Original Article

Clinical Deterioration and Lung Function Change in Patients With Concomitant Asthma and Bronchiectasis

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What is already known about this topic? Bronchiectasis is expected to worsen the clinical and functional outcomes in patients with asthma, but limited data are available regarding the long-term effects of bronchiectasis on the clinical course of asthma.

What does this article add to our knowledge? This study found that the presence and progression of bronchiectasis are associated with increased risk of moderate-to-severe acute clinical deterioration in patients with asthma.

How does this study impact current management guideline? This study suggests that it is necessary to evaluate the presence and severity of bronchiectasis in asthma patients with frequent clinical deteriorations.

BACKGROUND: Only limited data are available regarding the effects of bronchiectasis on the clinical course of asthma.
OBJECTIVE: This study evaluated longitudinal clinical outcomes according to bronchiectasis status in patients with asthma.
METHODS: This retrospective study included patients with asthma who underwent chest computed tomography and pulmonary function tests between January 2013 and December 2019. The annual incidence of episodes of moderate-to-severe acute clinical deterioration (exacerbations) and longitudinal changes in lung function were evaluated.
RESULTS: Of 667 patients with asthma, 251 had bronchiectasis. Patients with bronchiectasis had significantly more history of tuberculosis and nontuberculous mycobacterial lung disease, and lower forced expiratory volume in 1 second and forced vital capacity, compared with patients without bronchiectasis, although there was no difference in smoking intensity and inhaled corticosteroid treatment. Bronchiectasis was significantly associated with higher annual rates of severe and moderate-to-severe acute exacerbations; it was also associated with greater risk of acute exacerbation during follow-up. The severity and progression of bronchiectasis were independent risk factors for acute exacerbation. There were no significant differences in annual decline of lung function according to bronchiectasis status or bronchiectasis progression.
CONCLUSIONS: In patients with asthma, the presence and progression of bronchiectasis were significantly associated with increased risk of moderate-to-severe acute exacerbation, but they were not associated with longitudinal changes in lung function. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;■:■-■)

Key words: Asthma; Bronchiectasis; Exacerbation; Lung function

INTRODUCTION

Non−cystic fibrosis bronchiectasis (hereafter referred to as bronchiectasis) is a chronic inflammatory lung disease that is radiologically characterized by irreversible airway dilation; it is a common comorbidity in asthma patients. The prevalence of bronchiectasis is estimated to be less than 5% in the overall asthma population; it is much higher (25%−67.5%) in patients with severe and/or uncontrolled asthma.[1-3]

Although asthma and bronchiectasis are heterogeneous diseases with different pathophysiologies, they share similar clinical manifestations (eg, cough, sputum, dyspnea, and acute exacerbation).[4] Asthma is characterized by airway hyperresponsiveness predominantly based on eosinophilic inflammation, whereas bronchiectasis is characterized by medium-to-large bronchial dilation and mucus hypersecretion associated with intense neutrophilic inflammation.[5] Bronchiectasis causes chronic inflammation and recurrent bacterial infections of the airways because of impaired mucociliary clearance function.[6] Because an

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Abbreviations used
BMI- Body mass index
CT- Computed tomography
DL_{CO}- Diffusing capacity of the lungs for carbon monoxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
ICS- Inhaled corticosteroid
MPR- Medication possession ratio
NLR- Neutrophil to lymphocyte ratio
PFT- Pulmonary function test

infectious event is a common cause of acute exacerbation in asthma patients, bronchiectasis may be a risk factor for acute exacerbation of asthma.

In this context, bronchiectasis is expected to worsen the clinical and functional outcomes in patients with asthma, but limited data are available regarding the long-term effects of bronchiectasis on the clinical course of patients with asthma and bronchiectasis. Therefore, this study investigated the longitudinal clinical outcomes according to bronchiectasis status in patients with asthma.

METHODS

Study population

This retrospective study was conducted at 2 tertiary hospitals in South Korea (Seoul National University Hospital and Seoul Metropolitan Government—Seoul National University Boramae Medical Center) from January 1, 2013, to December 31, 2019. The inclusion criteria were as follows: a diagnosis of asthma confirmed by variable expiratory airflow limitation with pulmonary function tests (PFTs; positive bronchodilator response, positive bronchial provocation test, or excessive variation in lung function between visits); radiological evaluation with 1 or more chest computed tomography (CT) scans; and at least 2 PFTs during the follow-up period. The spirometric criteria for asthma followed the definition of the Global Initiative for Asthma (GINA) document at the time of the study (GINA 2019, Table E1; available in this article's Online Repository at www.jaci-inpractice.org).[7] Patients with a follow-up period less than 12 months were excluded because limited evaluation of long-term outcomes was possible in such patients.

The Charlson comorbidity index was calculated for each patient to estimate the severities of underlying comorbidities.[8] The history of inhaled corticosteroid (ICS) administration during the follow-up period was reviewed, and the medication possession ratio (MPR) was defined as the ratio of the duration of ICS administration to the follow-up period. Identification of identical bacteria 3 or more times in sputum samples with an interval of more than 1 month in stable status was considered chronic colonization by a potentially pathogenic microorganism (PPM).[9]

This study was approved by the institutional review board of Seoul National University Hospital (No: 2004-089-1117) and Seoul Metropolitan Government—Seoul National University Boramae Medical Center (No: 30-2020-7). The requirement for informed patient consent was waived because of the retrospective nature of the study.

