



Bronchodilator response as an independent predictor of severity in bronchiectasis

Yu Ri Kang^{1^}, Hyun Lee^{2^}, Hayoung Choi^{3^}, Seung Won Ra^{4^}, Yeon-Mok Oh^{5^}, Ki Hyun Seo¹, Jae Sung Choi¹, Ho Sung Lee¹, Jiwon Lyu¹, Jihye Lee^{1^}, Jin-Young Kim^{1^}, Kyeong-Deok Kim¹, Ju Ock Na¹

¹Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Korea; ²Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang University Hospital, Seoul, Korea; ³Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea; ⁴Division of Pulmonary Medicine, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea; ⁵Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Contributions: (I) Conception and design: YR Kang, JO Na; (II) Administrative support: JO Na; (III) Provision of study materials or patients: H Lee, H Choi, SW Ra, YM Oh, KH Seo, JS Choi, HS Lee, J Lyu, JO Na; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: YR Kang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Ju Ock Na, MD, PhD. Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, 31 Suncheonhyang 6-gil, Dongnam-gu, Cheonan-si, Chung cheongnam-do 31151, Korea. Email: juokna@schmc.ac.kr.

Background: Bronchodilator response (BDR) is occasionally observed in patients with bronchiectasis. However, clinical implications of BDR of bronchiectasis remain unclear. This multicenter observational cohort study aimed to compare clinical characteristics and severity in bronchiectasis between patients with BDR and without BDR.

Methods: We collected data from the Korean Multicenter Bronchiectasis Audit and Research Collaboration (KMBARC) registry, a multicenter observational cohort of non-cystic fibrosis bronchiectasis. We reviewed the medical records of 709 patients who underwent spirometry. We defined BDR as forced expiratory volume in one second (FEV₁) or forced vital capacity (FVC) improvement from pre-bronchodilator value by at least 200 mL and 12% for baseline or 1-year follow-up spirometry.

Results: Of the 709 patients, 7.3% exhibited BDR. Patients with BDR showed worse pulmonary function than those without BDR, both at baseline (FEV₁%, 52.7% *vs.* 65.3%) and at 1-year follow-up spirometry (52.2% *vs.* 62.9%). Inhaled corticosteroid (ICS)-containing agents were more frequently used in patients with BDR than those without BDR. Patients with BDR showed higher rates of emergency room visits (15.4% *vs.* 6.7%) and hospitalization (30.8% *vs.* 16.6%) than those without BDR. When measuring bronchiectasis severity with Bronchiectasis Severity Index, FACED [F: FEV₁; A: age; C: chronic colonization by *Pseudomonas aeruginosa*; E: radiological extension (number of pulmonary lobes affected), and D: dyspnea], and E-FACED (FACED plus exacerbations) scores, patients with BDR showed more severe bronchiectasis status than those without BDR.

Conclusions: In bronchiectasis, BDR is associated with poorer lung function, more frequent exacerbation, and increased disease severity.

Keywords: Bronchiectasis; bronchodilator response (BDR); pulmonary function test (PFT); exacerbation; severity

Submitted Apr 10, 2025. Accepted for publication Jul 25, 2025. Published online Oct 28, 2025.

doi: 10.21037/jtd-2025-713

View this article at: <https://dx.doi.org/10.21037/jtd-2025-713>

[^] ORCID: Yu Ri Kang, 0000-0001-5749-2040; Hyun Lee, 0000-0002-1269-0913; Hayoung Choi, 0000-0003-4812-0653; Seung Won Ra, 0000-0002-2458-8414; Yeon-Mok Oh, 0000-0003-0116-4683; Jihye Lee, 0000-0001-8737-8847; Jin-Young Kim, 0000-0002-1261-7312.

Introduction

Bronchiectasis is a chronic airway disease characterized by abnormal dilation of the bronchi (1). It presents symptoms such as chronic cough, wheezing, and dyspnea, and it is prone to recurrent airway infections and increased secretion of mucus. Although prevalence of comorbidities of bronchiectasis varies depending on factors such as patient population, study methodologies, and location, asthma and chronic obstructive pulmonary disease (COPD) are common comorbidities with bronchiectasis, with rates of 17–42% and 19–58%, respectively (2–5). When bronchiectasis coexists with these diseases, it appears difficult to treat or worse course of disease (6–9). Additionally, bronchiectasis often presents with abnormal lung function, including airflow obstruction and airway hyperresponsiveness (10–14). Therefore, bronchodilators and inhaled corticosteroids (ICSs) are frequently used. However, unlike COPD or asthma, the clinical efficacy of these treatment agents in patients with bronchiectasis is limited. Also, the study on clinical significance of bronchodilator response (BDR) in bronchiectasis is limited. A previous study found that a greater magnitude of BDR was associated with a poorer baseline forced expiratory volume in one second (FEV₁) percentage of predicted value, which was maintained throughout follow-up (11). However, no additional validation studies have been conducted.

Highlight box

Key findings

- Patients with bronchodilator response (BDR) had worse pulmonary function, higher rates of exacerbations, and increased disease severity compared to those without BDR.

What is known and what is new?

- Several studies have suggested that BDR may be present in patients with bronchiectasis, usually suggesting a more severe disease phenotype or overlap with other obstructive diseases.
- This study utilized a large, multicenter cohort to confirm that the presence of a BDR in patients with bronchiectasis is associated with poorer lung function, higher exacerbation rates, and greater disease severity. It was also verified that these results are maintained even in the absence of chronic obstructive pulmonary disease (COPD) and asthma.

What is the implication, and what should change now?

- This study indicates that BDR can play an important role as an independent marker of severity in bronchiectasis, which is crucial for consideration in disease management and treatment strategies.

Consequently, we categorized data obtained from the Korean Multicenter Bronchiectasis Audit and Research Collaboration (KMBARC) registry (15), a multicenter observational cohort of non-cystic fibrosis bronchiectasis, into patients exhibiting BDR and those without BDR. Our objective was to compare the clinical characteristics and other relevant factors between the BDR and non-BDR groups in the Korean bronchiectasis cohort. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-2025-713/rc>).

