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RESEARCH ARTICLE

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Clinical significance of BPI-ANCA detecting in COPD patients with *Pseudomonas aeruginosa* colonization

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Abstract

Background: Antineutrophil cytoplasmic autoantibodies against neutrophil granule bactericidal/permeability-increasing protein (BPI-ANCA) has been found in many inflammatory diseases, such as COPD, which can reduce the killing effect of BPI on Gram-negative bacteria. This study was aimed to assess the clinical significance of BPI-ANCA detecting in COPD patients with *Pseudomonas aeruginosa* (*P aeruginosa*) colonization.

Methods: A total of 216 COPD patients with lung *P aeruginosa* colonization, 244 patients with *P aeruginosa* infection from June 2015 to June 2018, and 100 healthy individuals were included. Serum BPI-ANCA, tumor necrosis factor (TNF)-α, and interleukin (IL)-6 and IL-1β levels were detected by ELISA, and the lung function of the patients was measured at stable clinical stages. Patients with COPD were grouped according to BPI-ANCA detection and GOLD criteria, and serum TNF-α, IL-6, and IL-1β levels and indices reflecting lung function were compared and analyzed between groups.

Results: Positive rate of BPI-ANCA in COPD patients with *P aeruginosa* colonization was 48.15%; and compared with BPI-ANCA(-) group, FEV_1%pred and FEV_1/FVC(%) in BPI-ANCA(+) patients were significantly decreased, while TNF-α, IL-6, and IL-1β levels were elevated. There were 31.73% and 36.54% BPI-ANCA(+) patients with severe and very severe airflow limitation, respectively, which was significantly higher than that in the BPI-ANCA(-) group. FEV_1%pred and FEV_1/FVC(%) were negatively correlated with TNF-α, IL-6, IL-1β, and NEU%. C-reactive protein (CRP) was negatively correlated with FEV_1%pred, yet not significantly correlated with FEV_1/FVC(%).

Conclusion: BPI-ANCA positivity is associated with inflammatory status in COPD patients with pulmonary *P aeruginosa* colonization and can be used as a potential biomarker assessing disease severity.

KEYWORDS

antineutrophil cytoplasm autoantibodies, bactericidal/permeability-increasing protein, chronic obstructive pulmonary disease, cytokines, *Pseudomonas aeruginosa*

Yongjian Tian and Tingting Zeng contributed equally.

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common chronic inflammatory disease impairing lung function. Lower respiratory microbial colonization often occurs during stable stage of this disease, of whom *Pseudomonas aeruginosa* (*P aeruginosa*) is the main colony.[1] Unlike bacteria infecting body in an acute way, *P aeruginosa* colonizing in the body usually cannot be easily killed and cleaned by bactericidal/permeability-increasing (BPI) protein—a kind of protein presented by neutrophil (NEU),[2] and on the contrary, it contributes to the production of autoantibody against BPI, unable it to clean pathogenic microorganism and inducing inflammatory responses.[3] The current study was retrospectively designed to evaluate pulmonary disease severity of COPD patients with *P aeruginosa* chronic colonization, via comparing the lung function and serum tumor necrosis factor (TNF)-α, interleukin(IL)-6 and IL-1β, and C-reactive protein (CRP) levels between patients seropositive for BPI-ANCA and those seronegative to explore the association of BPI-ANCA with patient's lung inflammation levels and explore the clinical significance of serum BPI-ANCA detection in COPD combined with *P aeruginosa* colonization.

