVC < 0.7 was associated with progression to COPD during a 3-year follow-up even after adjustment for demographics and smoking exposure (hazard ratio, 3.93; 95% CI, 2.71-5.72). We found similar results when we examined the association of prebronchodilator FEV_1/SVC < 0.7 or FEV_1/SVC less than the lower limit of normal with chest CT scan features and progression to COPD.

INTERPRETATION: Low FEV_1 to SVC in current and former smokers with normal spirometry results can identify individuals with CT scan features of COPD who are at risk for severe exacerbations and is associated with progression to COPD in the future.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01969344T4; URL: www.clinicaltrials.gov

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KEY WORDS: COPD; pulmonary; pulmonary function test; slow vital capacity; SVC

FOR EDITORIAL COMMENT, SEE PAGE 7

The diagnosis of COPD is based on the presence of airflow obstruction defined by the ratio of FEV_1/FVC of less than the lower limit of normal or 0.7.[1] About one-quarter of smokers with normal FEV_1 and FEV_1/FVC show visual emphysema on chest CT scanning.[2] Smokers with preserved lung function and COPD Assessment Test (CAT) score of $>$ 10 experience more respiratory exacerbations than those with CAT score of $<$ 10.[3] Many high-risk individuals with evidence of COPD features are not diagnosed formally with COPD based on current diagnostic criteria.[2-4]

In comparison with FVC, slow vital capacity (SVC) may reflect better the true vital capacity (VC) in obstructive lung disease because of possible underestimation of FVC that results from dynamic compression of the airways during the forced expiratory maneuver and reduced exhalation time.[5] In these settings, SVC may be more appropriate to calculate the FEV_1/VC according to the American Thoracic Society guidelines.[6] In a single-center study that included people referred for pulmonary function test and who showed a FEV_1/FVC and total lung

ABBREVIATIONS: CAT = COPD Assessment Test; LLN = lower limit of normal; mMRC = Modified Medical Research Council dyspnea; SVC = slow vital capacity; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study; VC = vital capacity

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capacity of more than the lower limit of normal (LLN), 20.4% of the participants demonstrated a FEV_1/SVC less than the LLN.[7] The frequency of obstructive lung disease diagnosis by health care provider was higher in participants with FEV_1/SVC less than the LLN compared with those with FEV_1/SVC equal to the LLN or more based on chart review of a randomly selected subgroup. The association of low FEV_1/SVC with objective features of obstructive lung disease like radiographic emphysema and progression to spirometric obstruction in the future among those at risk for COPD with normal FEV_1/FVC is unknown. We hypothesized that, in smokers with normal spirometry results according to the current standards, an FEV_1/SVC < 0.7 is associated with respiratory symptoms, chest CT scan emphysema, and increased likelihood of COPD developing. To investigate our hypothesis, we analyzed data from current and former smokers with normal spirometry results, defined as postbronchodilator FEV_1/FVC of ≥ 0.7 and FEV_1 % predicted of $\geq 80\%$, who were enrolled in the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS). We compared clinical, functional, and chest CT scan features between individuals with an FEV_1/SVC < 0.7 and individuals with an FEV_1/SVC ≥ 0.7.