Methods

Participants

We gathered data from the KMBARC registry, a multicenter observational cohort of non-cystic fibrosis bronchiectasis. The analysis included patients who were followed for one year between August 2018 and April 2021 while excluding those who did not undergo spirometry with a bronchodilator test from the study. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Spirometry and definition of BDR

Spirometry was performed at the initial visit and 1-year follow-up visit. By the KMBARC registry protocol, pre-bronchodilator and/or post-bronchodilator spirometry was conducted following the American Thoracic Society/European criteria (16). Absolute values for FEV₁ and forced vital capacity (FVC) were documented. The percentage of predicted values for FEV₁ and FVC was calculated using an automatic calculator based on an equation obtained from a representative Korean sample (17). We defined BDR as an improvement of at least 200 mL and 12% in either FEV₁ or FVC, comparing pre-bronchodilator and post-bronchodilator values. We applied this criterion to both baseline and 1-year follow-up spirometry. According to the results of pulmonary function tests (PFT), we classified them into an obstructive pattern, preserved ratio impaired spirometry (PRISm), and normal spirometry. We defined the obstructive pattern as post-bronchodilator FEV₁/FVC <0.7; PRISm as pre-bronchodilator FEV₁ <80% predicted with post-bronchodilator FEV₁/FVC ratio >0.7; and normal spirometry was defined as FEV₁ ≥80%, FVC ≥80% predicted with post-bronchodilator FEV₁/FVC ratio >0.7.

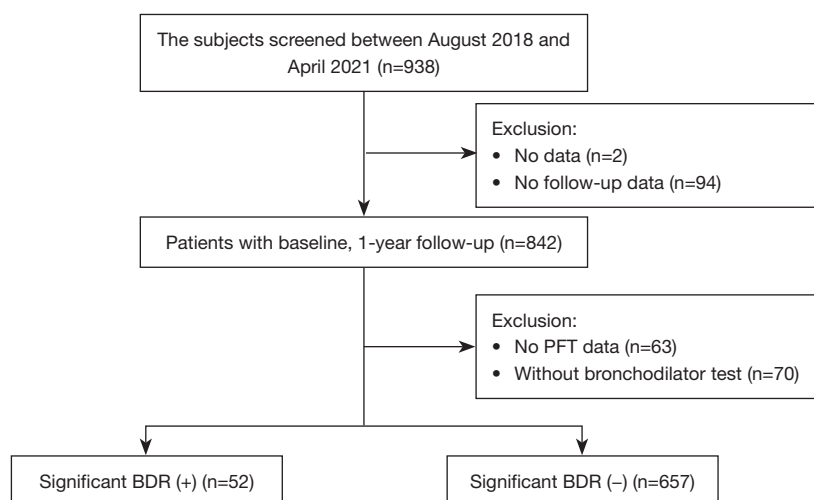


Figure 1 Study participants. BDR, bronchodilator response; PFT, pulmonary function test.

Other data collection

In addition to respiratory comorbidities such as asthma and COPD, other data on comorbidities and infections, including cardiovascular disease, diabetes mellitus, depression, anxiety, and *Mycobacterium tuberculosis*, non-tuberculous mycobacteria (NTM), *Pseudomonas aeruginosa*, were collected from medical records and patient history. We also analyzed bronchiectasis exacerbations (BEs) and severity indexes according to BDR. We defined acute exacerbations as a deterioration in ≥ 3 of the following symptoms persisting for at least 48 hours: (I) cough; (II) increased sputum volume and/or noticeable change; (III) sputum purulence; (IV) dyspnea and/or exercise intolerance; (V) fatigue and/or malaise; and (VI) hemoptysis. For acute exacerbations, we assessed the total acute exacerbation rate, number and rate of emergency room (ER) visits, hospitalizations, intensive care unit (ICU) hospitalizations, and hemoptysis due to acute exacerbation.

Disease severity was assessed using the multidimensional Bronchiectasis Severity Index (BSI) (18), FACED [F: FEV₁; A: age; C: chronic colonization by *Pseudomonas aeruginosa*, E: radiological extension (number of pulmonary lobes affected), and D: dyspnea] score (19) and the E-FACED (FACED plus exacerbations) score (20). Additional data, including respiratory medication and computed tomography (CT) imaging, were collected.

Statistical analysis

Continuous variables were presented using mean $\pm$ standard

deviation (SD) or median [interquartile range (IQR)]. Categorical variables were presented as percentages (%). Descriptive data between groups with and without BDR were compared using independent *t*-tests or Mann-Whitney tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. We performed regression analysis to evaluate the effect of BDR presence on lung function while controlling for the effects of asthma and COPD. Subgroup analysis was also conducted for patients without asthma or COPD. Also, we conducted multivariate logistic regression to determine whether the presence of BDR would cause more acute exacerbations even after adjusting for other key variables. Additionally, we included baseline parameters with a significance level of $P < 0.05$ in univariate analyses in the adjustment. Missing data were not included in the statistical analysis and were excluded from the total sample size. We performed all statistical analyses using the Stata/SE 17.0 software package (Stata Corporation, College Station, TX, USA). All tests were two-sided, and *P* values were significant at < 0.05 .

Results

Subject enrollment

Out of the 938 subjects screened between August 2018 and April 2021, we excluded 229 patients because two patients had no available data, 94 patients were lost to follow-up, 63 patients were without spirometry data, and 70 patients did not undergo a bronchodilator test (Figure 1). The remaining eligible cohort of 709 patients was subsequently

Table 1 Demographics and clinical characteristics of patients with bronchiectasis

Variables	Total (n=709)	Significant BDR (+) (n=52)	Significant BDR (-) (n=657)	P
Demographic factors				
Age, years	65 [59–71]	65 [59–72]	64 [59–71]	0.82*
Sex, female	55.1%	50%	55.6%	0.44
BMI, kg/m ²	23 [21–25]	24 [21–27]	23 [21–25]	0.006
Smoking status				
Never	65.0%	55.8%	65.8%	0.08
Former	30.9%	34.6%	30.5%	
Current	4.1%	9.6%	3.7%	
Comorbidities				
Cardiovascular diseases	30.8%	28.9%	30.9%	0.76
Diabetes	12.6%	13.5%	12.5%	0.84
Asthma	22.0%	36.5%	20.9%	0.009
COPD	39.4%	46.2%	38.8%	0.30
Depression	3.8%	0	4.1%	0.25**
Anxiety	2.8%	3.9%	2.7%	0.65**
Infection history				
Mycobacterium tuberculosis	33.1%	25.0%	33.7%	0.20
NTM	9.5%	9.6%	9.6%	>0.99**
Pseudomonas aeruginosa	30.0%	30.6%	30.0%	0.94
CT images				
Number of affected lobes	3.12±1.64	3.27±1.72	3.11±1.64	0.50
Right upper lobe	40.9%	44.2%	40.7%	0.62
Right middle lobe	58.8%	57.7%	58.9%	0.87
Right lower lobe	57.1%	61.5%	56.7%	0.50
Left upper lobe (upper division)	34.4%	32.7%	34.5%	0.79
Lingula	52.4%	57.7%	51.9%	0.42
Left lower lobe	72.0%	73.1%	72.0%	0.86

Data are presented as mean ± SD or median [IQR], and percentage. *, P values from Mann-Whitney test; **, P values from Fisher's exact test. BDR, bronchodilator response; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; IQR, interquartile range; NTM, non-tuberculous mycobacteria; SD, standard deviation.

categorized based on the presence or absence of a BDR.

