Original Article

Presence and sequence of bronchiectasis onset impact on the clinical characteristics in asthmatic patients

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Background: Asthmatic patients with comorbid bronchiectasis (ACB) show significantly severe condition with various inflammatory phenotypes; bronchiectasis is a heterogeneous disease caused by asthma and other multiple etiological factors. We aimed to investigate the inflammatory characteristics and their clinical significance in asthmatic patients according to the presence and onset time of bronchiectasis.

Methods: This prospective cohort study recruited outpatients with stable asthma. All the enrolled patients were divided into the non-bronchiectasis group and the ACB group, and the ACB group was separated into the bronchiectasis-prior group and the asthma-prior group. Demographic and clinical data were collected, and peripheral blood and induced sputum eosinophil counts, sputum pathogens, the fraction of exhaled nitric oxide (FeNO), lung function, and chest high-resolution computed tomography were examined.

Results: A total of 602 patients (mean age: 55.36±14.58 years) were included, of which 255 (42.4%) were males. Bronchiectasis was present in 268 (44.5%) patients, with 171 (28.41%) in the asthma-prior group and 97 (16.11%) in the bronchiectasis-prior group. For the asthma-prior group, the presence of bronchiectasis was positively correlated with age, presence of nasal polyps, severe asthma, ≥1 pneumonia in the last 12 months, ≥1 severe exacerbation of asthma in the last 12 months (SEA), peripheral blood eosinophil counts, and sputum eosinophil ratio; the extent and severity of bronchiectasis were positively correlated with ≥1 SEA and FeNO levels; and the bronchiectasis severity index (BSI) scores were positively correlated with ≥1 SEA and immunoglobulin E levels. For the bronchiectasis-prior group, bronchiectasis was positively correlated with previous pulmonary tuberculosis or pneumonia in childhood and ≥1 pneumonia in the last 12 months and negatively correlated with forced expiratory volume in one second (FEV_1) % and the FeNO level. The extent and severity of bronchiectasis were positively correlated with ≥1 pneumonia in the last 12 months and negatively correlated with FEV_1%. The BSI scores were positively correlated with the duration of bronchiectasis.

Conclusions: The sequence of bronchiectasis onset may indicate distinct inflammatory characteristics and may be helpful in targeted therapy for patients with asthma.

Keywords: Asthma; bronchiectasis; comorbidity; nasal polyps

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Introduction

Asthma and bronchiectasis are both common chronic respiratory diseases (1,2). Asthma affects 1–18% of the population and has received considerable attention (1). Asthma is a heterogeneous disease with distinct phenotypes demonstrating different underlying disease processes and therapeutic approaches (3). In contrast, bronchiectasis is a long-neglected chronic airway disorder, even though it is associated with poor quality of life and frequent exacerbations in many patients, adding a severe disease burden globally (2). Recently, several studies have investigated the prevalence and characteristics of asthma comorbid with bronchiectasis (ACB), indicating that bronchiectasis was diagnosed in 2–68% of patients with asthma, especially severe asthma (4-7). Bronchiectasis contributes to more frequent severe exacerbations and hospitalizations, decreased lung function, and poor prognosis in patients with asthma (8,9). Guidelines specifically recommend the investigation of bronchiectasis in patients with severe or poorly controlled asthma (1,10).

Asthma is primarily characterized by eosinophilic inflammation, while bronchiectasis is characterized by neutrophilic inflammation (1,11). Recent studies have noted at least two inflammatory phenotypes in ACB patients: chronic infectious bronchiectasis and eosinophilic bronchiectasis (4). Traditionally, neutrophilic inflammation caused by airway infection, which impairs mucociliary clearance and airway destruction and, in turn, predisposes the damaged airway to further infection, was regarded as the primary etiology of bronchiectasis (11). Several studies have shown that ACB patients experienced more episodes of pneumonia, increased pathogen isolation in the sputum, and lower fractional exhaled nitric oxide (FeNO) levels than pure asthmatic patients (5,8,12). In contrast, recent studies have shown that eosinophilic inflammation rather than chronic infection, may be involved in the formation and development of bronchiectasis in asthmatic patients. Serial records showed higher blood eosinophil counts in ACB patients than in pure asthmatic patients, indicating that bronchiectasis could be driven by an eosinophilic endotype (5,9,13). Additionally, other investigative series concluded that blood eosinophil counts and serum levels of immunoglobulin (Ig) Es were comparable in ACB and pure asthmatic patients (14,15). Generally, bronchiectasis is a heterogeneous disease due to multiple etiological factors, such as lower airway infection in children and previous pulmonary tuberculosis (PTB), in addition to asthma (10,11). Therefore, it is crucial to investigate the inflammatory characteristics of ACB patients based on the sequence of the onset of bronchiectasis and asthma.

Herein, we investigated inflammatory characteristics and the clinical significance in asthmatic patients according to the presence and onset time of bronchiectasis, and to explore targeted treatment accordingly. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1288/rc).

Highlight box

Key findings

- The sequence of bronchiectasis onset indicated distinct inflammatory characteristics in ACB, with eosinophilic inflammatory characteristics in asthma-prior group and non-eosinophilic chronic infectious inflammatory characteristics in bronchiectasis-prior group.

What is known and what is new?

- ACB presents as a significantly severe condition with various inflammatory phenotypes; bronchiectasis is a heterogeneous disease caused by multiple etiological factors.
- Previous studies rarely explored in the causality of asthma and bronchiectasis or defined asthma-induced bronchiectasis as a diagnosis of asthma preceding bronchiectasis. Herein, we investigated the distinct impact of bronchiectasis with asthma-induced or not on the clinical characteristics of patients with asthma.

What is the implication, and what should change now?

- We suggest that following up chest CT and lung function to investigate bronchiectasis is indispensable for patients with asthma, and medical history collection in details may play a role in the targeted therapy to ACB patients.

Methods

Study and participants

This prospective cohort study consecutively enrolled outpatients diagnosed with asthma aged 18–79 years at the Department of Respiratory Medicine and Otorhinolaryngology of Beijing Tongren Hospital from June 2019 to May 2022. Asthmatic diagnosis: Global Initiative for Asthma (GINA) criteria by definite asthmatic symptoms and lung function with hyperbronchodilator reversibility and/or airway hyperresponsiveness (1). None of the participants experienced any exacerbation or respiratory infection for at least one month. Severe

asthma was identified as an uncontrolled condition despite optimized treatment with high-dose inhaled corticosteroids (ICS) with a long-acting β_2-adrenoceptor agonist (LABA) or worsened when high-dose treatment was subsided (1). Severe exacerbation of asthma (SEA) was described as a life-threatening asthma attack requiring emergency department visit, hospitalization or oral corticosteroids administration (1). The exclusion criteria were as follows: (I) chronic obstructive pulmonary disease (COPD), active PTB, pneumonia, interstitial lung disease, or any other significant respiratory diseases; (II) post-pneumonectomy; (III) pleural effusion and other chest wall diseases; (IV) pregnant state; (V) active tumor; (VI) severe heart failure; (VII) autoimmune disease; (VIII) immunodeficiency disease.

Bronchiectasis is defined by the presence of both permanent bronchial dilatation on computed tomography (CT) and the clinical syndrome of cough, sputum production, and/or recurrent respiratory infections, according to the guidelines (10,16). All enrolled patients were divided into two groups according to whether they presented with bronchiectasis: the non-bronchiectasis group and the ACB group. Furthermore, we separated ACB group patients into the bronchiectasis-prior group and the asthma-prior group according to whether the onset of bronchiectasis was prior to asthma. Details of the bronchiectasis-prior group were as follows: (I) the typical clinical symptoms of bronchiectasis (especially purulent sputum production, hemoptysis, and/or recurrent respiratory infections) preceded or coincided with asthmatic symptoms (especially wheezing), (II) bronchiectasis diagnosed with chest high-resolution CT (HRCT) presented prior to or coincident with the asthmatic symptoms, or (III) diagnosis of bronchiectasis preceding or coincident with asthma; while the other patients were categorized as the asthma-prior group. Two independent respiratory physicians grouped the patients according to the above criteria, and a third senior respiratory physician made the final decision when there was a disagreement.

Demographic and clinical data were collected. Peripheral eosinophil counts, induced sputum eosinophils, sputum culture, total and specific immunoglobulin E (IgE) levels, FeNO, lung function, and chest imaging were examined.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Beijing Tongren Hospital, Capital Medical University (approval No. TRECKY2019-070). Written informed consent was obtained from all enrolled patients.

Pulmonary function test

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were tested using a spirometer (Jaeger, Germany). The procedure was performed according to the current ATS/ERS guidelines (17).

FeNO analysis

Patients were instructed to exhale through a disposable mouthpiece at 50 mL/s flow rate using a NIOX electrochemical analyzer (Aerocrine AB, Sweden) (18). The process was measured no less than three times, calculating the average values for analysis.

Induced sputum analysis

Induced sputum samples were obtained as previously described (19). Briefly, following inhalation of 200 μg salbutamol, sputum was induced with an ultrasonic nebulizer (PARIBOYSX, Germany) using inhaled hypertonic saline at 4.5% concentration. The samples were collected in sterile containers and analyzed within two hours. The sputum was stained with *Papanicolaou* stain. An independent investigator counted 400 non-squamous cells under a microscope. The sputum eosinophil ratio was expressed as the percentage of eosinophils in the total non-squamous cell count. Squamous epithelial cells/ the total cells <10% were considered adequate for the analysis.