Methods

This is a retrospective analysis of data from participants in SPIROMICS, a prospective observational cohort study conducted at multiple clinical centers across the United States (https://www.spiromics.org/spiromics/). The institutional review boards at each participating center approved the study protocol, and written informed consent was obtained from all participants (e-Appendix 1). Details of the study protocol have been published previously.[8] Briefly, participants 40 to 80 years of age who were either current or former smokers with $\geq$ 20 pack-years of smoking were enrolled in the study. An obstructive lung disease diagnosis other than asthma and COPD, BMI of $> 40\,kg/m^2$ at baseline, and unstable cardiovascular disease were exclusion criteria. Of 2,770 current and former smokers with at least a 20-pack-years history of smoking enrolled in SPIROMICS, we included 924 participants with normal baseline spirometry results, defined as a postbronchodilator FEV_1/FVC of ≥ 0.7 and FEV_1 % predicted of $\geq 80\%$ at enrollment. We used the reference spirometric values from the third National Health and Nutrition Examination Survey.[9] We excluded 70 participants with no available SVC data. The remained 854 participants entered the analysis. Participants underwent a baseline visit and up to three annual in-person follow-up visits. At baseline, participants answered questionnaires, including the modified Medical Research Council dyspnea (mMRC) questionnaire,[10] CAT,[11] and St. George's Respiratory Questionnaire.[12] At baseline and at each follow-up visit, participants underwent prebronchodilator and postbronchodilator spirometry assessments. Prebronchodilator spirometry and expiratory SVC maneuvers were performed according to American Thoracic Society/European Respiratory Society guidelines.[13] After four inhalations each of albuterol 90 µg/inhalation and ipratropium 18 µg/inhalation, spirometry and expiratory SVC maneuvers were repeated. Information regarding medical history, respiratory exposures, and current medications were collected. Six-minute walk distance in meters was tested and recorded as per SPIROMICS protocol.[8] Chest CT scans were performed at baseline according to study protocols.[14] Participants also received quarterly follow-up calls to assess health status and whether they had experienced an exacerbation.

Imaging

Baseline visit included high-resolution chest CT scans at maximum inspiration (total lung capacity) and maximal expiration (residual volume). We evaluated emphysema on high-resolution CT imaging by VIDA software. Percent emphysema was defined by using the percentage of voxels at maximum inspiration (total lung capacity by CT scan) with attenuation less than –950 Hounsfield units and gas trapping was quantified as the percentage of voxels at maximum expiration (residual volume by CT scan) with attenuation values of less than –856 Hounsfield units.[14] Parametric response mapping analysis was performed using the Imbio Lung Density Analysis software application (Imbio, LLC) to distinguish regions of emphysema from regions of nonemphysematous gas trapping, functional small airways disease.[15,16]

Definitions and Outcomes

In the main analysis, postbronchodilator FEV_1/SVC was calculated as the ratio of postbronchodilator FEV_1 to postbronchodilator SVC. Chronic bronchitis was defined based on the St. George's Respiratory Questionnaire results at baseline.[17] History of exacerbation was defined as self-report of respiratory exacerbation in the year before enrollment at the baseline visit. Exacerbation was defined as respiratory events for which the participant received antibiotics, steroids, or both or that were evaluated by a health care professional. Severe exacerbations were defined as exacerbations that required hospital admission or ED visit. Progression to COPD was defined as postbronchodilator FEV_1/FVC < 0.7 at a follow-up visit. After a postbronchodilator FEV_1/FVC < 0.7 at a follow-up visit, some individuals may have bounced back to postbronchodilator FEV_1/FVC of ≥ 0.7. For that reason, we also examined persistent COPD defined as a postbronchodilator FEV_1/FVC < 0.7 at a follow-up visit that did not bounce back to postbronchodilator FEV_1/FVC of ≥ 0.7 at the next visits.

Statistical Analysis

We stratified participants at the enrollment visit into those with FEV_1/SVC ≥ 0.7 and those with FEV_1/SVC < 0.7. We compared the characteristics of participants at the enrollment visit between the two groups using the Wilcoxon rank-sum test for continuous variables and the χ^2 or Fisher exact test for categorical variables. To identify factors associated with FEV_1/SVC < 0.7, we created parsimonious multivariate logistic regression models. Clinically relevant variables associated with $P < .1$ in the univariate analysis were considered for multivariate analysis. Variables were selected for the final model using a stepwise backward variable elimination process to minimize the Akaike information criterion.[18] We assessed for variable multicollinearity using correlation matrices and variance inflation factors.[19] We repeated the multivariate analysis after the multiple imputation by chained equations package (five datasets) to account for missing variables.[20,21]

