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Significance of Medication History at the Time of Entry into the COPDGene Study: Relationship with Exacerbation and CT Metrics

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Abstract

Background—Despite the importance of respiratory medication use in COPD, relatively little is known about which clinical phenotypes were associated with respiratory medications.

Methods—To determine the association between respiratory medication use and exacerbations or quantitative CT metrics, we analyzed medication history from 4,484 COPD subjects enrolled in the COPDGene Study.

Results—2,941 (65.6%) subjects were receiving one or more respiratory medications; this group experienced more frequent exacerbations in the year before study entry and had increased gas trapping, emphysema, and subsegmental airway wall area, compared to the patients who were on no respiratory medication. In subgroup analysis, subjects who were on triple therapy (long-acting beta2-agonist [LABA], long-acting muscarinic antagonist [LAMA], and inhaled corticosteroids [ICS]) had the highest frequencies of exacerbations and severe exacerbations and tended to have increased quantitative measures of emphysema and gas trapping on CT compared to other five groups. After adjustment for confounding variables, the triple therapy group experienced more exacerbations and severe exacerbations compared with other five groups. In addition, the LABA +LAMA+ICS group was more likely to have emphysema and gas trapping on CT than other groups in multivariable logistic analysis. Interestingly, the total number of respiratory medications was significantly associated with not only the frequency of exacerbations but also gas trapping and airway wall thickness as assessed by CT scan in multivariable analysis.

Conclusions—These results suggest that the use of respiratory medications, especially the number of medications, may identify a more severe phenotype of COPD that is highly susceptible to COPD exacerbations.

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Declaration of Interest Statement

The authors report no conflicts of interest. The authors are responsible for the content and writing of this paper.

Keywords

CT metrics; exacerbation; medication; triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of global morbidity and mortality, resulting in substantial economic and social burdens. COPD patients are treated with respiratory medications to reduce symptoms, decrease the frequency of exacerbations, and improve health status (1). A number of national and international guidelines for pharmacologic therapy of COPD recommend treatment with inhaled long-acting BDs (LABD) including long-acting beta-agonists (LABA) and long-acting muscarinic antagonist (LAMA) (1, 2). Combination inhaled medications (LABA, LAMA, and inhaled corticosteroid [ICS]) can be administered for symptomatic patients with severe airway obstruction. Despite the publication of these guidelines, significant care gaps have been reported in management of COPD (3), and little is known about the way that the respiratory medications are utilized in actual clinical practice. A Canadian study has shown that short-acting BDs (SABDs), most commonly salbutamol, are prescribed in the patients with COPD across the disease severity spectrum (4).

A previous study from Cincinnati also found that short-acting $beta_2$-agonist (SABA) was prescribed for 66% and short-acting muscarinic antagonist (SAMA) for 35% of COPD patients (5). Another study of a cohort of 133,737 patients with newly diagnosed COPD between 1999 and 2003 reported that the majority (80.0%) used a SABA, followed by 40.0% using SAMA, 33.2% using an ICS, and 16.0% using a LABA (6). In addition, multiple medications were commonly used, with 29% of patients taking 3 to 4 medication classes (6). Although many patients are treated with multiple medication classes, there are little data describing the clinical features of these subjects in real life scenarios in which medications are prescribed at the discretion of clinicians.

CT is an established technique for the detailed evaluation of various lung diseases. Quantitative CT in COPD provides information about the presence and extent of lung pathologic changes such as emphysema, airway disease, and air trapping (7). CT-based quantitative analyses can be used to classify COPD phenotypes (8). However, information about the relationship between these CT parameters and medication history is particularly limited.

To determine the pattern of pharmacologic therapy of COPD in actual clinical practice, we firstly evaluated the class and number of respiratory medications used to treat the disease in a cohort of former and current smokers with COPD that were enrolled in the COPD-Gene study. We compared the exacerbation frequency and CT parameters among patient groups divided by the category of respiratory medications with the goal of assessing the relationship between pharmacologic history and clinical or radiologic phenotype in COPD. In addition, we evaluated whether total number of respiratory medications used would be related with the frequency of exacerbations and CT metrics.

