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Clinical Features of Patients with Bronchiectasis with Comorbid Chronic Obstructive Pulmonary Disease in China

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Background: The prevalence of bronchiectasis with comorbid chronic obstructive pulmonary disease (COPD) is rising, which causes extremely high risk of exacerbation and mortality. We aimed to evaluate the differences in clinicopathological manifestations, immune function, and inflammation in bronchiectasis patients with comorbid COPD *vs.* patients who only have COPD.

Material/Methods: Clinicopathological characteristics, including common potentially pathogenic microorganisms, lung function, immune function, and inflammation were assessed in bronchiectasis patients with comorbid COPD and in patients who only had COPD.

Results: Compared to patients who only had COPD, patients with bronchiectasis with comorbid COPD had a higher positive rate of sputum bacteria (45.27% *vs.* 28.03%, $P<0.01$). Among them, *Pseudomonas aeruginosa* (*P. aeruginosa*) accounted for 25.19% in COPD (4.37%) ($P<0.01$). Likewise, patients with bronchiectasis with comorbid COPD had worse lung function, worse COPD assessment test scores, and worse Modified Medical Research Council scores. Moreover, compared with COPD only cases, patients with bronchiectasis with comorbid COPD had higher levels of white blood cells (WBC), neutrophils, C-reactive protein (CRP), and procalcitonin (PCT) (all $P<0.05$). Interestingly, the expression levels of Treg in patients with bronchiectasis with comorbid COPD were lower than in patients with COPD only ($P<0.05$). Th17 and Th17/Treg levels were higher ($P<0.05$). Furthermore, remarkable increased level of IL17 and IL-6 and decreased level of IL-10 and TGF-β were observed in the bronchiectasis combined COPD than in pure COPD (All $P<0.05$).

Conclusions: Our findings suggest that *P. aeruginosa* is the main pathogen of bacterial infection in bronchiectasis patients with comorbid COPD. These patients have more serious clinical manifestations and immune imbalance, which should be considered when providing clinical treatment.

MeSH Keywords: Bronchiectasis • Lung Diseases, Obstructive • *Pseudomonas aeruginosa*

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Background

Bronchiectasis is a chronic airway disease characterized by recurrent infection and chronic inflammation [1], in which repeated exacerbation can result in immune imbalance and pulmonary dysfunction. It has been reported that it has a prevalence rate ranging from 25% to 70% for patients with bronchiectasis and comorbid chronic obstructive pulmonary disease (COPD). While in moderate-to-severe COPD, the rate exceeds 50% [2,3]. Evidence shows that bronchiectasis patients with comorbid COPD (CBC) have more persistent heavy bacterial colonization and severe symptoms, higher frequency of exacerbations, worse lung function, and increased mortality compared to patients who only had COPD [4]. According to previous clinical observations, many CBC patients exhibit clinical characteristics outside the usual symptom profile, which is a considerable diagnostic challenge to clinicians. Limited evidence suggests that bronchiectasis patients with comorbid COPD show different patterns of colonization by or infection with potentially pathogenic microorganisms (PPMs) when compared to patients who only had COPD [4]. A higher rate of *Pseudomonas aeruginosa* (*P. aeruginosa*) isolation has been observed in patients with bronchiectasis with comorbid COPD than with pure COPD [5,6]. However, few studies have confirmed the association between *P. aeruginosa* and CBC. Colonization or infection by PPMs were reported to be associated with increased hospital mortality of COPD patients [7]. However, little is known about the molecular mechanisms underlying the persistence of PPMs involving *P. aeruginosa* colonization or infection in the lungs of patients with CBC.

Studies indicated that *P. aeruginosa* infection predisposes patients to inflammation, leads to a cycle of inflammation, and eventually induces bronchiectasis accompanied by dysfunctional immune response. Chronic *P. aeruginosa* infection inhibits activity of regulatory T cells (Tregs) and induces elicited T helper cell 17 (Th17) responses, which causes a decreased abundance of Tregs in peripheral blood and airway samples [8–10]. During bronchiectasis exacerbation, the function of Tregs is impaired, followed by suppression of immune cell activation and inhibition of inflammatory cytokine secretion, thus it is possible that the *P. aeruginosa* and dysfunctional Treg cell predispose bronchiectasis patients to developing COPD.