Baseline characteristics

We summarized baseline demographic details in *Table 1*. The median age was 65 [59–71], with females comprising 55.1% and 65.0% were non-smokers. Twenty-two percent

had a history of asthma, 39.4% had COPD, and 33.1%, 9.5%, and 30.0% had a history of *Mycobacterium tuberculosis*, NTM, and *Pseudomonas aeruginosa* infection, respectively.

As indicated in *Table 1*, out of 709 patients, 52 (7.3%) exhibited a BDR. Those with BDR had a higher body mass index (BMI) compared to those without. Asthma was more prevalent in individuals with BDR, while COPD and other

Table 2 Spirometry results and dyspnea scale for patients with bronchiectasis

Variables	Baseline				1-year			
	Total	Significant BDR (+)	Significant BDR (–)	P	Total	Significant BDR (+)	Significant BDR (–)	P
Pre-bronchodilator findings (n)	673	51	622		445	41	404	
FEV ₁ (L)	1.71±0.62	1.41±0.51	1.73±0.63	<0.001	1.64±0.62	1.37±0.39	1.67±0.63	0.003*
FEV ₁ (% pred)	64.32±19.35	52.71±17.21	65.28±19.22	0.003	61.91±19.56	52.23±17.96	62.89±19.46	<0.001
FVC (L)	2.61±0.79	2.48±0.80	2.62±0.79	0.35	2.58±0.80	2.45±0.67	2.59±0.82	0.39*
FVC (% pred)	73.33±16.03	68.55±19.19	73.73±15.70	0.03	72.46±16.65	68.09±18.35	72.90±16.42	0.01*
FEV ₁ change [1-year-baseline (L)]					–0.01±0.22	–0.01±0.36	–0.01±0.20	0.32*
FVC change [1-year-baseline (L)]					0.00±0.29	–0.02±0.43	0.00±0.27	0.92*
Post-bronchodilator findings (n)	653	49	604		399	38	361	
FEV ₁ (L)	1.76±0.63	1.59±0.49	1.78±0.63	0.04	1.72±0.63	1.52±0.42	1.74±0.64	0.053*
FEV ₁ (% pred)	66.59±19.02	59.75±16.94	67.05±19.08	0.009	64.86±19.63	58.29±18.40	65.55±19.65	0.03
FVC (L)	2.63±0.79	2.65±0.72	2.63±0.79	0.53	2.62±0.80	2.53±0.65	2.63±0.81	0.67*
FVC (% pred)	73.28±15.69	73.21±18.24	73.28±15.46	0.60	73.39±16.11	71.59±16.80	73.58±16.05	0.47
Lung function pattern								
Obstruction	13.6%	28.6%	12.4%	0.002	15.8%	26.3%	14.7%	0.06
PRISm	64.0%	66.3%	63.9%	0.84	64.6%	63.2%	64.7%	0.85
Normal spirometry	22.4%	6.1%	23.7%	0.005	19.6%	10.5%	20.6%	0.14
Dyspnea scale	709	52	657		548	46	502	
mMRC	1.04±0.83	1.25±0.84	1.03±0.82	0.04*	1.13±0.84	1.30±0.81	1.12±0.84	0.09*

*, P values from Mann-Whitney test. Data are presented as mean ± SD and percentage. Obstruction is defined as post-bronchodilator FEV₁/FVC ratio <0.7. PRISm is defined as FEV₁ <80% of predicted with post-bronchodilator FEV₁/FVC ratio >0.7. Normal spirometry is defined as FEV₁ ≥80%, FVC ≥80% of predicted with post-bronchodilator FEV₁/FVC ratio >0.7. BDR, bronchodilator response; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; mMRC, modified Medical Research Council; PRISm, preserved ratio impaired spirometry; SD, standard deviation.

comorbidities such as cardiovascular diseases, diabetes, depression, and anxiety, showed similar frequencies in those with and without BDR.

Chest CT images were available for 701 patients (98.9%). The mean number of affected lobes by bronchiectasis was 3.12±1.64. The left lower lobe (72.0%) was the most involved, followed by the right middle lobe (58.8%) and the right lower lobe (57.1%). Conversely, the upper division of the left upper lobe (34.4%) was the least commonly affected. There was no significant difference in the distribution and extent of bronchiectasis on CT between patients with and without BDR.

Spirometry and respiratory medications

A total of 673 patients underwent spirometry at enrollment,

and 445 patients underwent spirometry 1 year after enrollment. Bronchodilator testing was performed in 653 and 399 patients, respectively.

Among the total 709 patients, 52 demonstrated BDR. When viewed individually, among 673 patients who underwent baseline spirometry, 51 patients had BDR, and among 445 patients who underwent 1-year spirometry, 41 patients had BDR. Patients with BDR exhibited poorer pulmonary function compared to those without BDR on both baseline spirometry [FEV₁ (%), 52.7% *vs.* 65.3%] and 1-year follow-up spirometry [FEV₁ (%), 52.2% *vs.* 62.9%] (Table 2, Figure 2A). When considering the modified Medical Research Council (mMRC) grade, individuals exhibiting BDR displayed higher mMRC compared to those without BDR (1.25±0.84 *vs.* 1.03±0.82) (all P values