Radiological diagnosis and severity assessment of bronchiectasis by using HRCT

Chest HRCT (Philips Company, the Netherlands) was performed in full inspiration with 1-mm collimation. Bronchiectasis on HRCT was defined as follows: (I) lack of tapering in the bronchi, or (II) broncho-arterial ratio> 1, or (III) airway visibility within 1 cm of the costal pleural surface or contact with the mediastinal pleura (10). Smith scoring system was calculated to assess the extent of bronchiectasis in each lobe: 0, no bronchiectasis; 1, <25% of bronchiectasis; 2, 25–49% of bronchiectasis; 3, 50–74% of bronchiectasis; 4, ≥75% of bronchiectasis; the maximum score was 24. Patients with Smith scores ≥3 were categorized into the bronchiectasis group as previously described (7,20,21). Meanwhile, we used Bhalla scoring system to evaluate the severity of bronchiectasis, scores of 0 to 3 according to the broncho-arterial ratio in each lobe:

0, broncho-arterial ratio ≤1; 1, broncho-arterial ratio = 1–2; 2, broncho-arterial ratio = 2–3; 3, broncho-arterial ratio >3; the maximum score was 18, as described previously (22). Two thoracic radiologists independently assigned the Smith and Bhalla scores for each lobe, and the average represented the final score.

Prediction of future exacerbations, hospitalization and mortality using the Bronchiectasis Severity Index (BSI) tool

The BSI tool was used to identify patients at risk for future mortality, hospitalization, and exacerbations (23). The BSI scores included the following variables: age, body mass index (BMI), FEV_1%predicted, hospital admission within the last 2 years, number of exacerbations in the previous 12 months, MRC breathlessness score, *Pseudomonas* colonization, colonization with other organisms, and radiological severity (≥3 lobes involved or cystic bronchiectasis). We collected the variables data and calculated the BSI scores according to the BSI scoring system described by Hill *et al.* and Chalmers *et al.* (10,23).

Statistical analysis

Parametric, nonparametric, and categorical variables were presented as mean ± standard deviation (SD), median with interquartile ranges (IQR), and frequencies/percentages, respectively. The unpaired *t*-test or Mann-Whitney U test was applied to compare the statistical differences for continuous variables, while Pearson's Chi-squared test or Fisher's exact test was used for categorical variables, as appropriate. Pearson's or Spearman's test was performed to test the correlation between bronchiectasis severity and clinical parameters. Logistic regression and multivariate linear regression were used to calculate coefficients or odds ratios as appropriate, and covariates with P<0.05 were selected for analysis. Sex, age, BMI, and FEV_1% predicted were included in all models as potential confounders. A backward stepwise technique (entry level, 0.10; stay level, 0.05) was used to perform the analysis. Statistical analyses were performed using IBM SPSS Statistics for Windows 21.0 (IBM Corp., Armonk, NY, USA). P value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

A total of 1,865 outpatients with stable asthma were admitted to the outpatient departments. Of these, 602 (mean ± SD age, 55.36±14.58 years) were enrolled, of which 255 (42.4%) were males. The median duration of asthma was 7 years (range, 2–20). Bronchiectasis was present in 268 (44.5%) patients, with 171 (28.41%) in the asthma-prior group and 97 (16.11%) in the bronchiectasis-prior group. A total of 157 (26.1%) patients experienced at least one episode of pneumonia, and 104 (17.3%) patients experienced at least one episode of SEA in the last 12 months. Totally 290 (48.2%) patients suffered from chronic rhinosinusitis (CRS) and 197 (32.7%) from nasal polyps (NPs). The most common pathogen isolated from the sputum was *Pseudomonas aeruginosa*. Patient characteristics were shown in *Table 1* and *Figure 1*.

Characteristics of ACB group, asthma-prior group, and bronchiectasis-prior group versus non-bronchiectasis group

As shown in *Table 2*, compared to the non-bronchiectasis group, patients with bronchiectasis were older (P<0.001), had lower BMI (P=0.028), longer duration of asthma (P=0.01), higher rates of long-acting muscarinic antagonists (LAMA) and theophylline (P<0.05), higher ICS dose (P=0.006), increased occurrence rates of NPs (P=0.002), higher rate of previous PTB or pneumonia in childhood (P<0.001), higher frequency of severe asthma as well as pneumonia and SEA in the last 12 months (P<0.001), lower FEV_1% predicted (P<0.001), higher sputum eosinophil ratio (P<0.001), and a higher rate of isolation of *Pseudomonas aeruginosa* and *Aspergillus fumigatus* in the sputum (P<0.001). There were no significant differences in gender, smoking status, CRS history, atopy, comorbidity, peripheral blood eosinophil counts, FeNO, and other pathogens isolated from sputum between the two groups.

A comparison of the asthma-prior group and the bronchiectasis-prior group with the non-bronchiectasis group is also shown in *Table 2*. Patients with asthma preceding bronchiectasis were older (P=0.004), had a longer duration of asthma (P=0.003), a higher rate of using ICS + LABA (P=0.001), had higher ICS dose (P<0.001), increased occurrence rates of allergic rhinitis (P=0.002), CRS and NPs (P<0.001), higher frequency of severe asthma as well as pneumonia and SEA in the last 12 months (P<0.001), lower FEV_1% predicted (P=0.002), higher peripheral blood eosinophil counts, sputum eosinophil, total IgE, and FeNO (P<0.001), and positive sputum isolation rates of *Pseudomonas aeruginosa* (P=0.006) and *Klebsiella pneumoniae* (P=0.031) than without bronchiectasis group.

Table 1 Baseline patient characteristics (n=602)

Characteristics[†]	Values
Baseline characteristics	
Male sex, n (%)	255 (42.4)
Age, years	55.36±14.58
BMI, kg/m^2	25.17±4.10
Positive smoking status[‡], n (%)	170 (28.2)
Smoking index, pack-years	0 (0 to 4)
Duration of asthma, years	7 (2 to 20)
Age of onset of asthma, years	42.88±18.16
Bronchiectasis, n (%)	268 (44.5)
Asthma prior to bronchiectasis, n (%)	171 (28.41)
Bronchiectasis prior to asthma, n (%)	97 (16.11)
Duration of bronchiectasis, years	0 (0 to 15)
Age of onset of bronchiectasis, years	48.64±19.60
Previous PTB or pneumonia in childhood, n (%)	65 (10.8)
Medication history	
ICS + LABA, n (%)	399 (66.3)
LAMA, n (%)	24 (4.0)
LTRA, n (%)	77 (12.8)
Theophylline, n (%)	27 (4.5)
OCS, n (%)	20 (3.3)
Omalizumab, n (%)	9 (1.5)
For severe asthma and CRSwNP	6 (1.0)
For severe asthma without CRSwNP	2 (0.3)
For simple asthma with CRSwNP	1 (0.2)
Inhaled SABA only as needed, n (%)	9 (1.5)
ICS dose (fluticasone equivalent)[§], μg/d	320 (0 to 500)
macrolides usage >3 months duration, n (%)	3 (0.5)
Allergic disease, n (%)	
Allergic rhinitis	412 (68.4)
CRS	290 (48.2)
CRSwNP	197 (32.7)
Atopic dermatitis	62 (10.3)
Comorbidity, n (%)	
OSAHS	21 (3.5)
GERD	49 (8.1)
Hypertension	210 (34.9)
CAD	63 (10.5)
Stroke	30 (5.0)
2-DM	94 (15.6)
Asthma severity	
Severe asthma, n (%)	82 (13.6)
≥1 pneumonia in the last 12 months, n (%)	157 (26.1)
≥1 severe exacerbation of asthma in the last 12 months, n (%)	104 (17.3)
Postbronchodilator FEV_1% predicted, %	80.46±21.48
Inflammatory characteristics	
Peripheral blood eosinophil counts, ×10^9/L	0.30 (0.15 to 0.53)
Sputum eosinophil ratio, %	0 (0 to 2)
Total IgE, IU/mL	113.50 (40.15 to 324.25)
Atopy[¶], n (%)	271 (45.0)
Food allergen positive	106 (17.6)
Aeroallergen positive	230 (38.2)
FeNO, ppb	37 (21 to 54)
Pathogens isolated from the sputum, n (%)[&]	171 (28.4)
Pseudomonas aeruginosa	44 (7.3)
Klebsiella pneumoniae	38 (6.3)
Candida albicans	33 (5.5)
Hemophilus influenzae	25 (4.2)
Aspergillus fumigatus	19 (3.2)

[†], parametric data are expressed as the mean ± SD; nonparametric data are expressed as the median (25% to 75%); [‡], positive smoking status included ex- or current-smokers; [§], 2 μg beclomethasone = 2 μg budesonide = 1 μg fluticasone; [¶], food allergen positive, at least one positive allergen; aeroallergen positive, at least one positive aeroallergen; [&], other pathogens included *Escherichia coli* 11, *Staphylococcus aureus* 9, *Actinomyces odontolyticus* 8, *Acinetobacter baumannii* 6, *Enterococcus* 5, *Moraxella catarrhalis* 4, *Streptococcus pneumoniae* 2. BMI, body mass index; PTB, pulmonary tuberculosis; ICS, inhaled corticosteroids; LABA, long-acting β2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting β2-adrenoceptor agonist; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; OSAHS, obstructive sleep apnea hypopnea syndrome; GERD, gastroesophageal reflux disease; CAD, coronary artery disease; 2-DM, diabetes mellitus type 2; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide.