Methods

Study population

COPDGene is a multi-center study to examine the genetic epidemiology of smoking-related lung disease (9). The study enrolled 10,300 non-Hispanic whites or African-American individuals aged 45–80 years with a 10 or greater pack-year history of cigarette smoking from 21 clinical centers in the United States. Subjects were studied after obtaining informed consent under the research protocols approved by the institutional review board at each participating center. Participants underwent spirometry before and after the administration of SABA, 6-minute-walk test (6MWT), and chest CT scan and completed questionnaires collecting their medical histories and symptoms. 4,484 of 10,300 subjects met Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria for stage 1 or higher fixed airflow obstruction with a post-BD forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio lower than 0.7 (1).

Determination of medication group and measurements

Demographic data and medical and medication histories were collected via standardized questionnaires. A list of each patient's respiratory medications for treatment of breathing problems was obtained. Medication use in the following categories was recorded as being present or absent: SABA, SAMA, combination inhaler composed of SABA and SAMA, LABA, LAMA, ICS, combination inhaler composed of ICS and LABA, theophylline, and oral CS. Total number of respiratory medications was determined by adding those that the patients answered that they used among nine classes of medications. We divided the patients treated with one or more medications into six classes: (1) SABD alone (SABA or SAMA only); (2) LABD alone (LABA or LAMA only); (3) SABD+LABD (both SABD and LABD); (4) SABD+ICS (both SABD and ICS); (5) LABD+ICS (the patients treated with LABA and ICS or LAMA and ICS excluding the subjects who were on LABA, LAMA, and ICS); (6) LABA+LAMA+ICS (triple therapy).

GOLD severity was graded from 1 to 4 on the basis of FEV_1 data (1). Patients were classified into group A, B, C, and D according to the GOLD 2011 report which proposed a more complex multidimensional classification system with some modifications based on FEV_1, exacerbation history, and symptom scores using modified Medical Research Council (mMRC) dyspnea scale and St George's Respiratory Questionnaire (SGRQ) as previously described (10).

Exacerbations of COPD were defined by use of antibiotics or steroids and admission to the emergency room or hospital for respiratory flare-up (11). Severe exacerbations were defined as respiratory exacerbations were determined as exacerbations that resulted in presentation to the emergency room or hospital. Exacerbations of COPD during the year before study entry were self-reported and data were gathered at baseline.

Quantitative CT analysis

For participants in the COPDGene trial, analysis of the lung parenchyma and airways was performed on whole lung volumetric multi-detector CT scans of the chest obtained without

the administration of contrast material as previously described (9). Quantitative analysis of lung density was performed with the use of the Slicer software package (www.Slicer.org). Emphysema was defined by a lung attenuation value of less than −950 Hounsfield units on inspiratory scans and gas trapping was defined by that of less than −856 Hounsfield units on expiratory scans. Automated airway analysis including airway wall thickness and wall percentage area was performed with the use of Volumetric Information Display and Analysis (VIDA) Pulmonary Workstation 2 software (www.vida-diagnostics.com) as previously described (8, 9).

Statistical analysis

A chi-square test for categorical variables (e.g., sex, GOLD severity, GOLD group, presence of exacerbation) and a Mann-Whitney test for continuous variables (e.g., age, body mass index [BMI], FEV_1, number of exacerbations) to evaluate differences between the different groups. For statistical comparisons among multiple groups, Kruskal–Wallis analysis was carried out with Tukey post-hoc tests on rank-transformed data. A negative binomial regression model, adjusted for age, sex, pack years, BMI, and FEV_1 was used to model exacerbation frequency, given its skewed distribution. Multivariable logistic regression was applied to determine the association between the category of respiratory medication and the presence of emphysema or gas trapping on CT, adjusted for age, sex, pack-years, BMI, FEV_1, and type of CT scanner used. Correlations between number of respiratory medications and exacerbation frequency or CT metrics were determined using parametric testing methods with Pearson correlation coeffcients. Statistical analyses were conducted using SPSS software, version 19.0 and *p*-values of less than 0.05 were considered to indicate statistical significance.