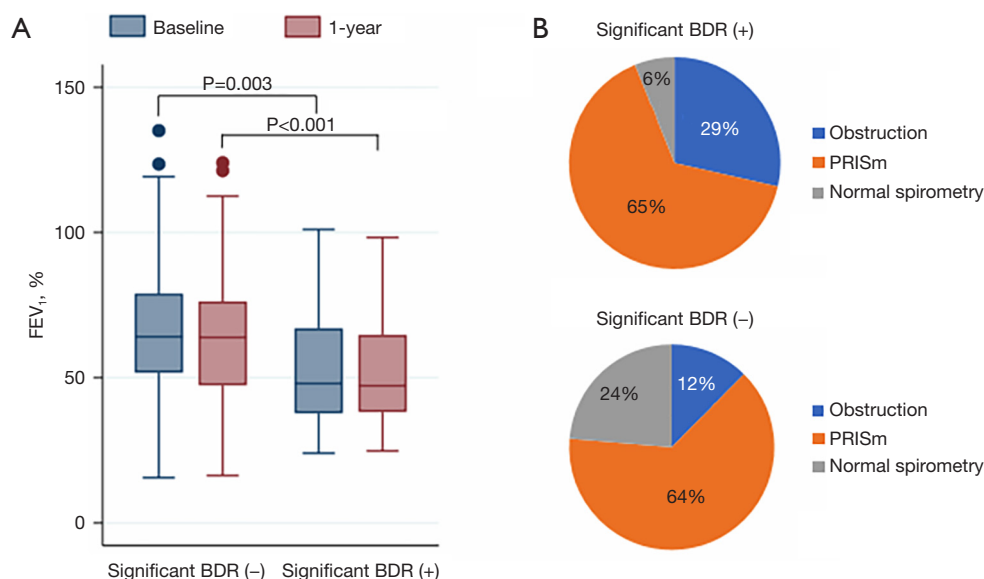


Figure 2 Change and pattern of spirometry. (A) One-year change in FEV₁ according to BDR. (B) Pattern of spirometry according to BDR. Obstruction is defined as post-bronchodilator FEV₁/FVC ratio <0.7. PRISm is defined as FEV₁ <80% of predicted with post-bronchodilator FEV₁/FVC ratio >0.7. Normal spirometry is defined as FEV₁ ≥80%, FVC ≥80% of predicted with post-bronchodilator FEV₁/FVC ratio >0.7. BDR, bronchodilator response; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry.

were <0.05) (Table 2).

Patients with BDR showed a higher percentage of obstructive spirometry results (post-bronchodilator FEV₁/FVC <0.7) and a lower percentage of normal spirometry results when compared with patients without BDR (37.3% vs. 14.5%, 7.8% vs. 20.3%, respectively. P values are <0.05). The percentage of PRISm was 54.9% and 61.9% of patients with and without BDR (P=0.32) (Figure 2B).

Long-acting beta-agonist (LABA) plus long-acting muscarinic antagonist (LAMA) was the most used inhaled agent in both patients with and without BDR (38.3% and 36.9%). ICS and ICS plus LABA agents were used significantly more frequently in patients with BDR than in patients without BDR (8.5% vs. 2.5%, 34.0% vs. 18.7%, respectively; P<0.05) (see Figure 3).

BEs and severity indexes, according to BDRs

We summarized the proportion of BEs in the past year at enrollment in Table 3. Among all patients, the proportion experiencing acute exacerbations was 19.2% (7.3% emergency room visits, 17.6% hospital admissions, and 0.6% ICU admissions, respectively). However, patients with BDR exhibited a significantly higher rate of acute

exacerbations (39.1%; emergency room visits 15.4%; hospital admissions 30.8%; ICU admissions 1.9%). The proportion of patients with hemoptysis events in total bronchiectasis patients was 14.3% without any differences according to BDR.

In terms of bronchiectasis severity with BSI, FACED, and E-FACED scores, it was confirmed that patients with BDR showed significantly more severe bronchiectasis than patients without BDR in all indices (7.8±3.9 vs. 6.8±3.6, 2.7±1.6 vs. 2.0±1.6, 3.2±2.0 vs. 2.3±1.9, respectively. All P values are <0.05). This trend was similar when categorizing the severity index. There was no significant difference in the proportion of patients classified as severe in the FACED and E-FACED scores (FACED score 5–7, E-FACED score 7–9) between the groups with and without BDR, but the proportion of patients classified as mild (FACED score 0–2, E-FACED score 0–3) was significantly lower in the group with BDR (detailed in Table 4).

Multinomial logistic regression was performed on several clinical variables to determine the risk of acute exacerbation in patients with bronchiectasis. As shown in Table 5, the risk of acute exacerbation increased approximately 2.9 times in patients with BDR compared to patients without BDR, a statistically significant result (P<0.05). On the other hand,

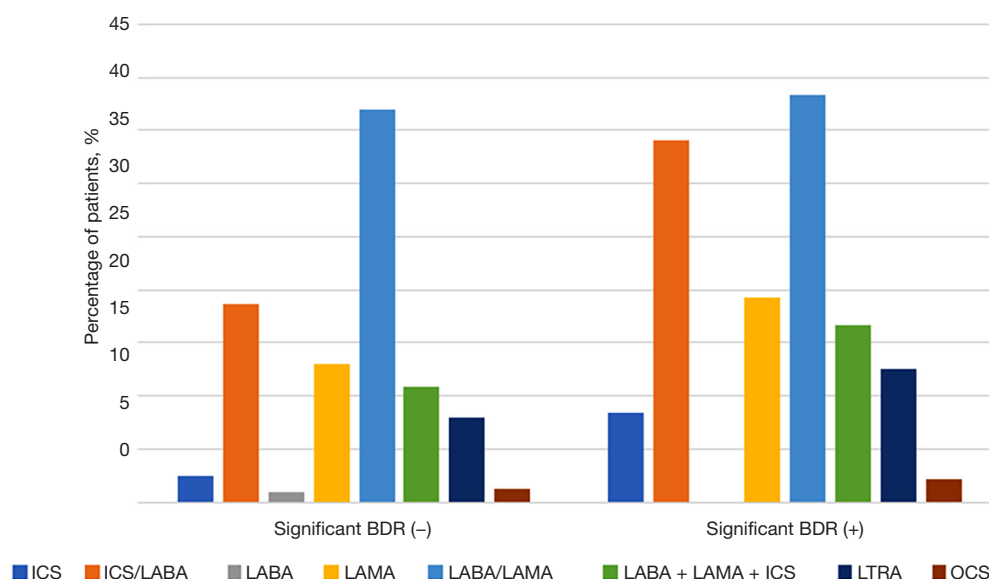


Figure 3 Respiratory drugs used in patients with bronchiectasis. BDR, bronchodilator response; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroids.

