Comparison of clinical characteristics between mild chronic bronchitis and severe chronic bronchitis in patients with chronic obstructive pulmonary disease

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Research

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Abstract

Background

Chronic bronchitis (CB) is associated with poor outcomes in patients with chronic obstructive pulmonary disease. The aim of this study was to identify the characteristics that distinguish chronic bronchitis (CB) from non-CB. In addition, the features of mild CB vs. severe CB were compared and a cut-off level was defined according to CAT1 and CAT2 scores.

Methods

This study was based on the Korea COPD Subgroup Study (KOCOSS) database, constructed in a multicenter COPD cohort study that recruited patients from 54 centers. CB was defined as CAT1 and CAT2 scores ≥3; severe CB was defined as CAT1 and CAT2 scores ≥4, while mild CB was defined as either a CAT1 or a CAT2 score < 4. Baseline characteristics, 1-year exacerbation rate, and 3-year FEV_1 decline were compared in non-CB vs. CB patients and in patients with mild CB vs. severe CB.

Results

Among the 2,162 patients enrolled in this study, 497 (23%) had CB. These patients were more likely than non-CB patients to be current smokers; they also had higher symptom and depression/anxiety scores. Lung function tests showed lower FEV_1, FEV_1/FVC, and DLco values in CB patients. Among CB patients, 67.6% had mild disease. Symptom and depression/anxiety scores were worse in patients with severe CB than in patients with mild CB. There were no significant differences in the lung function tests of the two groups. Analysis of 1-year exacerbation rates in CB patients and non-CB patients revealed that patients with CB more frequently had moderate-to-severe exacerbations (OR = 1.46, $p < 0.01$). More severe exacerbation was also present in patients with severe CB than in patients with mild CB (OR = 2.52, $p = 0.01$). The difference in annual FEV_1 decline rate did not significantly differ either between CB patients and non-CB patients or between patients with severe CB and patients with mild CB.

Conclusions

CB patients had worse symptoms and lung function than non-CB patients; CB patients also had more frequent moderate-to-severe exacerbation. Patients with severe CB had higher symptom scores and more frequent severe exacerbation than did patients with mild CB.

Background

Chronic obstructive pulmonary disease (COPD) causes substantial morbidity and mortality worldwide, although it is a preventable and treatable disease [1]. Awareness of COPD heterogeneity is necessary for patient-tailored treatment [2, 3]. There have been wide accepted phenotypes including chronic bronchitis (CB), emphysema, asthma-COPD overlap (ACO), frequent/rare exacerbator and rapid decliner [4]. Of the known phenotypes, CB is the most well-understood. It is associated with typical symptoms, poor health-related quality of life, reduced lung function, frequent exacerbation, and high mortality [5, 6]. Furthermore, the economic burden of CB is substantial [7–9].

Patients with CB frequently have chronic cough and sputum [10], but the diverse disease definitions complicate outcome assessments [11–14]. In 1978, the American Thoracic Society defined CB based on the presence of frequent cough and sputum production for 3 months per year over 2 consecutive years; however, there were some limitations using in both clinical and research field [15, 16]. A recent approach to the assessment of CB is the use of sub-questionnaires from the COPD Assessment Test (CAT) [15, 17]. In the eight sub-questionnaires, the scores range from 0 to 5 points [18–20]. CAT1 and CAT2 evaluate the severities of cough and sputum, respectively; the combination of their scores is a valid approach to CB diagnosis. The CAT score also allows symptoms to be ranked based on a score of 0–5. By defining different CB cut-off levels, disease stratification according to severity may be possible, but this has not yet been attempted.

The aim of this study was to identify the characteristics that distinguish CB from non-CB within a group of COPD patients, based on baseline characteristics, symptoms, exercise capacity, lung function, and exacerbation rates. In addition, distinct CAT1 and CAT2 cut-off scores were used to stratify patients with mild CB vs. severe CB. Forced expiratory volume in 1 second (FEV1) trajectories during a 3-year follow-up period were compared among non-CB, mild CB, and severe CB patients.

Methods

Study population and data collection

This study was based on the Korea COPD Subgroup Study (KOCOSS) database, constructed from a nationwide prospective cohort study—initiated in April 2012—that involved 54 medical centers in South Korea. The inclusion criteria were: age > 40 years and post-bronchodilator (FEV_1)/forced vital capacity (FVC) ≤ 70% of the normal predicted value. The data were collected from case reports recorded by a doctor or trained nurse. After a baseline evaluation, patients were examined at 6-month intervals. For this study, data until November 2020 were extracted from the KOCOSS database and used to compare the clinical characteristics of non-CB, mild CB, and severe CB patients.