Radiological findings

Bronchiectasis was diagnosed by chest CT as follows, in accordance with the criteria established by McGuinness et al[10]: lack of bronchial tapering; bronchial dilation when the internal diameter was larger than the diameter of the adjacent pulmonary artery; or visualization of peripheral bronchi within 1 cm of the costal pleural surface or adjacent mediastinal pleural surface. The chest CT findings were assessed visually by 3 readers; 2 pulmonologists (N.Y.K. and J.-K.L.) mainly reviewed images under supervision with consensus reading by 1 chest radiologist (K.N.J.).

Morphological classification of bronchiectasis was based on the Reid classification.[11] The extent of bronchiectasis was scored on the basis of semiquantitative measurements performed in each lobe: 0 points for no involvement of bronchiectasis; 1 point for 1% to 25% involvement; 2 points for 25% to 49% involvement; 3 points for 50% to 74% involvement; and 4 points for 75% to 100% involvement.[12,13] The total lung area was divided into 6 lobes, considering the lingular segment as a separate lobe. The bronchiectasis score was determined as the sum of the scores of each lobe. Changes in the degree of bronchiectasis were evaluated by comparison between the first and the last chest CT scans during the study period, and an increase in bronchiectasis score was defined as progression of bronchiectasis.

The FACED score was calculated for each patient included in the study. This score comprises a system to predict the prognosis of bronchiectasis; it consists of chronic colonization by *Pseudomonas aeruginosa*, dyspnea scale, forced expiratory volume in 1 second (FEV_1), age, and the number of lobes exhibiting bronchiectasis.[14] Tuberculosis-destroyed lung was defined as destruction of the lung parenchyma of more than 1 lobe because of previous pulmonary tuberculosis.[15]

Outcomes

The primary outcome was the annual incidence of moderate-to-severe acute exacerbations in patients with asthma, with or without bronchiectasis. Exacerbations were defined as an episode characterized by changes from the patient's previous status, which required additional treatment.[16] These additional treatments were characterized as either systemic steroids, antibiotics, or systemic steroids and antibiotics together. In the evaluation of acute exacerbation, antibiotic administration history was also regarded as an indicator of acute bronchiectasis exacerbation. We defined the severity of acute exacerbation as follows: moderate, event requiring initiation of oral antibiotics or steroid, or dose escalation of steroid in patients receiving steroid maintenance therapy; severe, event requiring a visit to the emergency room or hospitalization. A frequent exacerbator was regarded as a patient with a history of 2 or more moderate-to-severe acute exacerbations per year.[17]

The secondary outcome was longitudinal decline in lung function. The time at which chest CT was performed to evaluate bronchiectasis was the index date of the study; the clinical course was assessed thereafter. The PFTs after the index date were used to establish the association between bronchiectasis status and longitudinal changes in lung function.

Statistical analysis

Continuous variables are presented as means and SDs; categorical variables are presented as numbers and percentages. The χ^2 test or an independent 2-samples *t* test was used to assess differences between groups for all variables analyzed. Linear regression was performed to analyze the association between bronchiectasis status and annual rate of acute exacerbation; a logistic regression model was used to determine risk of acute exacerbation according to bronchiectasis status during the follow-up period. Multivariable analysis for risk of acute exacerbation was adjusted for age, sex, body mass index

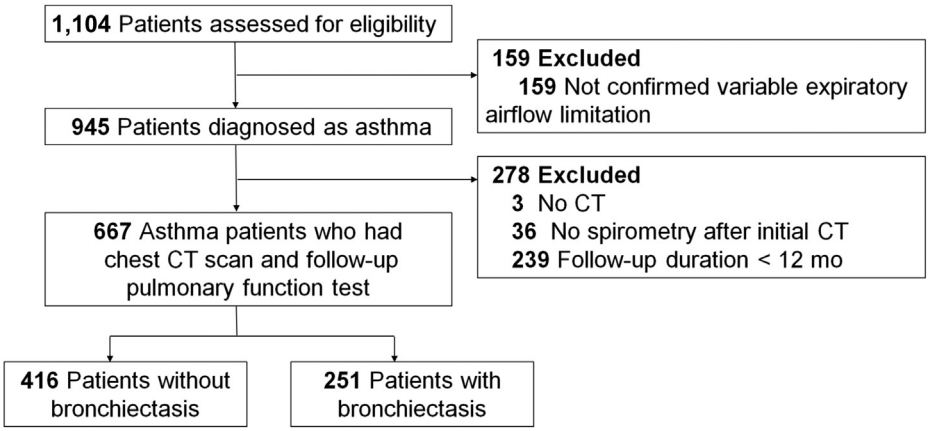

FIGURE 1. Flow diagram of the study population.

(BMI), Charlson comorbidity index, baseline FEV_1, ICS MPR, and blood neutrophil to lymphocyte ratio (NLR). Odds ratios and adjusted odds ratios were generated with 95% confidence intervals. Receiver operating characteristic curve analysis was performed to predict the risk of developing acute exacerbation of asthma according to bronchiectasis status. A linear mixed model was used to evaluate longitudinal changes in lung function according to bronchiectasis status. Multivariable models of lung function were adjusted for age, sex, height, baseline lung function, and ICS MPR. In all analyses, P less than .05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics

Of 1,104 patients assessed for eligibility, 667 asthma patients were finally included in this study following the application of inclusion and exclusion criteria (Figure 1). Of these 667 patients, 251 (37.6%) had bronchiectasis, and the remaining 416 (62.4%) had no bronchiectasis. The demographic and clinical characteristics of the study population are presented in Table I. The mean age of the patients was 66.6 years; 77.2% were men. The mean follow-up period was 3.96 years. Patients with bronchiectasis had significantly more past history of tuberculosis and nontuberculous mycobacterial lung disease, and lower absolute and predicted values of baseline FEV_1 and forced vital capacity (FVC), compared with patients without bronchiectasis. Patients with bronchiectasis included a greater proportion of never smokers than did patients without bronchiectasis, but there was no difference in the smoking intensity according to bronchiectasis status.