Table 3 Exacerbations events in patients with bronchiectasis

Variables	Baseline				1-year			
	Total	Significant BDR (+)	Significant BDR (-)	P	Total	Significant BDR (+)	Significant BDR (-)	P
Exacerbation events (n)	709	52	657		561	46	515	
Acute exacerbation	19.2%	39.1%	17.7%	<0.001	10.6%	25.0%	9.4%	0.005*
ER visit	7.3%	15.4%	6.7%	0.045**	3.0%	4.4%	2.9%	0.64
Mean ± SD	0.08±0.31	0.17±0.43	0.08±0.30	0.02*	0.04±0.24	0.04±0.21	0.04±0.25	0.59*
Admission	17.6%	30.8%	16.6%	0.01	9.6%	19.6%	8.7%	0.02
Mean ± SD	0.23±0.66	0.40±0.66	0.21±0.54	0.008*	0.13±0.47	0.24±0.52	0.12±0.47	0.02*
ICU admission	0.6%	1.9%	0.5%	0.26**	6.2%	10.9%	5.8%	0.19*
Hemoptysis	14.3%	17.3%	14.0%	0.51	6.2%	10.9%	5.8%	0.19*

Data are presented as mean ± SD and percentage. *, P values from Mann-Whitney test; **, P values from Fisher's exact test. BDR, bronchodilator response; ER, emergency room; ICU, intensive care unit; SD, standard deviation.

age, female gender, smoking, asthma, and COPD tended to be associated with acute exacerbations but did not show statistical significance.

Comparison of the groups with and without BDR in patients without asthma and COPD

We summarized baseline characteristics of patients excluding asthma and COPD in Table S1. Of 348 patients

without asthma and COPD, 15 (4.3%) exhibited a BDR. Unlike the total patient group results, there was no significant difference in BMI between the BDR group and the group without BDR. Comorbidities such as cardiovascular diseases, diabetes, depression, and anxiety showed similar frequencies in those with and without BDR.

Patients with BDR exhibited poorer pulmonary function compared to those without BDR on initial spirometry [FEV₁ (%), 60.9% vs. 73.3%] and 1-year follow-up spirometry

Table 4 Severity indexes in patients with bronchiectasis

Variables	Total	Significant BDR (+)	Significant BDR (–)	P
Severity index				
BSI	6.8±3.7	7.8±3.9	6.8±3.6	0.03*
0–4 (mild)	28.8%	18.8%	29.7%	0.23
5–8 (moderate)	46.9%	50.0%	46.6%	
≥9 (severe)	24.3%	31.2%	23.7%	
FACED	2.1±1.6	2.7±1.6	2.0±1.6	0.007
0–2 (mild)	58.4%	33.3%	60.7%	<0.001
3–4 (moderate)	33.2%	58.3%	31.0%	
5–7 (severe)	8.4%	8.3%	8.3%	
E-FACED	2.4±1.9	3.2±2.0	2.3±1.9	0.002
0–3 (mild)	76.7%	56.2%	78.5%	<0.001
4–6 (moderate)	19.9%	41.7%	18.0%	
7–9 (severe)	3.4%	2.1%	3.5%	
QoL questionnaire				
PHQ-9	5.1±5.7	5.3±6.2	5.1±5.6	0.71*
FSS	23.8±14.0	24.4±14.6	23.8±13.9	0.75

Data are presented as mean ± SD and percentage. *, P values from Mann-Whitney test. BDR, bronchodilator response; BSI, Bronchiectasis Severity Index; E-FACED, FACED plus exacerbations; FACED, F: FEV₁; A: age; C: chronic colonization by *Pseudomonas aeruginosa*; E: radiological extension (number of pulmonary lobes affected), and D: dyspnea; FSS, Fatigue Severity Scale; PHQ-9, Patient Health Questionnaire-9; QoL, quality of life; SD, standard deviation.

Table 5 Multivariable logistic regression for acute exacerbations of bronchiectasis

Variables	OR (95% CI)	SE	P
BDR	2.90 (1.52–5.50)	0.95	0.001
Age	0.98 (0.96–1.00)	0.01	0.05
Female	1.69 (0.93–3.09)	0.52	0.09
Smoking	1.57 (0.84–2.94)	0.50	0.16
Asthma	1.08 (0.67–1.73)	0.31	0.76
COPD	1.43 (0.95–2.15)	0.30	0.09

BDR, bronchodilator response; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; SE, standard error.

[FEV₁ (%), 58.0% *vs.* 72.6%] (Table S2). LABA plus LAMA was the most used inhaled agent in both patients with and without BDR (41.7% and 19.9%). Other inhaled agents, except LABA plus LAMA, oral corticosteroids (OCS) and leukotriene receptor antagonists (LTRA), were used in less than 10% of patients regardless of BDR and did not show statistically significant differences (Table S3).

Table 6 shows the results of a multivariate linear regression analysis that evaluated the impact of BDR on several lung function indicators and disease severity indicators while adjusting for asthma and COPD. Although the presence of asthma and COPD has a complex effect on decreased lung function and increased disease severity, it was found to have a statistically significant effect on lung function (especially FEV₁), FACED, and E-FACED even after adjusting for the effects of asthma and COPD.

Longitudinal subgroup classification based on BDR changes over 1-year

Among the 342 patients who underwent baseline and 1-year follow-up spirometry, including BDR testing, 16 patients exhibited BDR at baseline, 15 showed BDR at the 1-year follow-up, and 4 demonstrated BDR at both time points. The remaining 307 patients did not show BDR at either time point. There were no statistically significant differences in clinical characteristics when comparing these four groups.

However, analysis of pulmonary function revealed that patients with BDR at baseline had significantly lower FEV₁ (L) and FEV₁ (% predicted) compared to those without BDR in baseline spirometry (1.28±0.39 *vs.* 1.70±0.64 L, and 51.65%±17.11 *vs.* 63.27%±19.39%, respectively). Similarly, at the 1-year time point, those with BDR at the 1-year follow-up had significantly lower FEV₁ values (1.32±0.27 *vs.* 1.69±0.65 L, and 48.24%±12.38% *vs.* 63.20%±19.71%, respectively). FVC or post-bronchodilator spirometry parameters did not show significant differences across the groups.