Definition of CB and mild/severe CB

As recommended in previous studies, CAT1 (assessing cough) and CAT2 (assessing sputum) scores ≥ 3 were used to define CB [15, 21]. Patients with CAT1 and CAT2 scores ≥ 4 were considered to have severe CB; patients with either a CAT1 or a CAT2 score < 4 were considered to have mild CB.

Clinical parameters

Baseline characteristics collected at the initial patient visit included age, sex, smoking history, and body mass index (BMI). Symptoms and functional exercise capacity scores were also obtained, including the modified Medical Research Council (mMRC) dyspnea score, the CAT score, and the 6-minute walk distance test (6MWT) score. Additionally, the results of two psychological tests, the Beck Depression Inventory and the Beck Anxiety Inventory, were recorded.

Asthmatic features and markers associated with type 2 inflammation were analyzed, including history of asthma, asthma-COPD overlap (clinically diagnosed by a physician), fractional exhaled nitric oxide (FeNO), blood eosinophil count, and immunoglobulin E (IgE) level.

Pulmonary function test parameters (e.g., FEV1, FVC, FEV1/FVC, diffusion capacity of the lung for carbon monoxide [DLco], and residual volume/total lung capacity) were determined at baseline and annually for 3 years. Emphysema or bronchiectasis was diagnosed based on chest computed tomography findings interpreted by a radiologist. COPD medication regimens were categorized as long-acting beta-agonist or long-acting muscarinic antagonist, long-acting beta-agonist plus long-acting muscarinic antagonist, inhaled corticosteroid plus long-acting beta-agonist, and triple therapy. Both the occurrence and frequency of moderate-to-severe exacerbations and severe exacerbations during the first year of follow-up were analyzed. Moderate exacerbation was defined as a status requiring antibiotic or systemic corticosteroid therapy, administered in an outpatient clinic; severe exacerbation was defined as a status requiring an emergency room visit or hospital admission.

Statistical analyses

All statistical analyses were performed using R software (ver. 3.6.3; R Development Core Team, Vienna, Austria). Continuous variables are expressed as means ± standard deviations; categorical variables are expressed as numbers and percentages. The above-listed clinical parameters were compared between non-CB patients and CB patients, and between patients with mild CB vs. severe CB. Differences in the categorical and continuous values of two groups were determined using the χ^2 test and Student's *t*-test, respectively.

Negative binomial regression analysis was performed to predict the frequency of exacerbations in CB patients and non-CB patients. For the subgroup of CB patients, a regression model was used to predict the frequency of exacerbations in patients with severe vs. mild CB. The regression models were adjusted for age, sex, smoking history, and post-bronchodilator FEV1. They were also used to analyze moderate-to-severe and severe exacerbations.

The annual FEV1 decline over 3 years was assessed in a longitudinal analysis that used a linear mixed model in which the interaction was examined between time and CB. The interaction between time and the severity of CB (mild CB vs. severe) was also analyzed; the adjusted covariates were age, sex, and BMI. All analyses were repeated in the subset of patients who were ever-smokers (≥ 10 pack-years).

Results

Differences in general characteristics between non-CB patients and CB patients

Of the 2,162 COPD patients registered in the KOCOSS database between April 2012 and May 2021, 497 (23.0%) had CB as defined by the CAT score (both CAT1 and CAT2 ≥ 3) (Fig. 1). Differences in clinical characteristics between non-CB patients and CB patients are shown in Table 1. Compared with non-CB patients, CB patients were younger (69.2 ± 7.8 years vs. 68.3 ± 7.7 years, p = 0.02), more likely to be a current smoker (24.5% vs. 35.6%, p < 0.01), and had lower BMI (23.1 ± 3.4 vs. 22.6 ± 3.4, p < 0.01). There were no differences in the sex distribution. Symptom and functional exercise capacity scores were better in the non-CB group than in the CB group: mMRC (1.2 ± 0.8 vs. 1.6 ± 1.0, p < 0.01), total CAT score (12.0 ± 6.4 vs. 22.8 vs. 7.3, p < 0.01), and 6MWT (387.5 ± 117.5 m vs. 371.4 ± 109.8 m, p = 0.02). The two psychological scores showed that non-CB patients were less depressed (Beck Depression Inventory score, 6.1 ± 7.6 vs. 9.7 ± 9.7, p < 0.01) and less anxious (Beck Anxiety Inventory score, 3.8 ± 5.6 vs. 7.0 ± 9.1, p < 0.01) than CB patients. There were no significant differences in asthma history, asthma-COPD overlap, or type 2 inflammation markers (e.g., FeNO, blood eosinophil count, and IgE).