We performed a retrospective study with a total of 508 bronchiectasis patients with comorbid COPD and 503 patients who only had COPD to characterize and compare the sputum bacteriology results and clinical indexes between the 2 groups. Also, immune factors and inflammatory factors were further detected to uncover the pathomechanism in CBC.

Material and Methods

Study subjects

All CBC patients or pure COPD attended the respiratory outpatient clinics of Dongguan Fifth People's Hospital between January 2015 and September 2018. In this study, a total of 508 cases of stable bronchiectasis with comorbid COPD were diagnosed by high-resolution computed tomography (HRCT) [11] and pulmonary function, and 503 stable COPD patients diagnosed by pulmonary function test and confirmed negative for bronchiectasis by HRCT served as controls. Eligible patients had to remain exacerbation-free for 4 weeks. Patients with malignancy, upper respiratory tract infections, or antibiotic use within the last 4 weeks were excluded. After a written informed consent was signed by each patient, a simple questionnaire was used to collect data on demographics, including age, sex, smoking status, and body mass index (BMI). The constructed COPD assessment test (CAT) and Modified Medical Research Council (mMRC) questionnaires were used to assess CAT scores and mMRC scores at baseline by the subjects recruited [12,13]. The predicted values of FEV1 were estimated as previously reported [14]. The study was approved by the Ethics Committee of the Fifth People's Hospital of Dongguan (2017008).

HRCT scans and pulmonary function test

The presence of bronchiectasis was determined by HRCT examination for the following: bronchial abnormalities; adjacent and bronchus artery ratio >1; signet ring sign; double-track; bronchial unchanged; small, visible around aerosols; bronchial wall thickening; mucus filling; bronchus mosaic irrigation and air trapping; and bronchial artery increased. Lung function was evaluated with the EasyOne Spirometer (EasyOne Spirometer, Medizintechnik AG, Switzerland). When patients had forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) of <70% after inhalation of 400 μg salbutamol and chronic airway symptoms such as chronic cough, dyspnea, sputum production, or wheezing, they were identified as COPD cases. The predicted values of FEV1 were estimated as the previously reported [14].

Sputum and blood samples collection

Sputum was sampled in the morning when patients attended the respiratory outpatient clinics. For exacerbation patients, sputum was collected prior to treatment. After removal of oral cavity contents by thorough rinsing with distilled water, patients were instructed to expectorate and collect sputum in a 60-mL sterile plastic container for further bacterial culture and preparation of sol phase. Hypertonic saline (3–5%) was employed for sputum induction if no spontaneous sputum sample was available. Sputum samples with 25 leukocytes or greater and

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Table 1. Clinicopathological characteristics in bronchiectasis patients with comorbid COPD patients *vs.* COPD only.

Variables	Bronchiectasis with COPD (N=508, %)	COPD only (n=503, %)	*P*-value
Age (years)	63.7±14.8	64.9±12.5	0.164
Sex			
Male	320 (63.0)	324 (64.4)	0.638
Female	188 (37.0)	179 (35.6)	
BMI (kg/m^2)	21.1±3.93	22.5±5.99	<0.001
Smoke			
No	239 (47.0)	227 (45.1)	0.541
Yes	269 (52.9)	276 (54.9)	
Smoke (pack-year)	22.4±21.7	22.6±18.3	0.874

P-value from the chi-square test for categorical data or unpaired *t* test for quantitative data.

10 epithelial cells or lower under microscopic field (×100) were deemed eligible. Moreover, each subject simultaneously provided a 5-mL blood sample.

Quantitative identification of bacteria

Qualified sputum was further inoculated on a blood plate with chocolate tablet and China blue plate for bacterial culture. The conventional method was applied to identification of bacteria.

Detection of inflammatory biomarkers in serum

The peripheral blood samples were sent for routine blood tests and analysis of white blood cell (WBC), C-reactive protein (CRP), procalcitonin (PCT) levels following conventional methods.

