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ORIGINAL RESEARCH

Clinical Impact of the Bronchiectasis with Chronic Bronchitis Symptoms in COPD: Analysis of a Longitudinal Cohort

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Purpose: Bronchiectasis (BE) is a poor prognostic factor in COPD. However, it is not clear whether the poor prognosis is a result of BE alone or accompanying chronic bronchitis symptoms. Therefore, we investigated the effect of chronic bronchitis symptoms on clinical outcomes in COPD patients with BE.

Patients and Methods: We analyzed data of COPD patients from the Korean Obstructive Lung Disease (KOLD) cohort. The presence of BE was verified by chest computed tomography. Chronic bronchitis symptoms were determined using items in the symptomatic domain of the SGRQ, which is also used as an alternative definition of chronic bronchitis (CB). Patients were divided into four groups according to the presence of BE and CB symptoms: BE/CB, BE-only, CB-only, and no BE/CB. Demographic features and clinical outcomes were compared among these groups.

Results: In total, 389 COPD patients were included in the analysis. BE was present in 148 (38%) patients and CB symptoms were found in 123 patients (33.2%). The patients were divided according to BE and CB symptoms, and the numbers and percentages of each group were as follows: BE/CB, 52 (13.4%); BE-only, 96 (24.7%); CB-only, 77 (19.8%); no BE/CB, 164 (42.2%). No significant differences were observed in baseline characteristics of lung function, radiological findings, and inflammatory markers among the four groups. The proportion of annual exacerbators was higher in the BE/CB and CB-only groups than the other two groups. After adjusting other parameters, the BE/CB group was significantly associated with acute exacerbation of COPD (AE-COPD) (OR = 2.110, p = 0.045).

Conclusion: BE accompanying CB symptoms is associated with AE-COPD, while BE alone was not significantly associated. This finding suggests that it is more important to examine chronic bronchitis symptoms of BE to predict acute exacerbation than simply to identify BE in COPD patients.

Keywords: COPD, bronchiectasis, chronic bronchitis, exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease caused by chronic airway and systemic inflammation, accompanied by several comorbid conditions.[1,2]

With the widespread use of chest computed tomography (CT), the reported detection rate of coexisting bronchiectasis (BE) varies between 15% and 69% in patients with moderate to severe COPD.[3–6] The coexistence of BE is an independent factor associated with poor prognosis in COPD in terms of acute exacerbation[3,7,8] and mortality.[3,9]

However, some studies have reported no significant associations of BE with COPD exacerbations.[10,11]

Representative symptoms of BE are chronic cough and sputum, which are also typical clinical presentations of chronic bronchitis (CB). Symptoms of CB are related to poorer health-related quality of life,[12–14] accelerated decline in lung function,[12,15–17] and increased mortality,[14,18,19] as well as greater number and severity of COPD exacerbations.[20] Additionally, even in the general population, symptoms of chronic cough and sputum are among the substantial risk factors for developing airflow limitation and/or COPD.[21,22]

In these contexts, it is reasonable to doubt whether the poorer prognosis in COPD patients with BE is caused by the accompanying CB symptoms or BE per se.

BE is a heterogeneous disease with various clinical manifestations. In a recent cluster analysis of BE, four different clusters were identified as "Pseudomonas," "Other chronic infection," "Daily sputum," and "Dry BE".[23] In cluster analysis, clinical symptoms and bacterial colonization are important parameters to determine the clinical phenotype of BE, which is associated with quality of life, exacerbations, hospitalization, and death. Especially, the "Dry BE" phenotype, with a rate of 27% in the study population, had better lung function and prognosis than the others.

We hypothesized that the prognosis may be different according to the presence of symptoms in COPD patients with coexisting BE. Therefore, we investigated the effects of CB symptoms on clinical outcomes in COPD patients with BE in our longitudinal cohort.

Materials and Methods
Study Design
Patients
This study was carried out with the Korean Obstructive Lung Disease (KOLD) cohort, which enrolled 477 COPD patients on an outpatient basis from pulmonary clinics in 16 hospitals throughout South Korea between June 2005 and April 2014. From this KOLD cohort, 389 COPD patients were selected according to the following four criteria: post-bronchodilator ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) < 0.7 after administration of 400 μg of inhaled albuterol; smoking history > 10 pack-years; no or minimal abnormalities on chest radiography; and availability of chest CT at baseline.

Clinicophysiological Indices of COPD
Demographic and clinical data were collected, including age, sex, smoking status, history of exacerbations, etc. Dyspnea was assessed using the Modified Medical Research Council (mMRC) Dyspnea scale[24] and the health-related quality of life was assessed using the St. George Respiratory Questionnaire (SGRQ).[25] Spirometry was performed using Vmax 22 (SensorMedics, Yorba Linda, CA, USA; and PFDX instrument; MedGraphics, St. Paul, MN, USA) according to the guidelines of the American Thoracic Society.[26] Medication history, smoking status, mMRC score, and acute exacerbation history were obtained at each visit. COPD medications were defined as inhaled corticosteroid/ long acting β-2 agonist (ICS/LABA), long-acting muscarinic antagonist (LAMA), or others according to the prescription for more than two-thirds of the study period.