Table 1
Difference of clinical characteristics between non-CB and CB

	Non-CB (n=1665, 77.0%)	CB (n=497, 23.0%)	P-value
Age	69.2 ± 7.8	68.3 ± 7.7	0.02
Sex (male)	1554 (93.3%)	462 (93.0%)	0.85
Smoking Hx			<0.01
-Never	119 (7.2%)	39 (7.8%)	
-Ex-smoker	1135 (68.3%)	281 (56.5%)	
-Current smoker	408 (24.5%)	177 (35.6%)	
BMI	23.1 ± 3.4	22.6 ± 3.4	<0.01
mMRC	1.2 ± 0.8	1.6 ± 1.0	<0.01
CAT score	12.0 ± 6.4	22.8 ± 7.3	<0.01
6MWT	387.5 ± 117.5	371.4 ± 109.8	0.02
BDI score	6.1 ± 7.6	9.7 ± 9.7	<0.01
BAI score	3.8 ± 5.6	7.0 ± 9.1	<0.01
Asthma Hx	472 (28.6%)	158 (32.0%)	0.16
ACO	192 (21.1%)	71 (26.7%)	0.07
Emphysema	370 (44.0%)	133 (48.5%)	0.22
Bronchiectasis	97 (11.6%)	36 (13.1%)	0.55
GOLD stage			<0.01
- I	181 (10.9%)	29 (5.4%)	
- II	877 (52.7%)	237 (47.7%)	
- III	492 (29.6%)	175 (35.2%)	
- IV	114 (6.9%)	36 (11.3%)	
postBD FEV1 (L)	1.7 ± 0.6	1.6 ± 0.6	<0.01

Data are presented as n (%) or mean ± SD

BMI Body mass index, BDI Beck Depression Inventory, BAI Beck Anxiety Inventory, mMRC modified Medical Research Council,, CAT COPD Assessment Test, 6MWT 6-minute walk distance test, ACO Asthma-COPD overlap

LAMA long-acting muscarinic antagonist, LABA long-acting beta2-agonist, ICS inhaled corticosteroids

	Non-CB (n=1665, 77.0%)	CB (n=497, 23.0%)	P-value
postBD FVC (L)	3.3 ± 0.8	3.3 ± 0.8	0.09
FEV1/FVC	50.8 ± 12.6	47.8 ± 12.7	<0.01
DLco	64.8 ± 20.8	61.2 ± 20.3	<0.01
RV/TLC	0.4 ± 0.1	0.4 ± 0.1	<0.01
FeNO	26.8 ± 16.6	28.0 ± 18.3	0.70
Blood eosinophil count	225.2 ± 257.4	228.7 ± 216.9	0.79
IgE	239.5 ± 368.2	212.2 ± 296.4	0.27
Medications			
- LABA or LAMA	440 (26.4%)	105 (21.1%)	0.02
- LABA/LAMA	308 (18.5%)	76 (15.3%)	0.12
- ICS/LABA	195 (11.7%)	58 (11.7%)	1.00
- ICS/LABA/LAMA	365 (21.9%)	118 (23.7%)	0.43
M-S exacerbation (Y/N)	464 (37.5%)	177 (51.6%)	<0.01
MS exacerbation (Frequency)	0.9 ± 1.8	1.6 ± 2.6	<0.01
S exacerbation (Y/N)	124 (10.0%)	45 (13.1%)	0.12
S exacerbation (Frequency)	0.1 ± 0.5	0.3 ± 1.0	<0.01
Data are presented as n (%) or mean ± SD			
BMI Body mass index, BDI Beck Depression Inventory, BAI Beck Anxiety Inventory, mMRC modified Medical Research Council,, CAT COPD Assessment Test, 6MWT 6-minute walk distance test, ACO Asthma-COPD overlap			
LAMA long-acting muscarinic antagonist, LABA long-acting beta2-agonist, ICS inhaled corticosteroids			

The radiologic findings showed no significant differences between groups in presence of emphysema or bronchiectasis. Lung function tests showed that, compared with non-CB patients, CB patients had lower post-bronchodilator FEV1 (1.7 ± 0.6 vs. 1.6 ± 0.6, p < 0.01), lower FEV1/FVC (50.8 ± 12.6 vs. 47.8 ± 12.7, p < 0.01), and lower DLco (64.8 ± 20.8 vs. 61.2 ± 20.3, p < 0.01); thus, CB patients had a more advanced GOLD stage. Mono-bronchodilators were more often prescribed to non-CB patients (26.4% vs. 21.1%, p = 0.02); the prescription rates of dual bronchodilators, inhaled corticosteroid/long-acting beta-agonist, and triple agents did not significantly differ between groups. According to the baseline moderate-to-severe exacerbation history in the previous year, both the occurrence rate and the frequency were significantly

higher in CB patients than in non-CB patients (51.6% vs. 37.5%, $p < 0.01$ and 1.6 ± 2.6 vs. 0.9 ± 1.8, $p < 0.01$); according to the baseline severe exacerbation history, there was no significant difference in the occurrence rate but CB patients had more frequent exacerbations (0.3 ± 1.0 vs. 0.1 ± 0.5, $p < 0.01$). The general characteristics of non-CB patients and CB patients among ever-smokers are shown in Table S1.