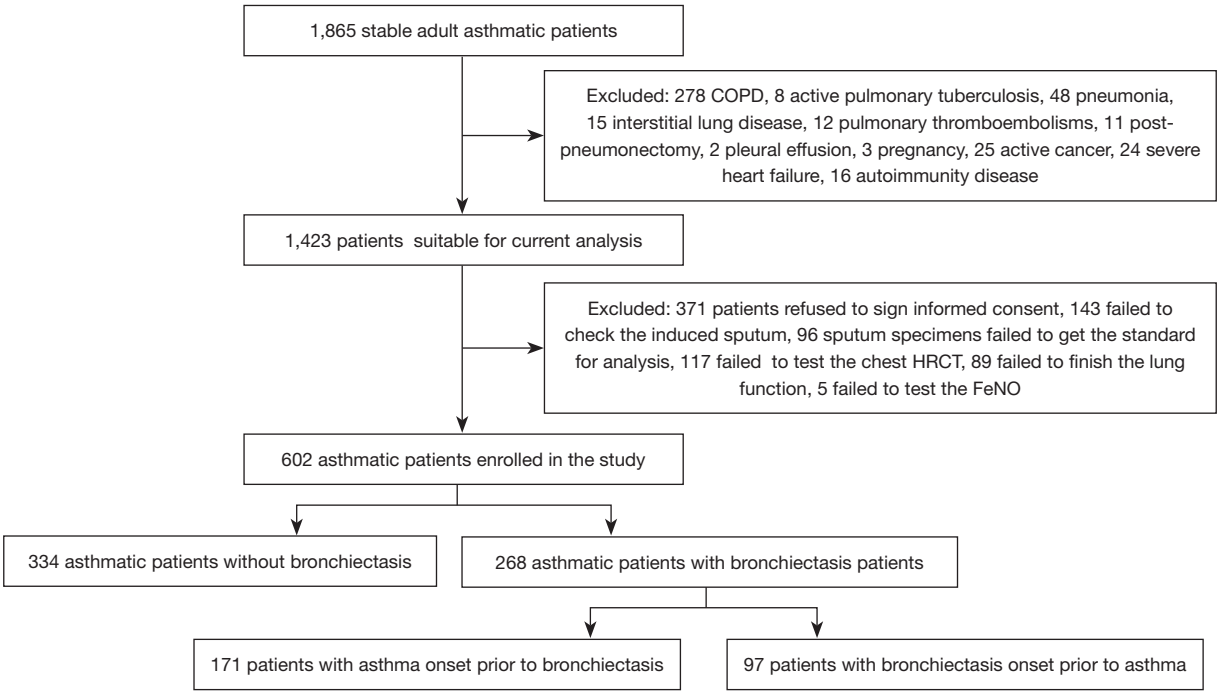

Figure 1 Protocol for the management of asthma in the study. A total of 1,865 stable adult asthmatic patients were admitted to the outpatient departments. Of these, 602 patients were ultimately enrolled in the study after screening. Among them, 268 patients had bronchiectasis, including 171 with asthma onset prior to bronchiectasis and 97 with bronchiectasis prior to asthma. COPD, chronic obstructive pulmonary disease.

Similarly, patients with bronchiectasis preceding asthma were older (P=0.001), had a higher rate of using ICS + LABA (P=0.003), had a higher frequency of severe asthma as well as pneumonia and experienced a SEA in the last 12 months (P<0.05), lower FEV_1% predicted (P<0.001), higher rate of positive sputum isolation of *Pseudomonas aeruginosa* (P<0.001), and *Aspergillus fumigatus* (P=0.001) when compared to asthma without bronchiectasis group. In contrast, patients with bronchiectasis preceding asthma showed decreased occurrence rates of allergic rhinitis, CRS, and NPs (P<0.001), lower peripheral blood eosinophil counts, lower rate of atopy and aeroallergen positive, and decreased total IgE and FeNO (P<0.01) when compared to asthma without bronchiectasis group. In addition, the bronchiectasis-prior group showed lower BMI, higher rates of LAMA (P<0.001) and theophylline use (P=0.010), higher frequency of previous PTB or pneumonia in childhood (P<0.001) and hypertension (P<0.05).

Coexistence of bronchiectasis correlates with disease severity and different inflammatory characteristics in asthmatic patients according to bronchiectasis onset prior or not

For the asthma-prior and non-bronchiectasis groups, the logistic analysis showed that the coexistence of bronchiectasis was positively correlated with age (OR: 1.035; 95% CI: 1.017–1.053), the presence of NPs (OR: 3.790; 95% CI: 2.348–6.115), severe asthma (OR: 2.076; 95% CI: 1.099–3.920), ≥1 pneumonia in the last 12 months (OR: 3.528; 95% CI: 2.062–6.038), ≥1 SEA in the last 12 months (OR: 2.052; 95% CI: 1.151–3.659) , peripheral blood eosinophil counts (OR: 2.181; 95% CI: 1.101–4.321) and sputum eosinophil ratio (OR: 1.260; 95% CI: 1.109–1.432).

For bronchiectasis-prior and non-bronchiectasis groups, the logistic analysis indicated that the coexistence of bronchiectasis was positively correlated with previous PTB or pneumonia in childhood (OR: 22.053; 95% CI: 8.504–

Table 2 Comparison of characteristics of ACB group, asthma-prior group and bronchiectasis-prior group versus non-bronchiectasis group

Characteristics[†]	Non-bronchiectasis group (n=334)	ACB group (n=268)	P value*	Asthma-prior group (n=171)	P value**	Bronchiectasis-prior group (n=97)	P value***
Baseline characteristics							
Male sex (n, %)	146, 43.7	109, 40.7	0.810	71, 41.5	0.638	38, 39.2	0.426
Age, years	52.40±14.67	59.05±13.60	<0.001	56.33±13.84	0.004	63.85±11.80	<0.001
BMI, kg/m^2	25.50±4.06	24.76±4.11	0.028	24.90±3.97	0.118	24.50±4.35	0.037
Positive smoking status[‡] (n, %)	93, 27.8	77, 28.7	0.810	46, 26.9	0.822	31, 32	0.431
Smoking index, pack-years	0 (0, 4)	0 (0, 3.75)	0.949	0 (0, 2)	0.674	0 (0, 5)	0.470
Duration of asthma, years	5.50 (1.00, 15.25)	8 (2, 20)	0.010	8 (3, 20)	0.003	7 (1, 30)	0.397
Age of onset of asthma, years	41.38±16.83	44.76±19.55	0.025	42.87±18.05	0.359	48.10±21.64	0.006
Duration of bronchiectasis, years		0 (0, 15)		0 (0, 0)		23 (9, 50)	
Age of onset of bronchiectasis, years		48.64±19.60		55.71±14.08		36.16±21.71	
Previous PTE or pneumonia in childhood (n, %)	13, 3.9	52, 19, 4	<0.001	8, 4.7	0.675	44, 45.4	<0.001
Medication history							
ICS + LABA (n, %)	217, 65	182, 67.9	0.448	135, 78.9	0.001	47, 48.5	0.003
LAMA (n, %)	6, 1.8	18, 6.7	0.002	6, 3.5	0.232	12, 12.4	<0.001
LTRA (n, %)	42, 12.6	35, 13.1	0.859	21, 12.3	0.925	14, 14.4	0.632
Theophylline (n, %)	9, 2.7	18, 6.7	0.018	9, 5.3	0.141	9, 9.3	0.010
OCS (n, %)	10, 3	10, 3.7	0.616	9, 5.3	0.205	1, 1	0.476
Omalizumab (n, %)	3, 0.9	6, 2.2	0.178	6, 3.5	0.081	0, 0	1
For severe asthma and CRSwNP	1, 0.3	5, 1.9	0.131	5, 2.9	0.032		
For severe asthma without CRSwNP	1, 0.3	1, 0.4	0.693	1, 5.8	0.563		
For simple asthma with CRSwNP	1, 0.3	0, 0	0.555	0, 0	0.661		
Inhaled SABA only as needed (n, %)	6, 1.8	3, 1.1	0.496	1, 0.6	0.270	2, 2.1	0.865
ICS dose (fluticasone equivalent) [§], μg/d	250 (0, 500)	320 (0, 640)	0.006	320 (160, 640)	<0.001	0 (0, 500)	0.171
Macrolides usage >3 months duration (n, %)	0, 0	3, 1.1	0.175	1, 0.585	0.339	2, 2.06	0.05
Allergic disease (n, %)							
Allergic rhinitis	233, 69.8	179, 66.8	0.436	141, 82.5	0.002	38, 39.2	<0.001
CRS	152, 45.5	138, 51.5	0.144	120, 70.2	<0.001	18, 18.6	<0.001
CRSwNP	92, 27.5	105, 39.2	0.002	95, 55.6	<0.001	10, 10.3	<0.001
Atopic dermatitis	40, 12	22, 8, 2	0.131	15, 8.8	0.274	7, 7.2	0.186
Comorbidity (n, %)							
OSAHS	10, 3	11, 4.1	0.461	9, 5.3	0.205	2, 2.1	0.888
GERD	30, 9	19, 7, 1	0.399	9, 5.3	0.138	10, 10.3	0.692
Hypertension	106, 31.7	104, 38, 8	0.070	61, 35.7	0.374	43, 44.3	0.022
CAD	30, 9	33, 12.3	0.184	16, 9.4	0.890	17, 17.5	0.017

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics[†]	Non-bronchiectasis group (n=334)	ACB group (n=268)	P value*	Asthma-prior group (n=171)	P value**	Bronchiectasis-prior group (n=97)	P value***
Stroke	20, 6	10, 3.7	0.206	6, 3.5	0.233	4, 4.1	0.481
2-DM	54, 16.2	40, 14.9	0.676	22, 12.9	0.326	18, 18.6	0.579
Asthma severity							
Severe asthma (n, %)	24, 7.2	58, 21.6	<0.001	40, 23.4	<0.001	18, 18.6	0.001
≥1 pneumonia in the last 12 months (n, %)	46, 13.8	111, 41.4	<0.001	51, 29.8	<0.001	60, 61.9	<0.001
≥1 severe exacerbation of asthma in the last 12 months (n, %)	39, 11.7	65, 24.3	<0.001	44, 25.7	<0.001	21, 21.6	0.012
Postbronchodilator FEV_1% predicted, %	85.49±17.55	74.19±24.16	<0.001	79.43±21.32	0.002	64.97±26.14	<0.001
Inflammatory characteristics							
Peripheral blood eosinophil counts, $\times10^9$/L	0.28 (0.15, 0.50)	0.31 (0.15, 0.58)	0.218	0.43 (0.23, 0.73)	<0.001	0.19 (0.10, 0.31)	<0.001
Sputum eosinophil ratio, %	0 (0, 1)	0 (0, 2.5)	<0.001	1 (0, 3)	<0.001	0 (0, 0.25)	0.137
Total IgE, IU/mL	99.10 (43.75, 291.75)	123.50 (32.53, 385.25)	0.341	219 (57.10, 471)	<0.001	52.30 (21.00, 180.00)	0.001
Atopy[¶] (n, %)	161, 48.2	110, 41	0.079	79, 46.2	0.669	31, 32	0.005
Food allergen positive	61, 18.3	45, 16.8	0.637	31, 18.1	0.970	14, 14.4	0.381
Aeroallergen positive	141, 42.2	89, 33.2	0.024	67, 39.2	0.512	22, 22.7	<0.001
FeNO, ppb	38 (23, 51)	37 (18, 56)	0.616	49 (34, 65)	<0.001	15 (9, 31.5)	<0.001
Pathogens isolated from the sputum (n, %)							
Pseudomonas aeruginosa	7, 2.1	37, 13.8	<0.001	12, 7	0.006	25, 25.8	<0.001
Klebsiella pneumoniae	26, 7.8	12, 4.5	0.097	5, 2.9	0.031	7, 7.2	0.853
Candida albicans	16, 4.8	17, 6.3	0.405	7, 4.1	0.722	10, 10.3	0.044
Hemophilus influenzae	12, 3.6	13, 4.9	0.442	8, 4.7	0.554	5, 5.2	0.690
Aspergillus fumigatus	4, 1.2	15, 5.6	0.002	7, 4.1	0.074	8, 8.2	0.001
Smith scores of bronchiectasis		7.99±4.89		6.73±3.81		10.21±5.74	
Bhalla scores of bronchiectasis		4.66±3.12		3.81±1.61		6.16±4.35	
BSI scores		6.80±4.51		5.13±3.50		9.75±4.59	