Spirometry was performed at 6-month intervals; diffusion capacity, lung volume, 6-minute walking distance (6MWD), and SGRQ score were determined annually. The emphysema index (EI), airway wall area percentage (AWA%), and air-trapping index (ATI) were determined from chest CT data, as reported previously.[27]

Detection of BE
All patients were in a stable condition at the time of CT and none had experienced an exacerbation. Two radiologists who were unaware of the patients' clinical condition participated in radiological interpretation of the CT scans for the presence, severity, radiological pattern, and distribution of BE; associated disease findings, such as emphysema and small airway diseases; and others. The presence of BE was based on the criteria published by Naidich et al. Lack of tapering of bronchi; dilation of bronchi when the internal diameter was larger than that of the adjacent pulmonary artery; or visualization of the peripheral bronchi within 1 cm of the costal pleural surface or adjacent mediastinal pleural surface.[28] In addition to assessing the type of BE (cylindrical, varicose, cystic), the severity of BE was evaluated using the modified Bhalla score.[8,29]

Defining Symptoms of Chronic Bronchitis and Classification of Patient Groups
Presence of the CB symptoms was evaluated by using items in the symptomatic domain of the SGRQ questionnaire.[30,31] Two questions inquire about symptoms of cough and sputum within one month, and these may be used as alternatives to investigations based on the classical definition. 1) How often do you complain of cough during the week? 2) How often do you complain of sputum production during the week? Patients who answered "most days of the week" or "several days of the week" to both of these questions were considered to have

CB.[30,31] Finally, we divided the patients into four groups according to the presence of BE and symptoms of CB: BE/CB (BE+/CB+), BE-only (BE+/CB−), CB-only (BE−/CB+), and no BE/CB (BE−/CB−) groups.

Analysis of Clinical Outcomes of COPD

Acute exacerbation of COPD (AE-COPD) was defined as an acute worsening of respiratory symptoms (dyspnea, cough, or sputum) requiring additional therapy.[1,2,32] Severe AE-COPD was defined as hospitalization or visiting the emergency department due to worsening of COPD.[1,2] The annual incidences of AE-COPD and severe AE-COPD were calculated by dividing total exacerbation number by follow-up duration. An annual exacerbator was defined when a COPD patient who experienced ≥ 1 exacerbations per year (annual incidence of AE-COPD ≥ 1). A frequent exacerbator was defined as ≥ 2 exacerbations or ≥ 1 severe exacerbations per year. Annual decline in post-bronchodilator FEV_1 was analyzed. Mortality data were collected during the follow-up period.

Statistical Analysis

All data were analyzed with SPSS 21.0 (IBM Corp., Armonk, NY, USA). Categorical data are described as number (percentage) and continuous variables are expressed as means ± standard deviation. We analyzed the clinical characteristics of the four groups with the Chi-square test and one-way analysis of variance (ANOVA) with Bonferroni post hoc analysis for categorical and continuous variables, respectively. Clinical characteristics were compared using Student's t test for continuous data and the Chi-square test for categorical data. Annual decline in post-bronchodilator FEV_1 was analyzed by random-slope and random-intercept mixed linear regression as described previously.[33] Association analyses were performed using Pearson's correlation coefficient among continuous data and logistic regression analysis when dependent data were categorical. Kaplan–Meier and Cox proportional hazard ratio analyses were conducted to evaluate time to exacerbation and mortality. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Ethics Statement

The study protocol was approved by the institutional review board of the Asan Medical Center (Approval No. 2005–0345) and the 16 other participating hospitals. Written informed consent was obtained from all patients.

Results

Baseline Characteristics

In total, 389 COPD patients from the KOLD cohort who fulfilled the inclusion criteria were included in the study (Figure 1). Baseline characteristics are presented in Table 1 patients had a mean age of 66.9 ± 7.4 years, 97.7% were male, and 29.0% were current smokers. The mean post-bronchodilator FEV_1 was 54.1% ± 16.1%, the median follow-up time was 6.8 years, and the mean

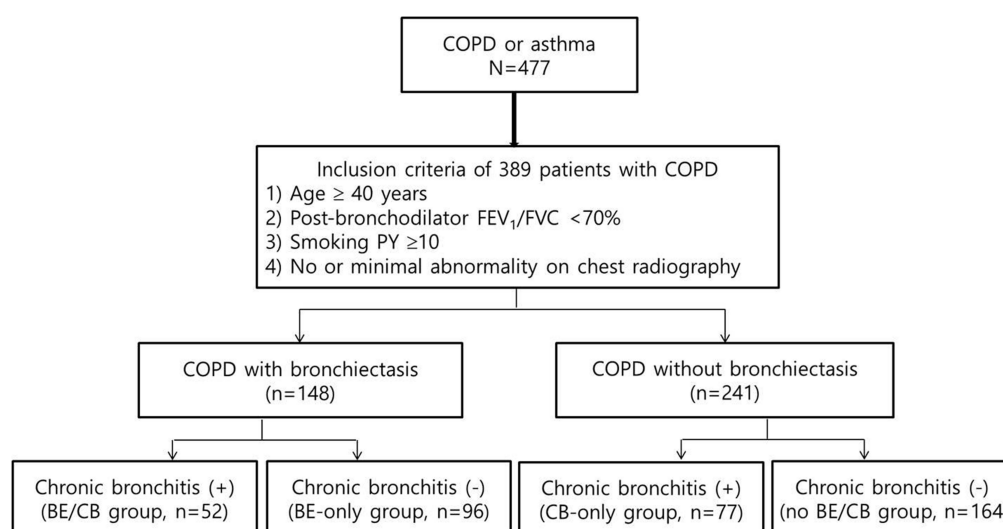
Figure 1 Flow diagram of enrollment.
Abbreviations: BE, bronchiectasis; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PY, pack-years.

