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Original Research

Changes in Lung Volumes with Spirometric Disease Progression in COPD

Mehrdad Arjomandi, MD[1,2] Siyang Zeng, MS[1,3] Jianhong Chen, MS[1,2] Surya P. Bhatt, MD[4] Fereidoun Abtin, MD[5] Igor Barjaktarevic, MD, PhD[5] R. Graham Barr, MD, PhD[6] Eugene R. Bleecker, MD[7] Russell G. Buhr, MD, PhD[5] Gerard J. Criner, MD[8] Alejandro P. Comellas, MD[9] David J. Couper, PhD[10] Jeffrey L. Curtis, MD[11,12] Mark T. Dransfield, MD[4] Spyridon Fortis, MD[9] MeiLan K. Han, MD, MS[11] Nadia N. Hansel, MD, MPH[13] Eric A. Hoffman, PhD[9] John E. Hokanson, MPH, PhD[14] Robert J. Kaner, MD[15] Richard E. Kanner, MD[16] Jerry A. Krishnan, MD, PhD[17] Wassim W. Labaki, MD, MS[11] David A. Lynch, MD[18] Victor E. Ortega, MD, PhD[19] Stephen P. Peters, MD, PhD[20] Prescott G. Woodruff, MD, MPH[2] Christopher B. Cooper, MD[5] Russell P. Bowler, MD, PhD[21] Robert Paine III, MD, PhD[16,21] Stephen I. Rennard, MD[22] Donald P. Tashkin, MD[6] and the COPDGene and SPIROMICS Investigators

Abstract

Background: Abnormal lung volumes representing air trapping identify the subset of smokers with preserved spirometry who develop spirometric chronic obstructive pulmonary disease (COPD) and adverse outcomes. However, how lung volumes evolve in early COPD as airflow obstruction develops remains unclear.

Methods: To establish how lung volumes change with the development of spirometric COPD, we examined lung volumes from the pulmonary function data (seated posture) available in the U.S. Department of Veterans Affairs electronic health records (n=71,356) and lung volumes measured by computed tomography (supine posture) available from the COPD Genetic Epidemiology (COPDGene®) study (n=7969) and the SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS) (n=2552) cohorts, and studied their cross-sectional distributions and longitudinal changes across the airflow obstruction spectrum. Patients with preserved ratio-impaired spirometry (PRISm) were excluded from this analysis.

Results: Lung volumes from all 3 cohorts showed similar patterns of distributions and longitudinal changes with worsening airflow obstruction. The distributions for total lung capacity (TLC), vital capacity (VC), and inspiratory capacity (IC) and their patterns of change were nonlinear and included different phases. When stratified by airflow obstruction using Global initiative for chronic Obstructive Lung Disease (GOLD) stages, patients with GOLD 1 (mild) COPD had larger lung volumes (TLC, VC, IC) compared to patients with GOLD 0 (smokers with preserved spirometry) or GOLD 2 (moderate) disease. In longitudinal follow-up of baseline GOLD 0 patients who progressed to spirometric COPD, those with an initially higher TLC and VC developed mild obstruction (GOLD 1) while those with initially lower TLC and VC developed moderate obstruction (GOLD 2).

Conclusions: In COPD, TLC, and VC have biphasic distributions, change in nonlinear fashions as obstruction worsens, and could differentiate those GOLD 0 patients at risk for more rapid spirometric disease progression.

1. San Francisco Veterans Affairs Healthcare System, San Francisco, California, United States
2. Department of Medicine, University of California, San Francisco, California, United States
3. Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, Washington, United States
4. University of Alabama at Birmingham, Birmingham, Alabama, United States
5. Department of Medicine, University of California, Los Angeles, California, United States
6. Columbia-Presbyterian Medical Center, New York, New York, United States
7. University of Arizona, College of Medicine, Tucson, Arizona, United States
8. Temple University, Philadelphia, Pennsylvania, United States
9. University of Iowa, Iowa City, Iowa, United States
10. University of North Carolina, Chapel Hill, North Carolina, United States
11. Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States
12. Medical Service, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, United States
13. Johns Hopkins Medical Institute, Baltimore, United States
14. Department of Epidemiology, School of Public Health, University of Colorado, United States
15. Weill Cornell Medical Center, New York, New York, United States

16. University of Utah, Salt Lake City, Utah, United States
17. University of Illinois at Chicago, Chicago, Illinois, United States
18. Department of Radiology, National Jewish Health Systems, Denver, Colorado, United States
19. Mayo Clinic, Scottsdale, Arizona, United States
20. Wake Forest School of Medicine, Winston-Salem, North Carolina, United States
21. Department of Medicine, National Jewish Health Systems, Denver, Colorado, United States
22. University of Nebraska Medical Center, Omaha, Nebraska, United States

Abbreviations:

BMI=body mass index; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **COPDGene**=COPD Genetic Epidemiology study; **CT**=computed tomography; **EHRs**=electronic health records; **FEF_{25-75}**=forced expiratory flow at 25% to 75%; **FEF_{75}**=maximum airflow after 75% of lung volume exhaled; **FEV_1**=forced expiratory volume in 1 second; **FRC**=forced residual capacity; **FVC**=forced vital capacity; **IC**=inspiratory capacity; **ILD**=interstitial lung disease; **NHANES**=National Health and Nutrition Examination Survey; **NIH**=National Institutes of Health; **PFT**=pulmonary function test; **PRISM**=preserved ratio-impaired spirometry; **$PRM^{Air\ trapping}$**=parametric response mapping of percentage air trapping; **PRM^{EMPH}**=parametric response mapping of functional small airway disease as measures of emphysema; **PRM^{fSAD}**=parametric response mapping of functional small airway disease; **RV**=residual volume; **SPIROMICS**=SubPopulations InteRmediate Outcome Measures In COPD Study; **SVC**=slow vital capacity; **TLC**=total lung capacity; **V1**=visit 1; **VA**=Veterans Affairs; **VAHCS**=Veterans Affairs Health Care System; **VC**=vital capacity; **VINCI**=VA Informational Computing Infrastructure

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Address correspondence to:

Mehrdad Arjomandi, MD
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine
University of California, San Francisco
San Francisco Veterans Affairs Medical Center
Building 203, Room 3A-128, Mailstop 111-D
4150 Clement Street, San Francisco, CA 94121
Phone: (415) 221-4810 x24393
Email: mehrdad.arjomandi@ucsf.edu

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Introduction

In chronic obstructive pulmonary disease (COPD), the general understanding in the field has been that as airflow obstruction progresses, air trapping and hyperinflation worsen, and vital capacity (VC) and inspiratory capacity (IC) decrease.[1-3] However, recent studies have suggested that in early disease, the development of spirometric COPD occurs from an increase in forced VC (FVC) while airflow obstruction (as measured by forced expiratory volume in 1 second [FEV_1]) remains unaffected,[4,5] a finding that is contrary to the current conventional wisdom. This finding triggered our interest to more precisely investigate how the lung volumes change during the development and progression of spirometric disease, as it remains unclear how underlying obstructive pathology may contribute to an increased FVC in early COPD.

This study aimed to examine the distributions of and changes in lung volumes with the development and progression of COPD. To achieve this goal, we first examined the differences in lung volumes by conducting cross-sectional analyses of patients with differing severity of COPD. Second, we examined the longitudinal changes in lung volumes in smokers with preserved spirometry to determine whether the changes in lung volumes mirrored the cross-sectional differences that we observed at baseline. For these analyses, we used the plethysmographic lung volume measurements from the pulmonary function test (PFT) results available in the U. S. Department of Veterans Affairs (VA) electronic health records (EHRs) and lung volume measurements derived from thoracic computerized tomography (CT) scans available in the National Institute of Health (NIH)-funded research cohorts of the COPD Genetic Epidemiology (COPDGene®) study and the SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS).

Methods

Study Design

Lung volumes measured by plethysmography in seated posture extractable from the VA EHR PFT data (n=71,356) and lung volumes measured by CT in supine posture from the COPDGene (n=7969) and SPIROMICS (n=2552) cohorts were examined over the spectrum of the spirometric airflow obstruction. VA EHR PFT data contained total lung capacity (TLC), VC, IC, residual volume (RV), and functional residual capacity (FRC). COPDGene CT data contained TLC and FRC while SPIROMICS CT data contained TLC and RV.