We also created multivariate linear regression models with percent emphysema, gas trapping, and parametric response mapping functional small airways disease as the dependent variables (outcomes) and FEV_1/SVC < 0.7 as the main independent variable

(exposure). Age, sex, race, smoking status at enrollment, and pack-years smoked were included as covariates in the models. We created zero-inflated negative binomial models to assess exacerbation rates, which included adjustment for age, sex, race, smoking status at enrollment, pack-years smoked, and diabetes mellitus as risk factors for exacerbations.[22] Follow-up time was included as an offset in the models as described previously.[23,24] We compared the frequency of participants who progressed to COPD during the study period using the χ^2 test. Interval-censored proportion hazards regression analysis was used to examine the association of $FEV_1/SVC < 0.7$ with progression to COPD during the follow-up period, with adjustment for age, sex, race, smoking status at enrollment, and pack-years smoked. We created a multivariate logistic regression model with persistent COPD as the dependent variable (outcome) and $FEV_1/SVC < 0.7$ as the main independent variable (exposure). Age, sex, race, smoking status at enrollment, and pack-years smoked were included as covariates in the models.

Although postbronchodilator spirometry is considered the gold standard for COPD diagnosis,[25] both prebronchodilator and postbronchodilator spirometry is associated with clinical, functional, and radiographic features of COPD.[26] Moreover, postbronchodilator spirometry is not always performed.[27] Therefore, we performed a sensitivity analysis that included 645 participants with a prebronchodilator $FEV_1/FVC \geq 0.7$ and FEV_1 % predicted of ≥ 80% at the enrollment. In the sensitivity analysis, we repeated the same approach as in the main analysis, but the FEV_1/SVC was computed using the prebronchodilator FEV_1 and SVC, and COPD was defined based on prebronchodilator $FEV_1/FVC < 0.7$. We examined the association of prebronchodilator $FEV_1/SVC < 0.7$ with clinical, functional, and radiographic features of COPD. An additional analysis that included 864 current or former smokers with a prebronchodilator FEV_1/FVC of the LLN or more and FEV_1 equal to the LLN or more at the enrollment[9] was performed to examine the association of prebronchodilator FEV_1/SVC less than the LLN with clinically relevant outcomes. All statistical analyses were conducted using R statistical software (R Foundation for Statistical Computing) except interval-censored proportion hazards regression analysis, which was conducted using SAS software (SAS Institute).

Results

Of 854 current and former smokers with normal spirometry results at enrollment, defined as postbronchodilator $FEV_1/FVC \geq 0.7$ and FEV_1 % predicted of ≥ 80%, 120 participants showed a postbronchodilator $FEV_1/SVC < 0.7$ and 734 participants showed an $FEV_1/SVC \geq 0.7$. Table 1 shows the characteristics of the two groups. In a parsimonious multivariate analysis, we identified factors associated with postbronchodilator $FEV_1/SVC < 0.7$. Older age with an OR of 1.91 for every 10 years (95% CI, 1.51-2.45), postbronchodilator FEV_1 % predicted (OR, 0.96 for every 1%; 95% CI, 0.94-0.97), and greater emphysema (OR, 1.13 for every 1% emphysema; 95% CI, 1.03-1.25) were associated with postbronchodilator $FEV_1/SVC < 0.7$ (Table 2). We repeated the multivariate analysis after multiple imputations to account for missing variables showing similar results (e-Table 1).

Chest CT Scan Features

After adjusting for demographics, pack-years smoking, and current smoking status, participants with postbronchodilator $FEV_1/SVC < 0.7$ showed greater percent emphysema by 0.45% (95% CI, 0.09-0.82), percent gas trapping by 2.52% (95% CI, 0.59-4.44), and percent parametric response mapping functional small airways disease by 2.78% (95% CI, 0.72-4.83) at baseline than those with $FEV_1/SVC \geq 0.7$ (Table 3).

