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Asthma and bronchiectasis exacerbation

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ABSTRACT Bronchiectasis and asthma are common respiratory diseases worldwide. However, the influence of asthma on bronchiectasis remains unclear. The objective of this study is to analyse the effects of asthma on bronchiectasis exacerbation.

Data from inpatients diagnosed with bronchiectasis with or without asthma at Shanghai Pulmonary Hospital (Shanghai, China) between January 2013 and December 2014 were retrospectively collected and analysed. 249 patients with only bronchiectasis and 214 patients with both bronchiectasis and asthma were included in the study. Follow-up records were used to evaluate the effect of asthma on bronchiectasis exacerbation.

The variables found to be independently associated with bronchiectasis exacerbations were age (OR 1.07, 95% CI 1.03–1.11; p<0.001), duration of symptoms (OR 1.06, 95% CI 1.03–1.09; p<0.001), the presence of asthma (OR 2.6, 95% CI 1.15–5.88; p=0.021), forced expiratory volume in 1 s <50% predicted (OR 4.03, 95% CI 1.75–9.26; p=0.001), isolation of *Pseudomonas aeruginosa* in sputum (OR 2.41, 95% CI 1.00–5.79; p=0.05) and lung lesion extension to more than two lobes (OR 2.73, 95% CI 1.16–6.45; p=0.022).

The existence of asthma was associated with an independent increase in risk of bronchiectasis exacerbation.

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Introduction

Non-cystic fibrosis bronchiectasis is characterised by irreversibly dilated bronchi and usually associated with chronic sputum production, bacterial colonisation of the lower respiratory tract, inflammation and frequent exacerbations [1]. Although its prevalence is unknown in most areas, with the development of high-resolution computed tomography (HRCT) scanning as a detection tool, bronchiectasis is increasingly recognised as an important respiratory disease in developing countries [2]. Patients with bronchiectasis suffer from recurrent acute exacerbations, which include airway infection and inflammation, often resulting in hospitalisation. Recurrent exacerbations can lead to progressive deterioration of lung function [3].

Asthma is a heterogeneous disease characterised by recurrent episodes with three distinct components: airway obstruction, airway hyperresponsiveness and airway inflammation [4]. These are often triggered by factors such as exercise, exposure to allergens or irritants, changes in weather or viral respiratory infections [5].

The coexistence of bronchiectasis and asthma has been observed in many patients. However, few studies have been undertaken to investigate the relationship between the two diseases. Therefore the purpose of this study is to evaluate the clinical characteristics of asthma in patients with bronchiectasis and analyse the effects of asthma on bronchiectasis exacerbation.

Methods

Subjects

Data were collected retrospectively from inpatients diagnosed with bronchiectasis with or without asthma at the Shanghai Pulmonary Hospital (Shanghai, China) between January 2013 and December 2014. Patients who had not received a chest HRCT scan examination or who had indecipherable HRCT scan images were excluded. Patients with other diseases (*e.g.* chronic obstructive pulmonary disease, allergic bronchopulmonary aspergillosis, α_1-antitrypsin deficiency, significant immunodeficiencies and respiratory carcinomas) were also excluded. All aspects of the study were performed in accordance with relevant guidelines and regulations.

Diagnosis of bronchiectasis and asthma

Diagnosis of bronchiectasis was performed using chest HRCT scans in suspected patients with coughing and expectoration, or long durations of haemoptysis. High-resolution images were obtained during full inspiration at 1-mm collimation and 10-mm intervals from the apex to the base of the lungs. The presence of bronchiectasis was confirmed based on the following criteria: 1) lack of tapering in the bronchi; 2) dilation of the bronchi where the internal diameter was larger than that of the adjacent pulmonary artery; or 3) visualisation of the peripheral bronchi within 1 cm of the costal pleural surface or the adjacent mediastinal pleural surface [6, 7]. An exacerbation is defined as the patient reporting four or more of the following symptoms: change in sputum production, increased dyspnoea, increased cough, fever >38°C, increased wheezing, decreased exercise tolerance, fatigue, malaise, lethargy, reduced pulmonary function, changes in chest sounds or radiographic changes consistent with a new infectious process [3]. The type of bronchiectasis was defined morphologically. Patients with small areas of bronchiectasis only visible in a single pulmonary segment were excluded, because this sign can appear in a large proportion of the healthy population [8].