Flowcytometry analysis of Th17 and Tregs

Patients with positive *P. aeruginosa* were recruited for Th17/Treg analysis. Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood samples before beginning therapy using Isopaque-Ficoll (Lymphoprep, Nycomed Pharma, Oslo, Norway). After gradient centrifugation and washing twice with Dulbecco's phosphate-buffered saline (DPBS)/10% fetal bovine serum (FBS, Bovogen, East Keilor, Vic, Australia) at 300 g for 10 min at room temperature, the cells were resuspended in 1 mL of DPBS/10% FBS and were either cryopreserved for future use or immediately activated and processed for flow cytometry. The identification of Th17 and Treg cells was performed using the Th17/Treg phenotyping kit (BD Biosciences, Mountainview, CA, USA) according to the instructions of the manufacturer.

ELISA analysis for inflammatory biomarkers

The standard curve was prepared and the 100-μL serum sample was added to the pore plate, placed on a shaking table, and incubated for 2.5 h. After washing the plate, we added antibody, incubated it for 1 h, washed the plate again, patted it dry, added 100 μL enzyme, incubated it for 45 min, then washed plate again and patted it dry. Then, we added substrate to each hole, incubated it for 30 min, added termination solution immediately on the enzyme marker (Thermo Fisher Scientific, Waltham, MA, USA), detected absorbance at the wavelength of 450 nm, drew a standard curve, and calculated the OD value of the sample.

Statistical analysis

The chi-square test was used to determine the differences in categorical data, while the unpaired *t* test was applied for analyzing the differences in measurement data between different groups. The Fisher's exact test was used when the expected number of observations was less than 5. All tests were two-sided and performed with the Statistical Product and Service Solutions (SPSS) version 17.0 software (SPSS, Inc., Chicago, IL, USA). *P*-values less than or equal to 0.05 were considered significant.

Results

Demographical characteristics in studied populations

The baseline characteristics of CBC patients and pure COPD ones are shown in Table 1. There was no significant difference in age, sex, or smoking between the 2 groups (all *P*>0.05).

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Table 2. Sputum PPMs during exacerbation in bronchiectasis combined COPD patients and COPD only.

PPMs	Bronchiectasis+COPD		COPD only		*P*-value
	Detected (%)		Detected (%)		
n	508		503		
P. aeruginosa	128	(25.19%)	22	(4.37%)	<0.001
Pneumonia klebsiella	16	(3.14%)	15	(2.98%)	0.877
Acinetobacter baumannii	22	(4.33%)	6	(1.19%)	0.002
Escherichia coli	6	(1.18%)	7	(1.39%)	0.766
Eosinophilic malt false unit cell packs	7	(1.37%)	6	(1.19%)	0.794
Haemophilus influenzae	20	(3.94%)	36	(7.16%)	0.025
Streptococcus pneumoniae	8	(1.57%)	32	(6.36%)	<0.001
Moraxella catarrhalis	6	(1.18%)	10	(1.99%)	0.304
Staphylococcus aureus	3	(0.59%)	1	(0.20%)	0.624
Fungus	14	(2.75%)	6	(1.19%)	0.074
Total	230	(45.27%)	141	(28.03%)	<0.001

However, the BMI status was significantly different between CBC patients and pure COPD cases.

Comparison of sputum PPMs between CBC patients and pure COPD ones

As shown in Table 2, the sputum cultivate bacterial species were observably different in CBC and COPD only patients. Over 10 different species of bacteria or fungi were isolated from these patients; 230 (45.27%) patients tested positive for pathogenic microorganisms in CBC group, and only 141 (28.03%) patients in the pure COPD group. The positive rate was remarkably discrepant between the 2 groups (P<0.01). The most commonly identified bacterial species was *P. aeruginosa* in 128 (25.19%) patients in the CBC group, which was significantly higher than in the pure COPD group with 22 (4.37%) (P<0.01).