Exacerbations

During a median follow-up time of 1,500 days (interquartile range, 1,062-1,954 days), data for exacerbations were available for 710 participants with $FEV_1/SVC \geq 0.7$ and for 120 participant with $FEV_1/SVC < 0.7$. Of 710 participants with postbronchodilator $FEV_1/SVC \geq 0.7$, 170 (23.9%) experienced at least one exacerbation, with 62 (8.7%) experiencing at least one severe exacerbation. Among 120 individuals with postbronchodilator $FEV_1/SVC < 0.7$, 42 (35%) experienced at least one exacerbation, with 17 (14.2%) experiencing at least one severe exacerbation. In multivariate analysis adjusted for demographics, pack-years smoking, current smoking status, and diabetes mellitus, postbronchodilator $FEV_1/SVC < 0.7$ was not associated with total exacerbation (incident rate ratio, 1.60; 95% CI, 0.97-2.64), but was associated with severe exacerbations (incident rate ratio, 2.60; 95% CI, 1.04-4.89) (Table 4).

Progression to COPD and Persistent COPD

During a median follow-up time of 1,460 days (interquartile range, 1,024-1,946 days), spirometric follow-up data were available for 727 participants with $FEV_1/SVC \geq 0.7$ and for 118 participants with $FEV_1/SVC < 0.7$. Of participants with $FEV_1/SVC \geq 0.7$, 12.7% demonstrated COPD, defined as postbronchodilator $FEV_1/FVC < 0.7$, whereas 42.4% of those with $FEV_1/SVC < 0.7$ demonstrated COPD during the follow-up period ($P < .001$). Figure 1 shows the COPD-free survival time in those with $FEV_1/SVC \geq 0.7$ and those with $FEV_1/SVC < 0.7$. The association of postbronchodilator $FEV_1/SVC < 0.7$ with progression to COPD during the follow-up period remained after adjusting for demographics, pack-years smoking, and current smoking status (hazard ratio, 3.93; 95% CI, 2.71-5.72) (Table 4). Postbronchodilator $FEV_1/SVC < 0.7$ also

TABLE 1] Baseline Characteristics in Smokers With Normal Spirometry Results[a] Stratified by Postbronchodilator $FEV_1/SVC < 0.7$ (n = 854)