Results

Subject characteristics

Of the 4,484 subjects with COPD analyzed, 2,941 (65.6%) received one or more respiratory medications at the time of entry into the COPDGene study. Univariate comparisons between the subjects without the use of respiratory medication and those taking one or more respiratory medications are summarized in Table 1. Compared to the patients who were on no respiratory medication, the medication group was older (63.8 ± 8.5 vs 61.7 ± 8.5 years, $p < 0.001$) and had fewer percentages of men (53.2 vs 61.2 %, $p < 0.001$) and current smokers (35.2 vs 58.8 %, $p < 0.001$) and a greater pack-year smoking history (53.7 ± 28.1 vs 47.6 ± 24.4 years, $p < 0.001$).

In addition, the patients treated with one or more respiratory medications had higher BMI, worse lung function (FEV_1 and FEV_1/FVC values), shorter 6MWT distance, and greater mMRC dyspnea score, SGRQ, and BODE (BMI, airflow obstruction, dyspnea, exercise capacity) index scores. The medication group had significantly higher proportions of patients with exacerbations and severe exacerbations in the 12 months preceding enrollment than did the group of no medication (56.2 vs 13.5 %, $p < 0.001$ and 27.6 vs 2.6 %, $p < 0.001$). In the patients with respiratory medication use, there were more frequent acute exacerbations and severe exacerbations in the year before study entry (2.51 ± 3.97 vs 0.27 ±

1.05, $p < 0.001$ and 0.56 ± 1.38 vs 0.04 ± 0.32, $p < 0.001$). Compared to the group with no medication, subjects on respiratory medications exhibited increased gas trapping, emphysema, subsegmental airway wall area, and 10 mm luminal perimeter (Pi10).

Respiratory medication used

We evaluated the class and total number of respiratory medications used. Regardless of whether the patients treated with single or multiple medications, the class of respiratory drug used most frequently was a SABA followed by a combination of ICS and LABA, a LAMA, a combination of SABA and SAMA, a ICS, a SAMA, a LABA, an oral CS, and a theophylline (Table S1). The observed trend in order of commonly used drug class was consistent in four groups categorized according to the severity of COPD. As the severity of COPD increased, the percentages of patients with the use of each medication were greater in all classes of medications. The most common number of respiratory medication classes used was three for all subjects, one for patients with mild COPD, and two for those with moderate disease (Table S2). The number of patients with no respiratory medication was reduced as the severity was increased, and those in the group with very severe COPD were just 1.7%.

Characteristics, exacerbations, and CT parameters by the category of respiratory medications

Out of the 2,941 patients received one or more respiratory medications, 2,923 patients were divided into six classes such as SABD, LABD, SABD+LABD, SABD+ICS, LABD+ICS, LABA+LAMA+ICS groups, after subjects taking ICS (13 patients), oral corticosteroids (3 patients), and theophylline (2 patients) as a single medication were excluded. A comparison of demographics, exacerbation frequency, and CT measurements according to the category of respiratory medications is shown in Table 2. Of the subjects divided into six medication classes, 2,707 (92.6%) underwent chest CT scan. Interestingly, the subjects who were on triple therapy with LABA, LAMA, and ICS (n = 1,056) were more than those receiving only BDs (n = 944) or those with the combination therapy of BDs and ICS (n = 923). The SABD group was significantly younger than other five groups. The LABA+LAMA+ICS group had poorer lung function (FEV_1 and FEV_1/FVC values) and greater BODE index scores as compared with other five groups. In the 12 months preceding enrollment, both frequencies of total exacerbation and severe exacerbation were highest in the LABA+LAMA+ICS group (3.39 ± 4.63 and 0.85 ± 1.76). For radiologic measurements, the SABD group showed the significant decrease in emphysema on chest CT than other five groups. In addition, the LABA+LAMA+ICS patients tended to have increased quantitative measures of emphysema and gas trapping. However, the subsegmental wall area percentage and Pi10 showed no significant differences in any group as compared with other five groups.