Radiological evaluation of bronchiectasis

Table II shows the radiological findings of initial and follow-up CT in patients with bronchiectasis. As a result of analyzing the reason for performing CT, 85 cases of 667 baseline CT scans were performed in association with acute exacerbation events. The remaining CTs were performed for other reasons, for example, screening, other comorbidities, chronic respiratory symptoms, and chest pain. Of 667 patients with asthma, 566 (84.9%) underwent follow-up chest CT; 226 (39.9%) had bronchiectasis. The mean interval between the index CT scan and the follow-up CT was 3.62 years. The most common type of Reid classification on chest CT was cylindrical, followed by varicose and cystic types. The baseline bronchiectasis and FACED scores were 2.58 and 1.63, respectively, indicating that bronchiectasis was mild in most patients. In follow-up CT analysis, the proportions of moderate and severe bronchiectasis increased slightly, consistent with the slight increase in severity determined by the bronchiectasis score.

Annual incidence of acute exacerbations according to bronchiectasis

The history of acute exacerbations during the follow-up period is presented in Table III. Patients with bronchiectasis had significantly higher annual rates of severe (0.15 ± 0.43 vs 0.08 ± 0.27; $P = .010$) and moderate-to-severe acute exacerbation (0.47 ± 0.79 vs 0.34 ± 0.63; $P = .018$); they also included a greater proportion of patients experiencing acute exacerbations during the follow-up period, compared with patients who did not exhibit bronchiectasis (49.8% vs 39.4%; $P = .009$). There was no difference in the proportion of frequent exacerbators between the 2 groups. Classification of moderate-to-severe acute exacerbation based on treatment with either steroids alone, antibiotics alone, or steroids plus antibiotics is described in Table III. The rate of use of steroids alone to treat exacerbations is the same between the groups (0.06 ± 0.19 with bronchiectasis and 0.06 ± 0.2 without bronchiectasis; $P = .914$). The rate of use of oral steroids plus antibiotics is also similar between the 2 groups (0.10 ± 0.26 vs 0.08 ± 0.23; $P = .317$). The rate of oral antibiotics alone trends toward being used more in the group with bronchiectasis than in the group without bronchiectasis (0.15 ± 0.38 vs 0.11 ± 0.28), but does not reach statistical significance ($P = 0.078$). The group with bronchiectasis had significantly more severe acute exacerbations with hospitalization than the group without bronchiectasis.

Low BMI, low baseline FEV_1, high ICS MPR, and high blood NLR were associated with greater risks of severe and moderate-to-severe acute exacerbations in multivariable analysis (Table IV). The existence of bronchiectasis remained an independent risk factor for severe and moderate-to-severe acute exacerbations despite adjustment for all other factors. Bronchiectasis score showed no association with annual rate of acute exacerbation (Table E2; available in this article's Online

TABLE I. Baseline and clinical characteristics of the study population*

Characteristics	Asthma with bronchiectasis (n = 251)	Asthma without bronchiectasis (n = 416)	*P* value
Follow-up period, y	4.16 ± 1.69	3.84 ± 1.68	.017
Age, y (range)	67.3 ± 10.4 (19–91)	66.1 ± 10.6 (20–88)	.160
Male sex, n (%)	191 (76.1)	324 (77.9)	.594
BMI, kg/m^2	23.4 ± 3.5	23.9 ± 3.6	.152
Smoking status, n (%) (n = 660)			.006
Never smoker	88 (35.2)	106 (25.9)	
Ex-smoker	134 (53.6)	227 (55.4)	
Current smoker	28 (11.2)	77 (18.8)	
Smoking intensity, pack-years (n = 579)	41.6 ± 24.0	43.4 ± 25.8	.471
Charlson comorbidity index	1.08 ± 0.87	1.24 ± 1.13	.052
History of tuberculosis, n (%)	58 (23.1)	58 (13.9)	.003
History of nontuberculous mycobacterial lung disease, n (%)	22 (8.8)	17 (4.1)	.013
Baseline lung function			
FEV_1, L	1.58 ± 0.51	1.77 ± 0.59	<.001
FEV_1, % predicted	67.2 ± 20.7	72.5 ± 20.1	.001
FVC, L	3.02 ± 0.83	3.28 ± 0.90	<.001
FVC, % predicted	87.4 ± 18.3	92.4 ± 18.1	.001
FEV_1/FVC ratio	53.6 ± 14.0	55.2 ± 13.9	.165
DL_{CO}, mL/mm Hg/min	14.4 ± 5.5	14.6 ± 5.1	.695
DL_{CO}, %	83.9 ± 23.6	82.7 ± 21.6	.572
Blood eosinophil count, cells/μL	227.2 ± 251. 7	240.0 ± 258.6	.485
Blood NLR	3.49 ± 4.26	3.62 ± 7.11	.673
ICS use, n (%)	180 (71.7)	290 (69.7)	.583
ICS MPR	0.50 ± 0.44	0.51 ± 0.43	.788

DL_{CO}, Diffusing capacity of the lungs for carbon monoxide; *ICS*, inhaled corticosteroid.
*Data are presented as n (%) or mean ± SD.

Repository at www.jaci-inpractice.org), but the progression of bronchiectasis confirmed on follow-up CT was associated with increased risks of severe and moderate-to-severe acute exacerbation (Table E3; available in this article's Online Repository at www.jaci-inpractice.org).