Table 1 Baseline Characteristics of the Subjects

Parameter (N=389)	Mean ± SD, n (%)
Age (years)	66.9 ± 7.4
Male	380 (97.7)
Smoking amount (pack-year)	45.9 ± 26.2
Current smoker	113 (29.0)
BMI (kg/m^2)	23.0 ± 3.2
6MWD (m)	427.8 ± 86.0
Dyspnea (mMRC)	1.7 ± 1.1
SGRQ	32.8± 17.6
Charlson's comorbidity score	1.30 ± 0.67
The presence of BE	148 (38.0)
The presence of CB	129 (33.2)
Lung function	
Pre BD FVC (% predicted)	78.1 ± 16.4
Post BD FVC (% predicted)	83.1 ± 15.9
Pre BD FEV$_1$ (% predicted)	48.9 ± 15.5
Post BD FEV$_1$ (% predicted)	54.1 ± 16.1
FEV$_1$/FVC (%)	46.8 ± 11.1
DLco (% predicted)	77.3 ± 23.9
FEV$_1$ decline (mL/year, n=341)	−24.73 ± 24.65
Medications (n=359)	
ICS/LABA	196 (54.6)
LAMA	151 (42.1)
Other medications*	12 (3.3)
Radiologic findings	
Emphysema index (%)	21.7 ±15.3
Airway Wall area (%)	17.6 ± 3.5
Air-trapping index	0.95 ± 0.03
Blood laboratory findings	
Leukocyte (×10^3/μL)	7.3 ± 2.0
Blood eosinophils (cells/μL)	273.6 ± 321.4
Hemoglobin (g/dL)	14.9 ± 1.3
Platelet (×10^3/μL)	239.2 ± 62.4
Protein (g/dL)	7.1 ± 0.5
Albumin (g/dL)	4.2 ± 0.4
Cholesterol (mg/dL)	171.9 ± 61.5
Hs-CRP (mg/dL)	0.4 ± 1.0
Creatinine (mg/dL)	1.0 ± 0.2

Notes: Data are presented as n (%) or mean ± SD. *Other medications, ICS (n=6), LABA [Onbrez® (indacaterol), n=5], Combivent® (ipratropium bromide/salbutamol, n=1).
Abbreviations: SD, standard deviation; BMI, body mass index; 6MWD, 6-minute walk distance; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire; BD, bronchodilator; BE, bronchiectasis; CB, chronic bronchitis; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; ICS, inhaled corticosteroid; LABA, long acting β2-agonist; LAMA, long acting muscarinic antagonist; hs-CRP, high-sensitivity C-reactive protein.

mMRC and SGRQ scores were 1.7 ± 1.1 and 32.8 ± 17.6, respectively.

BE was detected on chest CT in 148 (38%) patients. Agreement between the two radiologists was good in terms of detecting and scoring BE (Kappa index, 0.88) [intraclass correlation coefficient (ICC), 0.975 (95% CI = 0.969–0.979, $p < 0.001$)]. The median modified Bhalla score was 9.5 in patients with BE (range: 6.5–14.6) (Supplementary Table 1). CB symptoms were present in 33.2% of the total COPD patient population.

Comparison of Clinical Characteristics According to BE and CB Symptoms

About 35% of COPD patients with BE (52/148) had symptoms of CB and the patients were divided into the following four groups: BE/CB (n = 52, 13.4%), BE-only (n = 96, 24.7%), CB-only (n = 77, 19.8%), and no BE/CB (n = 164, 42.2%). Clinical characteristics of each group are presented in Table 2. Those in the BE/CB and CB-only groups were more likely to be current smokers and had higher mMRC scores compared to those in the BE-only and no BE/CB groups. The BE/CB group had a lower BMI compared to the CB-only and no BE/CB groups and higher mMRC and SGRQ scores compared to the BE-only and no BE/CB groups. The BE/CB and BE-only groups had shorter 6MWD than the CB-only group (Table 2).

Lung function and radiographic findings of EI, AWA%, and ATI did not differ among the four groups. The annual decline in lung function (post-bronchodilator FEV$_1$) did not show any difference among the groups. We were able to obtain medication history in 359 of the 389 patients. The proportion of patients who used ICS/LABA or LAMA during the follow-up was similar among the four groups. Inflammatory markers, including blood leukocyte count, blood eosinophil count and high-sensitivity C-reactive protein (hs-CRP) level, did not differ among the groups (Table 2).