Longitudinal changes in the lung volumes were computed for patients/participants who had both spirometric and lung volume data available in a follow-up visit. For the SPIROMICS cohort, although spirometry data were available from multiple visits, lung volume measurements were only available at baseline and 1-year follow-up visits (the 5-year SPIROMICS II CT-measured lung volumes were not available at the time of this analysis). For the COPDGene cohort, CT-measured lung volumes were available from 3 visits (baseline, 5-year, and 10-year visits). For the VA EHR cohort, we identified the patients with available full PFT data ≥1 year or ≥3 years after their index PFT. These timeframes were chosen to match the follow-up time intervals available from the SPIROMICS and COPDGene cohorts.

In all 3 cohorts, patients/participants with preserved ratio and impaired spirometry or PRISm (those with a normal FEV_1/FVC but reduced FEV_1, as defined originally by COPDGene investigators)[6] at any visit were excluded from the analysis, as they may have had a restrictive impairment affecting their lung volumes. Similarly, patients/participants who showed improvements in their follow-up spirometry, resulting in an improvement in their Global initiative for chronic Obstructive Lung Disease (GOLD) stage,[7] were also excluded from the analysis, as they may represent a subgroup with a reversible disease pathology distinct from the rest of the cohort. Overall, the longitudinal analysis included those whose spirometry at the follow-up visit stayed the same or worsened. Full study methods are available in the online supplement.

Statistical Analysis

For cross-sectional analyses, the distributions of the baseline lung volumes were examined across airflow obstruction as measured by the post-bronchodilator FEV_1 as a continuous variable. To understand the nature of the relationship between lung volumes and spirometry variables, we performed an initial exploratory evaluation using locally weighted scatterplot smoothing (LOWESS) analysis of the relative distribution of the lung volume variables versus FEV_1 and found that many lung volume variables had a nonlinear association with FEV_1. To generate better fits, we chose to examine the association of lung volumes versus partitions of FEV_1 based on the arbitrary but clinically well-known GOLD categorization.[7] To account for the random effect of study sites, the comparisons among each of the 5 baseline lung volume measurements (TLC, VC, RV, FRC, and IC) with respect to the baseline GOLD stages were assessed using mixed-effects linear regression, with a random effect of study sites and fixed effect covariates, including age, sex, height, and body mass index (BMI). BMI instead of weight was used as a covariate based on previous studies demonstrating BMI to have significant effects on lung volume measurements even in people with normal lung function.[8,9] Smoking status (current versus former) was also included as a covariate only in analyses of the COPDGene and SPIROMICS data, as it was not available in the VA EHR data, although all patients in the VA EHR cohort had a history of smoking.

Longitudinal changes in lung volume measurements and additional covariates (including changes in age, height, and BMI) were calculated by subtracting the follow-up values from those from baseline visit. Changes in lung volumes were stratified by the baseline GOLD stages of the patients/participants and then compared across the subsequent GOLD stages at follow-up visits. To account for the random effect of study sites, this analysis was performed using mixed-effects linear regression, with a random effect of sites within each of the 3 cohorts, and fixed effects of baseline age, sex, height, BMI, and smoking status as well as changes in age, height, BMI, and smoking status. The same modeling was examined for each of the baseline GOLD stages. To assess the pattern of change in lung volumes from initially mild disease onward, average changes in lung volumes for those smokers with preserved spirometry (denoted for simplicity of comparison terminology as GOLD 0) at baseline with respect to subsequent GOLD stages were examined using 1-sample *t*-tests with the null hypothesis of changes in lung volumes being zero. Comparisons of baseline lung volumes and their longitudinal changes for those patients/participants with GOLD 0 at baseline with respect to subsequent GOLD stages were examined using 2-sample *t*-tests. *P*-values and 95% confidence intervals (CI) for relative differences from mixed-effects linear regression modeling were estimated by Satterthwaite's degrees of freedom method via R package, "lmerTest." Statistical significance was defined as a *P*-value <0.05.

Results

Cross-Sectional Analyses of the Study Cohorts at Baseline

Veterans Affairs Electronic Health Record Cohort:

Characteristics of the patients included in the VA EHR cohort are shown in Table 1.[10,11] Between 1985 and 2020, *structured* EHR data for spirometry tests were available from

555,574 patients enrolled in the Veterans Affairs Health Care System (VAHCS) who had at least one documented diagnosis of smoking or obstructive lung disease (Figure 1). Among them, 293,779 had full pre- and post-bronchodilator spirometry. We then identified 203,043 patients aged ≥40 years with COPD or at risk for COPD who had records of tobacco use at any time before their index spirometry. A further 18,546 patients with diagnoses of interstitial or fibrotic lung diseases, or with allergic lung diseases (except for asthma) were excluded from our analysis. Among the remaining 184,497 patients, full PFT data (including pre- and post-bronchodilator spirometry and lung volume measurements by plethysmography) were available for 71,356 patients (baseline cross-sectional cohort). The cohort mostly consisted of men (68,722 or 96%) with an average age of 63±10 years.

COPDGene Cohort:

Characteristics of the participants in the COPDGene cohort are shown in Table 1. CT-measured TLC and FRC were available for 7969 participants, consisting of 4385 (55.0%) men and 3584 (45.0%) women with an average age of 60.1±9.1 years (Figure 2).

SPIROMICS Cohort:

Characteristics of the participants in the SPIROMICS cohort are shown in Table 1. CT-measured lung volumes including both TLC and RV were available for 2552 participants (Figure 3).

Cross-Sectional Distributions of Lung Volumes Across GOLD Stages of COPD at Baseline Visits

LOWESS analysis of the relative distribution of TLC, VC, and IC versus FEV_1 showed the presence of nonlinear relationships (Figure S1 in the online supplement). Further analyses were conducted using categories of FEV_1 based on GOLD categorization.

Cross-sectional analyses of all 3 cohorts showed a remarkably similar pattern of lung volume distributions across GOLD stages of COPD. In all 3 cohorts, patients/participants with GOLD 1 COPD had larger TLC values than those with GOLD 0, while those with GOLD 2 COPD had smaller TLC values than those with GOLD 1 (Figure 4). Those with GOLD 3 and GOLD 4 COPD had the expected trend of progressively larger TLC compared to those with GOLD 2. On the other hand, both RV and FRC showed progressively larger values in higher GOLD stages of COPD (Figure 5 and Figure 6). However, VC and IC were actually larger in patients/participants with GOLD 1 COPD compared to those in GOLD 0, but progressively smaller in those with more advanced disease (GOLD 3 and GOLD 4) (Figure 5 and Figure 6). Notably, slow vital capacity (SVC) obtained by spirometry in SPIROMICS at the baseline visit also showed a similar pattern of distribution, with larger SVC values in those with GOLD 1 than in those with GOLD 0, and progressively smaller SVC values in those with more advanced disease (GOLD 2 through GOLD 4) (Figure 7). Furthermore, baseline plethysmographic lung volumes were available for a limited number of participants in COPDGene (n=391); these volumes corroborated the pattern of VC and SVC distributions as seen in the other cohorts. (Figure 7).

Description of Longitudinal Cohorts

Longitudinal Veterans Affairs Electronic Health Record Cohort:

From the 71,356 patients in the VA EHR cohort, longitudinal PFT data ≥1 year after the index PFT were available for 9926 patients (Figure 1). On the follow-up PFT, the majority of these 9926 patients remained in the same spirometric GOLD stage as that at their baseline visit, while a smaller proportion progressed to more severe COPD, and another smaller proportion showed an improvement (Figure 8). The 1024 (10.3%) patients who showed improvements in their GOLD stage were excluded from this analysis. The final longitudinal cohort included 8902 (89.7%) patients whose GOLD stage remained the same or worsened on follow-up spirometric examination conducted ≥1 year after their index PFT (Table S1 in the online supplement). The median (25th percentile–75th percentile) number of years between the index and follow-up PFT for this group was 3.1 2.0–5.0 years.

When the follow-up time of ≥3 years from the index PFT was used, longitudinal full PFT data were available for 5084 patients, of whom 472 showed improvement in their COPD GOLD stage and were, thus, excluded from this analysis. The final longitudinal cohort included 4612 (90.7%) patients whose GOLD stage remained the same or worsened. The median (25th percentile–75th percentile) number of years between the index and follow-up PFT for this group was 4.9 (3.8–6.7) years.