*, ACB group versus non-bronchiectasis group; **, asthma-prior group versus non-bronchiectasis group; ***, bronchiectasis-prior group versus non-bronchiectasis group. [†], parametric data are expressed as the mean ± SD; nonparametric data are expressed as the median (25% to 75%). [‡], positive smoking status included ex- or current-smokers. [§], 2 μg beclomethasone = 2 μg budesonide = 1 μg fluticasone. [¶], food allergen positive, at least one positive allergen; aeroallergen positive, at least one positive aeroallergen. BMI, body mass index; ICS, inhaled corticosteroids; LABA, long-acting β2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting β2-adrenoceptor agonist; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; OSAHS, obstructive sleep apnea hypopnea syndrome; GERD, gastroesophageal reflux disease; CAD, coronary artery disease; 2-DM, diabetes mellitus type 2; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; BSI, bronchiectasis severity index; SD, standard deviation.

Table 3 Logistic regression analyses for factors associated with the presence of bronchiectasis in asthma-prior group and non-bronchiectasis group as well as bronchiectasis-prior group and non-bronchiectasis group

Variables	OR	95% CI	P value
Bronchiectasis in asthma-prior group and non-bronchiectasis group, logistic regression			
Age	1.035	1.017 to 1.053	<0.001
CRSwNP	3.790	2.348 to 6.115	<0.001
Severe asthma	2.076	1.099 to 3.920	0.024
≥1 pneumonia in the last 12 months	3.528	2.062 to 6.038	<0.001
≥1 severe exacerbation of asthma in the last 12 months	2.052	1.151 to 3.659	0.015
Peripheral blood eosinophil counts	2.181	1.101 to 4.321	0.025
Sputum eosinophil ratio	1.260	1.109 to 1.432	<0.001
Bronchiectasis in bronchiectasis-prior group and non-bronchiectasis group, logistic regression			
Previous PTB or pneumonia in childhood	22.053	8.504 to 57.191	<0.001
≥1 pneumonia in the last 12 months	6.211	3.013 to 12.802	<0.001
Postbronchodilator FEV_1% predicted	0.970	0.954 to 0.986	<0.001
FeNO	0.977	0.961 to 0.994	0.008

PTB, pulmonary tuberculosis; CRSwNP, chronic rhinosinusitis with nasal polyps; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; OR, odds ratio; CI, confidence interval.

57.191) and ≥1 pneumonia in the last 12 months (OR: 6.211; 95% CI: 3.013–12.802), and negatively correlated with post-bronchodilator FEV_1% predicted (OR: 0.970; 95% CI: 0.954–0.986) and FeNO (OR: 0.977; 95% CI: 0.961–0.994) (*Table 3*).

Extent and severity of bronchiectasis present severe condition, but different inflammatory characteristics is observed between asthma-prior and bronchiectasis-prior groups

In the asthma-prior group, univariate analysis and multivariate linear regression analysis showed that Smith scores were positively correlated with usage of LAMA (β coefficient, 5.728; 95% CI: 3.049–8.407), ≥1 SEA in the last 12 months (β coefficient, 1.245; 95% CI: 0.067–2.423), ≥1 pneumonia in the last 12 months (β coefficient, 1.733; 95% CI: 0.645–2.821), FeNO level (β coefficient, 0.015; 95% CI: 0.003–0.028), and negatively correlated with FEV_1% predicted (β coefficient, –0.050; 95% CI: –0.074 to –0.026) (*Tables 4,5*, *Figure 2A,2B*). Bhalla scores were positively correlated with duration of bronchiectasis (β coefficient, 0.139; 95% CI: 0.058–0.219), ICS dose (β coefficient, 0.001; 95% CI: 0.000–0.002), ≥1 SEA in the last 12 months (β coefficient, 0.547; 95% CI: 0.039–1.055), FeNO level (β coefficient, 0.006; 95% CI: 0.000–0.012) and isolation of *Hemophilus influenzae* in the sputum (β coefficient, 1.361; 95% CI: 0.308–2.414), and negatively correlated with BMI (β coefficient, –0.088; 95% CI: –0.143 to –0.032) (*Tables 6,7*, *Figure 2C,2D*). BSI scores were positively correlated with age (β coefficient, 0.385; 95% CI: 0.274–0.496), total IgE levels (β coefficient, 0.160; 95% CI: 0.054–0.266), the existence of coronary artery disease (β coefficient, 0.164; 95% CI: 0.058–0.270), ≥1 pneumonia in the last 12 months (β coefficient, 0.156; 95% CI: 0.053–0.259), ≥1 SEA in the last 12 months (β coefficient, 0.130; 95% CI: 0.024–0.236), and isolations of *Hemophilus influenzae* (β coefficient, 0.127; 95% CI: 0.025–0.229), *Pseudomonas aeruginosa* (β coefficient, 0.177; 95% CI: 0.073–0.281) and *Candida albicans* (β coefficient, 0.214; 95% CI: 0.111–0.317) in the sputum, and negatively correlated with FEV_1% predicted (β coefficient, –0.208; 95% CI: –0.318 to –0.098) and BMI (β coefficient, –0.162; 95% CI: –0.265 to –0.059) (*Tables 8,9*).

In the bronchiectasis-prior group, Smith scores were positively correlated with positive smoking history (β coefficient, 2.720; 95% CI: 0.662–4.778), ≥1 pneumonia in the last 12 months (β coefficient, 3.174; 95% CI: 1.145–

Table 4 Univariate analyses of correlated factors for Smith scores in asthma-prior group and bronchiectasis-prior group

Variables	Smith scores in asthma-prior group			Smith scores in bronchiectasis-prior group		
	r	95% CI	P value	r	95% CI	P value
Baseline characteristics						
Male sex	−0.011	−0.164 to 0.138	0.882	0.032	−0.174 to 0.223	0.752
Age	0.134	−0.012 to 0.278	0.080	−0.104	−0.294 to 0.069	0.311
BMI	−0.091	−0.242 to 0.066	0.237	−0.208	−0.370 to −0.021	0.041
Positive smoking status†	−0.104	−0.257 to 0.030	0.175	0.249	0.053 to 0.428	0.014
Smoking index	−0.111	−0.266 to 0.043	0.147	0.265	0.075 to 0.441	0.009
Duration of asthma	0.114	−0.041 to 0.267	0.139	0.220	0.038 to 0.407	0.030
Age of onset of asthma	−0.038	−0.218 to 0.156	0.620	−0.145	−0.331 to 0.031	0.157
Duration of bronchiectasis	0.179	0.011 to 0.337	0.019	0.042	−0.160 to 0.258	0.681
Age of onset of bronchiectasis	0.103	−0.047 to 0.236	0.179	−0.060	−0.221 to 0.118	0.560
Previous PTB or pneumonia in childhood	0.091	−0.088 to 0.263	0.235	0.005	−0.183 to 0.193	0.960
Medication history						
ICS + LABA	0.203	0.049 to 0.362	0.008	0.154	−0.053 to 0.356	0.132
LAMA	0.185	0.043 to 0.301	0.015	0.193	0.030 to 0.345	0.059
LTRA	0.023	−0.114 to 0.153	0.760	0.037	−0.160 to 0.220	0.717
Theophylline	0.030	−0.146 to 0.194	0.694	0.163	0.018 to 0.287	0.111
OCS	0.173	0.032 to 0.301	0.023	0.016	−0.023 to 0.065	0.873
Omalizumab	0.016	−0.063 to 0.083	0.838			
Inhaled SABA only as needed	−0.030	−0.077 to −0.012	0.701	0.070	−0.025 to 0.179	0.495
ICS dose	0.242	0.101 to 0.390	0.001	0.208	0.017 to 0.391	0.041
Macrolides usage >3 months duration	0.284	0.138 to 0.429	<0.001	0.124	−0.078 to 0.326	0.225
Allergic disease						
Allergic rhinitis	0.116	−0.053 to 0.286	0.130	−0.201	−0.374 to −0.005	0.048
CRS	0.095	−0.073 to 0.246	0.218	−0.089	−0.278 to 0.114	0.388
CRSwNP	0.080	−0.065 to 0.240	0.299	−0.166	−0.335 to 0.026	0.105
Atopic dermatitis	0.001	−0.148 to 0.142	0.991	−0.140	−0.317 to 0.058	0.173
Comorbidity						
OSAHS	−0.014	−0.173 to 0.140	0.860	−0.115	−0.251 to −0.002	0.260
GERD	0.162	−0.025 to 0.299	0.034	−0.041	−0.236 to 0.157	0.693
Hypertension	0.037	−0.117 to 0.192	0.631	−0.182	−0.358 to 0.014	0.075
CAD	−0.059	−0.190 to 0.091	0.443	−0.084	−0.286 to 0.124	0.411
Stroke	−0.024	−0.212 to 0.177	0.754	−0.164	−0.340 to 0.046	0.108
2-DM	−0.093	−0.232 to 0.055	0.227	−0.001	−0.196 to 0.207	0.993