Asthma diagnosis was confirmed according to the Global Initiative for Asthma (GINA) guideline at the time of diagnosis. Asthma was diagnosed for patients with symptoms such as episodic breathlessness, wheezing, cough and chest tightness, and whose spirometry showed bronchial reversibility of 12% and 200 mL from the prebronchodilator value or airway hyperresponsiveness as a 20% decrease in forced expiratory volume in 1 s (FEV_1) caused by a provocative histamine with a cumulative dose <2.4 mg [9, 10]. In accordance with the GINA guidelines, asthma symptom control assessment was based on the frequency of daytime and night-time asthma symptoms, reliever use and activity limitation.

Variables

The variables collected in this study included the following: general and anthropometric information (*i.e.* age, sex, body mass index and smoking history); history of respiratory illness (*i.e.* pertussis, tuberculosis and anaphylactic rhinitis); lung signs (moist or dry rales); serological indicators (*e.g.* C-reactive protein, erythrocyte sedimentation rate, albumin and immunoglobulin (Ig)); pulmonary function test results (*e.g.* predicted and absolute values of FEV_1 and forced vital capacity (FVC) and FEV_1/FVC ratio); and microbiological detection of sputum samples. Sputum samples were accepted if they contained <10 squamous epithelial cells and >25 leukocytes per low-powered field. Bronchiectasis exacerbations were recorded in patients within 1 year of their discharge from the hospital, using telephone or face-to-face interviews.

Statistics

The statistical packages SPSS (version 19.0; SPSS, Chicago, IL, USA) and GraphPad Prism (version 5; GraphPad Software, San Diego, CA, USA) were used for statistical analysis and drawing graphs, respectively.

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The data were tabulated as mean±SD in the case of quantitative variables and as absolute numbers and percentages in the case of qualitative variables. The Kolmogorov–Smirnov test was used to analyse the distribution of variables. In the bivariate analysis, the t-test for independent variables was used to analyse variables that were normally distributed and the Mann–Whitney U-test was used to analyse variables that were non-normally distributed. Qualitative variables were compared using the Chi-squared test. In multiple comparisons, quantitative variables were compared using one-way ANOVA. If a variable was found to be significant, the Student–Newman–Keuls q-test was used to analyse the comparison among groups in multiple comparisons. Depending on whether variables were normally or non-normally distributed, either a Spearman or a Pearson coefficient was calculated to assess the correlation between variables. In the case of elevated collinearity between two variables (Spearman correlation test >0.6), the variable with greater clinical significance was included in the final regression equation. A logistic regression model was used to determine the factors that were independently associated with bronchiectasis exacerbation. The variables that presented statistically significant differences ($p<0.05$) in the bivariate analysis and were of clinical interest were included as the independent variables in the first model. The forward stepwise technique (*i.e.* the Wald test) was then used to remove any variables with $p>0.1$ from the final model. The odds ratio and 95% confidence interval were calculated for the independent variables, with $p\leqslant 0.05$ considered to be significant.

Results

The data of 249 patients with bronchiectasis only and 214 patients with both bronchiectasis and asthma at Shanghai Pulmonary Hospital were included in the study. Of all 463 patients, 179 responded fully to the follow-up (102 patients with only bronchiectasis and 77 patients with both bronchiectasis and asthma). 97 patients had at least one bronchiectasis exacerbation within 1 year of their discharge from the hospital.

The baseline characteristics of subjects are shown in tables 1 and 2. There were statistical differences in age, duration of symptoms, previously experienced anaphylactic rhinitis, chest signs, distribution of bronchiectasis types, blood biochemical indicator levels, rate of *Pseudomonas aeruginosa* isolation and total IgE levels between the two groups. There was an elevated collinearity between age and duration of symptoms (Spearman

TABLE 1 Baseline and clinical characteristics of subjects with bronchiectasis, with and without asthma