Risk of acute exacerbation in the follow-up period according to bronchiectasis

We divided the study population into a group with at least 1 moderate-to-severe acute exacerbation during the follow-up period (exacerbators) and a group that did not (nonexacerbators) (Table E4; available in this article's Online Repository at www.jaci-inpractice.org). The exacerbators had a greater proportion of women, lower FVC and diffusing capacity of the lungs for carbon monoxide, higher blood NLR, and more medication use (ICS, long-acting antimuscarinic agent, leukotriene receptor antagonist, and methylxanthine), compared with the nonexacerbators. Notably, the exacerbators had significantly more bronchiectasis, more severe bronchiectasis (higher bronchiectasis score), and more progression of bronchiectasis.

Further analysis based on these results indicated that patients with bronchiectasis had a greater risk of acute exacerbation than did patients without bronchiectasis (1.47-fold for moderate, 1.72-fold for severe, and 1.50-fold for moderate-to-severe exacerbations) (Table V). Bronchiectasis progression was also an independent risk factor for developing severe and moderate-to-severe acute exacerbation during the follow-up period. The baseline severity of bronchiectasis based on the bronchiectasis score significantly predicted the risk of acute exacerbation during follow-up, especially in patients with severe acute exacerbation (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org).

Longitudinal changes in lung function according to bronchiectasis

We evaluated longitudinal changes in lung function according to bronchiectasis status (Table VI). There were no significant differences in the annual decline of FEV_1, FVC, or diffusing capacity of the lungs for carbon monoxide according to bronchiectasis status. With regard to the change in FEV_1/FVC ratio, patients with bronchiectasis changed to a restrictive pattern, whereas patients without bronchiectasis changed to an obstructive pattern; however, this trend was not statistically significant. Similarly, the progression of bronchiectasis was not significantly associated with longitudinal changes in lung function in either univariable or multivariable analyses (Table E5; available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this study, asthma patients with bronchiectasis were similar in age, BMI, smoking intensity, comorbidities, and ICS treatment; and they had significantly more past history of tuberculosis and nontuberculous mycobacterial lung disease and lower lung function, than patients without bronchiectasis. The group with asthma and bronchiectasis had more never smokers, and the nonbronchiectasis group had more current smokers, but the existence of asthma and/or bronchiectasis is difficult to fully explain the difference in the smoking status. This may be due to

TABLE II. Classification and severity in patients with bronchiectasis*

Characteristics	Bronchiectasis in initial CT (n = 251 of 667)	Bronchiectasis in follow-up CT (n = 226 of 566)
Time interval from initial CT, y		3.62 ± 1.77
Reid classification, n (%)		
Cylindrical	251 (100.0)	226 (100.0)
Varicose	48 (19.1)	52 (23.0)
Cystic	38 (15.1)	31 (13.7)
Bronchiectasis score	2.58 ± 2.22	2.73 ± 2.31
Tuberculosis-destroyed lung, n (%)	17 (6.8)	12 (5.3)
Chronic colonization of PPM, n (%)	10 (4.0)	9 (4.0)
FACED score criteria, *n* (%)		
PPM colonization (*Pseudomonas aeruginosa*)	1 (0.4)	3 (1.3)
Dyspnea, mMRC ≥ 3	7 (2.8)	7 (3.1)
Pre-bronchodilator FEV_1 < 50%	44 (17.5)	31 (13.7)
Age ≥ 70 y	122 (48.6)	150 (66.4)
Number of involved lobes ≥ 2	69 (27.5)	67 (29.6)
FACED score	1.63 ± 1.37	1.95 ± 1.28
FACED severity, n (%)		
Mild	190 (75.7)	162 (71.7)
Moderate	54 (21.5)	54 (23.9)
Severe	7 (2.8)	10 (4.4)

FACED, FEV_1, age chronic colonization by *Pseudomonas aeruginosa*, dyspnea scale, and the number of lobes exhibiting bronchiectasis; *mMRC,* modified Medical Research Council dyspnea scale; *PPM,* potentially pathogenic microorganism.
*Data are presented as n (%) or mean ± SD.

TABLE III. Classification and history of exacerbation based on the definition criteria

Variables	Asthma with bronchiectasis (n = 251)	Asthma without bronchiectasis (n = 416)	*P* value
Annual rate of acute exacerbation			
Moderate	0.32 ± 0.55	0.26 ± 0.50	.130
Steroid	0.06 ± 0.19	0.06 ± 0.20	.914
Antibiotics	0.15 ± 0.38	0.11 ± 0.28	.078
Steroid with antibiotics	0.10 ± 0.26	0.08 ± 0.23	.317
Severe	0.15 ± 0.43	0.08 ± 0.27	.010
Emergency room visit	0.02 ± 0.11	0.01 ± 0.07	.168
Hospitalization	0.13 ± 0.39	0.07 ± 0.25	.014
Moderate-to-severe	0.47 ± 0.79	0.34 ± 0.63	.018
Exacerbator during follow-up, n (%)	125 (49.8)	164 (39.4)	.009
Frequent exacerbator, n (%)	13 (5.2)	15 (3.6)	.326

the selection bias according to the small study population. Considering that there was no significant difference in smoking intensity between groups, the effect of differences in the smoking status may not be significant.