We divided the total patient population into two groups according to the presence (n = 148) or absence of BE (n = 241); COPD patients with BE had lower BMI and shorter 6MWD than those without BE. No differences were observed in terms of lung function, dyspnea, quality of life, or FEV$_1$ decline according to BE (Supplementary Table 1). In other words, the presence of BE alone did not have a serious impact on the severity of COPD. No significant differences were observed in the types (cylindrical, varicose, or cystic) and severity (modified Bhalla

Table 2 Comparison of Clinical Characteristics of Four Groups

Parameter (N=389)	BE/CB (n=52)	BE-Only (n=96)	CB-Only (n=77)	No BE/CB (n=164)	Overall *P* value
Age (years)	66.2 ± 7.9	68.5 ± 6.2[b]	65.3 ± 8.4	66.9 ± 7.2	0.035
Male	52 (100.0)	95 (99.0)	77 (100.0)[c]	156 (95.1)	0.036
Smoking amount (pack-year)	44.6 ± 22.3	46.3 ± 23.8	43.9 ± 27.2	47.1 ± 28.3	0.819
Current smoker	20 (38.5)[a, c]	22 (22.9)	30 (39.0)[a, c]	41 (25.0)	0.002
BMI (kg/m^2)	21.6 ± 3.3[b, c]	22.7 ±3.3	23.4 ± 2.6	23.5 ± 3.3	0.001
6MWD (m)	410.0 ± 85.5[b]	414.8 ±98.3[b]	446.3 ± 70.0	432.6 ± 83.6	0.042
Charlson's comorbidity score	1.29 ± 0.57	1.43 ± 0.96	1.29 ± 0.56	1.23 ± 0.53	0.160
Dyspnea (mMRC)	1.98 ± 1.09[a, c]	1.53 ± 1.06	1.86 ± 1.01[a, c]	1.54 ± 1.07	0.012
SGRQ	41.24 ± 18.62[a, c]	29.46 ± 16.11	38.41 ± 15.90	29.53 ± 17.55	<0.001
Lung function					
Pre BD FVC (% predicted)	80.6 ± 20.5	79.1 ± 16.2	76.4 ± 15.5	77.4 ±15.6	0.434
Post BD FVC (% predicted)	84.9 ± 19.6	82.4 ± 16.0	82.1 ± 13.7	83.4 ± 15.6	0.755
Pre BD FEV$_1$ (% predicted)	46.1 ± 18.1	49.6 ± 15.9	48.4 ± 14.1	49.5 ± 15.0	0.519
Post BD FEV$_1$ (% predicted)	50.3 ± 18.3	54.8 ± 16.9	53.4 ± 14.9	55.2 ± 15.3	0.252
FEV$_1$/FVC (%)	43.1 ± 12.0	46.9 ± 9.9	47.3 ± 11.2	47.7 ± 11.3	0.072
DLco (% predicted)	72.5 ± 21.3	79.8 ± 24.1	77.8 ± 21.5	76.9 ± 25.6	0.384
FEV$_1$ decline (mL/year, n=341)	−26.36 ± 25.99	−23.64 ± 21.56	−23.09 ± 29.69	−25.63 ± 23.17	0.836
Medications (n=359)					
ICS/LABA	25/48 (52.1)	41/84 (48.8)	44/75 (58.7)	86/152 (56.6)	0.573
LAMA	22/48 (45.8)	38/84 (45.2)	30/75 (40.0)	61/152 (40.1)	0.803
Other medications*	1/48 (2.1)	5/84 (6.0)	1/75 (1.3)	5/152 (3.3)	0.400
Radiologic findings					
EI (%)	25.5 ±15.4	21.6 ±16.2	19.6 ±14.5	21.5 ±15.2	0.257
AWA (%)	17.3 ± 3.0	18.1 ± 3.9	17.4 ± 3.9	17.4 ± 3.2	0.343
ATI	0.96 ± 0.03	0.95 ± 0.04	0.95 ± 0.03	0.94 ± 0.04	0.141
Blood laboratory findings					
Leukocyte (×10^3/μL)	7.5 ± 2.0	7.2 ± 1.7	7.3 ± 2.1	7.2 ± 2.1	0.759
Blood eosinophils (cells/μL)	309.0 ± 574.1	269.7 ± 253.9	270.4 ± 233.1	266.6 ± 286.8	0.876
Hemoglobin (g/dL)	15.0 ± 1.1	14.7 ± 1.4	14.8 ± 1.1	14.9 ± 1.4	0.502

(*Continued*)

Parameter (N=389)	BE/CB (n=52)	BE-Only (n=96)	CB-Only (n=77)	No BE/CB (n=164)	Overall P value
Platelet (×10³/μL)	250.7 ± 78.0	245.3 ± 65.1	240.1 ± 49.6	231.9 ± 60.3	0.187
Protein (g/dL)	7.1 ± 0.7	7.2 ± 0.5	6.9 ± 0.4[a, c]	7.1 ± 0.5	0.011
Albumin (g/dL)	4.2 ± 0.3	4.2 ± 0.6	4.2 ± 0.4	4.3 ± 0.3	0.324
Cholesterol (mg/dL)	173.9 ± 62.6	165.0 ± 70.9	157.6 ± 70.2[c]	181.4 ± 49.5	0.032
Hs-CRP (mg/dL)	0.4 ± 0.5	0.6 ± 1.9	0.3 ± 0.5	0.3 ± 0.6	0.320
Creatinine (mg/dL)	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	0.064