Longitudinal COPDGene Cohort:

Longitudinal data with follow-up pre- and post-bronchodilator spirometry and CT imaging were available from 5-year and 10-year follow-up visits (visits 2 and 3) for 3987 and 804 participants, respectively (Figure 2). Overall, 3712 (93.1%) and 750 (93.3%) participants whose subsequent GOLD category remained the same or worsened on follow-up spirometry at visits 2 and 3, respectively, were included in the longitudinal analysis (Table S2 in the online supplement). Visits 2 and 3 took place at a median (25th percentile–75th percentile) of 5.3 (5.0–5.8) and 9.9 (9.7–10.2] years after the baseline visit, respectively.

Table 1. Characteristics of Veteran Affairs Electronic Health Record Cohort Patients and COPDGene and SPIROMICS Study Participants

Characteristic	VA EHR	COPDGene	SPIROMICS
Demographics			
Number of Participants (n)	71,356	7969	2552
Age, years	63.4±10.0	60.1±9.1	63.6±8.9
Sex, Female n (%)	2634 (3.7%)	3584 (45.0%)	1158 (45.4%)
Race			
American Indian or Alaska native, n (%)	433 (0.6%)		11 (0.4%)
Asian, n (%)	247 (0.3%)		27 (1.1%)
Black or African American, n (%)	9029 (12.6%)	2459 (30.9%)	478 (18.7%)
Native Hawaiian or other Pacific, n (%)	548 (0.8%)		1 (<0.1%)
White, n (%)	49,939 (70.0%)	5510 (69.1%)	1964 (77.0%)
Declined to Answer, n (%)	1694 (2.4%)		
Mixed, n (%)			56 (2.2%)
Unknown or missing, n (%)	9466 (13.3%)		15 (0.6%)
Ethnicity			
Hispanic or Latino, n (%)	1549 (2.2%)	0 (0%)	118 (4.6%)
Not Hispanic or Latino, n (%)	60,089 (84.2%)	7969 (100%)	2433 (95.4%)
Declined to Answer, n (%)	1163 (1.6%)		
Unknown or Missing, n (%)	8555 (12.0%)		1 (<0.1%)
Height, cm	176±8	170±9	170±10
BMI, kg/m^2	27.9±6.0	28.3±5.9	27.4±5.3
Years of Follow-up	3.9±2.6	5.7±0.9	1.1±0.2
Current Smoker, n (%)		4035 (50.6%)	1012 (39.7%)
Smoking History, pack years		44.7±25.0	49.3±27.2
GOLD Stage			
GOLD 0	18,495 (25.9%)	3885 (48.8%)	798 (31.3%)
GOLD 1	14,912 (20.9%)	732 (9.2%)	384 (15.0%)
GOLD 2	19,877 (27.9%)	1737 (21.8%)	770 (30.2%)
GOLD 3	14,476 (20.3%)	1072 (13.4%)	419 (16.4%)
GOLD 4	3596 (5.0%)	543 (6.8%)	181 (7.1%)
Baseline Spirometric Indices			
FEV_1, L	2.24±0.85	2.27±0.97	2.09±0.91
FEV_1 ,% predicted	68±25	77±27	73±27
FVC, L	3.60±0.93	3.41±1.02	3.46±1.02
FVC, % predicted	82±18	90±18	92±19
FEV_1/FVC	0.61±0.14	0.65±0.17	0.59±0.17
FEV_1/FVC, % predicted	81±18	84±21	78±21
FEF_{25-75}, L	1.49±1.10	1.73±1.32	1.40±1.14
FEF_{25-75}, % predicted	54±40	65±45	56±42
Improvement in FEV_1 with Bronchodilator Administration, mL	155±204	98±165	192±171
Improvement in FEV_1 with Bronchodilator Administration, %	9.2±12.8	6.1±10.1	13.2±13.9
Bronchodilator Responsiveness by FEV_1, n (%)	18,142 (25.4%)	988 (12.4%)	785 (30.8%)
SVC, L			3.53±1.05
IC, L	2.61±0.81	2.38±0.91	
Baseline Lung Volumes	**Plethysmography**	**CT**	**CT**
TLC, L	6.76±1.41	5.71±1.41	5.09±1.33
TLC, % predicted	98±19		
RV, L	3.22±1.30		2.78±1.15
RV, % predicted	131±51		
RV/TLC	0.47±0.13		0.54±0.15
RV/TLC, % predicted	120±31		
FRC, L	4.15±1.34	3.40±1.14	

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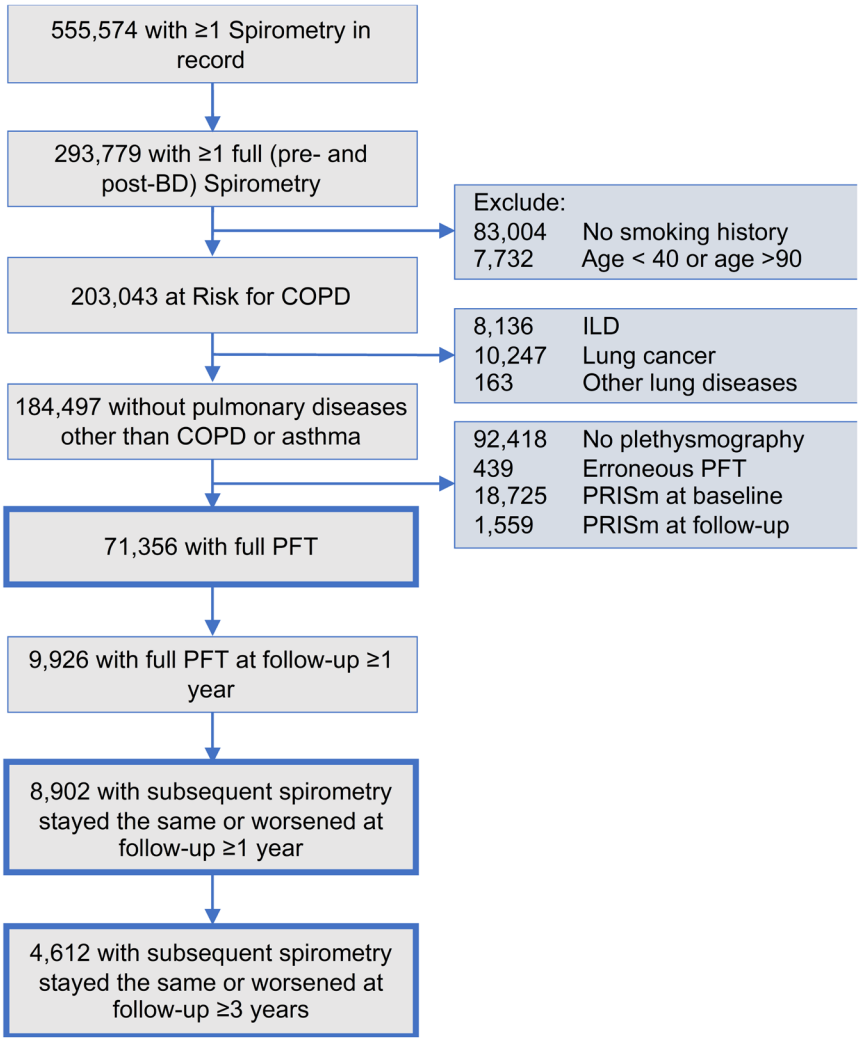
FRC, % predicted	116±36		
FRC/TLC	0.61±0.11	0.59±0.12	
FRC/TLC, % predicted	106 ±19		
VC, L	3.54 ±0.93		2.31±0.93
PRM^{EMPH}, %		6.2±10.7	6.8±10.7
PRM$^{Air\ trapping}$, %		17.1±13.7	
PRM^{fSAD}, %			21.1±15.3
Expiratory Lung Density <-856 HU, %		2.7± 1.2	25.7 ±21.7
Inspiratory Lung Density <-950 HU, %		0.8± 1.8	8.3 ±10.5

Data from participants of 3 cohorts are presented as mean ± standard deviation or number of patients with positive value for the variable (n) out of the total number of patients (N) and percentage of patients (%).