Parameter	Bronchiectasis	Bronchiectasis with asthma	p-value
Age years	55.7±13.38	52.0±11.54	**0.002**
Sex male:female n	86:163	78:136	0.668
BMI kg·m^{-2}	20.9±3.64	22.8±3.31	**<0.001**
Smoking	15.3	19.2	0.266
Duration of symptoms years	15.1±14.50	11.7±14.58	**0.001**
Previous pertussis	5.2	2.3	0.109
Previous tuberculosis	12.0	8.9	0.269
Previous anaphylactic rhinitis	9.2	18.9	**0.03**
Moist rales	57.0	35.5	**<0.001**
Dry rales	16.1	45.8	**<0.001**
***Pseudomonas aeruginosa* isolation**	29.3	19.7	**0.022**
FEV_1 L	1.60±0.75	1.69±0.74	0.212
FEV_1 % pred	61.4±23.17	63.3±24.02	0.418
FVC L	2.20±0.85	2.52±0.80	**<0.001**
FVC % pred	69.3±20.12	78.0±18.52	**<0.001**
FEV_1/FVC	71.2±14.21	65.7±14.54	**<0.001**
Type			
Cylindrical	42.4	63.7	
Cystic	25.1	11.0	
Mixed	32.5	25.3	**<0.001**
Location			
Unilateral	20.2	15.1	
Bilateral	79.8	84.9	0.219
Extent			
Affected lobes n	3.5±1.48	3.4±1.46	0.9
Affected segments n	7.5±3.80	8.0±3.96	0.317

Data are presented as mean±SD or %, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. Data presented in bold type are statistically significant.

TABLE 2 Serological indicators of subjects with bronchiectasis, with and without asthma

	Bronchiectasis	Bronchiectasis with asthma	p-value
Haemoglobin g·L^{-1}	126.1±14.77	131.8±15.93	**<0.001**
WBC ×10^{9} cells·L^{-1}	6.5±2.73	7.5±3.20	**<0.001**
Neutrophils %	59.6±11.90	64.7±14.02	**<0.001**
Eosinophils %	3.4±3.81	3.3±4.87	0.951
ESR mm·h^{-1}	39.3±29.91	27.1±23.25	**<0.001**
CRP IU·mL^{-1}	18.6±33.52	10.1±25.00	**<0.001**
Albumin mg·dL^{-1}	37.8±5.03	40.5±3.89	**<0.001**
CD4/CD8	1.9±1.47	1.9±1.41	0.466
IgG g·L^{-1}	15.5±7.30	11.8±3.74	**<0.001**
IgA g·L^{-1}	3.3±1.75	2.5±1.10	**<0.001**
IgM g·L^{-1}	1.2±0.60	1.2±0.65	0.099
C3	1.1±0.26	1.1±0.23	0.42
C4	0.3±0.12	0.3±0.09	0.33
Total IgE			
<100	64.9	40.9	
100–200	11.2	14.5	
>200	23.9	44.6	**<0.001**
P_{O_2} mmHg	83.8±18.75	78.0±16.04	**0.001**
P_{CO_2} mmHg	41.7±7.37	42.2±6.91	0.085
S_{pO_2} %	95.3±4.13	94.5±5.99	0.093

Data are presented as mean±SD or %, unless otherwise stated. WBC: white blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Ig: immunoglobulin; C: complement; P_{O_2}: oxygen tension; P_{CO_2}: carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. Data presented in bold type are statistically significant.

correlation test 0.119, p=0.011). Furthermore, 63.7% of patients in the group with coexisting asthma presented with cylindrical bronchiectasis. The severity of symptoms in patients with cylindrical bronchiectasis was moderate compared with that of patients with cystic or mixed bronchiectasis. There were significant differences in FVC % predicted, FEV1/FVC ratio and forced expiratory flow at 25% of FVC between the two groups. Patients with coexisting asthma had poorer small airway function than those without asthma.

The differential characteristics of patients who suffered at least one exacerbation and patients who did not exacerbate are shown in figures 1 and 2. Patients who had one or more exacerbations were older and presented with longer lasting symptoms, a higher prevalence of asthma, poorer pulmonary function test results and a wider extension of affected lobes.

The odds ratios and 95% confidence intervals of variables related to bronchiectasis exacerbations in all patients are illustrated in figure 3. Where OR=1, the variables have no risk in bronchiectasis exacerbation. Age, duration of symptoms, FEV1 <50% pred, extension to more than two lobes, isolation of *P. aeruginosa* from sputum samples and the presence of asthma were independent risk factors for bronchiectasis exacerbation in these patients.