In terms of exacerbation rate, BDR-positive groups tended to have a higher rate of patients experiencing acute exacerbations at baseline compared to the BDR-negative group (46.2% *vs.* 30.8% *vs.* 75.0% *vs.* 18.1%, for baseline only, 1-year only, both time points, and neither time point, respectively). This trend was also reflected in emergency room visits (18.8% *vs.* 20.0% *vs.* 25.0% *vs.* 7.5%) and hospitalization rates (43.8% *vs.* 20.0% *vs.* 50.0% *vs.* 16.0%). At the 1-year time point, none of the patients who

Table 6 Multivariate linear regression analysis for impact of BDR on lung function and severity indexes

Outcome	Coefficient	SD	t-value	P	Asthma coefficient	COPD coefficient
FEV ₁ (mL)	-261.2	84.5	-3.09	0.002	-237.9	-388.9
FEV ₁ (%)	-10.7	2.5	-4.29	<0.001	-4.5	-16.6
FVC (mL)	-97.5	115.4	-0.84	0.40	-210.3	-107.3
FVC (%)	-4.6	2.3	-2.00	0.046	-0.9	-7.7
1-year FEV ₁ (mL)	-265.0	93.3	-2.84	0.005	-229.7	-403.3
1-year FEV ₁ (%)	-9.8	2.8	-3.44	0.001	-5.3	-16.7
1-year FVC (mL)	-122.1	131.1	-0.93	0.35	-196.2	-123.8
1-year FVC (%)	-4.5	2.7	-1.71	0.09	-1.3	-8.0
FEV ₁ change [1-year-baseline (mL)]	0.8	36.5	0.02	0.98	8.3	11.7
FVC change [1-year-baseline (mL)]	-22.3	48.6	-0.46	0.65	-6.7	-9.5
BSI	0.94	0.54	1.74	0.08	0.03	1.60
FACED	0.55	0.23	2.40	0.02	0.14	0.99
E-FACED	0.77	0.28	2.78	0.006	0.13	1.13

Adjusted for asthma, COPD. BDR, bronchodilator response; BSI, Bronchiectasis Severity Index; COPD, chronic obstructive pulmonary disease; E-FACED, FACED plus exacerbations; FACED, F: FEV₁; A: age; C: chronic colonization by *Pseudomonas aeruginosa*, E: radiological extension (number of pulmonary lobes affected), and D: dyspnea; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; SD, standard deviation.

exhibited BDR at baseline and follow-up experienced acute exacerbations. In contrast, the rate of patients with acute exacerbations was significantly higher among those who had BDR at only one time point compared to the persistently BDR-negative group (25.0% *vs.* 35.7% *vs.* 8.1%, respectively), and this pattern persisted for hospitalization rates (12.5% *vs.* 33.3% *vs.* 8.8%).

No statistically significant differences were found in bronchiectasis severity index scores across the four groups (data not shown).

Discussion

In this study, the incidence of BDR among total bronchiectasis patients was 7.3%. Although the rate of co-existing asthma in the patient group with BDR was significantly higher than in the patient group without BDR, only 36.5% of patients had been diagnosed with asthma, and the proportion of patients with COPD history was even higher at 46.2% in patients with BDR. Patients with BDR exhibited worse pulmonary function compared to patients without BDR. Additionally, patients with BDR showed a higher risk of emergency room visits and hospital admissions. They also displayed a more severe disease

status as indicated by high scores on the BSI, FACED, and E-FACED scores compared to patients without BDR. The association of BDR with worse lung function and a higher proportion of patients experiencing acute exacerbations persisted even after adjusting for gender, age, history of asthma, and history of COPD.

The primary implication of this study is that BDR is associated with worse lung function, a higher risk of acute exacerbation, and increased disease severity. BDR may indicate the presence of asthma; however, other respiratory conditions, such as COPD and bronchiectasis, can also exhibit bronchial airway hyperreactivity (21,22). Some studies about COPD have suggested that airway reversibility has poor prognostic implications, while others have suggested that COPD patients with more significant airway reversibility have better long-term outcomes (23,24). For bronchiectasis, limited reports exist on the association between BDR and clinical characteristics and prognosis. An earlier study found that a greater magnitude of BDR was associated with poorer baseline FEV₁ percentage of predicted value and consistently poorer lung function throughout follow-up. However, BDR was not considered an indicator of lung function decline, suggesting it might be a pulmonary aging process (11). These results were

similar to those of our study, even if our study did not exclude patients with COPD and asthma, unlike the former study. Therefore, we suggest that BDR in bronchiectasis is associated with lower lung function.

We defined BDR as an improvement of at least 200 mL and 12% in either FEV₁ or FVC from the pre-bronchodilator value to the post-bronchodilator value, either for baseline spirometry or 1-year spirometry. This definition follows the 2005 European Respiratory Society (ERS)/American Thoracic Society (ATS) interpretive strategies for routine lung function tests (25). BDR assessed by FEV₁ is commonly used in routine clinical practice to differentiate asthma from COPD. However, it is noteworthy that up to 32% of patients with COPD may also exhibit a BDR (26). In a study focusing on BDR, it has been observed that FEV₁ is mainly affected by airflow limitation at high lung volumes. In contrast, FVC is primarily influenced by airflow at low lung volumes (27). In asthma, the degree of BDR is positively related to higher severity and increased disease-related mortality (28). On the other hand, in COPD, BDR may be associated with better exercise tolerance, less emphysema, more exacerbations, and lower mortality, indicating a more asthma-like phenotype (26,28). Bronchiectasis is characterized by impaired mucociliary clearance, increased bronchial secretions, and airway dilation due to chronic airway injury. These alterations in the airway can lead to airway obstruction, airflow limitation, and airway hyper-responsiveness in spirometry (29-32).