Notes: Data are presented as n (%) or mean ± SD. *Other medications, ICS (n=6), LABA [Onbrez® (indacaterol), n=5], Combivent® (ipratropium bromide/salbutamol, n=1). [a] P value < 0.05 compared CB-only group. [a] P value < 0.05 compared CB-only group. [c] P value < 0.05 compared no BE/CB group.
Abbreviations: SD, standard deviation; BE, bronchiectasis; CB, chronic bronchitis; BMI, body mass index; 6MWD, 6-minute walk distance; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire; BD, bronchodilator; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; ICS, inhaled corticosteroid; LABA, long acting β2-agonist; LAMA, long acting muscarinic antagonist; EI, emphysema index; AWA%, airway wall area percentage; ATI, air-trapping index; hs-CRP, high-sensitivity C-reactive protein.

score) of BE according to CB symptoms ($p = 0.805$) (Supplementary Table 2).

Comparison of Exacerbations of COPD According to BE and CB Symptoms

The median follow-up (interquartile range) was 6.83 (3.17–10.53) years. During the follow-up period, AE-COPD and severe AE-COPD occurred in 61.4% and 23.4% of the entire population, respectively; 114 (29.3%) were annual exacerbators (AE ≥ 1 per one year) and 54 (13.9%) were frequent exacerbators. Table 3 compares exacerbation and death rates among the four groups. A history of AE-COPD in the previous year was found in 20.1% of the total patient population. The incidence of AE-COPD in the previous year was higher in the BE/CB group than the BE-only and no BE/CB groups. The annual incidence of AE-COPD and severe AE-COPD did not differ among groups ($p = 0.545$, $p = 0.224$, respectively, Table 3). The proportion of annual exacerbators was higher in the BE/CB group than the BE-only group ($p = 0.037$) and no BE/CB group ($p = 0.033$) (Figure 2).

Of the 148 patients with BE, the proportion of annual exacerbators was higher in the BE/CB group than the BE-only group (40.4% vs 24.0%, respectively, $p = 0.037$, Table 3). Time to the first COPD exacerbation was shorter and the exacerbation risk was higher in the BE/CB group than the BE-only group (Supplementary Figure 1).

Logistic regression analysis was performed to analyze risk factors for annual exacerbation of COPD (exacerbations/year ≥ 1). Blood eosinophil count, hs-CRP level, the presence of BE, type of BE, and modified Bhalla score were not associated with annual AE-COPD. Table 4 lists the data: after adjusting other variables, including age, BMI, FEV₁, mMRC, and EI, the BE/CB group had a significant association with annual AE-COPD ($p = 0.045$). The CB-only group had a tendency to be associated with annual AE-COPD ($p = 0.088$), while the BE-only group did not ($p = 0.866$).

Comparison of Mortality According to BE and CB Symptoms

In total, 63 patients (16.2%) died during the follow-up period. The most common cause of death was respiratory failure (16 patients). Other causes were pneumonia (11 patients), lung cancer (8 patients), cancers other than lung cancer (7 patients), myocardial infarction (4 patients), and suicide (1 patient). The cause of death was unclear in 16 patients. As the cause of death

Table 3 Comparison of Exacerbation and Death of Four Groups

Parameter	Total (n=389)	BE/CB (n=52)	BE-Only (n=96)	CB-Only (n=77)	No BE/CB (n=164)	P value
History of AE in previous 1 year	78 (20.1)	16 (30.8)[a, b]	14 (14.6)	20 (26.0)	28 (17.0)	0.045
AE-COPD	239 (61.4)	32 (61.5)	54 (56.3)	50 (64.9)	103 (62.8)	0.655
Severe AE-COPD	91 (23.4)	15 (28.8)	14 (14.6)	23 (29.3)	39 (23.8)	0.077
AE-COPD/year	1.0 ± 3.1	1.0 ± 1.4	1.4 ± 5.9	0.9 ± 1.1	0.8 ± 1.4	0.545
Severe AE-COPD/year	0.1 ± 0.6	0.2 ± 0.4	0.1 ± 0.3	0.3 ± 1.1	0.1 ± 0.3	0.224
Annual exacerbator (AE/year ≥ 1)	114 (29.3)	21 (40.4)[a, b]	23 (24.0)	29 (37.7)	41 (25.0)	0.037
Frequent exacerbator (AE/year ≥ 2 or severe AE)	54 (13.9)	7 (13.5)	11 (11.5)	11 (14.3)	25 (15.2)	0.863
Overall mortality	63 (16.2)	10 (19.2)	13 (13.5)	12 (15.6)	28 (17.1)	0.810

Notes: [a]P value < 0.05 compared BE-only group. [b]P value < 0.05 compared no BE/CB group.
Abbreviations: BE, bronchiectasis; CB, chronic bronchitis; AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; severe AE-COPD, hospitalization or visit to ER; frequent exacerbator, AE-COPD/year ≥ 2 or severe AE-COPD/ year ≥ 1.

was unidentified in 25.4% of cases, only all-cause mortality was used for survival analysis. Kaplan–Meier survival curve analysis revealed no significant differences in mortality according to BE and/or CB symptoms (Figure 3). Clinical parameters associated with death were age, BMI, and 6MWD after adjusting other variables, including FEV_1, mMRC, frequent exacerbation, and EI (Table 5).