Discussion

Based on the results, we found that the patient's age, the duration of their symptoms, a FEV1 <50% predicted value, extension to more than two lobes, isolation of *P. aeruginosa* from sputum samples and the presence of asthma were associated with an increased risk in bronchiectasis exacerbation in patients with non-cystic fibrosis bronchiectasis.

According to previous studies, age and pulmonary function test results were associated with poor prognosis in patients with bronchiectasis [11, 12]. The high collinearity between FEV1 and FVC made it possible to choose FEV1 to represent the patient's functional state, as this is the variable most commonly used in the evaluation of airflow obstruction, which is the most common functional pattern in patients with bronchiectasis [13]. Other functional variables, such as those related to exercise tests, were not taken into account for the analysis because of their rare application [13–15]. In this study, age and FEV1 were associated with bronchiectasis exacerbation in these patients, which represents the progression of disease.

Other variables, such as the extent of bronchiectasis upon radiography and isolation of *P. aeruginosa* from sputum samples were also associated with bronchiectasis exacerbation in this study. The extent of bronchiectasis, quantified as the number of lobes affected, was included in the analysis. This is supported by

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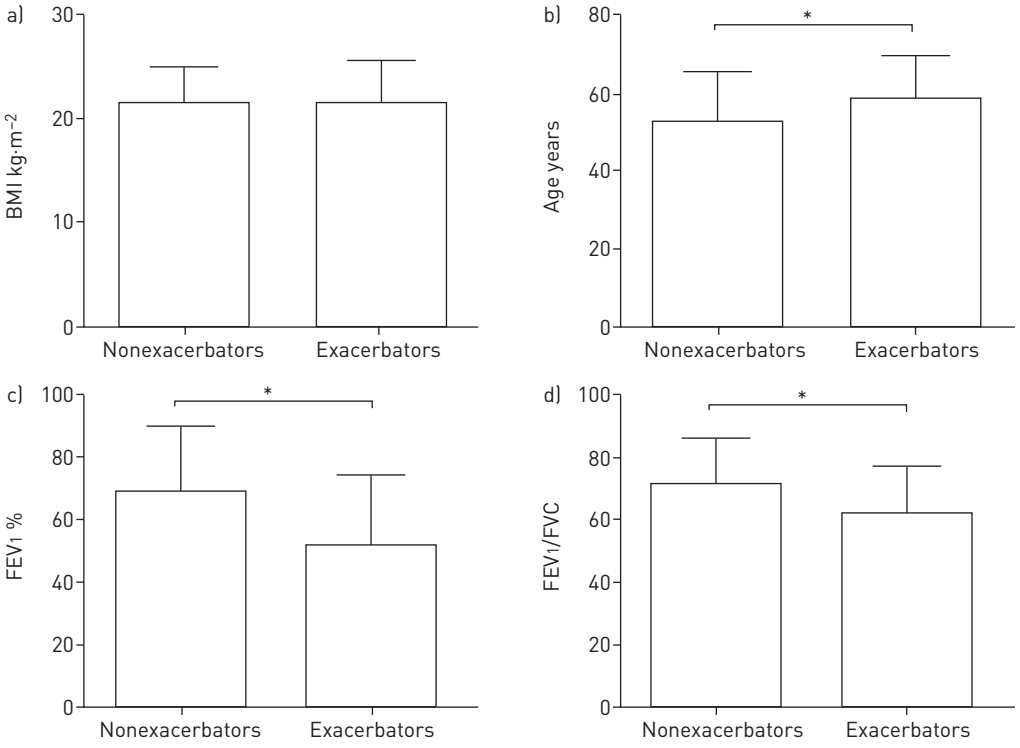


FIGURE 1 a) Body mass index (BMI); b) age; c) forced expiratory volume in 1 s (FEV_1) % predicted; and d) FEV_1/forced vital capacity (FVC) ratio of patients who underwent at least one exacerbation and patients who did not exacerbate. *: $p<0.05$.

authors who found that pulmonary extension can be used to assess the severity of bronchiectasis or its response on treatment as an isolated parameter [14, 16]. As its strong association with an increase in exacerbation and poorer function in patients with non-cystic fibrosis bronchiectasis [17–19], *P. aeruginosa* was an independent factor associated with bronchiectasis exacerbation in the present study.