Reference equations: for VA EHR, percentage predicted of normal values of spirometry and lung volumes were calculated using NHANES and Stocks and Quanjer predicted formulas, respectively;[10,11] COPDGene and SPIROMICS used NHANES reference equations for calculation of spirometric percentage predicted values.[10] Bronchodilator responsiveness was defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilators administration.

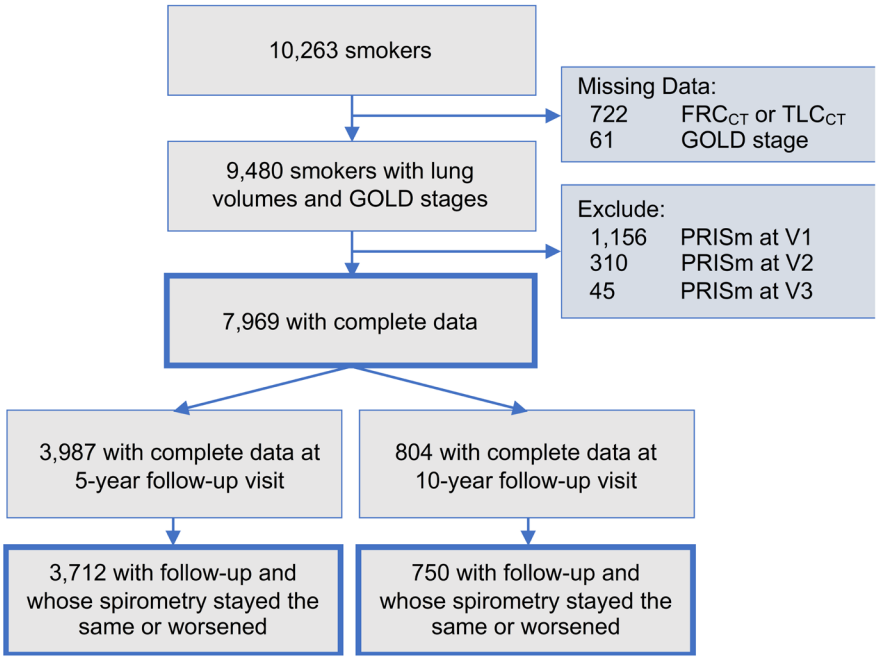
VA EHR=Veterans Affairs electronic health record cohort; COPDGene=COPD Genetic Epidemiology study; SPIROMICS=SubPopulation InteRmediate Outcome Measures In COPD Study; BMI=body mass index; GOLD=Global initiative for chronic Obstructive Lung Disease; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=forced expiratory flow at 25%-75%; FEF_{75}=maximum airflow after 75% of lung volume exhaled; SVC=slow vital capacity; IC=inspiratory capacity; CT=computed tomography; TLC=total lung capacity; RV=residual volume; FRC=functional residual capacity; VC=vital capacity; PRM^{EMPH}=parametric response mapping of functional small airway disease as measures of emphysema; PRM^{fSAD}=parametric response mapping of functional small airway disease; $PRM^{Air\ trapping}$=parametric response mapping of percentage air trapping; expiratory lung density <-856 HU=percentage of the lung voxels with attenuation <-856 Hounsfield unit on the expiratory CT images; inspiratory lung density <-950 HU=percentage of the lung voxels on inspiratory CT images with attenuation < -950 Hounsfield units; NHANES=National Health and Nutrition Examination Survey

Figure 1. Patient Selection Process Through the Department of Veterans Affairs Electronic Health Record Cohort



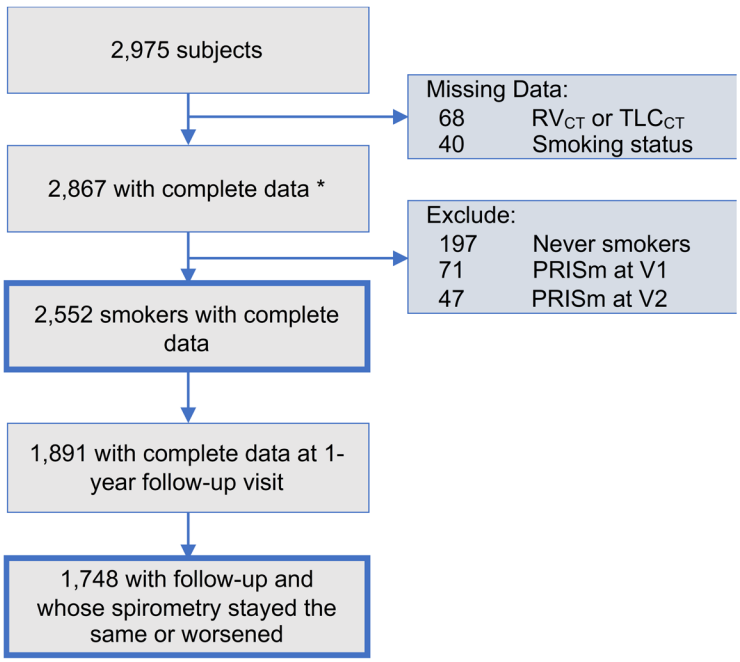
COPD=chronic obstructive pulmonary disease; ILD=interstitial lung disease; PFT=pulmonary function test; PRISm=preserved ratio-impaired spirometry

Figure 2. Participant Selection Process in the COPDGene Cohort



COPDGene=COPD Genetic Epidemiology; GOLD=Global initiative for chronic Obstructive Lung Disease; FRC=functional residual capacity; TLC=total lung capacity; PRISm=preserved ratio-impaired spirometry

Figure 3. Participant Selection Process in the SPIROMICS Cohort

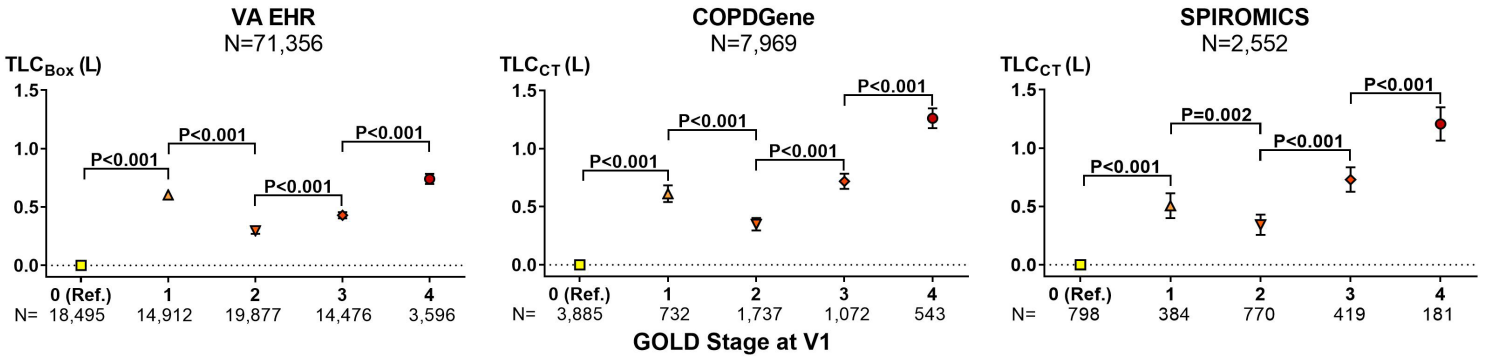


SPIROMICS=SubPopulations InteRmediate Outcome Measures In COPD Study; RV=residual volume; TLC=total lung capacity; PRISm=preserved ratio-impaired spirometry

Longitudinal SPIROMICS Cohort:

Longitudinal data with follow-up pre- and post-bronchodilator spirometry and CT data from the 1-year follow-up visit (visit 2) were available for 1891 participants (Figure 3). Overall, 1748 (92.4%) participants whose subsequent GOLD category remained the same or worsened on follow-up spirometry at visit 2 were included in the longitudinal analysis (Table S3 in the online supplement). The follow-up visit 2 took place at a median (25th percentile–75th percentile) of 1.0 (1.0-1.1) year after the baseline visit.