Lung function and clinicopathological characteristics in CBC patients and COPD only patients

As shown in Table 3, patients in the CBC group had poorer lung function when compared with the pure COPD group in terms of FEV1 (0.53±0.181 *vs.* 0.64±0.16, P<0.001), FEV1% (45.26±9.7 *vs.* 52.49±9.71, P<0.001), and FEV1/FVC (51.34+9.24 *vs.* 66.18+10.11, P<0.001). Likewise, those patients with CBC had a higher rate in advanced GOLD stage (P<0.001). Furthermore, compared with pure COPD patients, CBC patients had worse CAT scores (29.8±11.3 *vs.* 24.9±10.6, P<0.001) and mMRC scores (2.43±0.96 *vs.* 1.97±0.88, P<0.001). These poor clinical manifestations caused longer hospitalization times in the CBC group than in pure COPD patients (25.4±9.3 *vs.* 16.7±7.8, P<0.001).

Association between biomarkers of inflammatory and immune factors during exacerbation in CBC patients and COPD only patients

As described in Table 4, CBC was significantly associated with increased WBC and its ratio when compared to pure COPD patients in the exacerbation period (WBC: 12.54±7.26 *vs.* 10.65±4.47, P<0.001; ratio: 79.5±11.8% *vs.* 73.1±13.3%, P<0.001). Moreover, the CBC patients also had elevated PCT (0.563±0.172 *vs.* 0.354±0.203; P<0.001) and CRP (39.4±25.4 *vs.* 36.5±24.2; P<0.001) levels compared with pure COPD cases. However, no other significant association was observed. The CBC patients shown a higher rate of Th17 cells (3.56%±0.33% *vs.* 2.21±0.22%; P<0.001) and lower rate of Tregs (6.05±1.21% *vs.* 10.73±2.91%; P<0.001) than in the pure COPD cases (Figure 1). Consequentially, a higher Th17/Treg ratio was observed in CBC patients (59.74±8.76 *vs.* 26.58±9.54; P<0.001). In addition, several inflammatory factors were markedly different between the 2 groups. We observed that IL17 and IL-16 levels were significantly higher (8.32±1.61 *vs.* 6.20±0.74 and 4.24±1.22 *vs.* 3.21±1.50; P<0.001, respectively), and IL-10 (0.86±0.22 *vs.* 1.23±1.51; P<0.001) and TGF-β (92.4±11.8 *vs.* 110.4±9.73; P<0.001) levels were clearly lower than in pure COPD cases.

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Table 3. Lung function and clinicopathological characteristics in bronchiectasis combined COPD patients and COPD only.

Variables	Bronchiectasis combined COPD patients (N=508,%)	COPD only patients (N=503,%)	*P*-value
n	508	503	
FEV1 (L)	0.53±0.181	0.64±0.16	<0.001
FEV1 (% predicted)	45.26±9.7	52.49±9.71	<0.001
FVC (L)	0.68±0.12	0.63±0.14	<0.001
FVC (% predicted)	58.23±8.17	54.36±9.15	<0.001
FEV1/FVC	51.34±9.24	66.18±10.11	<0.001
GOLD stage			<0.001
I	91 (17.91%)	55 (20.87%)	
II	71 (13.97%)	206 (40.95%)	
III	167 (32.87%)	164 (32.60%)	
IV	179 (35.24%)	78 (5.56%)	
CAT score	29.8±11.3	24.9±10.6	<0.001
mMRC score	2.43±0.96	1.97±0.88	<0.001
Ventilatory disorder			<0.001
Obstructive	189 (37.20%)	471 (93.64%)	
Restrictive	88 (17.32%)	0 (0%)	
Mixed	231 (45.47%)	32 (6.36%)	
Number of readmissions (times)	3.86±0.47	2.14±0.58	<0.001
Hospitalization (days)	25.4±9.3	16.7±7.8	<0.001

P-value from the chi-square test for categorical data or unpaired *t* test for measurement data.

Table 4. Biomarkers of inflammatory and immune factor during exacerbation in bronchiectasis patients with comorbid COPD *vs.* patients who only had COPD.