Variable	Postbronchodilator $FEV_1/SVC \geq 0.7$ (n = 734)	Postbronchodilator $FEV_1/SVC < 0.7$ (n = 120)	*P* Value[b]
Age, y	59.13 ± 9.59	65.35 ± 9.02	< .001
Female sex	391 (53.3)	51 (42.5)	.036
White race	489 (66.6)	92 (76.7)	.037
BMI, kg/m^2	28.73 ± 5.05	29.12 ± 4.87	.36
Pack-years smoking	40.75 ± 24.29	50.31 ± 22.93	< .001
Currently smoking	387 (53.2)	45 (38.1)	.003
Asthma	107 (14.6)	19 (15.8)	.83
Congestive heart failure	10 (1.4)	2 (1.7)	.68
Diabetes mellitus	77 (10.6)	22 (18.5)	.019
Hypertension	296 (40.6)	65 (54.6)	.006
OSA	130 (17.7)	21 (17.5)	1
Stroke	26 (3.6)	4 (3.4)	1
History of exacerbation	97 (13.3)	14 (11.8)	.74
Bronchodilators	149 (20.3)	32 (26.7)	.14
Inhaled glucocorticoids	76 (10.4)	13 (10.8)	1
Chronic bronchitis	259 (37.1)	46 (41.8)	.40
MMRC ≥ 2	93 (12.8)	11 (9.2)	.34
CAT score ≥ 10	332 (49.0)	57 (49.6)	.99
Prebronchodilator FEV_1, L	2.71 ± 0.68	2.56 ± 0.66	.047
Prebronchodilator FEV_1 % predicted	94.17 ± 12.90	89.17 ± 11.52	< .001
Prebronchodilator FVC, L	3.61 ± 0.89	3.69 ± 0.97	.34
Prebronchodilator FVC % predicted	96.97 ± 12.61	97.02 ± 12.01	.76
Postbronchodilator FEV_1, L	2.87 ± 0.70	2.70 ± 0.67	.026
Postbronchodilator FEV_1 % predicted	99.76 ± 12.22	94.29 ± 9.94	< .001
Postbronchodilator FVC, L	3.67 ± 0.89	3.70 ± 0.94	.67
Postbronchodilator FVC % predicted	98.45 ± 12.01	97.63 ± 10.56	.44
Prebronchodilator SVC, L	3.61 ± 0.96	3.84 ± 1.05	.016
Postbronchodilator SVC, L	3.68 ± 0.92	4.03 ± 0.99	< .001
Bronchodilator response	86 (11.7)	19 (15.8)	.26
RV_{CT}, L	2.78 ± 0.72	3.15 ± 0.79	< .001
TLC_{CT}, L	5.38 ± 1.27	5.84 ± 1.33	< .001
RV_{CT} to TLC_{CT} ratio, %	52.56 ± 11.96	54.94 ± 11.89	.008
6-MWT distance, m	440.52 ± 94.96	426.77 ± 95.93	.30
Emphysema, %	1.53 ± 1.82	2.30 ± 2.25	< .001
Gas trapping, %	7.58 ± 9.53	12.09 ± 12.08	< .001
PRM^{fSAD}, %	8.01 ± 9.74	12.73 ± 12.27	< .001

Data are presented as No. (%) or mean ± SD, unless otherwise indicated. 6-MWT = 6-min walk test distance; CAT = COPD Assessment Test; MMRC= Modified Medical Research Council; PRM^{fSAD} = parametric response mapping functional small airways disease; RV_{CT} = residual volume by CT scan; SVC = slow vital capacity; TLC_{CT} = total lung capacity by CT scan.

[a]Normal spirometry results defined as postbronchodilator FEV_1 of ≥ 80% and postbronchodilator $FEV_1/FVC \geq 0.7$.

[b]Characteristics of participants between the two groups compared using a *t* test for continuous variable and the χ^2 or Fisher exact test for categorical variables.

was associated with persistent COPD after adjusting for demographics, pack-years smoking, and current smoking status (OR, 5.08; 95% CI, 3.09-8.37).

e-Table 2 shows the characteristics in participants who demonstrated persistent COPD and those who did not.

TABLE 2] Factors Associated With Abnormal Postbronchodilator FEV_1/SVC Ratio of < 0.7 Among Smokers With Normal Spirometry Results[a] (n = 854)

Variable	OR (95% CI)	*P* Value
Age, every 10 y	1.91 (1.51-2.45)	< .001
Pack-years, every 10 y	1.06 (0.99-1.14)	.09
Postbronchodilator FEV_1 % predicted	0.96 (0.94-0.97)	< .001
% Emphysema	1.13 (1.03-1.25)	.008
Female sex	0.68 (0.45-1.04)	.08

Variables tested but not retained for the final model include: residual volume to total lung capacity ratio, race, and current smoking. Data regarding percent emphysema, residual volume to total lung capacity ratio, and current smoking were missing in 7, 9, and 9 participants, respectively. We performed an additional analysis after multiple imputations accounting for missing values showing similar findings (e-Table 1). SVC = slow vital capacity.
[a]Normal spirometry results defined as postbronchodilator $FEV_1 \geq 80\%$ and postbronchodilator $FEV_1/FVC \geq 0.7$.

