Research Article

Clinical Differences between Eosinophilic and Noneosinophilic Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Multicenter Cross-Sectional Study

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Rationale. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is highly heterogeneous with a plethora of different etiologic factors and inflammatory presentations. COPD with higher blood eosinophil count is associated with increased readmission rates and better corticosteroid responses. However, the clinical features of eosinophilic AECOPD are not well explored. Thus, this study was aimed at exploring the clinical differences between eosinophilic and noneosinophilic AECOPD.

Methods. A total of 643 AECOPD patients were enrolled in this multicenter cross-sectional study. Finally, 455 were included, 214 in the normal-eosinophil AECOPD (NEOS-AECOPD) group, 63 in the mild increased-eosinophil AECOPD (MEOS-AECOPD) group, and 138 in the severe increased-eosinophil AECOPD (SEOS-AECOPD) group. Demographic data, underlying diseases, symptoms, and laboratory findings were collected. Multiple logistic regression analysis was performed to identify the independent factors associated with blood eosinophils (EOS). Correlations between blood EOS and its associated independent factors were evaluated. Results. The significant differences in 19 factors, including underlying diseases, clinical symptoms, and laboratory parameters, were identified by univariate analysis. Subsequently, multiple logistic regression analysis revealed that lymphocyte%, neutrophil% (NS%), procalcitonin (PCT), and anion gap (AG) were independently associated with blood EOS in AECOPD. Both blood EOS counts and EOS% were significantly correlated with lymphocyte%, NS%, PCT, and AG. Conclusions. Collectively, blood EOS was independently associated with lymphocyte%, NS%, PCT, and AG in AECOPD patients. Lymphocyte% was lower, and NS%, PCT, and AG were higher in eosinophilic AECOPD. Our results indicate that viral-dominant infections are the probable major etiologies of eosinophilic AECOPD. Noneosinophilic AECOPD is more likely associated with bacterial-dominant infections. The systemic inflammation in noneosinophilic AECOPD was more severe.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the most common chronic pulmonary disorder. It is found that the prevalence of COPD is gradually increasing in recent decades [1–3]. Wang et al. showed that the prevalence of COPD was 8.6%, indicating about 99.9 million patients in mainland China [3]. It is estimated that about 3.2 million people died from COPD worldwide in 2015 [2]. Globally, COPD is the third leading cause of death in recent years [1, 4]. Furthermore, COPD is a highly heterogeneous disease with different responses and outcomes [5, 6].
Although other potential biomarkers were identified [7] such as inflammatory mediators/proteins [8], miRNAs [9, 10], DNA methylation CpG sites [11, 12], single nucleotide polymorphisms [13, 14], and metabolites [15, 16], blood eosinophils (EOS) are considered to be stable, easily available, and acceptable markers in clinical practice [17, 18]. Generally, COPD is considered a Th1-dependent chronic airway inflammation. Neutrophils (NS), macrophages, and Th1 cells are the major immunological cells in COPD, whereas EOS, B cells, and Th2 cells are essential for asthma [1, 19–21]. However, evidence has proven that EOS are also increased in a group of COPD patients (not only in blood but also in sputum) and that higher blood EOS are associated with increased risk of readmission, severe lung function impairment, and longer hospital stay [LHS] [17, 22–26]. Some studies identified that inhaled corticosteroid (ICS) plus long-acting β2-agonist (LABA) and ICS plus LABA and long-acting muscarinic antagonist (LAMA) brought more benefits in eosinophilic COPD than in noneosinophilic COPD [27, 28]. Therefore, increased blood EOS was considered to be a “treatable trait” of COPD [18, 25]. Nevertheless, the clinical features of eosinophilic hospitalized AECOPD are still not well studied. Thus, this study was aimed at exploring the clinical differences between eosinophilic and noneosinophilic AECOPD.