Discussion

We found that COPD patients with BE accompanying CB symptoms (BE/CB group) were significantly associated with acute exacerbation, which was not the case in BE-only, CB-only, or no BE/CB groups. Based on our study, simply investigating symptoms of CB will improve prediction of prognosis in COPD patients with accompanying BE.

Because BE is included as one of the comorbidities of COPD in the 2014 GOLD guidelines,[1,2] accompanying BE

Figure 2 Proportion of annual exacerbators according to the presence of bronchiectasis/chronic bronchitis.
Abbreviations: annual exacerbator, AE-COPD/year ≥ 1; BE, bronchiectasis; CB, chronic bronchitis.

has been suggested to be a prevalent and important prognostic marker. We found the presence of BE in as many as 38% of the patients on chest CT, although we excluded patients showing abnormal findings on chest X-ray, including BE, at the time of enrollment.

BE is known to be associated with increased risk of exacerbations and mortality in patients with COPD. Recent studies indicated that patients with COPD and BE have increased risk of exacerbations,[3,7,8] severe airway obstruction,[7,8] and death.[3,6,8,9] However, coexisting BE has not always been linked with poorer outcome in COPD patients.[10,11] Bafadhel et al reported no differences in airway inflammation, exacerbation frequency, or bacterial load in COPD patients with BE.[10] In a prospective study, Jairam et al also found that the presence of BE was not associated with death or hospitalization due to exacerbation.[11] In the current study, when we divided the total patient population into two groups according to the presence or absence of BE, we also found no differences between the two groups in terms of exacerbation or mortality. The discrepancies in the results of these studies may be related to the heterogeneity of severity, types, or phenotypes of BE among patient populations. These findings suggest the need for better evaluation of the characteristics of individual patients in addition to the presence of BE, which could lead to individualized optimized treatment.

The severity of BE is often estimated using the Bhalla radiological scoring system, which is known to be correlated with physiological impairment and symptom severity.[8,34] Cystic BE is associated with poorer prognosis and more severe impairment of FEV_1 than other types of BE.[35,36] In the present study, the median modified Bhalla score of the patients with BE was 9.5 (range: 6.5–14.6), indicating that BE was less severe than in other studies reporting an association with poor outcome.[37] Additionally, the most common
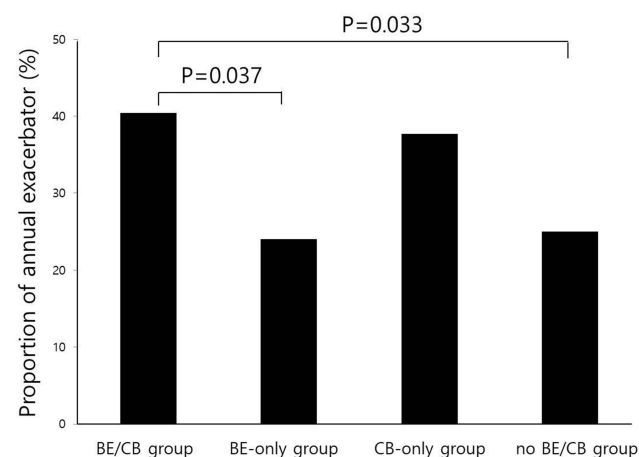
Table 4 Risk Factors Associated with Annual Exacerbation of COPD (Exacerbation /Year ≥ 1) in COPD Patients

Parameter (n=389)	Univariate Analysis			Multivariate Analysis[a]		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, yr	1.028	0.997–1.060	0.077	1.036	1.001–1.072	0.046
BMI, Kg/m^2	0.931	0.869–0.998	0.042	1.004	0.921–1.094	0.933
Post BD FEV$_1$ (% predicted)	0.969	0.954–0.983	<0.001	0.984	0.965–1.002	0.082
mMRC	1.403	1.140–1.727	0.001	1.187	0.922–1.530	0.184
6MWD (m)	1.000	0.997–1.002	0.728			
FEV$_1$ decline (mL/year)	1.002	0.993–1.011	0.672			
The presence of bronchiectasis	1.034	0.660–1.619	1.034			
Type of bronchiectasis						
Cylindrical	0.733	0.440–1.220	0.232			
Varicose	1.226	0.555–2.708	0.614			
Cystic	0.397	0.047–3.333	0.395			
Modified Bhalla score	1.051	0.994–1.111	0.078			
EI (%)	1.027	1.012–1.043	0.001	1.016	0.997–1.036	0.094
Hs-CRP (mg/dL)	0.982	0.771–1.251	0.883			
Blood eosinophils (cells/μL)	1.000	0.999–1.001	0.563			
Four groups according to BE, CB			0.040			0.082
No BE/CB group	Reference			Reference		
CB-only group	1.812	1.014–3.240	0.045	1.764	0.919–3.387	0.088
BE-only group	0.945	0.526–1.700	0.851	0.945	0.491–1.818	0.866
BE/CB group	2.032	1.053–3.921	0.034	2.110	1.016–4.382	0.045