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Smith scores in asthma-prior group			Smith scores in bronchiectasis-prior group		
	r	95% CI	P value	r	95% CI	P value
Asthma severity						
Severe asthma	0.315	0.207 to 0.425	<0.001	0.202	0.020 to 0.382	0.047
≥1 pneumonia in the last 12 months	0.192	0.017 to 0.339	0.012	0.425	0.227 to 0.582	<0.001
≥1 severe exacerbation of asthma in the last 12 months	0.315	0.171 to 0.438	<0.001	0.176	−0.026 to 0.356	0.084
Postbronchodilator FEV_1% predicted	−0.372	−0.494 to −0.236	<0.001	−0.470	−0.598 to −0.330	<0.001
Inflammatory characteristics						
Peripheral blood eosinophil counts	0.188	0.040 to 0.333	0.014	0.155	−0.032 to 0.342	0.131
Sputum eosinophil ratio	0.052	−0.117 to 0.204	0.496	−0.092	−0.271 to 0.109	0.370
Total IgE	0.155	−0.004 to 0.302	0.043	0.044	−0.184 to 0.251	0.666
Atopy	0.061	−0.094 to 0.203	0.428	0.113	−0.080 to 0.303	0.272
Food allergen positive	−0.012	−0.164 to 0.140	0.877	0.010	−0.203 to 0.203	0.926
Aeroallergen positive	0.012	−0.140 to 0.164	0.877	0.251	0.054 to 0.448	0.013
FeNO	0.242	0.091 to 0.378	0.001	−0.325	−0.479 to −0.151	0.001
Pathogens isolated from the sputum						
Pseudomonas aeruginosa	0.092	−0.036 to 0.229	0.229	0.380	0.180 to 0.569	<0.001
Klebsiella pneumoniae	0.134	0.015 to 0.239	0.081	−0.118	−0.287 to 0.061	0.252
Candida albicans	0.141	0.011 to 0.250	0.067	−0.081	−0.286 to 0.131	0.432
Hemophilus influenzae	0.102	−0.041 to 0.229	0.185	−0.015	−0.194 to 0.189	0.884
Aspergillus fumigatus	0.154	−0.016 to 0.292	0.044	0.058	−0.147 to 0.246	0.571

†, positive smoking status included ex- or current-smokers. BMI, body mass index; PTB, pulmonary tuberculosis; ICS, inhaled corticosteroids; LABA, long-acting β2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting β2-adrenoceptor agonist; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; OSAHS, obstructive sleep apnea hypopnea syndrome; GERD, gastroesophageal reflux disease; CAD, coronary artery disease; 2-DM, diabetes mellitus type 2; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide.

Table 5 Multivariate linear regression analyses for Smith scores in asthma-prior group

Variables	Smith scores in asthma-prior group, multivariate linear regression		
	β coefficients	95% CI	P value
Usage of LAMA	5.728	3.049 to 8.407	<0.001
≥1 severe exacerbation of asthma in the last 12 months	1.245	0.067 to 2.423	0.038
≥1 pneumonia in the last 12 months	1.733	0.645 to 2.821	0.002
Postbronchodilator FEV_1% predicted	−0.050	−0.074 to −0.026	<0.001
FeNO	0.015	0.003 to 0.028	0.019

LAMA, long-acting muscarinic antagonists; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; CAD, coronary artery disease.

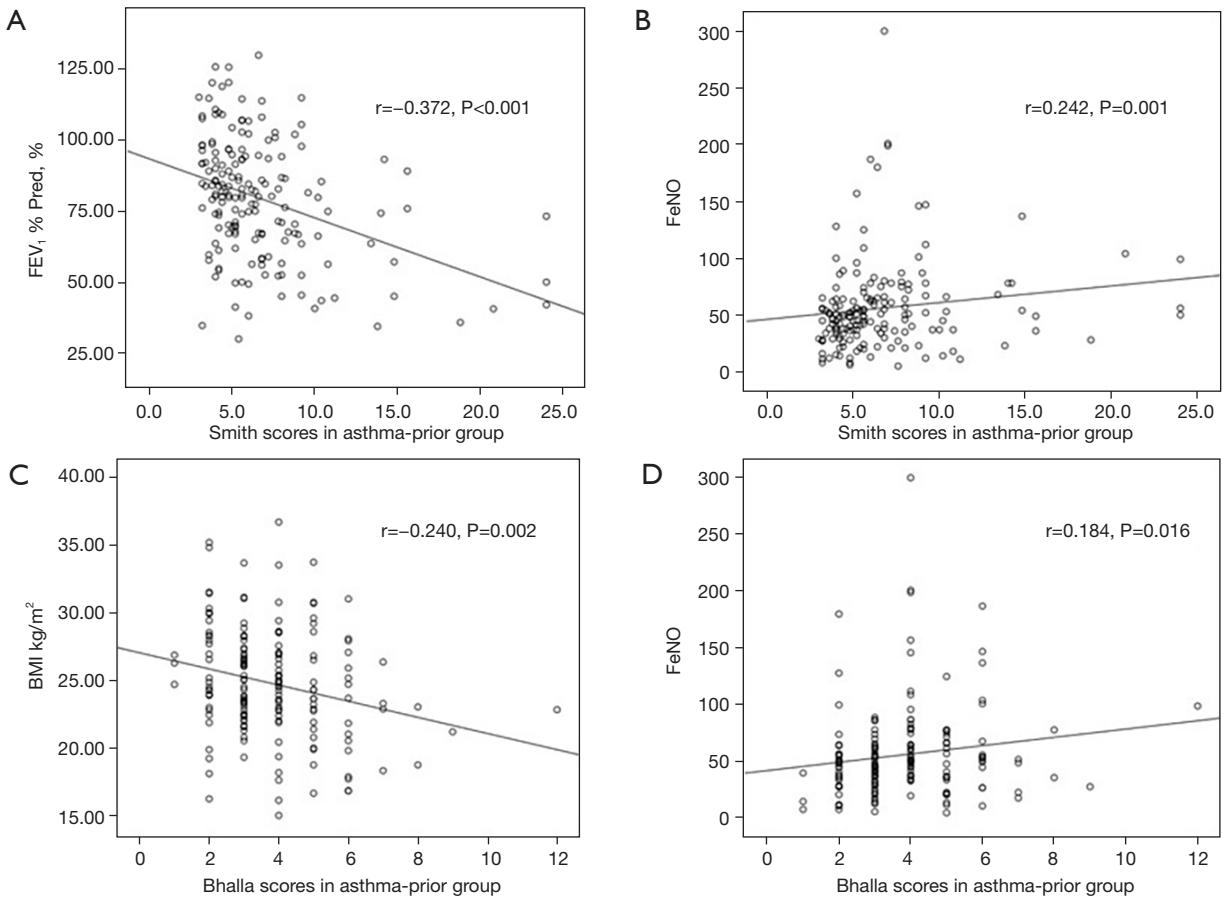

Figure 2 Correlation analysis in the asthma-prior group. (A) Scatter plot between Smith scores and postbronchodilator FEV_1% predicted. (B) Scatter plot between Smith scores and FeNO. (C) Scatter plot between Bhalla scores and BMI. (D) Scatter plot between Bhalla scores and FeNO. Abbreviations: FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; BMI, body mass index.

5.203), isolation of *Pseudomonas aeruginosa* in the sputum (β coefficient, 3.500; 95% CI: 1.254–5.745), while negatively correlated with BMI (β coefficient, −0.231; 95% CI: −0.453 to −0.010) and FEV_1% predicted (β coefficient, −0.060; 95% CI: −0.098 to −0.022) (*Tables 4*,*10*, *Figure 3A*,*3B*); Bhalla scores were positively correlated with ICS dose (β coefficient, 0.004; 95% CI: 0.001–0.007), ≥1 pneumonia in the last 12 months (β coefficient, 1.901; 95% CI: 0.334–3.468), and negatively correlated with FEV_1% predicted (β coefficient, −0.048; 95% CI: −0.078 to −0.017) (*Tables 6*,*11*, *Figure 3C*). BSI scores were positively correlated with age (β coefficient, 0.292; 95% CI: 0.167–0.418), duration of bronchiectasis (β coefficient, 0.159; 95% CI: 0.032–0.2287), and isolations of Pseudomonas (β coefficient, 0.446; 95% CI: 0.319–0.573) in the sputum, and negatively correlated with FEV_1% predicted (β coefficient, −0.449; 95% CI: −0.576 to −0.323) (*Tables 8*,*12*).