2 | MATERIALS AND METHODS

2.1 | Participants

We continuously collected 2053 outpatient and inpatient patients with COPD definitely diagnosed in the Second Affiliated Hospital of Nanchang University from June 2015 to June 2018, 460 of whom were enrolled eventually according to inclusion and exclusion criteria. All patients enrolled with COPD were diagnosed based on the GOLD Global Initiative[4] for COPD and in relative stable disease stages and with completed and detailed medical records. Patients combined with metabolic abnormalities, autoimmune diseases, malignant tumors, infection of other pathogens (such as, Klebsiella Pneumoniae, Escherichia coli, Acinetobacter baumannii, Staphylococcus aureus, Streptococcus hemolyticus), those suffering from surgery, severe stress, neuropsychiatric disorders that cannot cooperate to complete pulmonary function test because of any causes, and patients diagnosed with other lung diseases except for COPD including bronchiectasis, interstitial lung disease, asthma, tuberculosis, lung cancer, and sleep apnea syndrome were excluded from this study. Details of patients' inclusion and exclusion criteria are shown in Figure 1. COPD patients with *P aeruginosa* isolated from sputum culture, in whose course of 6 months, *P aeruginosa* was isolated in three or more consecutive sputum culture for at least 1 month, were considered to be *P aeruginosa* chronic colonization[5] (*P aeruginosa* colonization group), and *P aeruginosa* infection (*P aeruginosa* infection group) otherwise. *P aeruginosa* colonization group includes 152 males and 64 females, with an average age of 60.02 ± 11.17 years old. *P aeruginosa* infection group includes 182 males and 62 females, with an average age of 61.04 ± 13.23 years old. Another 100 healthy individuals from the medical center of the Second Affiliated Hospital were selected as healthy control, who were in good condition, without any evidence of malaise according to a thorough physical inspection and consultation. Detailed general and medical history information of each participant, including gender, age, height, weight, illness duration, smoking history, past medical history, and detailed physical examination data, was collected by medical record reviewing or telephone follow-up and is shown in Table 1. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University, and written informed consents were obtained from all eligible participants.

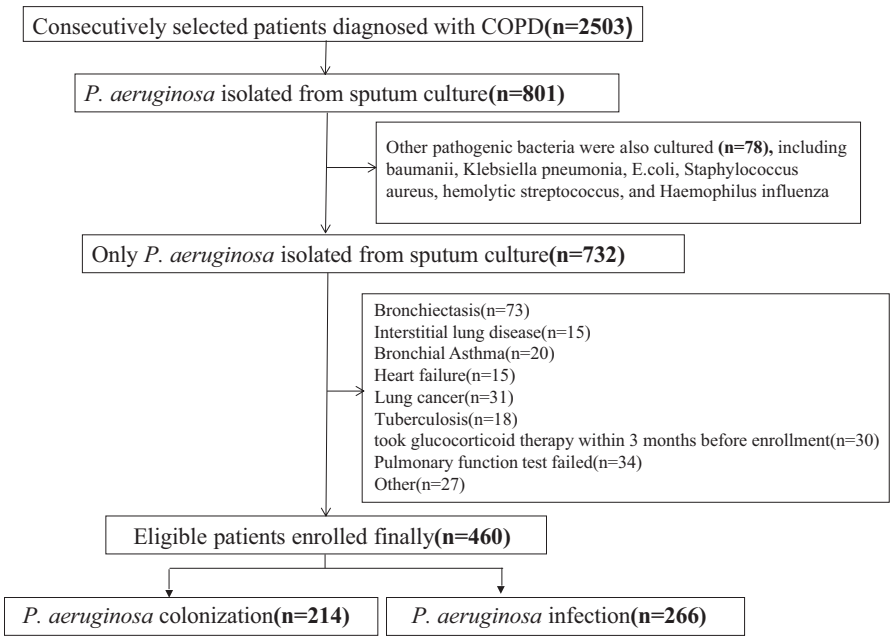

FIGURE 1 Flowchart of participants' inclusion and exclusion criteria

TABLE 1 General information of subjects and IgG-BPI-ANCA detection rate

Parameters	*Pseudomonas aeruginosa* colonization group	*Pseudomonas aeruginosa* infection group	HC group	*P*-value
Age (y)	60.03 ± 11.17	61.04 ± 13.23	58.63 ± 12.05	0.245†
Sex (n, %)				
Male	152 (70.37%)	182 (74.59%)	62 (62.00%)	0.066‡
Female	64 (29.63%)	62 (25.41%)	38 (38.00%)	
BMI (kg/m^2)	25.20 ± 3.22	24.65 ± 2.82	24.56 ± 3.41	0.101†
Smoking status (n, %)				
Never smoked	58 (26.85%)	74 (30.33%)	21 (21.00%)	0.054‡
Past smoking	119 (55.09%)	115 (47.13%)	48 (48.00%)	
Current smoking	39 (18.06%)	57 (23.37%)	31 (31.00%)	
Smoking history (pack-year)	43.06 ± 13.10	41.90 ± 12.68	40.14 ± 13.44	0.174†
Illness duration (y)	12.32 ± 5.23	10.77 ± 4.95	-	0.001†
Hospital admission within 6 mo				
Yes	116 (53.70%)	107 (43.85%)	-	0.035‡
No	100 (46.30%)	137 (56.15%)	-	
Family oxygen therapy				
Yes	18 (8.33%)	20 (8.20%)	-	0.958‡
No	198 (91.67%)	224 (91.80%)	-	
Taken glucocorticoid				
Yes	128 (59.26%)	142 (58.20%)	-	0.817‡
No	88 (40.74%)	102 (41.80%)	-	
BPI-ANCA (n, %)				
(+)	104 (48.15%)	6 (2.46%)	0 (0%)	0.000‡
(–)	112 (51.85%)	238 (97.54%)	0 (0%)	