Biomarkers	Bronchiectasis combined COPD (n=100)	Pure COPD (n=100)	*P*-value
WBC ($\times 10^9$/L)	12.54±7.26	10.65±4.47	<0.001
WBC ratio (%)	79.5±11.8	73.1±13.3	<0.001
CRP (mg/L)	39.4±25.4	36.5±24.2	<0.001
PCT (ng/mL)	0.563±0.172	0.354±0.203	<0.001
Th17 (%)	3.56±0.33	2.21±0.22	<0.001
Treg (%)	6.05±1.21	10.73±2.91	<0.001
Th17/Treg	59.74±8.76	26.58±9.54	<0.001
IL-17 (pg/mL)	8.32±1.61	6.20±0.74	<0.001
IL-6 (pg/mL)	4.24±1.22	3.21±1.50	<0.001
IL-10 (pg/mL)	0.86±0.22	1.23±1.51	<0.001
TGF-β1 (pg/mL)	92.4±11.8	110.4±9.73	<0.001

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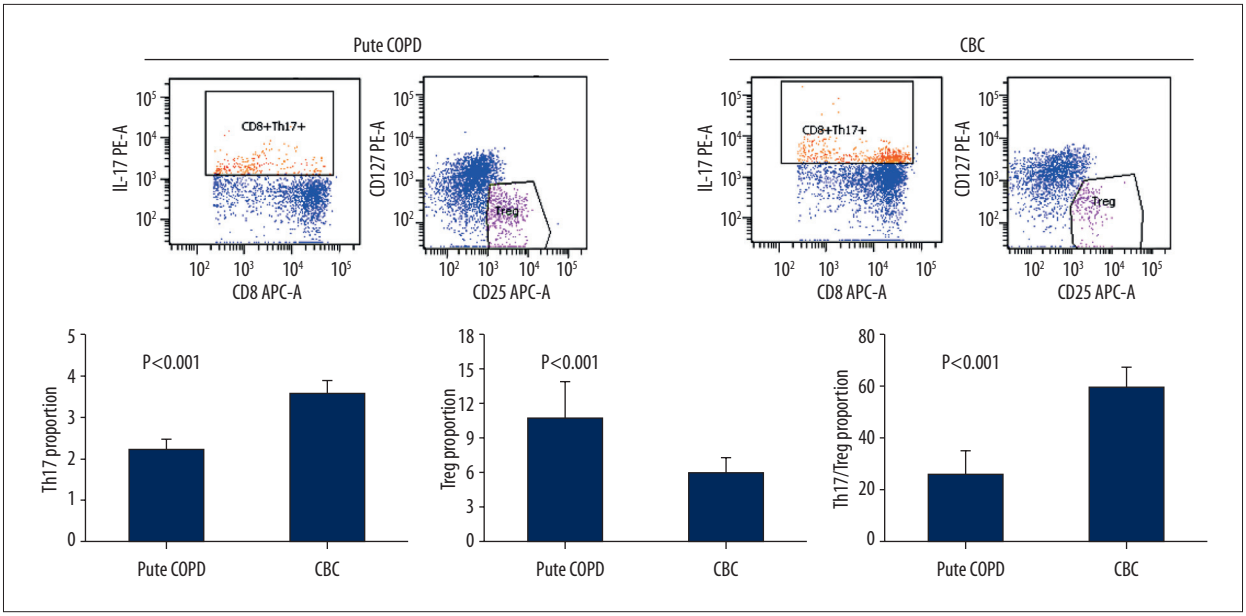

Figure 1. Comparison of Th17 cells and Tregs cells between CBC patients and pure COPD ones.

Discussion

To the best of our knowledge, this is the first study to evaluate the immunological characteristics of CBC patients with *P. aeruginosa* infection. Our study found that CBC was associated with increased infection rates of PPMs, especially *P. aeruginosa* colonization. These patients have more serious clinical manifestations due to evaluated levels of inflammatory biomarkers, including WBC, CRP, and PCT and incremental Th17/Treg conversion.