Our major findings indicated that having bronchiectasis in addition to asthma was associated with significantly higher rates of severe and moderate-to-severe episodes of clinical deterioration requiring acute treatment compared with patients with asthma and no bronchiectasis. This was consistent with previous findings, suggesting that bronchiectasis may contribute to severe or poorly controlled disease status; it may also cause acute exacerbations and frequent hospitalization in asthma patients with bronchiectasis.[1,18,19] In bronchiectasis patients, dysfunction of mucociliary clearance can result in chronic bacterial colonization, airway inflammation, and recurrent infection.[3] Our novel finding was that patients who have asthma and bronchiectasis have worse long-term outcomes than patients with asthma alone, despite adjustment for major clinical characteristics, including baseline lung function and treatment with ICS (ie, the main class of drugs used to control asthma). These observations strongly support the major guidelines that recommend evaluation of comorbid bronchiectasis in asthma patients with severe symptoms, severe disease status, or frequent exacerbations.[20,21]

There are various potential causes of bronchiectasis, and asthma may be 1 of them. According to the results of a Korean multicenter bronchiectasis registry study, the most common cause of bronchiectasis was idiopathic (40%), followed by tuberculosis (20%), asthma (5%), and nontuberculosis mycobacterial disease (4%).[22] Similarly, 23.1% and 8.5% of patients with bronchiectasis in this study group had a history of tuberculosis and nontuberculous mycobacterial lung disease, respectively. Theoretically, chronic airway inflammation and mucus hypersecretion arising from asthma can lead to recurrent infections and subsequent epithelial damage and ciliary dysfunction. This vicious circle of inflammation and infection serves as the pathogenesis of bronchiectasis.[1] This is consistent with a higher risk of bronchiectasis in patients with severe asthma with a longer history.[23] However, although previous study and our results show a close relationship between asthma and bronchiectasis, they have limitations to prove a clear causal link between asthma and bronchiectasis. The role of asthma in the development of bronchiectasis remains unclear, and further studies on this are needed in the future.

The extent and severity of bronchiectasis on CT are reportedly correlated with symptoms, airflow obstruction, and bronchiectasis exacerbation frequency.[24,25] We confirmed that the severity of bronchiectasis, analyzed semiquantitatively by CT, was significantly associated with the risk of acute exacerbation during a follow-up period of approximately 4 years. This was consistent with another result of this study (ie, bronchiectasis progressed in some patients during the follow-up period); furthermore, the radiological progression of bronchiectasis was an independent risk factor for acute exacerbation.

In this study, we found that a longer duration of ICS use during the follow-up period was associated with a greater risk of clinical deterioration in patients with asthma and bronchiectasis, suggesting that patients with poor clinical courses may have used ICS more frequently and in greater amounts. This was supported by our supplemental data, such that patients with a history of exacerbations had higher ICS MPR, higher ICS dose, and more non-ICS drug use than did patients without a history of exacerbations. An ICS is an essential medication to control airway inflammation and hyperresponsiveness and reduce future risks of both exacerbation and lung function decline in asthma patients.[7] However, in bronchiectasis patients, ICS use has no definite positive effects on lung function, acute exacerbation, or quality of life[26]; it also increases susceptibility to bacterial infection by

TABLE IV. Rate of acute exacerbation according to bronchiectasis status in patients with asthma

	Moderate		Severe		Moderate-to-severe	
Variables	**β ± SD**	***P* value***	**β ± SD**	***P* value***	**β ± SD**	***P* value***
Bronchiectasis	0.05 ± 0.04	.198	0.06 ± 0.03	.038	0.11 ± 0.05	.046
Age	−0.00 ± 0.00	.155	0.00 ± 0.00	.172	−0.00 ± 0.00	.698
Male sex	0.00 ± 0.05	.972	0.05 ± 0.03	.143	0.05 ± 0.07	.452
BMI	−0.01 ± 0.01	.125	−0.01 ± 0.00	.044	−0.02 ± 0.01	.032
Charlson comorbidity index	0.01 ± 0.02	.519	0.01 ± 0.01	.504	0.02 ± 0.03	.415
Baseline FEV_1	−0.08 ± 0.04	.043	−0.07 ± 0.03	.007	−0.15 ± 0.05	.004
ICS medication possession ratio	0.30 ± 0.05	<.001	0.12 ± 0.03	<.001	0.42 ± 0.06	<.001
Blood NLR	0.00 ± 0.00	0.261	0.01 ± 0.00	<.001	0.01 ± 0.00	.007

**P* values were corrected for multiple comparisons with all variables.

TABLE V. Risk of acute exacerbation in follow-up period according to bronchiectasis status*

	Moderate		Severe		Moderate-to-severe	
Variables	**aOR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**
Bronchiectasis	1.47 (1.05−2.07)	.026	1.72 (1.10−2.69)	.017	1.50 (1.07−2.11)	.018
Bronchiectasis score	1.06 (0.97−1.16)	.195	1.13 (1.02−1.26)	.017	1.08 (0.99−1.19)	.092
FACED score (n = 251)	0.89 (0.70−1.13)	.325	0.93(0.69−1.26)	.657	0.87 (0.69−1.12)	.259
FACED severity						
Mild	Reference		Reference		Reference	
Moderate	0.86 (0.43−1.70)	.658	0.56 (0.24−1.33)	.188	0.71 (0.35−1.44)	.347
Severe	0.30 (0.03−2.67)	.280	1.20 (0.21−6.96)	.843	0.57 (0.10−3.25)	.531
Bronchiectasis progression (n = 566)	1.34 (0.79−2.29)	.279	2.81 (1.52−5.21)	.001	1.77 (1.04−3.04)	.037

aOR, Adjusted odds ratio; *FACED,* FEV_1, age, chronic colonization by *Pseudomonas aeruginosa*, dyspnea scale, and the number of lobes exhibiting bronchiectasis.
*All analyses were adjusted for age, sex, BMI, Charlson comorbidity index, baseline FEV_1, ICS MPR, and NLR.