Abbreviations: BMI, body mass index; BPI-ANCA, antineutrophil cytoplasmic autoantibodies against neutrophil granule bactericidal/permeability-increasing protein; HC, healthy control.
†Tested by one-way ANOVA test
‡Tested by chi-square test

2.2 | Detection of serum BPI-ANCA, TNF-α, IL-6, and IL-1β

Three milliliter fasting venous blood was collected to detect serum IgG-BPI-ANCA, TNF-α, IL-6, and IL-1β using ELISA, with reagents supplied by EUROIMMUN Medical Laboratory Diagnostics Stock Company (IgG-BPI-ANCA) and R&D Systems (Minneapolis, MN, USA) (TNF-α, IL-6, and IL-1β). For IgG-BPI-ANCA detection, optical density (OD) was determined by Multiskan Mk3 Enzyme labeled meter (Thermo Fisher Scientific, Shanghai, China), at the end of antigen and antibody reaction, and cutoff value was defined as $0.2 \times OD_{calibration}$. When ratio ($OD_{sample}$ to cutoff)>1, BPI-ANCA was considered positive, and negative otherwise. All assay aforementioned were conducted in strict accordance with manufacturers' protocols and standard operating procedure (SOP) of the Second Affiliated Hospital of Nanchang University, and repeated twice with included blinded quality controlled samples, and the inter- and intra-batch CVs were lower than 5%.

2.3 | Measurement of lung function

Pulmonary function tests were performed using a German-born Master Screen Diffusion Pulmonary Function Tester. Lung ventilation function tests were performed in strict accordance with the quality control standards of the American Thoracic Society. Lung volume measurements and flow rate capacity curves were performed to evaluate patients' pulmonary function. Each item was conducted three times repeatedly, and the best value of FEV_1%pred and FEV_1/FVC(%) was taken as the measurement result. The severity of COPD airflow limitation was classified according to the GOLD guidelines[6]: mild ($FEV_1 \geq 80\%$ predicted); moderate ($50\% \leq FEV_1 < 80\%$ predicted); severe: ($30\% \leq FEV_1 < 50\%$ predicted); and very severe: ($FEV_1 < 30\%$ predicted).

2.4 | Statistical analysis

The analysis was performed using SPSS 23.0 software. The normality and variance homogeneity of the measurement data were analyzed by

TABLE 2 Comparison of general data between patients with BPI-ANCA(+) and BPI-ANCA(-) of patients with COPD combined with *Pseudomonas aeruginosa* colonization

Parameters	BPI-ANCA(+) (n = 104)	BPI-ANCA(−) (n = 112)	*P*-value
Age (y)	61.08 ± 10.12	59.05 ± 12.02	0.992†
Sex			
Male	75 (72.12%)	77 (68.75%)	0.588‡
Female	29 (27.88%)	35 (31.25%)	
BMI (kg/m^2)	25.49 ± 2.94	24.92 ± 3.26	0.288†
Smoking status (n, %)			
Never smoked	19 (24.04%)	33 (29.47%)	0.079‡
Past smoking	68 (59.62%)	50 (50.89%)	
Current smoking	17 (16.34%)	30 (19.64%)	
Smoking history (pack-year)	44.71 ± 14.64	41.27 ± 11.02	0.052†
FEV1%pred	50.31 ± 7.94	52.91 ± 7.14	0.012†
FEV1/FVC (%)	48.35 ± 8.95	50.61 ± 6.27	0.037†

Abbreviations: BMI, body mass index; BPI-ANCA, antineutrophil cytoplasmic autoantibodies against neutrophil granule bactericidal/permeability-increasing protein; CRP, C-reactive protein; FEV1%pred: predicted% forced expiratory volume in 1 min; FEV_1/FVC: forced expiratory volume in one second/forced vital capacity ratio; NEU, neutrophil.
†Tested by independent data *t* test.
‡Tested by chi-square test.