Differences in general characteristics of mild CB vs. severe CB

Among the 497 CB patients, 336 (67.6%) had mild disease and 161 (32.4%) had severe disease (Fig. 1). The clinical characteristics of these two groups are presented in Table 2. There were no significant differences in age, sex, smoking history, or BMI. The symptom and functional exercise capacity scores were consistent with an unfavorable outcome in the severe vs. mild CB groups: mMRC (1.8 ± 1.1 vs. 1.5 ± 0.9, $p < 0.01$), total CAT score (27.3 ± 6.8 vs. 20.7 ± 6.5, $p < 0.01$), and 6MWT (353.0 ± 110.9 m vs. 379.9 ± 108.5 m, $p = 0.03$). The psychological scores indicated more depression and anxiety in the severe CB group than in the mild CB group (Beck Depression Inventory score: 11.4 ± 10.6 vs. 8.8 ± 9.1, $p = 0.04$; Beck Anxiety Inventory score: 10.5 ± 11.6 vs. 5.2 ± 7.0, $p < 0.01$). There were no significant differences between groups with respect to asthma history, asthma-COPD overlap, and markers of type 2 inflammation (e.g., FeNO, blood eosinophil count, and IgE level).

Table 2
Difference of clinical characteristics between mild CB and severe CB

	Mild CB (n=336, 67.6%)	Severe CB (n=161, 32.4%)	P-value
Age	68.4 ± 7.8	67.9 ± 7.4	0.53
Sex (male)	313 (93.2%)	149 (92.5%)	0.95
Smoking Hx			0.41
-Never	27 (8.0%)	12 (7.5%)	
-Ex-smoker	196 (58.3%)	85 (52.8%)	
-Current smoker	113 (33.6%)	64 (39.8%)	
BMI	22.7 ± 3.3	22.3 ± 3.5	0.30
mMRC	1.5 ± 0.9	1.8 ± 1.1	<0.01
CAT score	20.7 ± 6.5	27.3 ± 6.8	<0.01
6MWT	379.9 ± 108.5	353.0 ± 110.9	0.03
BDI score	8.8 ± 9.1	11.4 ± 10.6	0.04
BAI score	5.2 ± 7.0	10.5 ± 11.6	<0.01
Asthma Hx	104 (31.2%)	54 (33.8%)	0.65
ACO	50 (29.1%)	21 (22.3%)	0.30
Emphysema	90 (48.9%)	43 (47.8%)	0.96
Bronchiectasis	23 (12.5%)	13 (14.4%)	0.80
GOLD stage			0.76
- I	18 (5.4%)	11 (6.8%)	
- II	165 (49.1%)	72 (44.7%)	
- III	117 (34.8%)	58 (36.0%)	
- IV	36 (10.7%)	20 (12.4%)	
postBD FEV1 (L)	1.6 ± 0.6	1.5 ± 0.5	0.32

Data are presented as n (%) or mean ± SD

BMI Body mass index, BDI Beck Depression Inventory, BAI Beck Anxiety Inventory, mMRC modified Medical Research Council,, CAT COPD Assessment Test, 6MWT 6-minute walk distance test, ACO Asthma-COPD overlap

LAMA long-acting muscarinic antagonist, LABA long-acting beta2-agonist, ICS inhaled corticosteroids

	Mild CB (n=336, 67.6%)	Severe CB (n=161, 32.4%)	P-value
postBD FVC (L)	3.3 ± 0.8	3.2 ± 0.9	0.36
FEV1/FVC	47.8 ± 12.9	47.8 ± 12.4	0.99
DLco	61.7 ± 20.8	60.1 ± 19.2	0.46
RV/TLC	0.4 ± 0.1	0.4 ± 0.1	0.90
FeNO	30.5 ± 20.5	22.0 ± 9.8	0.08
Blood eosinophil count	228.2 ± 212.7	229.8 ± 225.8	0.95
IgE	223.3 ± 280.2	191.4 ± 325.4	0.46
Medications			
- LABA or LAMA	77 (22.9%)	28 (17.4%)	0.20
- LABA/LAMA	51 (15.2%)	25 (15.5%)	1.00
- ICS/LABA	37 (11.0%)	21 (13.0%)	0.61
- ICS/LABA/LAMA	79 (23.5%)	39 (24.2%)	0.95
M-S exacerbation (Y/N)	114 (47.9%)	63 (60.0%)	0.051
MS exacerbation (Frequency)	1.4 ± 2.4	1.9 ± 2.9	0.13
S exacerbation (Y/N)	22 (9.2%)	23 (21.9%)	<0.01
S exacerbation (Frequency)	0.2 ± 0.9	0.4 ± 1.1	0.07
Data are presented as n (%) or mean ± SD			
BMI Body mass index, BDI Beck Depression Inventory, BAI Beck Anxiety Inventory, mMRC modified Medical Research Council,, CAT COPD Assessment Test, 6MWT 6-minute walk distance test, ACO Asthma-COPD overlap			
LAMA long-acting muscarinic antagonist, LABA long-acting beta2-agonist, ICS inhaled corticosteroids			