TABLE VI. Annual decline in lung function according to bronchiectasis status

		Univariable		Multivariable*	
Variables	**Patients**	**β ± SE**	***P*-value**	**β ± SE**	***P*-value**
FEV_1, mL/y			.894		.812
Without bronchiectasis	416 of 667	−14.7 ± 4.4		−15.2 ± 5.0	
With bronchiectasis	251 of 667	−15.8 ± 4.6		−7.1 ± 6.2	
FVC, mL/y			.916		.877
Without bronchiectasis	416 of 667	−30.7 ± 5.7		−35.3 ± 5.4	
With bronchiectasis	251 of 667	−31.5 ± 7.0		−34.0 ± 7.1	
FEV_1/FVC ratio/y			.745		.727
Without bronchiectasis	416 of 667	−0.03 ± 0.09		−0.05 ± 0.10	
With bronchiectasis	251 of 667	0.03 ± 0.11		0.01 ± 0.11	
DL_{CO}, %/y			.073		.063
Without bronchiectasis	416 of 667	−1.44 ± 0.28		−1.49 ± 0.25	
With bronchiectasis	251 of 667	−0.51 ± 0.43		−0.64 ± 0.40	

DL_{CO}, Diffusing capacity of the lungs for carbon monoxide; *SE,* standard error.
*Adjusted for age, sex, height, baseline lung function (FEV_1, FVC, or DL_{CO}), and ICS MPR.

inducing partial immunosuppression and hospitalization for respiratory infection.[27-29] Considering these contradictory effects of ICS use, further research is needed regarding its risks and benefits in asthma patients with bronchiectasis, including differences in the benefit of ICS use according to patient phenotype.

We demonstrated that the presence and progression of bronchiectasis were not significantly associated with longitudinal changes in lung function. Some previous studies suggested that comorbid bronchiectasis may increase the severity of airway obstruction,[23,30] but the present study is rare in that it confirmed longitudinal changes in lung function. However, when interpreting these results, it is important to consider that 56.7% of the study population had generally well-controlled asthma and did not experience moderate-to-severe exacerbations during the follow-up period. The progression of bronchiectasis was mild during the study period, and the indolent and less-variable changes in bronchiectasis (compared with cancer or active infections) may have been responsible for the small effect on lung function.

This study had several limitations. First, it was a retrospective cohort study; thus, the evidence level was moderate. Second, the

patients in this study were undergoing chest CT and PFTs while receiving active treatment at tertiary hospitals; this may have led to selection bias. Because the subjects of this study had a high proportion of patients receiving periodic examination and maintenance treatment, there is a limit to generalizing the study results to asthma patients without considering the individual patient's condition. In particular, this study does not include cost-effectiveness analysis. Based on the results of this study, it may be helpful to evaluate the presence and progression of bronchiectasis in asthma patients with frequent exacerbations or poorly controlled conditions, but additional studies are needed to determine whether chest CT screening is recommended for asthma patients universally. Third, it is limited to clearly classify asthma exacerbation and bronchiectasis exacerbation in a retrospective analysis. These 2 events may appear together in actual clinical course. For the purpose of complementing this, history of antibiotics use was included in the operational definition of acute exacerbation, in addition to the definition of conventional asthma exacerbation. This is based on the assumption that acute exacerbation occurring in the concomitant condition of asthma and bronchiectasis would be different from that of patients with only asthma. And acute exacerbation of asthma is often caused by infectious causes similar to that of bronchiectasis. Fourth, the severity of bronchiectasis was radiologically evaluated by semiquantitative measurements. Advanced quantitative analysis and computational evaluation may improve the accuracy of evaluation in future studies.

In conclusion, in patients with asthma, the presence and progression of bronchiectasis were associated with increased risk of moderate-to-severe acute exacerbation; they were not associated with longitudinal changes in lung function.

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This study was approved by the Institutional Review Board of Seoul National University Hospital (No: 2004-089-1117) and Seoul Metropolitan Government—Seoul National University Boramae Medical Center (No: 30-2020-7). The informed consent of subjects was waived owing to retrospective design of this study under approval of the institutional review board.

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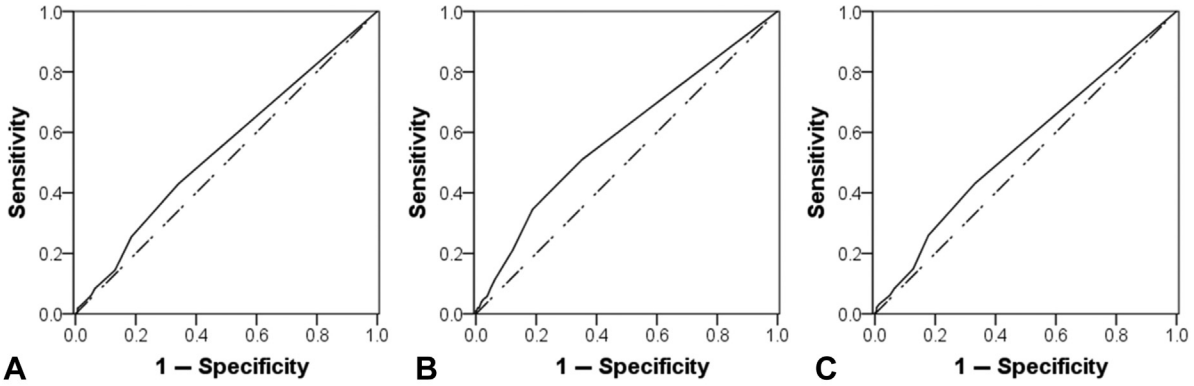

FIGURE E1. Receiver operating characteristic curves to predict the risk of acute exacerbation of asthma according to bronchiectasis status. Bronchiectasis score is presented as a solid line, with the reference value as a dashed line. **A** Moderate exacerbation (area under the curve [AUC] 0.55; 95% CI 0.50–0.59; $P = .049$). **B** Severe exacerbation (AUC 0.59; 95% CI 0.53–0.65; $P = .003$). **C** Moderate-to-severe exacerbation (AUC 0.55; 95% CI 0.51–0.60; $P = .021$).