Discussion

Asthma with distinct phenotypes has recently drawn increasing attention as a common and heterogeneous disease (1,3). Bronchiectasis is a common chronic respiratory disease in China (2) and is characterized by airway impairment, recurrent infections, and progressive damage to lung function (2,24). Recent studies have focused on bronchiectasis overlapping with other chronic respiratory diseases, especially asthma (13), and have demonstrated that the prevalence of asthma comorbid with bronchiectasis was notably high and increased from year to year (6,25). Bronchiectasis can be due to diverse underlying etiologies, such as congenital defects, aspiration, and previous lower

Table 6 Univariate analyses of correlated factors for Bhalla scores in asthma-prior group and bronchiectasis-prior group

Variables	Bhalla scores in asthma-prior group			Bhalla scores in bronchiectasis-prior group		
	r	95% CI	P value	r	95% CI	P value
Baseline characteristics						
Male sex	–0.074	–0.222 to 0.087	0.336	–0.035	–0.239 to 0.177	0.731
Age	0.035	–0.096 to 0.162	0.654	–0.104	–0.300 to 0.073	0.311
BMI	–0.240	–0.375 to –0.097	0.002	–0.066	–0.278 to 0.143	0.522
Positive smoking status†	–0.084	–0.238 to 0.070	0.277	0.084	–0.106 to 0.274	0.414
Smoking index	–0.094	–0.241 to 0.068	0.220	0.093	–0.085 to 0.277	0.365
Duration of asthma	0.063	–0.108 to 0.231	0.411	0.433	0.249 to 0.586	<0.001
Age of onset of asthma	–0.077	–0.245 to 0.087	0.314	–0.320	–0.511 to –0.136	0.001
Duration of bronchiectasis	0.184	0.014 to 0.342	0.016	0.191	–0.015 to 0.381	0.060
Age of onset of bronchiectasis	–0.009	–0.159 to 0.130	0.910	–0.238	–0.397 to –0.073	0.019
Previous PTB or pneumonia in childhood	0.168	0.009 to 0.289	0.028	0.175	–0.030 to 0.372	0.087
Medication history						
ICS + LABA	0.123	–0.031 to 0.285	0.109	0.288	0.089 to 0.463	0.004
LAMA	0.109	–0.077 to 0.271	0.156	0.325	0.157 to 0.471	0.001
LTRA	–0.030	–0.158 to 0.105	0.694	0.173	–0.028 to 0.343	0.090
Theophylline	–0.022	–0.196 to 0.155	0.775	0.096	–0.112 to 0.287	0.348
OCS	0.159	0.000 to 0.288	0.037	0.134	0.113 to 0.263	0.191
Omalizumab	0.013	–0.065 to 0.085	0.871			
Inhaled SABA only as needed	–0.042	–0.089 to –0.027	0.584	0.143	0.064 to 0.251	0.161
ICS dose	0.218	0.071 to 0.630	0.004	0.353	0.163 to 0.525	<0.001
Macrolides usage >3 months duration	0.105	–0.046 to 0.256	0.173	0.196	–0.004 to 0.396	0.055
Allergic disease						
Allergic rhinitis	0.060	–0.116 to 0.243	0.432	–0.219	–0.406 to –0.027	0.031
CRS	0.073	–0.096 to 0.240	0.342	–0.122	–0.325 to 0.109	0.234
CRSwNP	0.132	–0.025 to 0.277	0.085	–0.201	–0.371 to –0.022	0.048
Atopic dermatitis	0.006	–0.146 to 0.173	0.940	–0.152	–0.342 to 0.109	0.138
Comorbidity						
OSAHS	–0.017	–0.158 to 0.116	0.822	–0.090	–0.282 to 0.082	0.381
GERD	0.084	–0.104 to 0.251	0.272	0.074	–0.160 to 0.281	0.473
Hypertension	–0.058	–0.212 to 0.092	0.452	–0.055	–0.260 to 0.148	0.591
CAD	–0.032	–0.166 to 0.102	0.679	–0.186	–0.360 to 0.003	0.068
Stroke	–0.073	–0.249 to 0.143	0.342	–0.151	–0.380 to 0.180	0.140
2-DM	–0.055	–0.215 to 0.098	0.476	–0.061	–0.248 to 0.137	0.553

Table 6 (*continued*)

Table 6 (*continued*)

Variables	Bhalla scores in asthma-prior group			Bhalla scores in bronchiectasis-prior group		
	r	95% CI	P value	r	95% CI	P value
Asthma severity						
Severe asthma	0.248	0.101 to 0.374	0.001	0.299	0.120 to 0.450	0.003
≥1 pneumonia in the last 12 months	0.058	−0.109 to 0.221	0.455	0.473	0.279 to 0.636	<0.001
≥1 severe exacerbation of asthma in the last 12 months	0.178	0.028 to 0.321	0.020	0.170	−0.044 to 0.362	0.096
Postbronchodilator FEV_1% predicted	−0.164	−0.311 to 0.010	0.032	−0.457	−0.585 to −0.318	<0.001
Inflammatory characteristics						
Peripheral blood eosinophil counts	0.148	0.001 to 0.287	0.054	0.108	−0.100 to 0.309	0.291
Sputum eosinophil ratio	0.025	−0.131 to 0.171	0.747	−0.155	−0.345 to 0.061	0.131
Total IgE	0.070	−0.075 to 0.203	0.366	0.000	−0.199 to 0.224	0.996
Atopy	0.038	−0.124 to 0.182	0.626	0.110	−0.088 to 0.304	0.282
Food allergen positive	0.066	−0.085 to 0.218	0.391	−0.009	−0.213 to 0.195	0.931
Aeroallergen positive	0.044	−0.107 to 0.196	0.565	0.253	0.056 to 0.450	0.013
FeNO	0.184	0.018 to 0.325	0.016	−0.366	−0.536 to −0.182	<0.001
Pathogens isolated from the sputum						
Pseudomonas aeruginosa	0.138	−0.023 to 0.290	0.072	0.286	0.098 to 0.456	0.005
Klebsiella pneumoniae	0.039	−0.125 to 0.196	0.610	−0.113	−0.264 to 0.025	0.270
Candida albicans	0.062	−0.120 to 0.228	0.417	−0.161	−0.349 to 0.054	0.114
Hemophilus influenzae	0.188	0.048 to 0.297	0.014	0.004	−0.130 to 0.132	0.968
Aspergillus fumigatus	0.104	−0.045 to 0.241	0.177	0.019	−0.200 to 0.227	0.855

†, positive smoking status included ex- or current-smokers. BMI, body mass index; PTB, pulmonary tuberculosis; ICS, inhaled corticosteroids; LABA, long-acting β2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting β2-adrenoceptor agonist; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; OSAHS, obstructive sleep apnea hypopnea syndrome; GERD, gastroesophageal reflux disease; CAD, coronary artery disease; 2-DM, diabetes mellitus type 2; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide.

Table 7 Multivariate linear regression analyses for Bhalla scores in asthma-prior group

Variables	Bhalla scores in asthma-prior group, multivariate linear regression		
	β coefficients	95% CI	P value
BMI	−0.088	−0.143 to −0.032	0.002
Duration of bronchiectasis	0.139	0.058 to 0.219	0.001
ICS dose	0.001	0.000 to 0.002	0.004
≥1 severe exacerbation of asthma in the last 12 months	0.547	0.039 to 1.055	0.035
FeNO	0.006	0.000 to 0.012	0.035
Hemophilus influenzae isolated from the sputum	1.361	0.308 to 2.414	0.012

BMI, body mass index; ICS, inhaled corticosteroids; FeNO, fractional exhaled nitric oxide.

Table 8 Univariate analyses of correlated factors for BSI scores in asthma-prior group and bronchiectasis-prior group

Variables	BSI scores in asthma-prior group			BSI scores in bronchiectasis-prior group		
	r	95% CI	P value	r	95% CI	P value
Baseline characteristics						
Male sex	0.044	−0.108 to 0.195	0.570	−0.141	−0.343 to 0.060	0.167
Age	0.500	0.368 to 0.631	<0.001	0.292	0.097 to 0.487	0.004
BMI	−0.097	−0.248 to 0.054	0.206	−0.168	−0.369 to 0.033	0.101
Positive smoking status†	0.102	−0.049 to 0.253	0.183	0.148	−0.053 to 0.350	0.147
Smoking index	0.066	−0.086 to 0.217	0.394	0.052	−0.152 to 0.255	0.615
Duration of asthma	0.124	−0.027 to 0.275	0.106	0.269	0.073 to 0.466	0.008
Age of onset of asthma	0.283	0.137 to 0.428	<0.001	−0.064	−0.267 to 0.140	0.536
Duration of bronchiectasis	0.169	0.019 to 0.318	0.027	0.352	0.161 to 0.542	<0.001
Age of onset of bronchiectasis	0.458	0.323 to 0.593	<0.001	−0.183	−0.384 to 0.017	0.072
Previous PTB or pneumonia in childhood	0.151	0.000 to 0.301	0.049	0.167	−0.034 to 0.368	0.102
Medication history						
ICS + LABA	−0.063	−0.215 to 0.088	0.412	0.147	−0.054 to 0.349	0.150
LAMA	0.093	−0.058 to 0.244	0.226	0.281	0.085 to 0.476	0.005
LTRA	0.073	−0.078 to 0.224	0.343	0.029	−0.175 to 0.232	0.781
Theophylline	0.216	0.068 to 0.365	0.004	0.095	−0.108 to 0.298	0.354
OCS	0.044	−0.108 to 0.196	0.569	0.050	−0.153 to 0.254	0.625
Omalizumab	−0.062	−0.213 to 0.090	0.423			
Inhaled SABA only as needed	0.063	−0.088 to 0.215	0.412	−0.087	−0.290 to 0.116	0.395
ICS dose	0.036	−0.116 to 0.188	0.640	0.171	−0.030 to 0.372	0.094
macrolides usage >3 months duration	0.063	−0.088 to 0.215	0.412	0.087	−0.116 to 0.290	0.396
Allergic disease						
Allergic rhinitis	−0.247	−0.394 to −0.100	0.001	−0.312	−0.506 to −0.119	0.002
CRS	−0.225	−0.373 to −0.077	0.003	−0.363	−0.553 to −0.173	<0.001
CRSwNP	−0.318	−0.462 to −0.174	<0.001	−0.308	−0.502 to −0.114	0.002
Atopic dermatitis	0.066	−0.086 to 0.217	0.394	0.067	−0.136 to 0.271	0.512
Comorbidity						
OSAHS	−0.046	−0.198 to 0.105	0.548	0.087	−0.116 to 0.290	0.396
GERD	0.171	0.022 to 0.321	0.025	0.093	−0.110 to 0.295	0.367
Hypertension	0.228	0.080 to 0.376	0.003	0.071	−0.132 to 0.274	0.489
CAD	0.276	0.130 to 0.422	<0.001	0.049	−0.155 to 0.252	0.636
Stroke	0.029	−0.122 to 0.181	0.703	−0.057	−0.260 to 0.147	0.580
2-DM	0.031	−0.121 to 0.183	0.689	0.055	−0.149 to 0.258	0.594

Table 8 (*continued*)

Table 8 (*continued*)