K-S test and Levene's test. The results of normal distribution measurement data were expressed as mean ± SD. Differences in measurement data among multiple groups were compared by one-way ANOVA test followed by post hoc LSD test, and independent data *t* test was used to compare data between the two groups. Count data were expressed as percentage, and the data were compared by chi-square tests. Pearson correlation analysis was performed to assess correlations between indices. $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics and anthropometrics of participants

Positive rate of BPI-ANCA was 48.15% in 216 COPD patients with *P aeruginosa* colonization, highest compared to those with *P aeruginosa* infection and healthy controls, and perinuclear antineutrophil cytoplasmatic antibodies (p-ANCA) and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) were negative (not listed in the results). And illness duration and numbers of patients admitted to hospital within 6 months before enrollment was also significant between groups. Differences in general information such as age, gender, and smoke exposure among groups were not statistically significant. See details in Table 1.

3.2 | Anthropometric comparison between COPD patients with *P aeruginosa* colonization positive for BPI-ANCA and negative

A total of 216 COPD patients with *P aeruginosa* colonization were divided into BPI-ANCA (+) group (n = 104) and BPI-ANCA(−) group (n = 112) according to serum BPI-ANCA test results, with general data compared between groups. Results showed that there was no significant difference in baseline data between groups. Lung function in BPI-ANCA(+) patients was worse than the BPI-ANCA(−) group, FEV_1%pred and FEV_1/FVC(%) being lower (50.31 ± 7.94 vs 52.91 ± 7.14, $P = 0.012$ and 48.35 ± 8.95 vs 50.61 ± 6.27, $P = 0.037$, respectively). See Table 2.

3.3 | Comparison of serum TNF-α, IL-6, IL-1β, CRP, and NEU% between patients positive for BPI-ANCA and negative

In Table 3, serum levels of inflammatory markers (including TNF-α, IL-6, IL-1β, and CRP) and NEU% of COPD patients combined with *P aeruginosa* colonization were compared. TNF-α, IL-6, IL-1β, CRP, and NEU% levels in the BPI-ANCA(+) group were all higher than that in the BPI-ANCA (−) group, as shown in Table 3.

3.4 | Association of FEV_1%pred and FEV_1/FVC(%) with serum inflammatory markers

Pulmonary function indicators FEV_1%pred and FEV_1/FVC(%) were negatively correlated with inflammatory markers: TNF-α ($r = -0.582$, $r = -0.589$), IL-6 ($r = -0.521$, $r = -0.579$), IL-1β ($r = -0.346$, $r = -0.388$), NEU% ($r = -0.543$, $r = -0.582$), and CRP were negatively correlated with FEV_1%pred ($r = -0.159$, $P = 0.019$), but not significantly correlated with FEV_1/FVC (%), $P = 0.264$. See Table 4.

3.5 | TNF-α, IL-6, and IL-1β levels of COPD patients with different severity of airflow limitation

The distribution of the number of COPD patients with different severity of airflow limitation in the BPI-ANCA(+) group and BPI-ANCA

TABLE 3 Serum inflammatory markers were compared between the two groups

Parameters	BPI-ANCA(+) (n = 104)	BPI-ANCA(−) (n = 112)	*P-value*
TNF-α (pg/mL)	45.69 ± 19.93	33.31 ± 14.58	0.000
IL-6 (pg/mL)	40.61 ± 12.60	29.25 ± 7.86	0.000
IL-1β (pg/mL)	21.95 ± 7.29	14.37 ± 6.15	0.000
NEU%	64.14 ± 9.48	61.66 ± 8.33	0.042
CRP (mg/L)	8.41 ± 1.09	5.34 ± 1.14	0.000

Data were expressed as mean ± SD and tested by group *t* test.
Abbreviations: BPI-ANCA, antineutrophil cytoplasmic autoantibodies against neutrophil granule bactericidal/permeability-increasing protein; CRP, C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; NEU, neutrophil; TNF-α, tumor necrosis factor-α.

(−) group is shown in Table 5. The number of patients with very severe airflow limitation in the BPI-ANCA(+) group (n = 104) was significantly higher than that in the BPI-ANCA(−) group [38 (36.54%) vs 22 (19.64%)], and the difference was statistically significant ($P = 0.018$). Serum TNF-α (65.73 ± 14.45 pg/mL), IL-6 (54.18 ± 11.88 pg/mL), and IL-1β (3.97 ± 1.08 pg/mL) levels in patients with very severe airflow limitation were significantly higher than those in the mild, moderate, and severe groups ($P < 0.001$).