TABLE E1. Spirometric criteria for diagnosis of asthma from GINA 2019 document

Confirmed variable expiratory airflow limitation	
Documented excessive variability in lung function* (1 or more of the tests below)	The greater the variations or the more occasions excess variation is seen the more confident the diagnosis
AND documented expiratory airflow limitation	At a time when FEV_1 is reduced, confirm that FEV_1/FVC is reduced (it is usually > 0.75 in adults)
Positive bronchodilator reversibility test* (more likely to be positive if bronchodilator medication is withheld before test: SABA $\geq$ 4 h, LABA $\geq$ 15 h)	Increase in FEV_1 of $> 12\%$ and > 200 mL from baseline, 10−15 min after 200−400 μg albuterol or equivalent (greater confidence if increase is $> 15\%$ and > 400 mL)
Excessive variability in twice-daily PEF over 2 wk*	Average daily diurnal PEF variability $> 10\%$†
Significant increase in lung function after 4 wk of anti-inflammatory treatment	Increase in FEV_1 by $> 12\%$ and > 200 mL (or PEF‡ by $> 20\%$) from baseline after 4 wk of treatment, outside respiratory infections
Positive exercise challenge test*	Fall in FEV_1 of $> 10\%$ and > 200 mL from baseline
Positive bronchial challenge test (usually only performed in adults)	Fall in FEV_1 from baseline of $\geq 20\%$ with standard doses of methacholine or histamine, or $\geq 15\%$ with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits* (less reliable)	Variation in FEV_1 of $> 12\%$ and > 200 mL between visits, outside of respiratory infections

FEV_1, Forced expiratory volume in 1 second; *FVC,* forced vital capacity; *GINA,* Global Initiative for Asthma; *LABA,* long-acting beta-2 agonist; *PEF,* peak expiratory flow; *SABA,* short-acting beta-2 agonist.
*These tests can be repeated during symptoms or in the early morning.
†Daily diurnal PEF variability is calculated from twice-daily PEF as ([day's highest minus day's lowest]/mean of day's highest and lowest), and averaged over 1 wk.
‡For PEF, use the same meter each time because PEF may vary by up to 20% between different meters.

TABLE E2. Rate of acute exacerbation according to bronchiectasis score in patients with asthma

	Moderate		**Severe**		**Moderate-to-severe**	
Variables	**β ± SD**	***P* value***	**β ± SD**	***P* value***	**β ± SD**	***P* value***
Bronchiectasis score	0.01 ± 0.01	.443	0.01 ± 0.01	.062	0.02 ± 0.01	.134
Age	−0.00 ± 0.00	.171	0.00 ± 0.00	.139	−0.00 ± 0.00	.770
Male sex	0.01 ± 0.05	.915	0.05 ± 0.03	.108	0.06 ± 0.07	.380
BMI	−0.01 ± 0.01	.128	−0.01 ± 0.00	.048	−0.02 ± 0.01	.034
Charlson comorbidity index	0.01 ± 0.02	.551	0.01 ± 0.01	.522	0.02 ± 0.03	.445
Baseline FEV_1	−0.08 ± 0.04	0.040	−0.07 ± 0.03	.009	−0.15 ± 0.05	.005
ICS MPR	0.30 ± 0.05	<.001	0.13 ± 0.03	<.001	0.43 ± 0.06	<.001
Blood NLR	0.00 ± 0.00	0.269	0.01 ± 0.00	<.001	0.01 ± 0.00	.008

BMI, Body mass index; *FEV_1,* forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MPR, medication possession ratio; NLR, neutrophil to lymphocyte ratio.
**P* values were corrected for multiple comparisons with all variables.

TABLE E3. Rate of acute exacerbation according to bronchiectasis progression in patients with asthma

	Moderate		**Severe**		**Moderate-to-severe**	
Variables	**β ± SD**	***P* value***	**β ± SD**	***P* value***	**β ± SD**	***P* value***
Bronchiectasis progression	0.08 ± 0.06	.222	0.15 ± 0.04	.001	0.22 ± 0.08	.008
Age	−0.00 ± 0.00	.592	0.00 ± 0.00	.152	−0.00 ± 0.00	.739
Male sex	0.02 ± 0.05	.638	0.04 ± 0.04	.247	0.07 ± 0.07	.346
BMI	−0.01 ± 0.01	.208	−0.01 ± 0.00	.043	−0.02 ± 0.01	.049
Charlson comorbidity index	0.02 ± 0.02	.407	0.01 ± 0.01	.617	0.02 ± 0.03	.384
Baseline FEV_1	−0.08 ± 0.04	.055	−0.08 ± 0.03	.009	−0.15 ± 0.06	.006
ICS MPR	0.30 ± 0.05	<.001	0.11 ± 0.03	.001	0.41 ± 0.06	<.001
Blood NLR	0.00 ± 0.00	.190	0.01 ± 0.00	<.001	0.01 ± 0.00	.005

**P* values were corrected for multiple comparisons with all variables.
BMI, Body mass index; *FEV_1,* forced expiratory volume in 1 second; *ICS,* inhaled corticosteroid; *MPR,* medication possession ratio; *NLR,* neutrophil to lymphocyte ratio.