Prebronchodilator Analysis

The prebronchodilator analysis included 645 participants with prebronchodilator FEV_1/FVC of ≥ 0.7 and FEV_1 % predicted of ≥ 80%, and it showed similar results to the postbronchodilator analysis, except that no association was found of prebronchodilator $FEV_1/SVC < 0.7$ with percent gas trapping, small airway disease, and exacerbations, as opposed to the main analysis findings (e-Tables 3-7).

LLN Analysis

The LLN analysis included 864 participants with prebronchodilator FEV_1/FVC = the LLN or more and FEV_1 equal to the LLN or more, and it showed similar results to the postbronchodilator analysis, except that no association was found of prebronchodilator FEV_1/SVC less than the LLN with small airway disease and exacerbations, as opposed to the main analysis findings (e-Tables 8, 9).

TABLE 3] Association of Postbronchodilator FEV_1 to SVC Ratio of < 0.7 With Chest CT Scan Features in Smokers With Normal Spirometry Results[a] (n = 854)

Variable	β (95% CI)	*P* Value
% Emphysema	0.45 (0.09-0.82)	.014
% Gas trapping	2.52 (0.59-4.44)	.010
% PRM^{fSAD}	2.78 (0.72-4.83)	.0081

Each row represents a model. All models included the following covariates: age, sex, race, smoking status, and smoking pack-years at the enrollment. Data regarding % emphysema, % gas trapping, % PRM^{fSAD}, and current smoking were missing in 7, 4, 96, and 9 participants, respectively. PRM^{fSAD} = parametric response mapping functional small airways disease; SVC = slow vital capacity.
[a]Normal spirometry results defined as postbronchodilator $FEV_1 \geq 80\%$ and postbronchodilator $FEV_1/FVC \geq 0.7$.

Discussion

Among current and former smokers who were not diagnosed with COPD based on normal postbronchodilator spirometry results,[25] we found that participants with postbronchodilator $FEV_1/SVC < 0.7$ experienced more emphysema, gas trapping, and severe exacerbations and that they were more likely to demonstrate COPD relative to those patients with postbronchodilator $FEV_1/SVC \geq 0.7$. We found similar results when we examined the association of prebronchodilator $FEV_1/SVC < 0.7$ or FEV_1/SVC less than the LLN with chest CT scan features and progression to COPD.

Vital capacity can be measured either at forced expiration (FVC), at slow expiration (SVC), or at inspiration (inspiratory VC).[28] Although SVC and FVC in theory should be the same in a healthy population with normal lungs, SVC usually is larger than FVC, especially in obese people or those with airways disease.[29,30] In individuals with no obstructive lung disease, the difference between SVC and FVC increases with increasing BMI and age.[29,30] Current lung function test interpretation guidelines acknowledge that inspiratory or expiratory SVC may be a better estimate of VC than FVC, but they do not provide specific recommendations regarding whether SVC should be used to calculate the FEV_1/VC.[6] Nevertheless, professional organizations have proposed the FEV_1 to VC instead of the FEV_1/FVC as a diagnostic criterion for COPD at certain times.[31] The FEV_1/SVC may be more sensitive than the FEV_1/FVC to diagnose COPD, likely because FVC often may underestimate the true VC. The FVC maneuver increases intrathoracic pressure, which may lead to the collapse of small airways before the end of expiration, an effect that also shortens exhalation time. In individuals with mild obstructive lung disease, this phenomenon may result in pseudonormalization of the FEV_1/FVC, whereas in those with substantial obstructive lung disease, it may result in preserved ratio impaired spirometry results.[32-34] Using the FEV_1/SVC instead of the FEV_1/FVC results in an increase in the reported prevalence of COPD[35,36] and may lead to overdiagnosis, in particular among elderly individuals.[7]

TABLE 4] Association of Postbronchodilator FEV_1 to SVC Ratio of < 0.7 With Exacerbations and Progression to COPD in Smokers With Normal Spirometry Results[a]