Patients with mild CB vs. severe CB did not significantly differ in chest computed tomography findings concerning emphysema or bronchiectasis, nor in terms of lung function test results and medication use. While the rate and frequency of moderate-to-severe exacerbations tended to be higher in patients with severe CB than in patients with mild CB, the differences were not statistically significant. Severe exacerbation occurred in a significantly larger number of patients with severe CB, compared with patients who had mild CB (21.9% vs. 9.2%, $p < 0.01$). There was also a larger number of severe exacerbations in the severe CB group than in the mild CB group, but this difference was not statistically significant (0.4 ±

1.1 vs. 0.2 ± 0.9, p = 0.07). The general characteristics of patients with mild CB vs. severe CB who were ever-smokers are presented in Table S2.

Association of chronic bronchitis and frequency of exacerbation

Negative binomial regression analysis revealed an association between the frequency of exacerbation and CB (Table 3). Compared with non-CB patients, patients with CB had a larger annual number of moderate-to-severe exacerbations (OR = 1.46, p < 0.01). The frequency of severe exacerbation did not significantly differ between groups. Regression analysis to explore an association between CB severity and the frequency of exacerbation (Table 4) showed a significant relationship for severe exacerbation but not for moderate-to-severe exacerbation. The same results were obtained in the group of ever-smokers, although CB was also significantly associated with the frequency of severe exacerbation (OR = 1.52, p < 0.04) (Tables S3, S4).

Table 3
Frequency of exacerbations for CB compared with non-CB patients

	Moderate-to-severe exacerbation			**Severe exacerbation**		
	OR	95%CI	p-value	OR	95%CI	p-value
CB	1.46	1.20-1.79	<0.01	1.40	0.96-2.03	0.08
Age	1.00	0.99-1.01	0.87	1.00	0.97-1.02	0.81
Sex (male)	0.76	0.53-1.09	0.13	0.40	0.19-0.81	0.01
Smoking Hx	1.06	0.89-1.26	0.52	0.96	0.68-1.36	0.81
FEV1	0.36	0.31-0.43	<0.01	0.16	0.11-0.22	<0.01
CB Chronic bronchitis						

Table 4
Frequency of exacerbations for severe CB compared with mild CB

	Moderate-to-severe exacerbation			Severe exacerbation		
	OR	95%CI	p-value	OR	95%CI	p-value
Severe CB	1.29	0.92-1.82	0.14	2.52	1.23-5.32	0.01
Age	1.01	0.98-1.03	0.62	1.02	0.97-1.06	0.51
Sex (male)	0.70	0.34-1.45	0.33	0.19	0.03-1.11	0.08
Smoking Hx	1.13	0.83-1.55	0.42	0.91	0.44-1.92	0.80
FEV1	0.36	0.27-0.49	<0.01	0.08	0.03-0.17	<0.01
CB Chronic bronchitis						

Association of chronic bronchitis and lung function decline

Linear mixed model analysis revealed no significant differences in the annual rate of FEV1 decrease either between non-CB patients and CB patients (p = 0.61) (Fig. 2) or between patients with mild CB vs. severe CB (p = 0.88). Analysis of ever-smokers produced similar results (non-CB vs. CB, p = 0.36; mild CB vs. severe CB, p = 0.25).

Discussion

Our analysis of a nationwide COPD cohort database revealed differences in clinical characteristics between non-CB patients and CB patients. By stratifying CB patients into patients with mild disease and patients with severe disease based on CAT sub-questionnaires, we were able to quantify the degrees of symptoms. The results showed that, compared with patients who had mild CB, patients with severe CB had worse outcomes in terms of respiratory symptoms, functional exercise capacity, and depression and anxiety scores; they also had more frequent severe exacerbations.

The clinical significance of the CB phenotype in COPD is well-established. CB is associated with poor health-related quality of life [22–25], poor functional exercise capacity [26], low lung function [11, 22, 23, 27, 28], more frequent exacerbations [11, 17, 22, 23, 27], and higher mortality [24, 29]. Consistent with those previous findings, our study showed higher mMRC and CAT scores, worse 6MWT performance, worse lung function, and more frequent exacerbations in CB patients than in non-CB patients. In most studies, including ours, CB patients were younger and had lower BMI; however, conflicting results have also been reported [11, 23, 26, 27, 30]. Furthermore, in our study and other studies, CB was strongly associated with a history of smoking [11, 23, 31]. In a study concerning the association of CB with mental health, Meek et al. found poor outcomes for CB patients in terms of emotional and mental health sections of the 36-Item Short Form Health Survey (SF-36). Their assessment of SF-36 items related to depression

showed that CB patients had higher scores for all of those items. Our CB patients also had higher depression and anxiety scores, compared with non-CB patients.