Variables	BSI scores in asthma-prior group			BSI scores in bronchiectasis-prior group		
	r	95% CI	P value	r	95% CI	P value
Asthma severity						
Severe asthma	0.142	−0.008 to 0.292	0.064	0.142	−0.060 to 0.344	0.166
≥1 pneumonia in the last 12 months	0.262	0.115 to 0.408	0.001	0.301	0.107 to 0.495	0.003
≥1 severe exacerbation of asthma in the last 12 months	0.281	0.135 to 0.427	<0.001	0.138	−0.064 to 0.34	0.178
Postbronchodilator FEV_1% predicted	−0.431	−0.568 to −0.294	<0.001	−0.563	−0.731 to −0.395	<0.001
Inflammatory characteristics						
Peripheral blood eosinophil counts	0.045	−0.106 to 0.197	0.557	−0.094	−0.297 to 0.109	0.359
Sputum eosinophil ratio	−0.150	−0.300 to 0.001	0.051	−0.102	−0.305 to 0.101	0.320
Total IgE	0.291	0.146 to 0.436	<0.001	−0.072	−0.275 to 0.131	0.482
Atopy	−0.004	−0.156 to 0.148	0.960	−0.031	−0.234 to 0.173	0.766
Food allergen positive	0.035	−0.117 to 0.187	0.651	−0.029	−0.233 to 0.174	0.777
Aeroallergen positive	0.053	−0.099 to 0.204	0.493	0.045	−0.158 to 0.249	0.658
FeNO	−0.072	−0.224 to 0.079	0.347	−0.333	−0.525 to −0.141	0.001
Pathogens isolated from the sputum						
Pseudomonas aeruginosa	0.233	0.085 to 0.380	0.002	0.584	0.418 to 0.749	<0.001
Klebsiella pneumoniae	0.113	−0.038 to 0.264	0.141	−0.063	−0.267 to 0.140	0.538
Candida albicans	0.263	0.116 to 0.409	0.001	0.100	−0.103 to 0.303	0.330
Hemophilus influenzae	0.190	0.041 to 0.339	0.013	0.074	−0.129 to 0.277	0.472
Aspergillus fumigatus	0.255	0.108 to 0.401	0.001	0.279	0.083 to 0.474	0.006

†, positive smoking status included ex- or current-smokers. BMI, body mass index; PTB, pulmonary tuberculosis; ICS, inhaled corticosteroids; LABA, long-acting β2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting β2-adrenoceptor agonist; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; OSAHS, obstructive sleep apnea hypopnea syndrome; GERD, gastroesophageal reflux disease; CAD, coronary artery disease; 2-DM, diabetes mellitus type 2; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; BSI, bronchiectasis severity index.

respiratory tract infections besides asthma (10,16,26), with different clinical manifestations and prognoses. Therefore, we investigated the distinct impact of bronchiectasis with asthma-induced or not on the clinical characteristics of patients with asthma.

As asthma and bronchiectasis shares several symptomatic and physiological similarities, it is sometimes challenging to establish whether bronchiectasis is a comorbidity of asthma or an intrinsic component of airway remodeling within the history of asthma (4). Previous studies rarely explored in the causality of asthma and bronchiectasis or defined asthma-induced bronchiectasis as a diagnosis of asthma preceding bronchiectasis (6,27,28). Notably, bronchiectasis tends to be neglected for a long time, while most patients are already in a severe or exacerbation stage when first diagnosed (2). Therefore, we combined clinical symptoms and chest HRCT findings to identify the onset of bronchiectasis.

Consistent with previous findings, the present study showed that advanced age and severe asthma were risk factors for the presence of bronchiectasis in patients with asthma, while the presence, extent and BSI scores of bronchiectasis were related to more frequent asthma exacerbations and pneumonia (6,15,23,29). Structural abnormalities are common in HRCT among patients with

Table 9 Multivariate linear regression analyses for BSI scores in asthma-prior group

Variables	BSI scores in asthma-prior group, multivariate linear regression		
	β coefficients	95% CI	P value
Age	0.385	0.274 to 0.496	<0.001
Postbronchodilator FEV_1% predicted	–0.208	–0.318 to –0.098	<0.001
Pseudomonas aeruginosa isolated in the sputum	0.177	0.073 to 0.281	0.001
Candida albicans isolated in the sputum	0.214	0.111 to 0.317	<0.001
Total IgE level	0.160	0.054 to 0.266	0.003
CAD	0.164	0.058 to 0.270	0.003
BMI	–0.162	–0.265 to –0.059	0.002
≥1 pneumonia in the last 12 months	0.156	0.053 to 0.259	0.003
Hemophilus influenzae isolated from the sputum	0.127	0.025 to 0.229	0.015
≥1 severe exacerbation of asthma in the last 12 months	0.130	0.024 to 0.236	0.016

BSI, bronchiectasis severity index; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; CAD, coronary artery disease; BMI, body mass index.

Table 10 Multivariate linear regression analyses for Smith scores in bronchiectasis-prior group

Variables	Smith scores in bronchiectasis-prior group, multivariate linear regression		
	β coefficients	95% CI	P value
BMI	–0.231	–0.453 to –0.010	0.041
Positive smoking status[†]	2.720	0.662 to 4.778	0.010
≥1 pneumonia in the last 12 months	3.174	1.145 to 5.203	0.003
Postbronchodilator FEV_1% predicted	–0.060	–0.098 to –0.022	0.002
Pseudomonas aeruginosa isolated from the sputum	3.500	1.254 to 5.745	0.003

[†], positive smoking status included ex- or current-smokers. BMI, body mass index; FEV_1, forced expiratory volume in 1 second.

severe asthma, as bronchial wall thickness and bronchiectasis have been described in 80–90% of patients with severe asthma (5,30). Chronic inflammation leads to structural changes in the airway over time, followed by reduced secretion clearance, and subsequent recurrent respiratory infections, which may be the mechanism underlying the development of bronchiectasis in asthmatic patients (5).

Unlike traditionally characterized by neutrophilic airway inflammation (11), our investigation showed that the prominent feature of bronchiectasis induced by asthma is eosinophilic airway inflammation, manifested by increased peripheral blood eosinophil counts and sputum eosinophil ratio. The extent and severity of bronchiectasis were positively related to FeNO, which indicated eosinophilic airway inflammation (1), and the BSI scores indicating future exacerbation, hospitalization, and mortality of bronchiectasis were also positively related to IgE levels. Several recent studies have also shown that eosinophilic inflammation may play a causative role in the development of bronchiectasis in patients with asthma (9,31), and the underlying pathway of eosinophilic inflammation that destroys airway structure needs to be explored further. Additionally, our study showed that the existence of bronchiectasis was related to NPs in asthma-prior patients. On the one side, patients with NPs had a significantly higher frequency of asthma exacerbations (7,32); on the other side, discharge of mucus from the upper to the lower airways may act as an irritative stimulus for the bronchial epithelium, promoting an exaggerated recall and activation of the eosinophils via the innate immunity pathway through

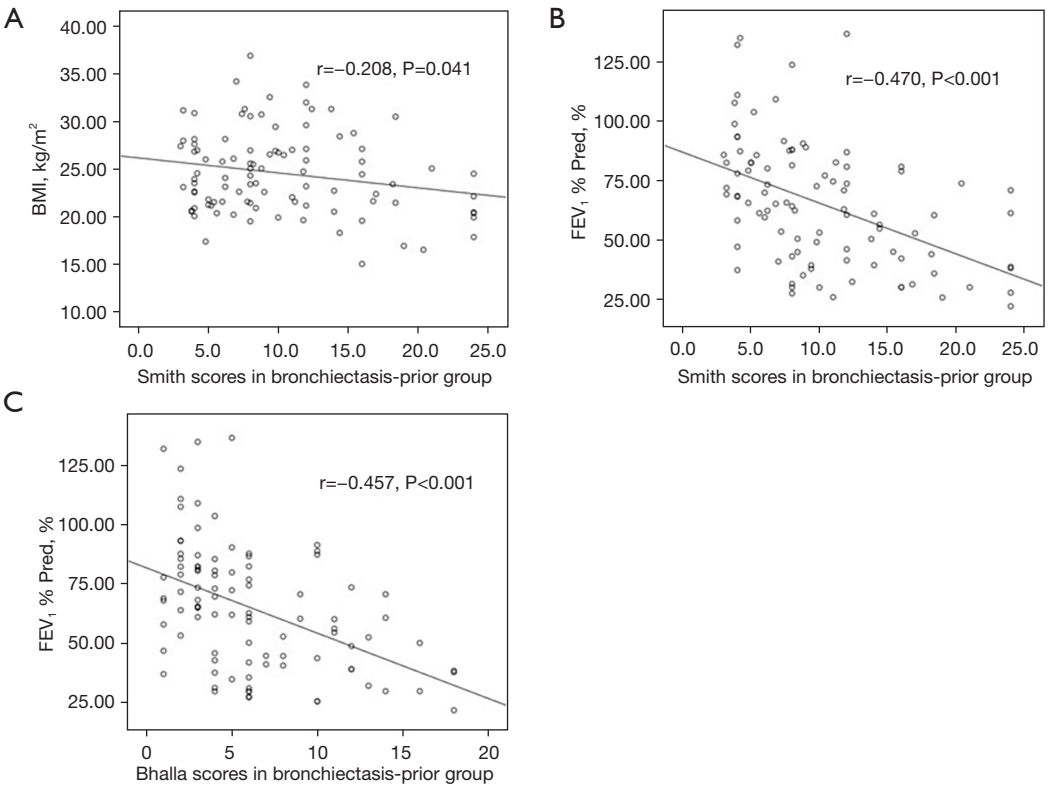

Figure 3 Correlation analysis in the bronchiectasis-prior group. (A) Scatter plot between Smith scores and BMI. (B) Scatter plot between Smith scores and postbronchodilator FEV_1% predicted. (C) Scatter plot between Bhalla scores and postbronchodilator FEV_1% predicted. Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second.

Table 11 Multivariate linear regression analyses for Bhalla scores in bronchiectasis-prior group

Variable	Bhalla scores in bronchiectasis-prior group, multivariate linear regression		
	β coefficients	95% CI	P value
ICS dose	0.004	0.001 to 0.007	0.004
≥1 pneumonia in the last 12 months	1.901	0.334 to 3.468	0.018
Postbronchodilator FEV_1% predicted	−0.048	−0.078 to −0.017	0.002

ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 second; CI, confidence interval.