In our study, LABA plus LAMA was the most commonly used inhaled agent in patients with and without BDR. ICS and ICS plus LABA agents were used significantly more frequently in patients with BDR than in patients without BDR (8.5% *vs.* 2.5%, 34.0% *vs.* 18.7%, respectively; $P < 0.05$). In the patient group without asthma and COPD, other inhaled agents were used in less than 10% of cases, but LABA plus LAMA was used in 41.7% of cases with BDR and 19.9% without BDR. Bronchiectasis guidelines state that using bronchodilators or ICS depends on comorbid conditions such as asthma or COPD (33,34). Chronic bronchial inflammation in bronchiectasis is characterized by the infiltration of mononuclear cells or neutrophils and is associated with inflammatory factors such as interleukin-6, interleukin-8, and tumor necrosis factor- α . Studies have demonstrated a correlation between these factors (30,31), and an approach suggests that corticosteroids may exhibit potential anti-inflammatory effects by reducing inflammatory cells in the airways and inhibiting the release of inflammatory cytokines and chemokines (35-39). Several

studies have confirmed that using ICS in bronchiectasis improves clinical symptoms and quality of life (36,37), and other studies show synergy in anti-inflammatory effects when using ICS and LABA together (40,41). However, in the case of bronchiectasis, where the risk of recurrent airway infection is high (42), it is important to exercise caution when prescribing ICS based solely on BDR without evidence of Th2 inflammatory markers (e.g., blood eosinophil count or immunoglobulin E and fractional exhaled nitric oxide) (43). In bronchiectasis, airflow limitation is not uncommon, and dyspnea is common, leading to frequent use of bronchodilators (44). Inhaled β_2 agonists and anticholinergics can improve symptoms and lung function in patients with bronchiectasis (45). One study found that daily use of tiotropium over 6 months did not reduce acute exacerbations but improved lung function (46). Also, another study aimed at determining whether the use of an inhaled dual bronchodilator (LABA and LAMA) for 12 months for bronchiectasis, either as monotherapy or in combination with ICS, reduces the number of BEs requiring antibiotic treatment is currently underway (47). When examining the bronchiectasis subgroup in studies on obstructive airway diseases, particularly chronic obstructive airflow limitation (FEV₁/FVC < 0.7 ; with or without FEV₁ reversibility to bronchodilators), the benefits of bronchodilators were confirmed in patients with asthma. Additionally, one study showed the benefit of using ICS together in the presence of asthma (35). However, this study only included baseline and 1-year data, did not analyze changes in lung function, symptoms, and severity due to the use of ICS and bronchodilators, and there is no evidence for the simultaneous use of bronchodilators in patients without dyspnea. So future research on this is needed.

Our study has several limitations that should be further considered. First, this study was an observational study, and only the characteristics such as demographics, spirometry, acute exacerbation, and severity index according to BDR status were roughly known, making it challenging to confirm treatment response based on actual treatment. Second, we defined BDR according to the 2005 ERS/ATS criteria (≥ 200 mL and $\geq 12\%$ improvement in FEV₁ or FVC). However, the most recent ERS/ATS guidelines [2022] recommend expressing BDR relative to the predicted value, with a threshold of $> 10\%$ of the predicted value. Because we conducted our study in a setting before 2018, predicted values were not separately collected, and applying the 2022 criteria would have required reverse calculation from actual values and percentage predicted, introducing

potential sources of error. Moreover, the 2022 criteria have been primarily validated in COPD and asthma populations, and no studies have applied these definitions to patients with bronchiectasis. Future studies comparing the impact of the 2005 versus 2022 BDR criteria in bronchiectasis cohorts are warranted to clarify their clinical relevance in this population. Third, asthma and COPD may have been underestimated because they were reported by the patient in medical histories. Also, we collected only baseline and 1-year data, so the analysis of items that can change over time, such as lung function and T2 inflammatory markers, is limited. Finally, BDR was assessed based on its presence at either the baseline or 1-year spirometry rather than requiring both tests. We made this decision due to the study's observational nature, where not all patients underwent spirometry at both time points, and PFTs were performed at widely spaced intervals (baseline and 1 year). Although limiting the analysis to patients with complete longitudinal data might have allowed for more direct comparisons, such a restriction could introduce selection bias. Moreover, in the subgroup of patients who underwent both tests, we found that only a minority exhibited consistent BDR across time points, suggesting that BDR may represent a dynamic and variable physiological trait rather than a fixed characteristic. This temporal variability should be considered when interpreting the clinical significance of BDR in chronic airway diseases, and it highlights the need for future studies with more frequent and longitudinal follow-ups of pulmonary function to better characterize BDR trajectories over time.

Conclusions

Our study described the characteristics of the BDR in bronchiectasis. BDR was associated with worse lung function, a higher rate of acute exacerbations, and higher severity, and these patterns persisted even after adjusting for gender, age, history of asthma, and history of COPD. ICS and bronchodilators are commonly used in bronchiectasis, especially when there is a BDR, but it is not clear how each drug affects the course. Further research will be needed to assess the effectiveness of these drugs in bronchiectasis.

Acknowledgments

The authors thank all members of the Korean Multicenter Bronchiectasis Audit and Research Collaboration (KMBARC) registry. The abstract of this study was published as a conference abstract in the 28th Congress of

the Asian Pacific Society of Respiriology (APSR 2023).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-2025-713/rc>

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-2025-713/prf>

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-2025-713/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. O'Donnell AE. Bronchiectasis - A Clinical Review. *N Engl J Med* 2022;387:533-45.
2. Ringshausen FC, de Roux A, Diel R, et al. Bronchiectasis in Germany: a population-based estimation of disease prevalence. *Eur Respir J* 2015;46:1805-7.
3. Quint JK, Millett ER, Joshi M, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016;47:186-93.
4. Weycker D, Hansen GL, Seifer FD. Prevalence and incidence of noncystic fibrosis bronchiectasis among US