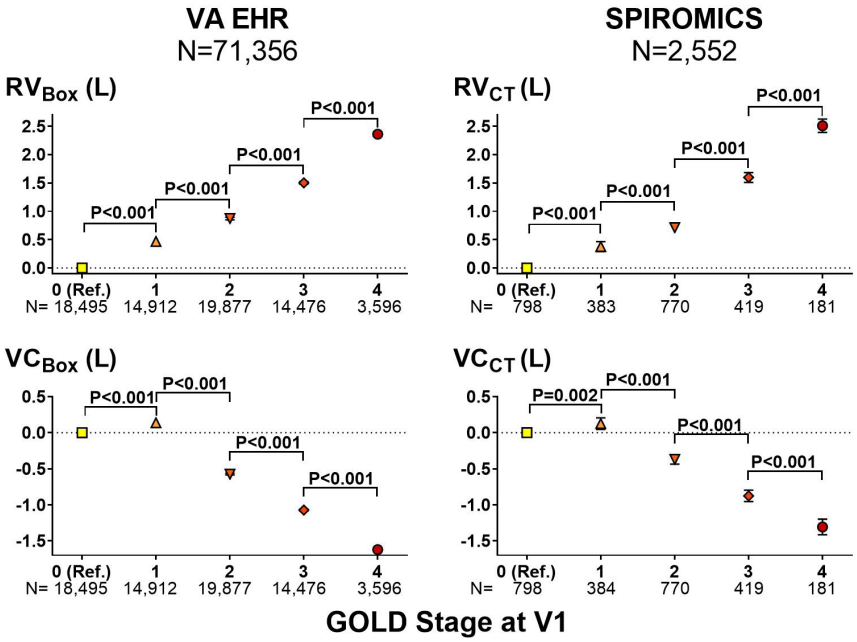
Figure 4. Distributions of Total Lung Capacity Across GOLD Stages of COPD at Baseline Visit



Coefficient (ß or parameter estimate) and 95% confidence interval for relative differences in total lung capacity from regression modeling with adjustment for age, sex, height, and body mass index (in VA EHR, COPDGene, and SPIRMICS cohorts). All 3 cohorts show similar patterns of distribution across GOLD stages of COPD.

GOLD= Global initiative for chronic Obstructive Lung Disease; COPD=chronic obstructive pulmonary disease; VA EHR= Veterans Affairs electronic health record cohort; COPDGene=COPD Genetic Epidemiology; SPIROMICS= SubPopulations InteRmediate Outcome Measures In COPD Study; TLC=total lung capacity; CT=computed tomography; V1=visit 1

Figure 5. Distributions of Residual Volume and Vital Capacity across GOLD Stages of COPD at the Baseline Visit



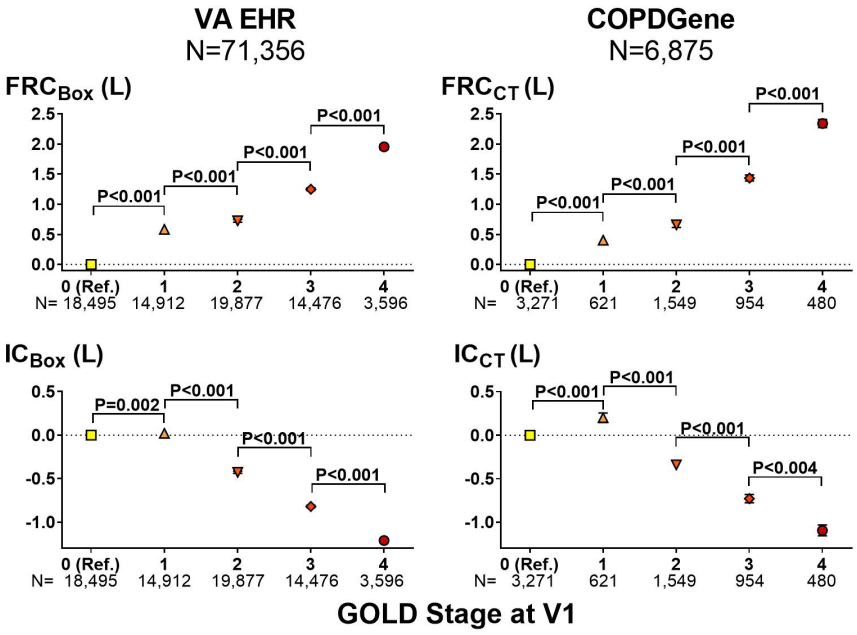
Coefficient (ß or parameter estimate) and 95% confidence interval for relative differences in RV and VC from regression modeling with adjustment for age, sex, height, and body mass index in VA EHR, COPDGene, and SPIRMICS cohorts. All 3 cohorts show similar patterns of distribution across GOLD stages of COPD.

GOLD= Global initiative for chronic Obstructive Lung Disease; COPD=chronic obstructive pulmonary disease; VA EHR= Veterans Affairs electronic health record cohort; SPIROMICS= SubPopulations InteRmediate Outcome Measures In COPD Study; RV=residual volume; CT=computed tomography; VC=vital capacity; V1=visit 1; COPDGene=COPD Genetic Epidemiology

Longitudinal Changes in Lung Volumes with Progression of Obstruction Across GOLD Stages

In longitudinal analyses, we examined changes in lung volumes as the spirometric disease progressed to more severe GOLD stages of COPD. The proportions of patients/participants who experienced disease progression were similar among all 3 cohorts (Figure 8). Overall, longitudinal changes in lung volumes at follow-up visits in the 3 cohorts corroborated the nonlinear pattern of distribution observed in the cross-sectional analysis of those lung volumes at baseline visits (Figure 9 for VA EHR; Figure S2 for COPDGene in the online supplement; and Figure S3 for SPIROMICS in the online supplement). The VA EHR and COPDGene cohorts' data from longer follow-up times showed similar trends as their respective shorter follow-up data (Figure S4 and Figure S5 in the online supplement). Given that a small number of patients/participants progressed to advanced (GOLD stages 3 and 4) COPD, we focused our analysis on patients with GOLD 0 classification at baseline who progressed to GOLD 1 or GOLD 2 disease, as described below.

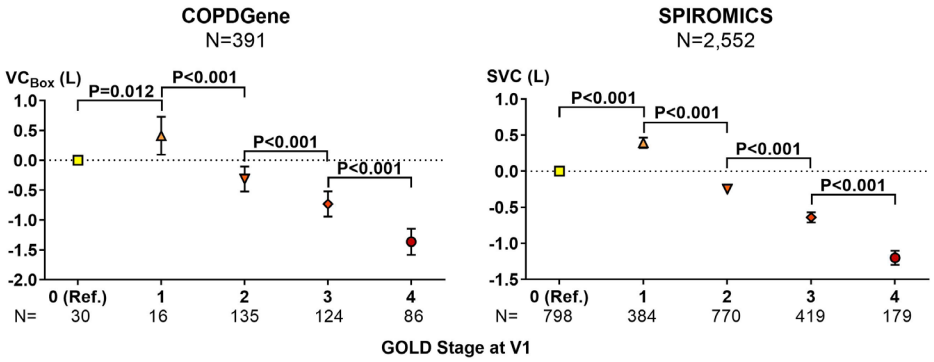
Figure 6. Distributions of Functional Residual Capacity and Inspiratory Capacity Across GOLD Stages of COPD at the Baseline Visit



Coefficient (ß or parameter estimate) and 95% confidence interval for relative differences in functional residual capacity FRC and IC from regression modeling with adjustment for age, sex, height, and body mass index in the VA EHR, COPDGene, and SPIRMICS cohorts. All 3 cohorts show similar patterns of distribution across GOLD stages of COPD.

GOLD= Global Initiative for Obstructive Lung Disease; COPD=chronic obstructive pulmonary disease; VA EHR= Veterans Affairs electronic health record cohort; COPDGene=COPD Genetic Epidemiology; FRC=functional residual capacity; CT=computed tomography IC=inspiratory capacity; V1=visit 1

Figure 7. Distributions of Slow Vital Capacity in SPIROMICS and Physiologically-Measured Vital Capacity in the COPDGene Cohort Across GOLD Stages of COPD at the Baseline Visit



Coefficient (ß or parameter estimate) and 95% confidence interval for relative differences in SVC (measured by spirometry in the SPIROMICS cohort) and plethysmographic VC (available in a limited number of participants in the COPDGene cohort from a single center) from regression modeling with adjustment for age, sex, height, and body mass index in the SPIROMICS cohort. Physiologically-measured SVC showed a similar pattern of distribution across GOLD stages of COPD as CT-measured VC in SPIROMICS.