Many studies have reported the relationship between bronchiectasis, allergic diathesis and asthma [20–22]. According to Säynäjäkangas *et al.* [22], asthma is common in hospitalised bronchiectasis patients and appears to be a consequence of this disease. However, the prevalence of asthma in patients with bronchiectasis ranged from 2.7% to 42% in other studies [23–25]. Although the sample sizes were insufficient in these studies, they indicated the role of asthma in bronchiectasis exacerbation. Patients with asthma in our study were 2.6 times more likely to suffer exacerbation than those without asthma, independent of other variables. The prognostic value of the presence of asthma could suggest the existence of a new phenotype of patients with bronchiectasis with asthma, probably related to the exacerbation and prognosis. As we know, asthma is a phenotypically heterogeneous chronic disease of the airways, characterised by either predominant eosinophilic, neutrophilic or even mixed eosinophilic/neutrophilic inflammatory patterns [26]. Mucus hypersecretion, oxidative stress and airway remodelling were all involved in asthma and bronchiectasis. In addition, the micro-organisms separated from the lower respiratory airway of asthma patients may play a role in bronchiectasis exacerbation [27, 28]. Inhaled corticosteroids in asthma patients can affect immunity, including an increased risk of pneumonia [29], while bacterial infection is a main predisposing factor in acute exacerbation in bronchiectasis patients. However, further studies are needed to demonstrate the real connection between asthma and the prognosis of bronchiectasis.

There are several limitations to this study. The first is that there is an inherent risk of selection bias (perhaps Berkson's bias [30]) based on its retrospective design. Thus we conducted a cross-sectional and observational study which might minimise the risk of selection bias. Besides, the patients were continuously recruited in strict accordance with the inclusion and exclusion criteria. Furthermore, we made efforts to contact patients many times for follow-up, despite the fact that the rate of loss to follow-up is high. Another limitation of this study is that some questionnaires that reflect the psychological impact on patients, such as the modified Medical Research Council dyspnoea scale and the Quality of Life Bronchiectasis questionnaire were not included in this retrospective study [31, 32]. Another limitation of the study is that we did not bring the status of treatment into the analysis, which was associated with the compliance of patients and might have an effect on the results of the analysis.