To our knowledge, the present study is the first to stratify CB patients according to disease severity, then to analyze the clinical characteristics of patients with mild CB vs. severe CB. A previous study classified the severity of cough and sputum by using CAT1 and CAT2 scores [32]. Similar to our findings, the previous study showed that patients with more severe cough or sputum had higher mMRC scores and more frequent exacerbations. Patients with severe symptoms also had poor outcomes in terms of anxiety, depression, fatigue, physical function, social ability, sleep disturbance, and pain interference, as determined using the Patient-Reported Outcome Measurement Information System Scores (PROMIS-29). These results are consistent with our findings and highlight the broader implications of severe cough and sputum in patients with severe CB. In our study, there were no significant differences in baseline characteristics (age, sex, and BMI) between patients with severe vs. mild CB; while patients with severe CB were more likely to be current smokers, the difference between groups was not statistically significant. However, patients with severe CB experienced more frequent severe exacerbations than did patients with mild CB (OR = 2.52); thus, patients with severe CB should be more carefully monitored.

Although our study showed worse lung function in CB patients than in non-CB patients, the 3-year follow-up data showed no significant differences in the FEV1 decline rate between groups. Similar results were obtained in patients with mild CB vs. severe CB. However, according to the Coronary Artery Risk Development in Young Development in Young Adults (CARDIA) study, a prospective cohort study that repeatedly measured lung function in young adults over 30 years, the presence of cough or sputum was significantly associated with an excess annual decline in both FEV1 (−2.71 ml/year, $p < 0.01$) and FVC (−1.94 ml/year, $p = 0.03$) [33]. In the Rotterdam Study, the rate of FEV1 decline during a median 6.5 years of follow-up was higher in CB patients (−38 ml/year, $p = 0.02$) [23]. The Copenhagen City Heart Study evaluated 5-year lung function test results and found excessive FEV1 decline in men with chronic mucus hypersecretion (22.6 ml/year, 95% confidence interval, 8.2–37.4) [34]. Thus, our follow-up interval of 3 years may have been insufficient to detect statistically significant differences between CB patients and non-CB patients. Moreover, 3-year follow-up data regarding FEV_1 were available for only 24% of our patients, which may have led to bias in the results. Further studies involving longer durations may demonstrate that disease severity is an important factor contributing to lung function decline in CB patients.

In this study, CB severity was stratified using CAT sub-questionnaires and various cut-off values. Questionnaires for CB were developed by the American Thoracic Society in 1978 and they are frequently used to define the disease [16, 25, 35]. However, there may be recall bias during long-term evaluations and the definitions of CB are complicated; thus, other parameters have been used in some studies, including chronic cough, physician diagnosis, and the presence of cough and sputum for 3 months over > 1 year [12, 13, 36]. Symptom-based scores (e.g., SGRQ and CAT) have also been employed [11, 15, 17, 21, 27]. Such scoring systems allow symptom severity to be quantified based on cut-off values, rather than subjective definitions. In this study, CB was defined as both CAT1 and CAT2 scores ≥ 3, as initially

recommended by Lim et al. [21]. This cut-off value results in similar proportions of CB among COPD patients, as determined using classically defined CB. In addition, Lim et al. showed that a CAT-based definition explained computed tomography airway parameters, such as mean wall thickness and mean wall area. In a previous study, we showed that patients with CAT score-defined CB shared clinical characteristics and outcomes with patients who had classically defined CB [15]. While cut-off values have not been validated in other populations, a recent study based on Subpopulations and Intermediate Outcomes Measures in COPD Study (SPIROMICS) data suggested CAT1 and CAT2 cut-off scores of ≥ 2 [17]. Further studies are needed to validate a CAT score-based definition of CB in other populations.

Our study had two main limitations. First, the CAT definition of CB has been validated only in the Korean population [37, 38]; thus, as noted above, further studies are needed to support its general use. However, the CAT questionnaire is a universal tool for measuring quality of life in patients with COPD. Second, the KOCOSS cohort mostly consisted of patients examined and treated at tertiary hospitals; therefore, it may not represent the entire COPD population. The strengths of our study included its novel stratification of CB severity such that the patients' clinical characteristics could be analyzed in relation to disease severity. In addition, lung function decline (based on 3-year follow-up data) was compared between non-CB patients and CB patients; it was also compared between patients with mild CB vs. severe CB. Finally, our study included a large number of patients, drawn from a nationwide database that had been enrolling patients for 7 years at the time of data extraction.