Using negative binomial regression model, the LABA+LAMA+ICS group experienced significantly more exacerbations and severe exacerbations compared with other five groups. The odds ratio (OR) of exacerbation for the triple therapy group was 2.08 (95% confidence interval [CI] 1.82–2.38) and that of severe exacerbation was 1.91 (95% CI 1.57–2.33) as compared with the SABD group (Table 3).

To better understand the relationship between pharmacologic history and quantitative measures of emphysema or gas trapping, multivariable logistic analysis was performed. In the 4,843 subjects without COPD (normal control), the 90th percentile values for emphysema and gas trapping were 4.7% and 23.1%, respectively. Individuals with CT measurements exceeding these values were regarded as meeting CT criteria for the presence of emphysema and gas trapping (12). Table 4 showed that the LABA + LAMA + ICS group had the highest OR for the presence of emphysema or gas trapping in multivariable logistic analysis controlling for age, sex, BMI, FEV_1, and type of CT scanner used.

Correlation between number of respiratory medications and other parameters

In COPDGene study, total number of respiratory medications significantly correlated with the frequencies of exacerbations and severe exacerbations for the year prior to enrollment and the extents of gas trapping and Pi10 assessed by chest CT in COPD subjects (Table 5).

Discussion

To our knowledge, this is the first large real-life study, which examines in detail the association between respiratory medication use and clinical phenotypes in COPD patients. We found that the number of respiratory medications positively correlated with worse clinical outcomes (e.g., exacerbations) and more severe CT phenotypes. Those on triple therapy had the highest frequency of exacerbations and burden of CT disease in subgroup analysis. These results have suggested that the number of respiratory medications can provide useful clinical information and may be a marker of severe disease in COPD.

In COPDGene study, 34.4% of COPD patients were not treated with any respiratory medication. As only 59.1% subjects among COPD patients answered that they were diagnosed with COPD by doctor or other health professional at the time of entry, this lack of treatment may be caused by underdiagnosis of COPD, suggesting a need for greater screening in high risk individuals. Pharmacologic therapy is one of most crucial parts for COPD (13), and thus it is important to understand the practical patterns of taking respiratory medications for patients with COPD. COPD patients received one or more respiratory medications had worse lung function and experienced more frequent acute exacerbations and severe exacerbations in the year before study entry as compared to the patients who were on no respiratory medication. SABA was most frequently used to control breathing problems, consistent with previous findings (4-6, 14).

Unlike previous studies (5, 6), the second most commonly used medication was the combination inhaler of LABA and ICS, followed by LAMA, reflecting a change in prescribed medications by clinicians. In the current study, 13% of all COPD patients used single respiratory medication. The most common number of respiratory medication classes was three for COPD patients, supporting that a lot of COPD patients are treated with multiple respiratory medications (6).

We attempted to reduce the complexity of respiratory medication use by dividing the cohort into 6 groups. Among these groups, there were more subjects who were on triple therapy with LABA, LAMA, and ICS than those receiving only BDs or those with the combination

therapy of BDs and ICS. Unfortunately, studies comparing the effect of adding LABA+ICS and LAMA to LABA+ICS or LAMA alone for patients with COPD are limited (15-20). A recent 12-week study demonstrated that adding LABA/ICS (budesonide/ formoterol) to tiotropium improved lung function, health status, and symptoms and reduced severe exacerbations (15).

However, a different study found that addition of fluticasone/salmeterol to tiotropium did not statistically influence rates of COPD exacerbation (16). Though the beneficial effect on lung function has been consistently reported with triple therapy compared with LABD (15–18), data on exacerbation reduction have varied (15, 16, 19). There is little published data on superior efficacy of the triple therapy over LABD+ICS (17, 18, 20). A retrospective analysis revealed that the triple therapy was associated with 40% reduced risk of death compared with LABA+ICS with reduction of exacerbations and hospitalizations (20). It is an intriguing finding that the individuals with triple therapy are over one-third of COPD patients with medication use in medical practice, although the clinical benefit of triple therapy has not been definitively confirmed.