Notes: [a]Adjusted for age, FEV$_1$, BMI, mMRC, EI, and four groups according to BE, CB.
Abbreviations: BD, bronchodilator; FEV$_1$, forced expiratory volume in 1 second; BMI, body mass index; mMRC, modified Medical Research Council; 6MWD, 6-minute walk distance; EI, emphysema index; hs-CRP, high-sensitivity C-reactive protein; BE, bronchiectasis; CB, chronic bronchitis; OR, odds ratio; CI, confidential interval.

type of BE was cylindrical, which has been shown to be associated with relatively better lung function and prognosis than other types of BE.[35,36] We analyzed the risk factors for exacerbation/mortality with the modified Bhalla score (data not shown) or type of BE, and found no significant associations.

The presence of chronic infection with pathogenic bacteria or *Pseudomonas aeruginosa* seems to predict poor prognosis.[23,38] Again, the presence of chronic infection with *Pseudomonas* is associated with more severe disease, poorer clinical, functional, and radiological features, and poorer quality of life and long-term outcomes.[38] Based on cluster analysis, Aliberti et al reported that the "Pseudomonas," "Other chronic infection," and "Daily sputum" clusters had poorer prognosis than the "Dry BE" cluster with the least evidence of chronic infection and no daily sputum and the "Pseudomonas" cluster had the poorest prognosis.[23]

Recently, multimodality indicators, such as the BE Severity Index (BSI) score and FACED (FEV$_1$, age, colonization, extension, dyspnea) score, have been developed to effectively evaluate the severity of BE by considering various clinical factors along with radiological findings.[39,40] Both of these indices also include the presence of chronic bacterial colonization including *P. aeruginosa*. However, these indices and sputum examination are not easily applicable in daily clinical practice.

Practically and theoretically, chronic inflammation of the airways by bacterial colonization causes chronic mucus hypersecretion.[41] Chronic excessive airway inflammation induced by bacterial infection and colonization is thought to underlie the pathogenesis of BE, and chronic mucus hypersecretion is also considered to be a typical symptom of BE. However, not all patients with BE have cough and/or sputum.[23]
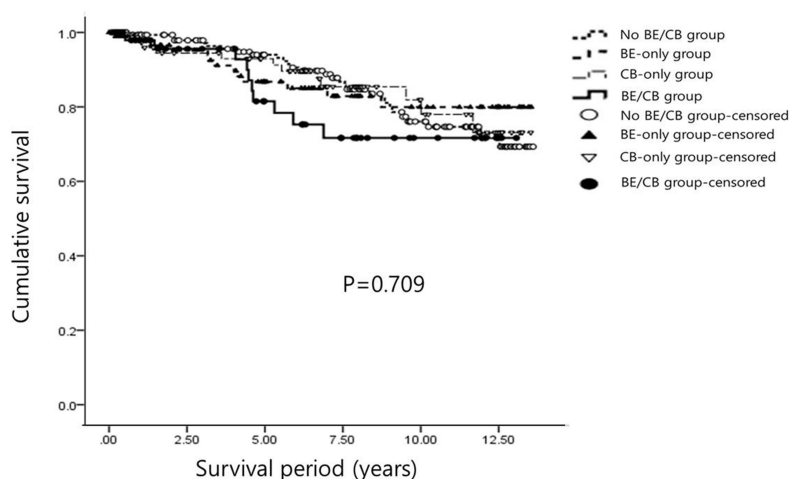
Figure 3 Kaplan–Meier survival analysis among groups.
Abbreviations: BE, bronchiectasis; CB, chronic bronchitis.

Previous studies of BE have reported that isolation of potentially pathogenic microorganisms (PPMs) and/or *P. aeruginosa* was associated with chronic symptoms of cough and sputum.[23,38,42] Because poor prognostic indicators, including isolation of PPMs and/or *P. aeruginosa*, are likely to be seen in patients with chronic mucus hypersecretion,[23,38,41–43] the poor prognosis is also probably related to the CB symptoms in COPD patients with BE. Chronic bacterial colonization and chronic mucus hypersecretion cannot be thought of separately.

Symptoms of CB have been considered to be important clinical phenotypes and prognostic markers of COPD.[12–20] CB is classically defined as chronic cough and sputum production for 3 months/year for at least 2 consecutive years.[44] Instead of using the classic CB definition, we used the SGRQ CB definition as evidence of chronic mucus hypersecretion.[30,31]

The SGRQ has been used extensively in clinical trials and large cohort studies of COPD, and the SGRQ CB definition has been considered to be similar[30,31] or superior[45] to the classic CB definition in predicting future exacerbation risk. When we applied the classic definition of CB, only 121 patients responded to the questionnaire and only 52 patients responded they had had symptoms compatible with the definition. The classic CB questionnaire inquires about symptoms for the previous 2 years, and some patients may have difficulty in recalling the details. This may be one of the reasons why the response rate to the classic questionnaire was lower than that of CB-related questions in SGRQ, which asked about symptoms only for the past 4 weeks.