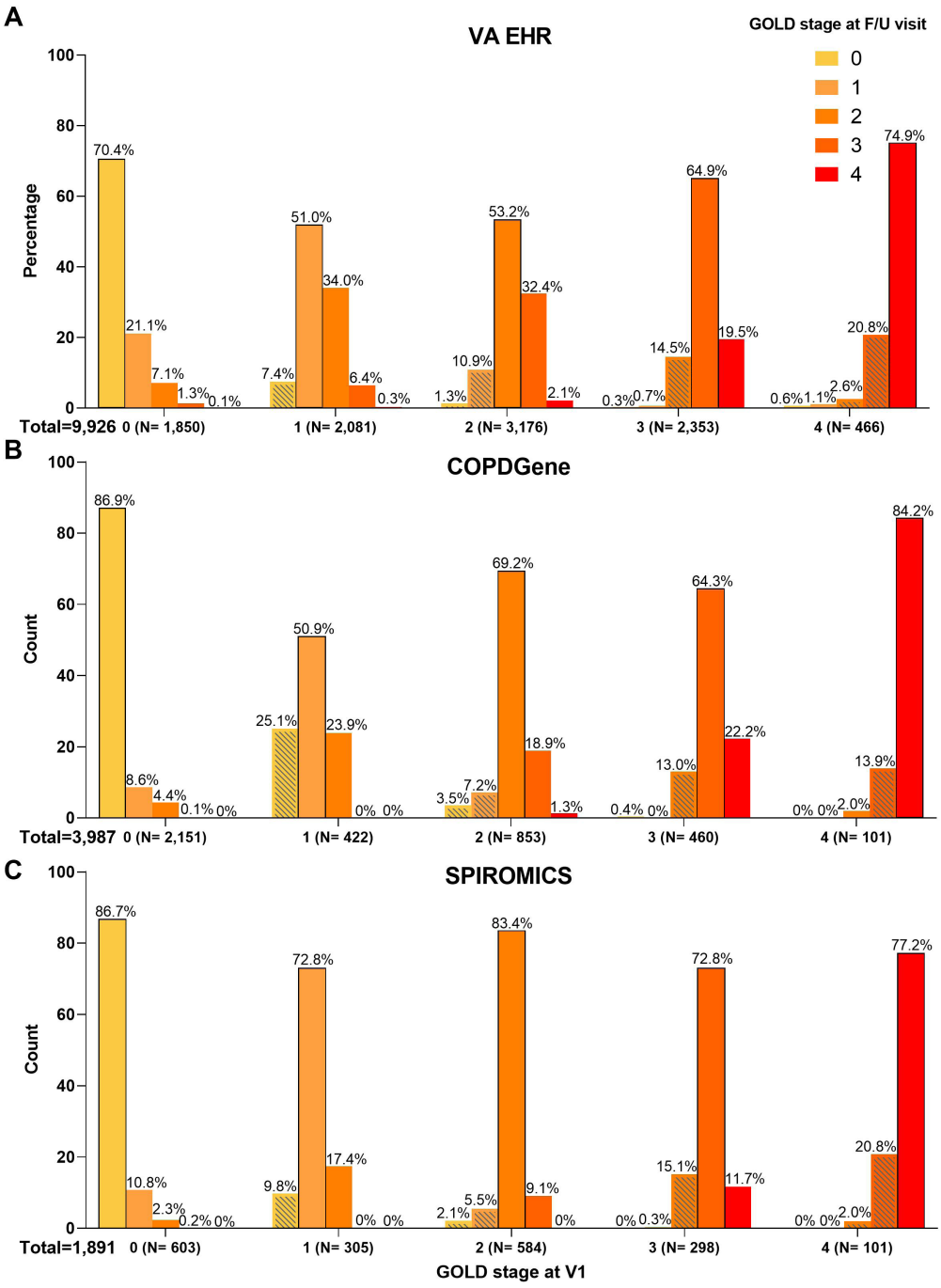
SPIROMICS= SubPopulations InteRmediate Outcome Measures In COPD Study; COPDGene=COPD Genetic Epidemiology; GOLD= Global initiative for chronic Obstructive Lung Disease; COPD=chronic obstructive pulmonary disease; VC=vital capacity; SVC=slow vital capacity; CT=computed tomography

High Baseline Total Lung Capacity, Vital Capacity, and Inspiratory Capacity Were Associated with Spirometric Progression to GOLD 1 Rather Than to GOLD 2 Disease

To better understand the nature of the nonlinear pattern of change in lung volumes with progression of spirometric disease in early COPD, we examined whether stratification by lung volumes could identify subgroups of GOLD 0 patients at baseline who have diverging disease progression. We found that among baseline GOLD 0 patients who progressed to spirometric COPD, those with higher lung volumes went on to develop mild obstruction (GOLD 1) while those with lower TLC and VC went on to develop moderate obstruction (GOLD 2).

In the VA EHR longitudinal analysis using ≥1-year follow-up data (median follow-up time of 3.1 years), those who progressed to GOLD 1 had higher TLC and VC (absolute and percentage predicted) values at baseline than those who

Figure 8. COPD GOLD Stage Status at Second Follow-up Visit Stratified by Starting GOLD Stage at the Baseline Visit