4 | DISCUSSION

Chronic obstructive pulmonary disease is a kind of obstructive lung disease characterized by long-term and chronic breathing problems and airflow limitation and usually gets worse over time. Tobacco smoking, air pollution, and occupation exposure are primary causes of chronic inflammation.[7] *P aeruginosa* is a common opportunist, colonizing in the body for long time without inflammatory responses while causing serious infection during existing disease—for example, COPD.[8] As a chronic disease, COPD is, *P aeruginosa* colonizing in patients usually have enough time to form a biofilm, which helps it escape from body immune system, ensuring its long-term colonization and even probably resulting in patients' acute exacerbation of COPD(AECOPD) during certain condition.[9] NEU can differentiate into antigen-presenting cell functioning in tumor microenvironment and some chronic inflammatory environments, expressing MHC class II molecules and related costimulatory molecules involved in adaptive immune response regulation.[10] On the other hand, a large number of NEU and macrophages infiltrating in the airway and releasing inflammatory factors impair lung function in patients with COPD as well. BPI, a cationic antimicrobial peptide, presenting in human and mammalian NEU, can directly exert toxic effects on Gram-negative bacteria (GNB) and neutralize free lipopolysaccharide (LPS).[11] When *P aeruginosa* invades the body, BPI can neutralize endotoxin and help kill intracellular and extracellular bacteria related to *P aeruginosa's* being quickly cleaned from body; while *P aeruginosa* is chronically colonized in the lung, BPI and microbial antigen are simultaneously engulfed and in the same way presented to MHC class II molecules on the surface of cells, the body then producing both protective antibodies against microbial antigens and autoreactive antibodies against BPI.[12] BPI, like other ANCA antigens, originates from polymorphonuclear leukocyte (PMN) and is exposed on the surface of PMN cells once released; binding of ANCA to this membrane-bound antigen activates PMN and leads to the release of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, which destroy lung structure and promote the inflammatory response of NEU.[13] Currently, the impact of BPI-ANCA on the clinical manifestations of chronic airway infections and elevated levels of cytokines in the serum of patients with COPD, and their relationship to disease severity remains unknown.

TABLE 4 Correlation of FEV_1%pred and FEV_1/FVC(%) with inflammatory markers

	FEV_1%pred		FEV_1/FVC(%)	
Parameters	*r*	*P*-value	*r*	*P*-value
TNF-α	−0.582	0.000	−0.589	0.000
IL-6	−0.521	0.000	−0.579	0.000
IL-1β	−0.346	0.000	−0.388	0.000
CRP	−0.159	0.019	−0.076	0.264
NEU (%)	−0.543	0.000	−0.582	0.000

Abbreviations: CRP, C-reactive protein; FEV1%pred, predicted% forced expiratory volume in 1 min; FEV1/FVC, forced expiratory volume in one second/forced vital capacity ratio; IL-1β, interleukin 1β; IL-6, interleukin 6; NEU, neutrophil; TNF-α, tumor necrosis factor-α.

Results of the current study showed that illness duration of *P aeruginosa* colonization group was longer (12.32 ± 5.23 vs 10.77 ± 4.95 year) and more patients in *P aeruginosa* colonization group admitted to hospital within 6 months before enrollment. As mentioned before, chronic disease characteristic of COPD was one of the requirements for *P aeruginosa* to form biofilm and against being cleaned, so it is reasonable that there is significant difference in illness duration between groups. And serum BPI-ANCA positivity in the *P aeruginosa* colonization group (48.15%) was higher than patients with *P aeruginosa* infection (2.46%) in the present study. However, positive rate of BPI-ANCA here was lower compared to what reported by Lachenal et al,[14] which might cause by different sample size, illness duration and subtypes of *P aeruginosa*. What's more, in the current study we detected IgG-BPI-ANCA only, considering that it is the main type of autoantibody against BPI.