Exacerbation frequency is associated with older age, lower BMI, lower FEV_1% predicted, and history of prior exacerbations and co-morbidities (21). There are little data about the comparative risk of exacerbations depending on the class of respiratory medications in patients with COPD. In the present study, we investigated the association between the medical history taking various categories of medications commonly used and acute exacerbations in patients with COPD. We found that both frequencies of exacerbation and severe exacerbation in the 12 months preceding enrollment were highest in the LABA +LAMA+ICS group in univariate analysis. After adjustment for confounding variables, the subjects who were on triple therapy had statistically higher rates of exacerbations and severe exacerbations as compared to those on other respiratory medication classes. These results suggest that the medication history taking the triple therapy may be a marker of disease severity in medication aspect of COPD.

An important and novel finding in this study is the association between respiratory medication use and CT measurements, especially a history of triple therapy and emphysema. A previous study has demonstrated that radiologic indices of airway disease are closely associated with higher SGRQ and emphysema is associated with BODE (22). Quantitative measures of lung structural changes such as emphysema and airway wall thickness are also related to COPD exacerbations, independent of the severity of airway obstruction (8). We found that the subjects on any respiratory medication had higher gas trapping, emphysema, subsegmental airway wall area, and Pi10 than did subjects using no respiratory medication. In subgroup analysis, those on LABA+LAMA+ICS (triple therapy) were more likely to have emphysema than others. Additionally, subjects who used more respiratory medications had higher gas trapping and airway wall thickening (Pi10). These results suggest that the use of multiple respiratory medications could be used to identify subjects with more severe disease on CT.

The number of respiratory medications has been ignored in many studies, although it is one of most essential parts in the management of COPD patients. Previously, Yu and colleagues

have shown that COPD patients using multiple long-acting inhalers experience significantly more exacerbations than those using a single long-acting inhaler (23). In this study, we found that the number of respiratory medications was significantly associated with the frequency of exacerbations or severe exacerbations. The relationship of medication number with frequent exacerbations is likely explained by prescription patterns or poor adherence (23, 24). For instance, multiple inhaler users have a significantly higher discontinuation rate than single inhaler users (24). Furthermore, COPD patients with more severe disease may continue to suffer acute exacerbations despite aggressive medication therapy (25). The multiple respiratory medication use may be a marker of more severe disease. Our results suggest that the number of respiratory medications can help identify those patients who experience frequent acute exacerbations and severe exacerbations of COPD as well as more severe disease on CT.

A potential limitation of our study for data on acute exacerbations and severe exacerbations in the 12 months preceding enrollment is recall bias. Other limitations include how exacerbations of COPD were defined. We defined the frequency of acute exacerbations of COPD during the year before study entry by calculating the sum of episodes of emergency room visit, hospitalization, and treatment with antibiotics or systemic glucocorticoids for lung problems. This method may differ from other studies that report exacerbations divided by the type of treatment (8) and can lead to inflation of exacerbation number. Finally, this is observational study, and we were not able to assess prescribing patterns of physicians nor are there longitudinal data on medication use available to determine if subjects who did experience exacerbations during the study were more likely to be prescribed triple therapy.

Conclusion

We used a large well-characterized cohort of current and prior smokers with COPD to show that the number of respiratory medications is associated with increased frequency of exacerbations as well as gas trapping and airway wall thickness on CT scan. These findings suggest that the number of respiratory medications could be used as an inexpensive screen to identify individuals at high risk for exacerbations or who might high disease burden on quantitative CT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Subject characteristics