Table 12 Multivariate linear regression analyses for BSI scores in bronchiectasis-prior group

Variables	BSI scores in bronchiectasis-prior group, multivariate linear regression		
	β coefficients	95% CI	P value
Pseudomonas aeruginosa isolated from the sputum	0.446	0.319 to 0.573	<0.001
Postbronchodilator FEV_1% predicted	−0.449	−0.576 to −0.323	<0.001
Age	0.292	0.167 to 0.418	<0.001
Duration of bronchiectasis	0.159	0.032 to 0.287	0.015

FEV_1, forced expiratory volume in 1 second; BSI, bronchiectasis severity index; CI, confidence interval.

inflammatory factors' production and stimulation (31). Eventually, recurrent exacerbations and inflammatory stimuli may drive the formation of bronchiectasis in asthma.

As shown in the current results, *Hemophilus influenzae* isolated from sputum was associated with the severity and BSI scores of bronchiectasis in the asthma-prior group. Previous investigations indicated that *Hemophilus influenzae* is not only a common potentially pathogenic microorganism colonizing the bronchiectasis airway (33) but is also increased in the sputum of patients with severe asthma (12), suggesting that it may be involved in the formation and development of bronchiectasis in patients with asthma.

Corticosteroids are potent drugs that suppress eosinophilic inflammation, and partially severe asthmatic patients may require oral corticosteroids to maintain stability (1). ICS play an established role in managing ACB (10). Consistently, our results showed that bronchiectasis severity was positively associated with increased inhaled corticosteroids use in the asthma-prior group. Notably, corticosteroids are potentially associated with the risk of PTB and pneumonia (34). As bronchiectasis induced by asthma presents prominent eosinophilic airway inflammation, patients may benefit even more from the type-2 targeted biologic therapy compared to the simple asthmatic patients.

Several studies have highlighted the therapeutic response of type-2 targeted biological therapy in severe asthmatic patients with bronchiectasis or NPs (35,36). Crimi *et al.* discovered that mepolizumab, an anti-interleukin (IL)-5 receptor, could effectively improve asthma symptom control and reduce annual exacerbations and corticosteroid intake in all patients with severe eosinophilic asthma, even in the subgroup with coexisting bronchiectasis (35). Similarly, a real-world multicenter study showed that benralizumab, an anti-IL-5 receptor α, can improve nasal outcome, asthma control, and lung function, and decrease eosinophilic inflammation in patients with severe eosinophilic asthma coexisting with NPs (36). Whether type-2 targeted biologic therapy can benefit patients with asthma-induced bronchiectasis in the early stages remains to be further explored. As suggested by the guidelines, bronchodilators may have an acceptable safety profile in bronchiectasis induced by asthma (10). Our project showed that the usage of bronchodilators increased with the development of bronchiectasis in the asthma-prior group. The airway clearance technique and pulmonary rehabilitation were recommended for partial bronchiectasis patients according to the guidelines (10,16); however, further research is needed to evaluate the latent benefits and risks for the asthma-induced bronchiectasis subgroup.

The current study indicated that the existence of bronchiectasis was related to previous PTB or pneumonia in childhood in the bronchiectasis-prior group. As against Western countries, childhood pneumonia caused by measles, pertussis, and PTB is the most commonly identified cause of acquired bronchiectasis in China (2). As against asthma-induced bronchiectasis patients, patients with bronchiectasis preceding asthma manifested a non-eosinophilic inflammation with lower FeNO, and the extent of bronchiectasis was positively associated with *Pseudomonas aeruginosa* isolated from the sputum. Previous studies have also shown that the eosinophilic inflammatory marker FeNO, which also reflects antimicrobial activity (37), is decreased in bronchiectasis, particularly when colonized by *Pseudomonas aeruginosa* (38). Moreover, the present study indicated that the existence and severity of bronchiectasis increased the frequency of pneumonia but did not affect the frequency of acute exacerbations of asthma in the bronchiectasis-prior group. The presence of bronchiectasis was more likely to be a combination than a factor promoting asthma to become more severe and exacerbated when the onset of bronchiectasis preceded asthma. Furthermore, the onset of bronchiectasis before asthma tends to be characterized by non-eosinophilic inflammation with recurrent pneumonia. This finding may be of great significance in guiding the precise treatment of asthma in the future.

As patients with the bronchiectasis-prior present with predominantly non-eosinophilic inflammation, increased corticosteroids usage may increase the risk of pneumonia without achieving symptomatic control. Guidelines for asthma suggested that type-2 targeted biologic therapy, such as anti-IgE, anti-IL-5, and anti-IL4R, should be recommended for stage 5 asthmatic patients with evidence of type 2 inflammation (1). One recent case series showed that treatment with biologics targeting type 2 inflammation leads to clinical improvement, including a reduction in corticosteroid courses, respiratory exacerbations, and systemic antibiotic courses in patients with asthma overlapping bronchiectasis (39). Our current findings suggest that there may be no additional benefit of using type-2 targeted biologic therapy for non-eosinophilic inflammation in bronchiectasis-prior patients. However, due to the potential infection risk of ICS, biologic therapy preceding ICS may benefit patients with type 2 inflammation in the bronchiectasis-prior group. Macrolides exert immunomodulatory effects on neutrophil-mediated

lung damage suppression and enhancement of cilia function to promote mucociliary clearance. Guidelines for bronchiectasis recommend long-term treatment with macrolide antibiotics to reduce exacerbation in patients with recurrent exacerbations (11). Patients with neutrophil-predominant severe asthma tend to show a decline in exacerbation rate, improved peak expiratory flow, and improved quality of life when treated with macrolides (40). One retrospective study suggested that macrolides may be helpful as an add-on therapy in severe asthma-bronchiectasis overlapping patients (41). Owning to the non-eosinophilic inflammatory and recurrent pneumonia characteristics in the present study, bronchiectasis-prior patients may have benefited from macrolides therapy. Unfortunately, only three patients with bronchiectasis received long-term macrolide therapy in the present study, and further follow-up studies may provide more objective evidence.

It is well known that smoking history is a predisposing factor for COPD, but not asthma (1). The extent of bronchiectasis was correlated with a positive smoking history in the current study, consistent with previous findings (42). Particulates released by smoking might be involved in airway remodeling in patients with bronchiectasis-prior similar to COPD.

Comparably with asthma-induced bronchiectasis, the existence, severity, and BSI scores of bronchiectasis were associated with deteriorated lung function in the bronchiectasis-prior group. Regardless of etiology, clinicians and researchers should be aware of the presence of bronchiectasis in patients with asthma. Regular follow-up chest CT and lung function are necessary for the early detection and treatment of bronchiectasis in asthmatic patients. Meanwhile, the dose of the inhaled drug was positively correlated with the severity of bronchiectasis, regardless of the onset of bronchiectasis, indicating that the severity of bronchiectasis affected the step-treatment strategy by clinicians. Recent studies focused on the nutritional status and nutrient deficiency to the prognosis of bronchiectasis (43-45). As an indicator of nutritional status, BMI is a predictor of prognosis in bronchiectasis, and a lower BMI is linked to the severity and increased mortality in bronchiectasis patients (43,44). The present study presented that the severity of bronchiectasis was related to a lower BMI, regardless of the sequence of bronchiectasis onset in asthmatic patients. In summary, these results suggested that the severity of bronchiectasis was significantly associated with poor nutritional status and prognosis, and it should be closely monitored in asthmatic patients.

The British Thoracic Society guidelines recently recommended the BSI scoring system to predict further outcomes in bronchiectasis patients (10). Our results showed that BSI scores were positively related to *Pseudomonas aeruginosa* isolation and age and negatively correlated with FEV_1%predicted in the bronchiectasis-prior group, consistent with variables included in the BSI tool, indicating that the BSI tool is strongly predictive of the future outcomes in bronchiectasis preceding asthma patients (23). Notably, in the asthma-prior group, the BSI scores were positively related to the total IgE level and severe asthma exacerbation, suggesting that the coexistence of asthma acts as an adverse factor in bronchiectasis outcomes. Consistently, recent research indicated that the coexistence of asthma was an independent risk factor of bronchiectasis exacerbation (46). Whether the BSI tool is a perfect outcome predictor for asthma-induced bronchiectasis remains to be confirmed in the follow-up studies, and adding asthmatic factors to the BSI tool may be a better predictive system.

Limitations

This study has several limitations. First, there may be a selection bias because an assessment of the onset of bronchiectasis may be affected by the patients' statement of history. Second, since the patients were enrolled at the respiratory and otorhinolaryngology departments, the rate of bronchiectasis in asthma could not reflect the epidemiological prevalence, although a correlation can be established. Longitudinal randomized controlled studies are necessary to determine the intrinsic causality and mechanisms of asthma and bronchiectasis. Third, we classified patients with "bronchiectasis diagnosed with HRCT coincident with the asthmatic symptoms" into the bronchiectasis-prior group, among which there were possibly a small number of asthma-induced bronchiectasis patients. Fourth, although the diagnosis of asthma in our study was strictly based on GINA guidelines, a small proportion of bronchiectasis patients with asthmatic components might be included. The differences and intrinsic correlations between bronchiectasis patients with asthmatic components and bronchiectasis combined with asthma in physiological and inflammatory characteristics, progression, treatment principles, and prognosis need further exploration.

Conclusions

The coexistence of asthma and bronchiectasis is a complex phenomenon. For patients with asthma, it is necessary to undergo follow-up chest CT and lung function to investigate bronchiectasis. The sequence of bronchiectasis onset may indicate distinct inflammatory characteristics. Meanwhile, detailed medical history collection is necessary to deliver targeted therapy for asthma comorbid with bronchiectasis.

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Footnote

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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 (as revised in 2013). This study was approved by the Ethics Committee of the Beijing Tongren Hospital, Capital Medical University (approval No. TRECKY2019-070). Written informed consent was obtained from all enrolled patients.

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