Thomsen et al[15] reported that COPD patients with elevated levels of CRP and NEU count usually had higher risk of AECOPD, even those with relative moderate symptoms. The present study detected TNF-α, IL-6, IL-1β, CRP, and NEU% levels in COPD patients with *P aeruginosa* colonization and found that inflammatory markers were higher in patients seropositive for BPI-ANCA than those negative, indicating a link between BPI-ANCA positivity and inflammatory status in COPD patients with *P aeruginosa* colonization. A 10-year study followed 46 patients with cystic fibrosis and *P aeruginosa* colonization drawn conclusion basically consistent with us—it showed that 15/28 BPI-ANCA(+) patients developed adverse outcomes

TABLE 5 Serum levels of TNF-α, IL-6, and IL-1β at different levels of COPD airflow limitation

	Mild	Moderate	Severe	Very severe	*P*-value
BPI-ANCA group (n,%)					
(+)	11 (10.58%)	22 (21.15%)	33 (31.73%)	38 (36.54%)	0.018†
(−)	21 (18.75%)	35 (31.26%)	37 (30.35%)	22 (19.64%)	
TNF-α (pg/mL)	10.81 ± 6.05	28.5 ± 10.25	42.10 ± 9.04	65.73 ± 14.45	<0.000‡
IL-6 (pg/mL)	9.63 ± 4.77	18.81 ± 8.76	32.75 ± 8.95	54.18 ± 11.88	<0.000‡
IL-1β (pg/mL)	3.97 ± 1.08	6.49 ± 2.49	13.96 ± 6.93	27.28 ± 10.43	<0.000‡

Abbreviations: BPI-ANCA, antineutrophil cytoplasmic autoantibodies against neutrophil granule bactericidal/permeability-increasing protein antibodies; IL-1β, interleukin 1β; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α.
†Tested by chi-square test.
‡Tested by one-way ANOVA test.

(*P* = 0.01), while only 2/18 BPI-ANCA(−) patients did so,[16] suggesting the close association of inflammation and poor prognosis in COPD patients with *P aeruginosa* colonization with serum BPI-ANCA positivity. Besides, pulmonary function test showed that indices including FEV_1%pred and FEV_1/FVC (%) decreased significantly in COPD patients with *P aeruginosa* colonization positive for BPI-ANCA, which is basically consistent with the findings of Seema Singh et al.[17]

Cytokines act as the main inflammatory mediator to regulate the aggregation and activation of inflammatory cells, which will release more proteases or oxidants to further aggravate the damage of airway epithelium and lung tissue. Previous research has showed that TNF-α was involved in the process of NEU activation during airway inflammation, resulting in a large amount of NEU infiltrating in the airway mucosa and enhancing the solubility of extracellular elastin, which is responsible for airway restructure,[18] while both IL-6 and IL-1β played regulatory role in immune responses and participated in disease development and tissue damage.[19] Zhou et al[20] reported that serum IL-1β in COPD patients was significantly elevated compared to healthy controls (43.33 ± 5.70 vs 28.60 ± 5.07 pg/mL), and Celli BR et al[21] detected serum inflammatory markers for 3 years revealing that with serum IL-6 elevated, mortality of COPD patients increased significantly. All mentioned above showed that inflammatory markers such as IL-6 and IL-1β were good indicator of poor outcomes for COPD patients. Correlation analysis demonstrated that TNF-α, IL-6, IL-1β, and NEC% levels were negatively related to lung function indicators including FEV_1%pred and FEV_1/FVC(%), and CRP was correlated with FEV_1%pred negatively. Considering that serum cytokine levels were susceptible to multiple factors, for example, IL-6 levels were seriously affected by nutritional status and its levels usually elevated in patients with lower BMI or dystrophy.[22] We, in the current study, selected COPD patients with *P aeruginosa* colonization in a relatively stable illness stage and excluded those with chronic consumptions such as heart failure, diabetes mellitus, and malignant neoplasm and those with dystrophia to minimize the influence of confounding factors.

A total of 216 patients studied currently were grouped according to severity of COPD airflow limitation based on the GOLD criteria. Results showed that the proportion of patients with very severe airway limitation in BPI-ANCA(+) patients were 36.54%, higher than that in the BPI-ANCA(−) group, and inflammatory indicator levels in patients with very severe airflow limitation were higher compared to other groups, suggesting that inflammation levels of COPD patients with *P aeruginosa* colonization and seropositive for BPI-ANCA might be higher compared to those seronegative and should be paid more attention during disease management.

In conclusion, our study suggests that BPI-ANCA positivity is associated with inflammatory status in COPD patients with pulmonary *P aeruginosa* colonization and can be used as a potential biomarker assisting physicians in disease management.

CONFLICT OF INTERESTS

All authors declared that they have no conflict of interests.

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