Characteristic	No respiratory medication (n = 1,543)	One or more respiratory medications (n = 2,941)	*p*-value
Age (years)	61.7 ± 8.8	63.8 ± 8.5	<0.001
Male sex (%)	61.2	53.2	<0.001
Current smoker (%)	58.8	35.2	<0.001
Smoking history (pack-years)	47.6 ± 24.4	53.7 ± 28.1	<0.001
BMI (kg/m^2)	27.5 ± 5.3	28.1 ± 6.5	0.026
FEV_1 after BD use (% of predicted value)	74.5 ± 17.2	48.5 ± 20.1	<0.001
GOLD severity (%)			<0.001
1	38.8	6.7	
2	52.2	38.0	
3	8.4	35.1	
4	0.6	20.3	
GOLD group (%)			<0.001
A	66.1	10.1	
B	22.9	25.7	
C	4.6	5.1	
D	6.4	59.1	
FEV1/FVC (%)	61.3 ± 8.0	47.5 ± 13.2	<0.001
6 MWT (ft)	1452 ± 347	1115 ± 389	<0.001
mMRC dyspnea score	0.8 ± 1.2	2.5 ± 1.3	<0.001
SGRQ score	18.8 ± 17.2	46.4 ± 19.6	<0.001
BODE index	0.9 ± 1.2	3.4 ± 2.0	<0.001
Exacerbation in the year before enrollment			
Patient with exacerbation (%)	13.5	56.2	<0.001
Exacerbation per patient	0.27 ± 1.05	2.51 ± 3.97	<0.001
Patient with severe exacerbation (%)	2.6	27.6	<0.001
Severe exacerbation per patient	0.04 ± 0.32	0.56 ± 1.38	<0.001
CT measurements			
% Emphysema	5.5 ± 6.3	14.9 ± 13.3	<0.001
% Gas trapping	23.6 ± 15.0	42.4 ± 20.6	<0.001
Subsegmental wall area (%)	64.2 ± 2.5	65.8 ± 2.4	<0.001
Pi10	3.7 ± 0.1	3.7 ± 0.1	<0.001

Data are presented as mean ± SD or %.

BD, bronchodilator; BMI, body mass index; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; Pi10, 10 mm luminal perimeter; SGRQ, St George's Respiratory Questionnaire; 6MWT, 6-minute-walk test.

Table 2

Characteristics, exacerbation frequency, radiologic measurements by the category of respiratory medications

	SABD	LABD	SABD+LABD	SABD+ICS	LABD+ICS1	LABA + LAMA + ICS	*p*-value
			Characteristics				
Number	527	92	325	126	797	1,056	
Age (years)	61.2 ± 9.0*	67.7 ± 7.4	65.3 ± 8.4	63.8 ± 9.1	64.0 ± 8.6	64.1 ± 7.8	<0.001
Male sex (%)	58.6	53.3	55.4	48.4	50.2	52.8	
Smoking history (pack-years)	51.3 ± 28.4	55.5 ± 25.0	56.6 ± 29.0	59.1 ± 40.6	52.5 ± 27.7	54.1 ± 27.1	<0.001
BMI (kg/m^2)	28.4 ± 6.8	29.4 ± 6.0	27.1 ± 5.9	26.8 ± 6.0	28.6 ± 6.6	28.0 ± 6.5	<0.001
FEV_1 after BD use (% of predicted value)	57.0 ± 20.0	57.5 ± 19.4	49.0 ± 19.1	53.4 ± 23.6	50.9 ± 20.0	40.7 ± 21.6*	<0.001
FEV_1/FVC (%)	53.4 ± 12.0	51.8 ± 10.8	46.7 ± 13.7	48.6 ± 13.7	49.5 ± 13.0	42.6 ± 12.5*	<0.001
BODE index	2.6 ± 1.9	2.1 ± 1.8	3.2 ± 1.8	3.2 ± 2.1	3.1 ± 2.0	4.1 ± 1.8*	<0.001
Number of medications	1.3 ± 0.6	1.2 ± 0.4	2.5 ± 0.8	2.6 ± 0.8	2.6 ± 1.1	3.5 ± 1.1*	<0.001
			Exacerbations				
Exacerbation per patient	1.49 ± 2.79	0.98 ± 2.10	1.62 ± 2.65	2.35 ± 4.04	2.59 ± 4.01	3.39 ± 4.63*	<0.001
Severe exacerbation per patient	0.39 ± 1.00	0.16 ± 0.45	0.29 ± 0.72	0.44 ± 1.04	0.59 ± 1.32	0.75 ± 1.76*	<0.001
			CT measurements				
% Emphysema	8.7 ± 10.2*	13.2 ± 11.0	15.7 ± 12.6	12.3 ± 11.7	13.0 ± 12.1	19.7 ± 14.3*	<0.001
% Gas trapping	33.0 ± 20.2	40.3 ± 16.7	43.5 ± 19.1	39.4 ± 20.0	40.5 ± 20.3	48.8 ± 19.6*	<0.001
Subsegmental wall area (%)	66.0 ± 2.5	64.8 ± 2.4	65.6 ± 2.4	66.2 ± 2.3	66.1 ± 2.5	65.6 ± 2.2	0.002
Pi10	3.7 ± 0.2	3.7 ± 0.1	3.7 ± 0.1	3.7 ± 0.2	3.7 ± 0.1	3.7 ± 0.1	0.001