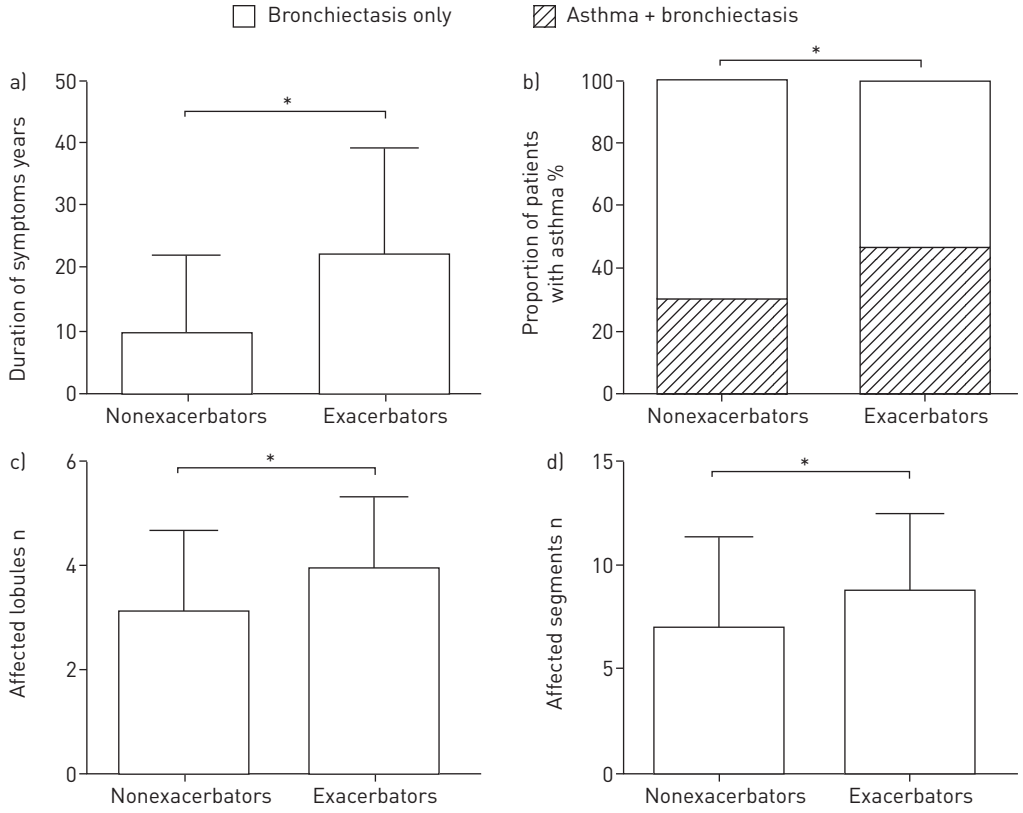
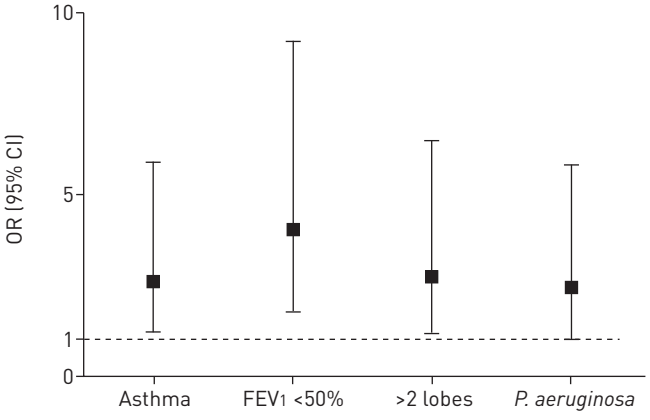
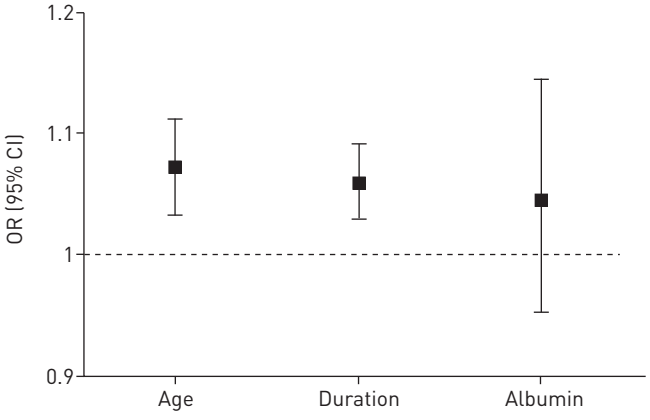


FIGURE 2 a) Duration of symptoms; b) proportion of asthma; c) number of affected lobules; d) number of affected segments of patients who suffered exacerbation (at least once) and patients who did not exacerbate. *: p<0.05.

In summary, our results suggest that the presence of asthma are associated with an independent increase in the risk of bronchiectasis exacerbation in patients with non-cystic fibrosis bronchiectasis. Further studies are needed to confirm our results with respect to the prognostic value of asthma in patients with non-cystic fibrosis bronchiectasis, and the role played by exacerbations in this relationship.



	OR (95% CI)	p-value
Asthma	2.60 (1.15–5.88)	0.021
FEV_1 <50%	4.03 (1.75–9.26)	0.001
Extent >2 lobes	2.73 (1.16–6.45)	0.022
P. aeruginosa isolation	2.41 (1.00–5.79)	0.05



	OR (95% CI)	p-value
Age	1.07 (1.03–1.11)	<0.001
Duration of symptoms	1.06 (1.03–1.09)	<0.001
Albumin	1.05 (0.95–1.15)	0.353

FIGURE 3 Factors associated with bronchiectasis exacerbation in all subjects according to the logistic regression analysis. FEV_1: forced expiratory volume in 1 s; *P. aeruginosa*: *Pseudomonas aeruginosa*.

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