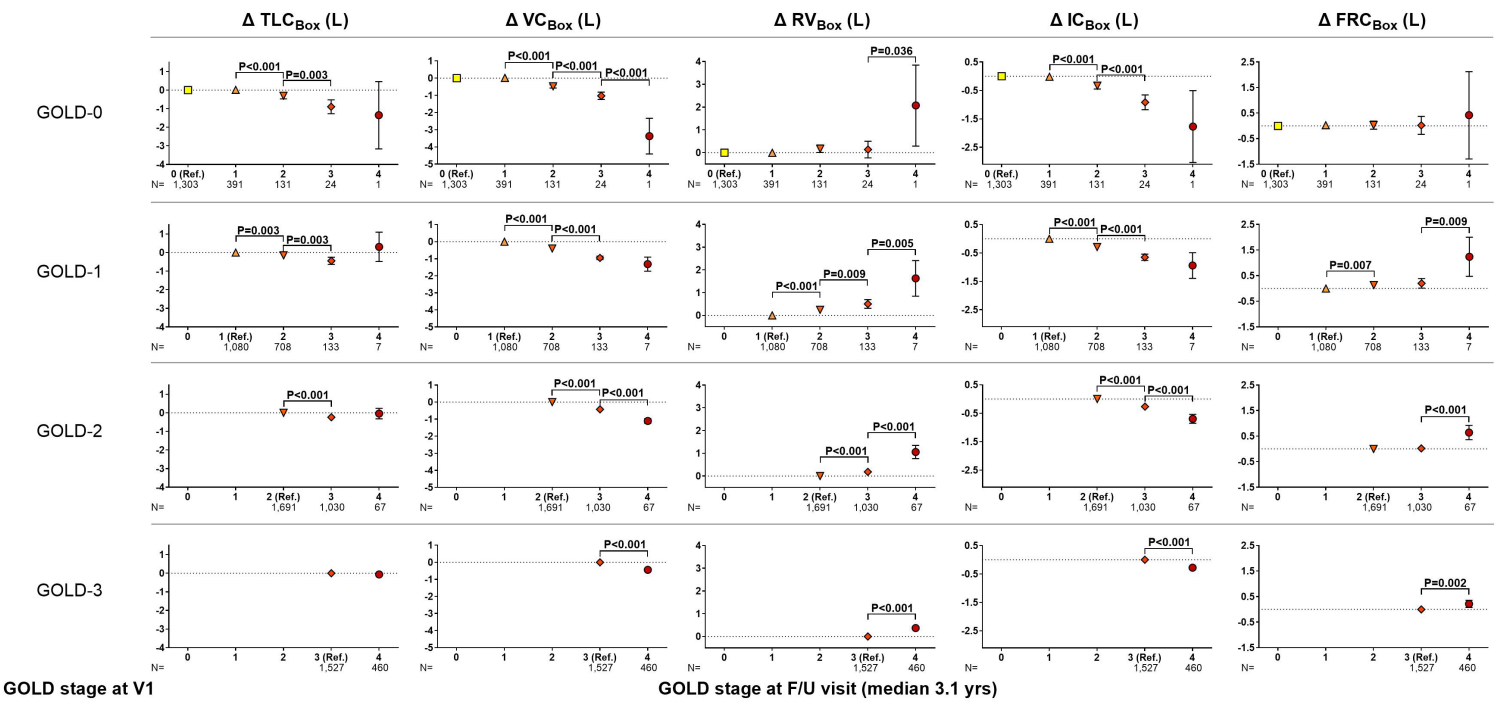


Bar plots show the distribution of the GOLD stage status for patients/participants at their follow-up (V2) stratified by their first visit (V1) GOLD stage status in the 3 cohorts of VA EHR (Panel A), COPDGene (Panel B), and SPIROMICS (Panel C). The x-axis shows the GOLD stage of the patients/participants in V1. The bar plots of different shades of orange show the GOLD stage distribution of those patients/participants during their V2. Most patients/participants maintained their V1 (baseline) GOLD category (bar plot outlined with a black line), but some showed spirometric progression of their disease to a more severe GOLD stage, while others showed improvement in their spirometry (bar plots with hatched lines), moving to a lower GOLD stage. The percentages show the number of patients/participants in each V2 GOLD stage category as a proportion of the V1 GOLD stage category. Patients/participants with PRISm at any visit were excluded and are not shown in this graph.

COPD=chronic obstructive pulmonary disease; GOLD= Global initiative for chronic Obstructive Lung Disease; VA EHR= Veterans Affairs electronic health record cohort; COPDGene=COPD Genetic Epidemiology; SPIROMICS= SubPopulations InteRmediate Outcome Measures In COPD Study; F/U= follow-up visit; V1=first visit; V2=second visit; PRISm=preserved ratio-impaired spirometry

remained at GOLD 0 or those who progressed to GOLD 2 (Table 2). In the COPDGene cohort analysis using 5-year follow-up data, those progressing to GOLD 1 had higher TLC and IC absolute values (CT-measured with no predicted values available) than those who remained at GOLD 0 or those who progressed to GOLD 2 (TLC comparison for GOLD 0 versus GOLD 2 was not statistically significant) (Table 2). In the SPIROMICS cohort analysis, those who progressed to GOLD 1 had higher TLC and VC absolute values (CT-measured with no predicted values available) than those

Figure 9. Longitudinal Changes in Total Lung Capacity, Vital Capacity, Residual Volume, Inspiratory Capacity, and Functional Residual Capacity with Disease Progression in COPD in the Veterans Affairs Electronic Health Record Cohort



Changes (Δ) in the TLC, VC, RV, IC, and FRC with disease progression in patients from different GOLD stages of COPD in the VA EHR cohort are represented using regression coefficient (ß or parameter estimate) and 95% confidence interval with adjustment for age, sex, height, and body mass index. Each row represents the changes in patients from one baseline GOLD category of COPD (e.g., changes for patients with baseline GOLD 0 in the first row and patients with baseline GOLD 1 in second row, etc.). Lung volumes and capacities in the VA EHR cohort were measured by plethysmography (Box) in seated position.

COPD=chronic obstructive pulmonary disease; Δ=changes; TLC=total lung capacity; VC=vital capacity; RV=residual volume; IC=inspiratory volume; FRC=functional residual capacity; GOLD= Global initiative for chronic Obstructive Lung Disease; V1=first visit; F/U=follow-up visit; VA EHR= Veterans Affairs electronic health record cohort

who remained at GOLD 0 or those who progressed to GOLD 2 (VC comparison for GOLD 0 versus GOLD 1 was not statistically significant) (Table 2).

Interestingly, in the VA EHR cohort, even in those who stayed in GOLD 0, there was a significant decline in TLC over time (the decline in VC was not significant in adjusted values) (Table 3). In those whose spirometric disease progressed to mild obstruction (GOLD 0 to GOLD 1), the decline was smaller although not statistically different. On the other hand, in those whose spirometric disease progressed to moderate obstruction (GOLD 0 to GOLD 2), there was a significantly larger decline in TLC, VC, and IC compared to both those who stayed in GOLD 0 and those who progressed to GOLD 1. In the COPDGene cohort, spirometric disease progression to moderate obstruction (GOLD 0 to GOLD 2) was also associated with a significant differential decline in TLC and IC (Table 3).

Discussion

In this analysis of cross-sectional and longitudinal data from 3 large cohorts of patients with a history of smoking or COPD, we found a nonlinear pattern of change in lung volumes across the spectrum of spirometric disease progression. This phenomenon has not been described previously and appears paradoxical to the conventional understanding of COPD pathophysiology. The distributions of lung volumes, regardless of whether they were measured by plethysmography or CT, were nearly identical in the 3 large cohorts of real-world patients and research participants. In particular, we found a biphasic pattern of distribution of TLC values across GOLD 0 to GOLD 4 stages of COPD: TLC showed a peak in GOLD 1, a trough in GOLD 2, and a subsequent peak in GOLD 4. In contrast, both RV and FRC had progressively larger values across all GOLD stages of COPD. These patterns resulted in the IC and VC values being the highest in patients with GOLD 1 disease compared to those with GOLD 0 or more advanced spirometric disease (GOLD 2 to GOLD 4). Longitudinal analysis of the lung volumes data corroborated these nonlinear patterns of distributions observed in the cross-sectional analysis.

To better understand the unanticipated finding of biphasic distributions of lung volumes with spirometric disease progression, we examined the changes in lung volumes in the population of GOLD 0 patients who progressed from GOLD 0 stage to GOLD 1 (mild) disease

Table 2. Comparison of Baseline Lung Volumes of Patients with GOLD 0 Stage at Baseline Progressing to Other Spirometric GOLD Stages at the Follow-Up Visit

		GOLD Stage at Follow-up Visit			*P*-values for Differences in Baseline Lung Volume		
Baseline Lung Volume		GOLD 0	GOLD 1	GOLD 2	GOLD 0 vs. GOLD 1	GOLD 0 vs. GOLD 2	GOLD 1 vs. GOLD 2
VA EHR							
TLC	L	6.34	6.84	6.58	<0.001	0.015	0.013
	% predicted	94%	99%	95%	<0.001	0.123	0.004
VC	L	4.00	4.15	3.94	0.001	0.287	0.001
	% predicted	93%	97%	90%	<0.001	<0.001	<0.001
IC	L	3.10	3.04	2.99	0.149	0.059	0.486
	% predicted	89%	85%	85%	<0.001	0.009	0.962
RV	L	2.34	2.69	2.63	<0.001	<0.001	0.522
	% predicted	101%	113%	112%	<0.001	<0.001	0.944
FRC	L	3.24	3.80	3.58	<0.001	<0.001	0.013
	% predicted	93%	107%	102%	<0.001	<0.001	0.015
COPDGene							
TLC	L	5.33	5.94	5.71	<0.001	0.007	0.174
IC	L	2.68	2.87	2.60	0.014	0.412	0.029
FRC	L	2.73	3.11	3.26	<0.001	<0.001	0.159
SPIROMICS							
TLC	L	4.52	4.92	4.33	0.014	0.430	0.042
VC	L	2.64	2.65	2.21	0.946	0.021	0.036
RV	L	1.89	2.28	2.12	<0.001	0.086	0.316

P-values represent the *P*-values for comparison of baseline lung volumes between patients progressing from GOLD 0 stage at baseline to different spirometric GOLD stages at follow-up visit using 2-sample *t*-test. Percentage predicted of normal values in the VA EHR were calculated using Stocks and Quanjer predicted formulas.[11] Percentage predicted of normal values for CT measures in the COPDGene and SPIROMICS were not available.