Variable	IRR (95% CI)	*P* Value
Total exacerbations	1.60 (0.97-2.64)	.07
Severe exacerbations	2.60 (1.04-4.89)	.040
	HR (95% CI)	
Progression to COPD	3.93 (2.71-5.72)	< .001
	OR (95% CI)	
Persistent COPD	5.08 (3.09-8.37)	< .001

For exacerbation analysis, data for 830 participants were available. Zero-inflated negative binomial regression models with postbronchodilator $FEV_1/SVC < 0.7$ as the main independent variable (exposure) and total exacerbations and severe exacerbations as the dependent variables (outcome) were performed. Models included the following covariates: age, sex, race, current smoking status, smoking pack-years, and diabetes mellitus in the count negative binomial regression and an intercept-only model in the zero component. Follow-up time was included as an offset in the models. For progression to COPD analysis, data for 845 participants were available. Interval-censored proportion hazards regression model for progression to COPD included the following covariates: age, sex, race, smoking status, and smoking pack-years. For progression to persistent COPD analysis, a logistic regression model was created with the same covariates. HR = hazard ratio; IRR = incident rate ratio; SVC = slow vital capacity.

[a]Normal spirometry results defined as postbronchodilator $FEV_1 \geq 80\%$ and postbronchodilator $FEV_1/FVC \geq 0.7$.

Nevertheless, in the absence of a true gold standard for COPD diagnosis, the usefulness of a diagnostic test is related highly to its association with the clinical, functional, and radiographic features of a disease.[37] The main purpose of this analysis was not to evaluate FEV_1/SVC as a tool to diagnose the COPD. Instead, we decided to evaluate the usefulness of FEV_1/SVC in individuals at risk for development, but without COPD according to current guidelines.[1] Our goal was to use the information commonly obtained by routine spirometry further, which could be useful for identifying early airflow abnormalities predictive of the development of COPD.[38]

In our analysis, $FEV_1/SVC < 0.7$ was not associated with high mMRC, CAT score, or chronic bronchitis, likely because the participants in the study had relatively preserved lung function and they were fairly asymptomatic. In a similar study by Saint-Pierre et al[7] that included adults with a prebronchodilator FEV_1/FVC of more than the LLN and total lung capacity of more than the LLN, the average of mMRC was only 1.5 in those FEV_1/SVC less than the LLN and in those with FEV_1/SVC equal to the LLN or more, the average of mMRC was 0.5. Our data contribute to the published literature by showing that, among smokers with normal postbronchodilator spirometry results, a postbronchodilator $FEV_1/SVC < 0.7$ was associated with greater radiographic emphysema and gas trapping relative to those with postbronchodilator $FEV_1/SVC \geq 0.7$. The association of $FEV_1/SVC < 0.7$ with emphysema is not surprising, because emphysema may result in expiratory airway collapse and increase in the difference between SVC and FVC.[39] Thus, individuals with low to normal FEV_1 who do not meet the criteria