For statistical comparisons among multiple groups, Kruskal–Wallis analysis was carried out with Tukey post-hoc tests on rank-transformed data.

BD, bronchodilator; BMI, body mass index; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; Pi10, 10 mm luminal perimeter; SABD, short-acting bronchodilator.

* $p < 0.05$ versus the other 5 groups.

Table 3

Adjusted ORs of exacerbations by the category of respiratory medications

	Exacerbation			Severe exacerbation		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
SABD	1.00			1.00		
LABD	0.79	0.57–1.08	0.144	0.59	0.33–1.05	0.073
SABD+LABD	1.13	0.94–1.36	0.183	0.83	0.63–1.11	0.218
SABD+ICS	1.60	1.23–2.04	<0.001	1.16	0.80–1.66	0.440
LABD+ICS	1.74	1.51–2.00	<0.001	1.57	1.28–1.93	<0.001
LABA+LAMA+ICS	2.08	1.82–2.38	<0.001	1.91	1.57–2.33	<0.001

Analyses were controlled for age, sex, pack-years, BMI, and FEV_1.

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; OR, odds ratio; SABD, short-acting bronchodilator.

Table 4

Respiratory medication category associated with emphysema and gas trapping on CT

	Emphysema			Gas trapping		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
SABD	1.00			1.00		
LABD	2.50	1.36–1.61	0.003	2.26	1.09–4.70	0.029
SABD+LABD	2.37	1.62–3.47	<0.001	1.84	1.17–2.89	0.009
SABD+ICS	1.43	0.86–2.37	0.167	2.60	1.41–4.79	0.002
LABD+ICS	1.86	1.39–2.48	<0.001	1.94	1.38–2.72	<0.001
LABA+LAMA+ICS	3.46	2.56–1.66	<0.001	2.28	1.61–3.23	<0.001

Logistic regression analyses were controlled for age, sex, pack years, BMI, FEV_1, and type of CT scanner used.

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; OR, odds ratio; SABD, short-acting bronchodilator.

Table 5

Correlation between number of respiratory medications and other parameters

	Unadjusted		Adjusted*	
	Coefficient	***p*-value**	**Coefficient**	***p*-value**
Exacerbations per patient	0.426	<0.001	0.236	<0.001
Severe exacerbations per patient	0.287	<0.001	0.161	<0.001
Emphysema percentage	0.426	<0.001	0.036	0.183
Gas trapping percentage	0.471	<0.001	0.054	0.046
Subsegmental wall area (%)	0.258	<0.001	0.034	0.205
Pi10	0.250	<0.001	0.079	0.003

Pearson correlation coefficients were used to evaluate the correlation between number of respiratory medications and numbers of exacerbations or CT metrics.

Pi10, 10 mm luminal perimeter.

*Adjusted for age, sex, pack-years, BMI, FEV1, and medication class.