- adults in 2013. *Chron Respir Dis* 2017;14:377-84.
5. Choi H, Yang B, Nam H, et al. Population-based prevalence of bronchiectasis and associated comorbidities in South Korea. *Eur Respir J* 2019;54:1900194.
6. Polverino E, Dimakou K, Hurst J, et al. The overlap between bronchiectasis and chronic airway diseases: state of the art and future directions. *Eur Respir J* 2018;52:1800328.
7. Huang JT, Cant E, Keir HR, et al. Endotyping Chronic Obstructive Pulmonary Disease, Bronchiectasis, and the “Chronic Obstructive Pulmonary Disease-Bronchiectasis Association”. *Am J Respir Crit Care Med* 2022;206:417-26.
8. Ni Y, Shi G, Yu Y, et al. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2015;10:1465-75.
9. Du Q, Jin J, Liu X, et al. Bronchiectasis as a Comorbidity of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *PLoS One* 2016;11:e0150532.
10. Radovanovic D, Santus P, Blasi F, et al. A comprehensive approach to lung function in bronchiectasis. *Respir Med* 2018;145:120-9.
11. Guan WJ, Gao YH, Xu G, et al. Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications. *J Thorac Dis* 2016;8:14-23.
12. Jeong HJ, Lee H, Carriere KC, et al. Effects of long-term bronchodilators in bronchiectasis patients with airflow limitation based on bronchodilator response at baseline. *Int J Chron Obstruct Pulmon Dis* 2016;11:2757-64.
13. Martinez-Garcia MA, Polverino E, Aksamit T. Bronchiectasis and Chronic Airway Disease: It Is Not Just About Asthma and COPD. *Chest* 2018;154:737-9.
14. McShane PJ, Naureckas ET, Tino G, et al. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2013;188:647-56.
15. Lee H, Choi H, Sim YS, et al. KMBARC registry: protocol for a multicentre observational cohort study on non-cystic fibrosis bronchiectasis in Korea. *BMJ Open* 2020;10:e034090.
16. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* 2019;200:e70-88.
17. Choi J, Paek D, Lee J. Normal Predictive Values of Spirometry in Korean Population. *Tuberc Respir Dis* 2005;58:230-42.
18. Chalmers JD, Goeminne P, Aliberti S, et al. The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med* 2014;189:576-85.
19. Martínez-García MÁ, de Gracia J, Vendrell Relat M, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *Eur Respir J* 2014;43:1357-67.
20. Martinez-Garcia MA, Athanazio RA, Girón R, et al. Predicting high risk of exacerbations in bronchiectasis: the E-FACED score. *Int J Chron Obstruct Pulmon Dis* 2017;12:275-84.
21. Choi JY, Kim SK, Lee JH, et al. Differences in clinical significance of bronchodilator responses measured by forced expiratory volume in 1 second and forced vital capacity. *PLoS One* 2023;18:e0282256.
22. Tashkin DP, Celli B, Decramer M, et al. Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008;31:742-50.
23. Hanania NA, Celli BR, Donohue JF, et al. Bronchodilator reversibility in COPD. *Chest* 2011;140:1055-63.
24. Marín JM, Ciudad M, Moya V, et al. Airflow reversibility and long-term outcomes in patients with COPD without comorbidities. *Respir Med* 2014;108:1180-8.
25. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
26. Fortis S, Comellas A, Make BJ, et al. Combined Forced Expiratory Volume in 1 Second and Forced Vital Capacity Bronchodilator Response, Exacerbations, and Mortality in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2019;16:826-35.
27. Albert P, Agusti A, Edwards L, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax* 2012;67:701-8.
28. Betancor D, Villalobos-Vilda C, Olaguibel JM, et al. The New ERS/ATS 2022 Bronchodilator Response Recommendation: Comparison With the Previous Version in an Asthma Cohort. *Arch Bronconeumol* 2023;59:608-11.
29. King PT. The pathophysiology of bronchiectasis. *Int J Chron Obstruct Pulmon Dis* 2009;4:411-9.
30. Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. *Eur Respir J* 2008;31:396-406.
31. Chalmers JD, Hill AT. Mechanisms of immune dysfunction and bacterial persistence in non-cystic fibrosis bronchiectasis. *Mol Immunol* 2013;55:27-34.

32. Wei P, Yang JW, Lu HW, et al. Combined inhaled corticosteroid and long-acting β 2-adrenergic agonist therapy for noncystic fibrosis bronchiectasis with airflow limitation: An observational study. *Medicine (Baltimore)* 2016;95:e5116.
33. Hill AT, Sullivan AL, Chalmers JD, et al. British Thoracic Society Guideline for bronchiectasis in adults. *Thorax* 2019;74:1-69.
34. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017;50:1700629.
35. Kapur N, Bell S, Kolbe J, et al. Inhaled steroids for bronchiectasis. *Cochrane Database Syst Rev* 2009;(1):CD000996.
36. Tsang KW, Tan KC, Ho PL, et al. Inhaled fluticasone in bronchiectasis: a 12 month study. *Thorax* 2005;60:239-43.
37. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, et al. Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. *Respir Med* 2006;100:1623-32.
38. Hernando R, Drobnic ME, Cruz MJ, et al. Budesonide efficacy and safety in patients with bronchiectasis not due to cystic fibrosis. *Int J Clin Pharm* 2012;34:644-50.
39. Martínez-García MÁ, Soler-Cataluña JJ, Catalán-Serra P, et al. Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. *Chest* 2012;141:461-8.
40. Mak JC, Nishikawa M, Shirasaki H, et al. Protective effects of a glucocorticoid on downregulation of pulmonary beta 2-adrenergic receptors in vivo. *J Clin Invest* 1995;96:99-106.
41. Pang L, Knox AJ. Synergistic inhibition by beta(2)-agonists and corticosteroids on tumor necrosis factor-alpha-induced interleukin-8 release from cultured human airway smooth-muscle cells. *Am J Respir Cell Mol Biol* 2000;23:79-85.
42. Chalmers JD, Chang AB, Chotirmall SH, et al. Bronchiectasis. *Nat Rev Dis Primers* 2018;4:45.
43. Shoemark A, Shteinberg M, De Soyza A, et al. Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study. *Am J Respir Crit Care Med* 2022;205:894-902.
44. Chalmers JD, Polverino E, Crichton ML, et al. Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). *Lancet Respir Med* 2023;11:637-49.
45. Martínez-García MÁ, Oscullo G, García-Ortega A, et al. Rationale and Clinical Use of Bronchodilators in Adults with Bronchiectasis. *Drugs* 2022;82:1-13.
46. Jayaram L, Vandal AC, Chang CL, et al. Tiotropium treatment for bronchiectasis: a randomised, placebo-controlled, crossover trial. *Eur Respir J* 2022;59:2102184.
47. Morton M, Wilson N, Homer TM, et al. Dual bronchodilators in Bronchiectasis study (DIBS): protocol for a pragmatic, multicentre, placebo-controlled, three-arm, double-blinded, randomised controlled trial studying bronchodilators in preventing exacerbations of bronchiectasis. *BMJ Open* 2023;13:e071906.

Cite this article as: Kang YR, Lee H, Choi H, Ra SW, Oh YM, Seo KH, Choi JS, Lee HS, Lyu J, Lee J, Kim JY, Kim KD, Na JO. Bronchodilator response as an independent predictor of severity in bronchiectasis. *J Thorac Dis* 2025;17(10):7515-7527. doi: 10.21037/jtd-2025-713