In the present study, we divided the total patient population into two groups according to CB symptoms, and found that COPD patients with CB symptoms were associated with more severe dyspnea and poorer quality of life than those without CB symptoms. This result is consistent with those of previous studies reporting poor prognosis of COPD patients with CB symptoms.[12–14] Notably, COPD patients with non-symptomatic BE (BE-only group) had dyspnea and quality of life scores similar to patients in the no BE/CB group, indicating that the presence of BE alone is not clinically significant. Additionally, symptomatic BE with CB symptoms (BE/CB group) but not CB alone was the only significant factor for acute exacerbation of COPD in multivariate analysis. These findings suggest that symptomatic BE has greater clinical significance than BE per se or CB symptoms alone (Table 2, Supplementary Table 1, Supplementary Table 2).

To our knowledge, this is the first study to evaluate the significance of combining symptoms of CB in COPD patients with BE.

This study had some limitations. First, our cohort included a relatively small number of patients with a significant smoking history recruited only from the pulmonary clinic at a tertiary university hospital, so our results may not fully represent the general COPD population of Korea. Second, we did not examine the sputum microbiology. We regarded that CB symptoms per se may reflect bacterial colonization to some degree. Colonization by bacteria was shown to be associated with an increase in daily symptoms of CB in COPD patients.[41] However, from a clinical perspective, sputum surveillance for COPD patients with symptomatic BE is important in developing a better treatment strategy. Lastly, we did not consider

Table 5 Risk Factors for Mortality by Cox Proportional Hazards Model

Parameter (n=389)	Univariate Analysis			Multivariate Analysis[a]		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, yr	1.114	1.072–1.158	<0.001	1.084	1.037–1.133	<0.001
Post BD FEV$_1$ (% predicted)	0.940	0.922–0.958	<0.001	0.978	0.956–1.002	0.069
BMI (Kg/m2)	0.769	0.711–0.832	<0.001	0.885	0.811–0.966	0.006
mMRC	2.037	1.592–2.607	<0.001	1.313	0.943–1.828	0.107
6MWD (m)	0.991	0.988–0.993	<0.001	0.996	0.993–1.000	0.030
FEV$_1$ decline (mL/year)	1.008	0.998–1.017	0.115			
Frequent exacerbation	3.582	2.105–6.095	<0.001	1.725	0.927–3.208	0.085
EI (%)	1.048	1.031–1.065	<0.001	1.013	0.993–1.033	0.193
The presence of bronchiectasis	1.143	0.684–1.910	0.610			
Hs-CRP (mg/dL)	1.098	0.938–1.285	0.247			
Blood eosinophils (cells/μL)	1.000	0.999–1.001	0.758			
Four groups according to BE, CB			0.710			
No BE/CB group	Reference					
CB-only group	0.947	0.481–1.863	0.846			
BE-only group	0.956	0.495–1.846	0.720			
BE/CB group	1.458	0.707–3.006	0.307			

Notes: [a]Adjusted for age, FEV$_1$, BMI, mMRC, 6MWD, frequent exacerbation, and EI.
Abbreviations: BD, bronchodilator; FEV$_1$, forced expiratory volume in 1 second; BMI, body mass index; mMRC, modified Medical Research Council; 6MWD, 6-minute walk distance; frequent exacerbation, >2 exacerbation or >1 admission to hospital or visiting the emergency department/year; EI, emphysema index; hs-CRP, high-sensitivity C-reactive protein; BE, bronchiectasis; CB, chronic bronchitis; HR, hazard ratio; CI, confidential interval.

airway inflammatory markers. Increased airway inflammatory markers such as sputum eosinophil numbers and sputum IL-1b are associated with the subset of COPD exacerbations.[46] Recent reports have shown that the measurement of blood eosinophils is comparable to that of airway eosinophils.[47] We measured blood eosinophil count as a marker of eosinophilic airway inflammation and found no association with exacerbation.

Conclusion

BE accompanying CB symptoms is associated with AE-COPD, while non-symptomatic BE is not significantly associated. Symptomatic BE is more important for predicting prognosis than the presence of BE per se in COPD patients. These results suggest that it is more important to identify symptoms of BE to predict acute exacerbation than simply detecting the presence of BE in COPD patients.

Abbreviations

COPD, chronic obstructive pulmonary disease; BE, bronchiectasis; CB, chronic bronchitis; SGRQ, St. George Respiratory Questionnaire; AE-COPD, acute exacerbation of COPD; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; mMRC, Modified Medical Research Council; 6MWD, 6-minute walk distance; hs-CRP, high-sensitivity C-reactive protein; EI, emphysema index; AWA%, airway wall area percentage; ATI, air-trapping index; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest for this work.

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