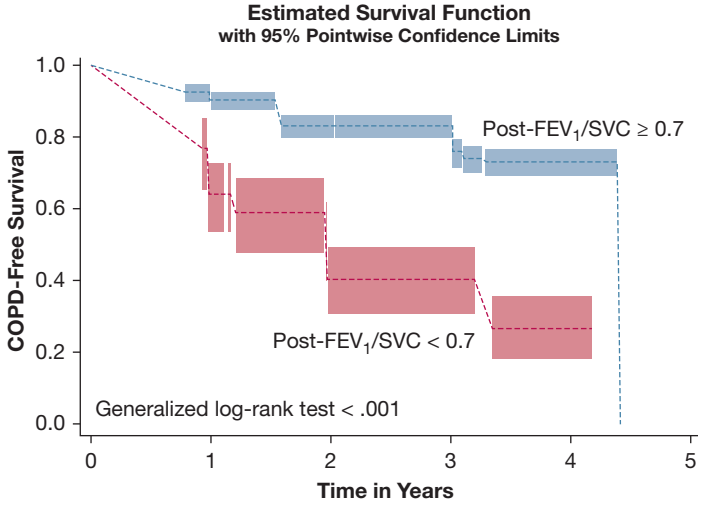

Figure 1 – *Line graph showing COPD-free survival in smokers with normal spirometry results (postbronchodilator $FEV_1 \geq 80\%$ and postbronchodilator $FEV_1/FVC \geq 0.7$; n = 845) stratified by postbronchodilator FEV_1/SVC: postbronchodilator $FEV_1/SVC \geq 0.7$ (blue) and postbronchodilator $FEV_1/SVC < 0.7$ (red). Interval-censored proportion hazards regression analysis was used to examine the association of $FEV_1/SVC < 0.7$ with progression to COPD during the follow-up period. SVC = slow vital capacity.*

for COPD diagnosis using the FEV_1/FVC often have an abnormal FEV_1/SVC. Consistent with our findings, the study by Saint-Pierre et al[7] showed that individuals with an FEV_1/SVC less than the LLN demonstrated a higher airway resistance and residual volume than patients with FEV_1/SVC equal to the LLN or more and were more likely to be diagnosed with obstructive lung diseases such as asthma and COPD relative to patients with FEV_1/SVC equal to the LLN or more. We must note that in this cohort of current or formers smokers with normal spirometry results, approximately 15% of the participants self-reported asthma, which may be associated with different clinical features (ie, emphysema, exacerbations, and progression to airways obstruction) than those in individuals without history of asthma.

In contrast to several studies focused mainly on the association of low FEV_1/SVC and the clinical characteristics of COPD,[7] we also evaluated the outcomes over at least 3 years of follow-up, thus allowing for longitudinal evaluation of the significance of an abnormal FEV_1/SVC. Our findings add to other recent reports demonstrating that other physiologic abnormalities may precede formal diagnosis of COPD.[4,40,41] Air trapping based on radiographic lung volumes predicts accelerated spirometry decline and progression to COPD in smokers without obstruction.[4,33,40,41] Based on the above, we conclude that FEV_1/SVC can be a simple, routinely available spirometric index that can identify individuals who may benefit from early intervention such as smoking cessation. Confirmation of obstructive lung disease by an objective measurement like FEV_1/SVC may motivate smokers to quit smoking,[42,43] which is the only proven intervention that can modify disease progression. A study showed that pharmacotherapy in COPD patients with mild-to-moderate lung function impairment also may be beneficial.[44] An ongoing multicenter randomized controlled trial aims to examine the effect of bronchodilators in symptomatic smokers with preserved spirometry.[45]

Apart from its retrospective nature, our study has some limitations. SPIROMICS was not a population-based study. We analyzed a cohort of heavy smokers older than 40 years; thus, any generalization warrants caution. We did not take into consideration other risk factors for obstructive lung disease like occupational exposure. Given the lack of widely accepted reference values for FEV_1/SVC in the US population, we used the 0.7 as a cutoff for the FEV_1/VC for the main analysis. Nevertheless, we observed similar findings when we examined the association of FEV_1/SVC less than the LLN with radiographic features and progression to COPD in those with FEV_1 equal to the LLN or more and FEV_1/FVC equal to the LLN or more. In this regard, a study by Bhatt et al[46] demonstrated that fixed ratio is actually superior to the LLN in the ability to predict hospitalization, mortality, or both.

In conclusion, an $FEV_1/SVC < 0.7$ or LLN may be used as a metric of early obstruction and may be useful tool in identifying individuals at increased risk of COPD. An $FEV_1/SVC < 0.7$ or LLN in current and former smokers with normal spirometry results can identify individuals with increased emphysema, gas trapping, and risk of progressing to COPD in the future. Further research should evaluate whether the FEV_1/SVC should be used in addition to the current diagnostic criteria to identify individuals at high risk for COPD who potentially may benefit from early interventions like smoking cessation or pharmacotherapy.

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