TABLE E4. Baseline and clinical characteristics according to history of moderate-to-severe exacerbation in the study population*

Characteristics	Exacerbator (n = 289)	Nonexacerbator (n = 378)	*P* value
Follow-up period, y	4.08 ± 1.66	3.87 ± 1.71	.106
Age, y (range)	66.8 ± 10.5 (29–91)	66.4 ± 10.6 (19–87)	.588
Male sex, *n* (%)	202 (69.9)	313 (82.8)	<.001
Body mass index, kg/m^2	23.6 ± 3.8	23.8 ± 3.4	.316
Smoking status, n (%) (n = 660)			.009
Never smoker	99 (34.6)	95 (25.4)	
Ex-smoker	148 (51.7)	213 (57.0)	
Current smoker	39 (13.6)	66 (17.6)	
Smoking intensity, pack-years (n = 579)	42.3 ± 25.1	43.2 ± 25.2	.673
Charlson comorbidity index	1.17 ± 1.11	1.19 ± 1.00	.492
Baseline lung function			
FEV_1, L	1.62 ± 0.57	1.76 ± 0.55	<.001
FEV_1, % predicted	69.8 ± 22.0	71.1 ± 19.3	.368
FVC, L	2.98 ± 0.86	3.34 ± 0.87	<.001
FVC, % predicted	88.2 ± 19.0	92.3 ± 17.6	.013
FEV_1/FVC ratio	55.4 ± 14.6	53.9 ± 13.5	.186
DL_{CO}, mL/mm Hg/min	13.7 ± 5.4	15.2 ± 5.1	.001
DL_{CO}, %	80.3 ± 25.2	85.4 ± 19.6	.016
Blood eosinophil count, cells/μL	259.5 ± 338.0	216.6 ± 166.1	.284
Blood NLR	3.97 ± 5.25	3.27 ± 6.81	.006
ICS use, n (%)	243 (84.1)	227 (60.1)	<.001
ICS MPR	0.64 ± 0.30	0.41 ± 0.43	<.001
Mean dose of ICS			.001
Low	181 (74.5)	197 (86.8)	
Medium	49 (20.2)	22 (9.7)	
High	13 (5.3)	8 (3.5)	
Long-acting antimuscarinic agent use, n (%)	113 (39.1)	120 (31.7)	.049
Leukotriene receptor antagonist use, n (%)	96 (33.2)	44 (11.6)	<.001
Methylxanthine use, *n* (%)	102 (35.3)	33 (8.7)	<.001
Chronic colonization of PPM, n (%) (n = 289)	8 (2.8)	4 (1.1)	.141
Bronchiectasis, *n* (%)	125 (43.3)	126 (33.3)	.009
Bronchiectasis score	1.15 ± 2.02	0.84 ± 1.69	.008
FACED score (*n* = 251)	1.58 ± 1.29	1.67 ± 1.44	.741
FACED severity			.434
Mild	97 (77.6)	93 (73.8)	
Moderate	26 (20.8)	28 (22.2)	
Severe	2 (1.6)	5 (4.0)	
Bronchiectasis progression (n = 566)	39 (13.5)	30 (9.2)	.013
Annual rate of acute exacerbation			
Moderate	0.65 ± 0.61	0	<.001
Severe	0.25 ± 0.49	0	<.001
Moderate-to-severe	0.90 ± 0.82	0	<.001
Frequent exacerbator, n (%)	28 (9.7)	0 (0.0)	<.001

DL_{CO}, Diffusing capacity of the lungs for carbon monoxide; *FACED,* FEV_1, age, chronic colonization by *Pseudomonas aeruginosa*, dyspnea scale, and the number of lobes exhibiting bronchiectasis *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICS,* inhaled corticosteroid; *MPR,* medication possession ratio; *NLR,* neutrophil to lymphocyte ratio; *PPM,* potentially pathogenic microorganism.

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

TABLE E5. Annual decline in lung function according to longitudinal changes of bronchiectasis

		Univariable		Multivariable*	
Variables	**Patients**	**β ± SE**	***P* value**	**β ± SE**	***P* value**
FEV_1, mL/y			.611		.710
No progression	497 of 566	−15.1 ± 3.5		−20.4 ± 3.7	
Progression	69 of 566	−11.2 ± 8.7		−16.4 ± 8.6	
FVC, mL/y			.954		.763
No progression	497 of 566	−28.9 ± 5.0		−32.4 ± 5.0	
Progression	69 of 566	−31.3 ± 10.5		−35.2 ± 10.5	
FEV_1/FVC ratio/y			.215		.202
No progression	497 of 566	−0.03 ± 0.08		−0.06 ± 0.08	
Progression	69 of 566	0.27 ± 0.23		0.24 ± 0.23	
DL_{CO}, %/y			.055		.064
No progression	497 of 566	−0.93 ± 0.26		−1.06 ± 0.24	
Progression	69 of 566	−2.32 ± 0.72		−2.21 ± 0.67	

DL_{CO}, Diffusing capacity of the lungs for carbon monoxide; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICS,* inhaled corticosteroid; *MPR,* medication possession ratio; *SE,* standard error.

*Adjusted for age, sex, height, baseline lung function (FEV_1 or FVC. or DL_{CO}), and ICS MPR.