GOLD=Global initiative for chronic Obstructive Lung Disease; VA EHR=Veterans Affairs electronic health record cohort; TLC=total lung capacity; VC=vital capacity; IC=inspiratory capacity; RV=residual volume; FRC=functional residual capacity; COPDGene=COPD Genetic Epidemiology study; SPIROMICS=SubPopulation InteRmediate Outcome Measures In COPD Study

versus those who progressed from GOLD 0 stage to GOLD 2 (moderate) disease. We found that progression from GOLD 0 to GOLD 1 was associated with larger baseline lung volumes than progression from GOLD 0 to GOLD 2, i.e., high baseline TLC, IC, and VC values were predictive of future progression to GOLD 1, while lower baseline values were predictive of progression to more advanced spirometric disease (GOLD 2). Remarkably, those patients progressing to GOLD 2 not only had smaller lung volumes at baseline than those who progressed to GOLD 1 but also had their lung volumes relatively diminished. Overall, these findings imply the presence of an inhomogeneous population among the smokers with preserved spirometry (GOLD 0 stage) with diverging predispositions for spirometric disease development. Furthermore, these findings imply that stratification by lung volumes (TLC, VC, and IC) at GOLD 0 stage could help identify those susceptible to more rapid progression of their spirometric disease.

Our study does not provide any mechanistic explanation for the observed pattern of lung volume changes. It is also possible that different disease mechanisms might underlie the progression from GOLD 0 to GOLD 1 versus to GOLD 2 disease. Several pathological factors have been described to contribute to changes in lung volumes in COPD.[2,12-16] However, it is unclear whether these pathological factors begin to affect the lungs concurrently or sequentially, and whether they affect all at-risk populations in a similar manner. The biphasic pattern that we observed in this analysis suggests that different pathologies may develop or become important at different stages of the disease in different at-risk individuals. For example, the higher baseline TLC and VC in those progressing from GOLD 0 to GOLD 1 may be due to a disproportionately higher rate of loss of lung elastance in the setting of a relatively lower burden of small airway disease, resulting in lung expansion with lesser air trapping (an emphysematous phenotype). Conversely, the lower baseline and subsequent decline in TLC, VC, and IC values among those progressing to GOLD 2 may be due to a higher burden of small airway disease in the presence of a slower loss of lung elastance, resulting in more air trapping with relatively lesser thoracic expansion in the early stages of disease progression (a small airway phenotype). Disruption of connective tissue is also recognized as a potential mechanism.[17,18] However, lung connective tissue is organized into an extremely complex 3-dimensional network,[19,20] and it is reasonable to speculate that disruption of different portions of the network by similar mechanisms could have very disparate effects.[21] Further research with quantification of various pathologic mechanisms can lead to a better understanding of the nature and sequence of the

Table 3. Comparison of Changes in Lung Volumes of Patients with GOLD 0 Stage at Baseline Progressing to Other Spirometric GOLD Stages at the Follow-Up Visit

		GOLD Stage at Follow-up Visit			*P*-values for Differences in Baseline Lung Volume Change (Δ)		
Baseline Lung Volume		GOLD 0	GOLD 1	GOLD 2	GOLD 0 vs. GOLD 1	GOLD 0 vs. GOLD 2	GOLD 1 vs. GOLD 2
VA EHR							
Δ TLC	ml	-124[a]	-89	-427[a]	0.539	0.001	0.001
	% predicted	-1.54%[a]	-1.09%	-6.23%[a]	0.592	<0.001	<0.001
Δ VC	ml	-130[a]	-144[a]	-670[a]	0.646	<0.001	<0.001
	% predicted	-0.30%	-0.11%	-12.93%[a]	0.805	<0.001	<0.001
Δ IC	ml	-163[a]	-195[a]	-522[a]	0.386	<0.001	<0.001
	% predicted	-5.77%[a]	-6.91%[a]	-16.65%[a]	0.290	<0.001	<0.001
Δ RV	ml	5	55	243[a]	0.410	0.010	0.073
	% predicted	-3.22%[a]	-2.53%	4.94%	0.783	0.032	0.084
Δ FRC	ml	38	106[a]	95	0.232	0.528	0.916
	% predicted	0.44%	1.79%	1.42%	0.394	0.697	0.895
COPDGene							
Δ TLC	ml	-25	-56	-180[a]	0.475	0.022	0.113
Δ IC	ml	-79[a]	-129[a]	-364[a]	0.299	0.012	<0.001
Δ FRC	ml	32[a]	69[a]	146[a]	0.285	0.099	0.308
SPIROMICS							
Δ TLC	ml	-20	0.4	33	0.754	0.731	0.842
Δ VC	ml	-51	61	30	0.121	0.619	0.856
Δ RV	ml	33	-60	3	0.078	0.789	0.594

[a]Represents significant (*P*<0.001) changes (Δ) from baseline in each GOLD category using one-sample *t*-test.

The changes in lung volumes were calculated by subtracting baseline lung volume from lung volume at follow-up visit (lung volume at follow up - volume at baseline). *P*-values represent the *P*-values for comparison of changes (Δ) in lung volumes between patients progressing from GOLD 0 stage at baseline to different spirometric GOLD stage at follow-up visit using 2-sample *t*-test. Percentage predicted of normal values in the VA EHR were calculated using Stocks and Quanjer predicted formulas.[11] Percentage predicted of normal values for CT measures in the COPDGene and SPIROMICS were not available.

GOLD=Global initiative for chronic Obstructive Lung Disease; VA EHR=Veterans Affairs electronic health record cohort; TLC=total lung capacity; VC=vital capacity; IC=inspiratory capacity; RV=residual volume; FRC=functional residual capacity; COPDGene=COPD Genetic Epidemiology study; SPIROMICS=SubPopulation InteRmediate Outcome Measures In COPD Study

pathologies that contribute to the observed nonlinear lung volume changes with spirometric disease progression in COPD. By understanding these mechanisms, we may be able to better apply prognostic biomarkers and design targeted therapy for the different stages of COPD.

Our study has several limitations. First, the PFT data of the VA EHR cohort, which were obtained at different centers across the country over several decades using various PFT machines, were unlikely to have been fully harmonized; therefore, it may have been problematic to group them together. However, there is no clear reason to believe that any systematic or technical errors in the PFT measurements could have produced the consistent pattern of change in lung volume across GOLD stages we observed. Second, the smoking status of the patients in the VA EHR cohort was only characterized as "ever smoker" and their cumulative smoking burden was not certain, although it is known that most veterans begin smoking early in life and have a heavier smoking burden than the general public.[22,23] While these considerations may have a bearing on the generalizability of the findings from the VA EHR data, there is no clear reason for this bias to produce the pattern that we observed. Finally, the lung volumes measured in the 3 cohorts examined herein were obtained using different methods of plethysmography (in the seated position) and CT scanning (in the supine position); moreover, the CT scanning algorithms in COPDGene and SPIROMICS were not harmonized. In addition, neither the COPDGene nor the SPIROMICS CT scan protocols included spirometry gating; therefore, CT-measured lung volumes may have underestimated the TLC and/or overestimated the RV compared to the plethysmographic measurements in the VA EHR cohort. Despite these limitations, the remarkably similar patterns of lung volume distribution across the GOLD stages of COPD in 3 independent cohorts of real-world patients and research participants provide robust confirmation that the observed patterns were not simply the result of technical variability.

In conclusion, our cross-sectional and longitudinal analyses of data from 3 large cohorts showed a remarkably similar pattern of change in lung volumes as spirometric disease progressed in COPD, regardless of whether the lung volumes were measured by plethysmography or CT. The TLC, VC, and IC values showed nonlinear patterns of change as the disease progressed. While the underlying pathology of these nonlinear patterns of change remain to be investigated, the observed patterns highlight the heterogeneity of disease development in COPD and suggest the contribution of

distinct pathophysiologic mechanisms at different stages of the disease in different individuals. Moreover, baseline lung volumes seem to predict the risk of more rapid spirometric disease progression in COPD, making a case for more routine incorporation of lung volume measurement in assessment of tobacco-exposed persons at risk for COPD in early disease. Further research on these mechanisms could help in understanding the heterogeneity of disease in COPD and with identification of appropriate biomarkers and design of therapies targeting its specific phenotypes.

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Data Sharing Statements: The VA EHR dataset generated and analyzed during the current study was created through the VA Informatics and Computing Infrastructure (VINCI) resource and is available on VINCI digital platform to the VA, VA-affiliated, and VA-approved investigators. Availability of the VA data is subject to the U.S. Department of Veterans Affairs regulations. Clinical and research data along with the definition of variables are available on NIH dbGaP for COPDGene (phs000179.v6.p2) and SPIROMICS (phs001119.v1.p1).

Declaration of Interest

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