Sputum culture is the criterion standard for diagnosing respiratory pathogen infection. Previous studies have shown that bronchial dilation is mainly caused by haemophilus influenzae and *P. aeruginosa* [15]. With the exception of *P. aeruginosa*, haemophilus influenzae have also be studied and suggested that bronchiectasis is associated with increased risk of bronchiectasis combined with comorbid COPD [16]. Overlapped PPMs have been recognized as the major pathological mechanism of coexistence of bronchiectasis and COPD, of which *P. aeruginosa* was the most frequency found pathogenic bacterium in bronchiectasis patients [17]. Consistent with most previous studies, the association between presence of PPMs in the sputum and bronchiectasis combined COPD was confirmed in our study, which further suggests the *P. aeruginosa* is a biomarker of bronchiectasis for COPD patients. *P. aeruginosa* causes airway and systemic inflammatory responses and lung function impairment [18]. Thus, *P. aeruginosa* colonization is a difficult clinical problem, and special attention should be paid to *P. aeruginosa*. Early detection and effective prevention and treatment may reduce the incidence of CBC and improve the prognosis of such patients. In this study, we found that the sputum-cultivated bacterial species were obvious different between CBC and pure COPD patients, and during the acute exacerbation period, the pathogens of sputum culture in CBC patients were mainly Gram-negative bacteria. The sputum culture prioritized Gram-negative bacteria, of which the *P. aeruginosa* was the most commonly identified. However, the pure COPD patients had lower sputum-culture positive rates; and the sputum culture gave priority to Gram-positive bacteria.

Haemophilus influenzae was the main positive bacterium in the pure COPD patients. Because *P. aeruginosa* has multiple drug resistance, controlling *P. aeruginosa* colonization is a worldwide problem. The Chinese government has limited the use of broad-spectrum antibiotics; therefore, new effectively therapeutic strategies to combat inflammation caused by the PPMs are imperative.

In the present study, CBC patients showed worse pulmonary function, more readmissions times, and longer duration of hospitalization, and more of these patients had advanced GOLD stage and had higher CAT scores and mMRC scores, which suggests worse prognosis of CBC than pure COPD. These results are in accordance with a previous study [18]. Accumulating evidence has revealed the significant association of coexistent bronchiectasis with morbidity and mortality of COPD. The shared molecular mechanism might explain the progression of these 2 diseases. Studies have confirmed that inflammatory markers, including IL-17, IL-6, and IL-10, were positively correlated with airway inflammation and remodeling [19]. The development of bronchiectasis is closely related to immune disorders. Many studies have confirmed that the pathogenesis of bronchiectasis may be related to the loss of function of T cells [20,21], and studies have found that cellular

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immune responses participate in the regulation of inflammatory response in bronchiectasis [22]. Th17 and Treg cells are 2 $CD4^+$ T cell subsets with adverse functions, mediating pro-inflammatory and anti-inflammatory action that act in balance to regulate immune response [23]. Th17/Treg level predicts progression of COPD and good lung function. Evidence suggests that abnormal inflammation in bronchiectasis influences the development of comorbidities in COPD, including BR [24].

In our study, we found the CBC patients had higher levels of inflammatory markers and worse immune imbalance compared to patients with only COPD. Previous reports have established airway luminal activation of Th-17 pathway in bronchiectasis. We hypothesized that immune imbalance could accelerate the progression of bronchiectasis with comorbid COPD.

This observational study with a relatively large sample size has some limitations. First, all subjects were voluntary participants at a single center, which may cause selection bias. Second, the severity of bronchiectasis was not evaluated, which may have resulted in low population representativeness. Finally, we did not evaluate the effects of bronchiectasis, serum inflammatory biomarkers, or PPMs on COPD prognosis. These limitations may have affected our results regarding the association between the tested variables and risk of bronchiectasis combined with comorbid COPD, and limit the clinical value of our study.

Conclusions

Our study identified *P. aeruginosa* colonization, increased level of serum inflammatory factors, and immune imbalance as risk factors for CBC patients. Immune imbalance might play a vital role in bronchiectasis development in COPD. Prospective studies with large sample sizes are needed for evaluating the immune imbalance and its effect on CBC.

Conflicts of interest

None.

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