Conclusion

Our study compared clinical characteristics between non-CB patients and CB patients. Consistent with previous studies, we found that CB patients had poorer respiratory, exercise capacity, and psychological scores; reduced lung function; and more frequent exacerbations. Regression analysis showed that CB patients had more frequent moderate-to-severe exacerbations than did non-CB patients, based on a 1-year follow-up assessment. Using different CAT score cut-off scores, we distinguished mild CB from severe CB, then compared the clinical features of these two groups. Patients with severe CB had higher respiratory, exercise capacity, and psychological scores. At the 1-year follow-up assessment, patients with severe CB had more frequent severe exacerbations, as determined in a regression model. These results highlight the need for physicians to carefully monitor patients with severe symptoms.

Abbreviations

COPD
Chronic obstructive pulmonary disease
CB
Chronic bronchitis
ACO
Asthma-COPD overlap
ATS

American Thoracic Society
CAT score
COPD Assessment Test score
KOCOSS
Korea COPD Subgroup Study
FEV_1
Forced expiratory volume in 1 second
FVC
Forced vital capacity
CRF
Form of case report
BMI
Body mass index (BMI).
mMRC scale
Modified medical research council scale
6MWT
6-minute walk distance test
BDI score
Beck depression inventory score
BAI score
Beck anxiety inventory score
FeNO
Fractional exhaled nitric oxide
IgE
Immunoglobulin E (IgE)
PFT
Pulmonary function test
DLco
Diffusion capacity of the lung for carbon monoxide
RV
Residual volume
TLC
Total lung capacity
CT
Computed tomography
LABA
Long-acting beta-agonist
LAMA
Long-acting muscarinic antagonist
ICS

Inhaled corticosteroid
SF-36 score
36-Item Short Form Health Survey score
PROMIS-29
Patient-Reported Outcome Measurement Information System Scores
CARDIA study
Coronary Artery Risk Development in Young Development in Young Adults study

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of each medical center participating in KOCOSS (see the Supplementary Material for a list of those committees). Written informed consent was collected from all participating patients.

Consent to publication

Not applicable

Availability of data and materials

The datasets supporting the conclusions of this article are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None

Authors' contributions

JYC and CKR were involved in the design of the study. All authors were involved in data acquisition. JYC and CKR were involved in data analysis. All authors were involved in the interpretation of the data and in the writing and critical review of the manuscript. All authors read and approved the final manuscript.

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Figures

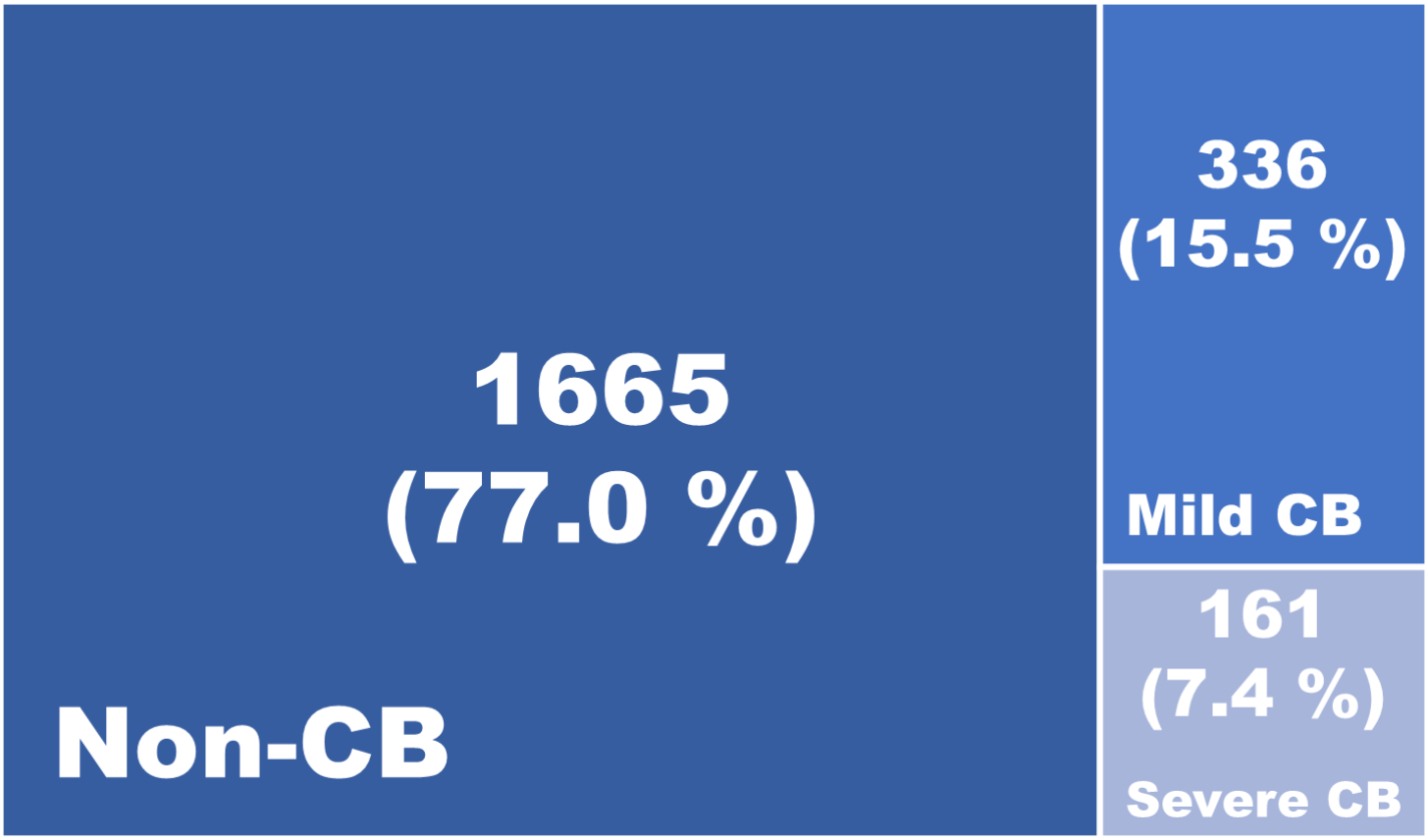

Figure 1

Distribution of non-CB, mild CB and severe CB

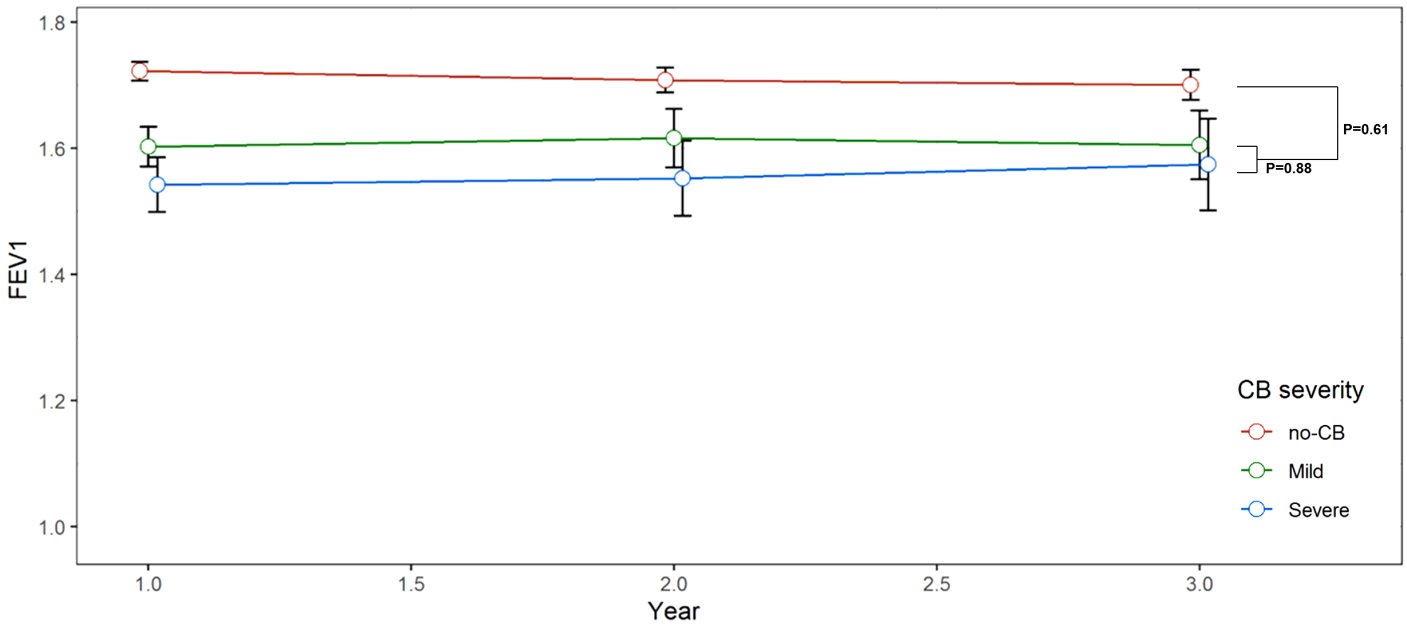

Figure 2

FEV1 trajectories of non-CB, mild and severe CB

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