Additionally, the optimal cutoff value of blood EOS is still not determined. With the cutoff of EOS% ≥ 2% and/or EOS counts ≥ 200 cells/μL, Couillard et al. showed that the risk of 12-month COPD-related readmission in eosinophilic AECOPD was increased and LHS was not different, as compared to noneosinophilic AECOPD [22]. With a cutoff of 300 cells/μL, Qi et al. found that sputum microbiome richness and plasma IL-6 levels in eosinophilic AECOPD decreased more significantly than in noneosinophilic AECOPD, after 7 days of treatment [29]. Cheng and Lin demonstrated that the ICS response in COPD with EOS% > 3% was better than that in noneosinophilic COPD [30]. Therefore, in our study, the patients with AECOPD were divided into three subgroups considering both blood EOS counts and EOS% (Figure 1).

2. Methods

2.1. Study Design and Population. This multicenter cross-sectional study was performed at the Respiratory Department of the Second Affiliated Hospital of Chongqing Medical University and the First People’s Hospital of Sining City from January 2017 to January 2020. This study was approved by the Research Ethics Committees of the Second Affiliated Hospital of Chongqing Medical University (No. 2019-23) in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients by the responsible physician or an appropriately trained staff member. Standard care and treatments were provided according to current clinical guidelines [1, 5].

2.2. Sample Size Determinations. As for the sample size, a minimum total of 159 (53 in each group) was required to detect at least a 25% difference in effect size for an 80% power, assuming α = 0.05 and allocation ratio = 1 : 1 : 1. Furthermore, 20% more patients (64 in each group) were recruited.

2.3. Inclusion and Exclusion Criteria. The inclusion criterion was COPD exacerbation requiring hospitalization with age ≥ 40 years. Exclusion criteria were as follows (in descending order): asthma (n = 71), bronchiectasis (n = 65), nonrespiratory failure patients without lung function test (n = 33), other chronic lung diseases (n = 22), history of malignant diseases (n = 17), systemic steroid use within the last 2 weeks (n = 15), antibiotics use within the last 2 weeks (n = 13), pneumonia (n = 11), liver failure (n = 10), renal failure (n = 9), interstitial lung diseases (ILDs) (n = 9), active pulmonary tuberculosis (TB) (n = 8), immunocompromised status (organ transplant, immunosuppressive agent use, and HIV infection) (n = 8), dysphagia and aspiration (n = 6), hospital-acquired pneumonia (HAP) (n = 5), dementia (n = 2), and pulmonary thromboembolism (PTE) (n = 1). A total of 643 patients with hospitalized AECOPD were recruited, of which 188 were excluded. In the end, 214 were NEOS-AECOPD patients, 63 were MEOS-AECOPD patients, and 178 were SEOS-AECOPD patients (Figure 1).

2.4. Definitions. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [1], the diagnosis of COPD was established by a pulmonologist based on a history of exposure to risk factors, such as smoking, biomass fuel exposure, and occupational dust; clinical presentations; and airflow obstruction measured by spirometry (a postbronchodilator fixed ratio of FEV1/FVC < 0.7). AECOPD was defined as an event in the natural course of the disease characterized by acute changes in clinical symptoms beyond normal day-to-day variation, resulting in additional therapy [1]. Connective tissue disease (CTD) was defined as having a previous rheumatologist diagnosis of a specific CTD, such as systemic lupus erythematosus, Sjogren’s syndrome, systemic sclerosis, and rheumatoid arthritis. Both blood EOS counts and EOS% were considered to set the cutoff values of EOS. Normal-eosinophil AECOPD (NEOS-AECOPD) was defined as AECOPD with EOS% < 2% and EOS counts < 200 cells/μL. Mild increased-eosinophil AECOPD (MEOS-AECOPD) was defined as AECOPD with EOS% 2%-2.99% and/or EOS counts 200-299 cells/μL. Severe increased-eosinophil AECOPD (SEOS-AECOPD) was defined as AECOPD with EOS% ≥ 3% and/or EOS counts ≥ 300 cells/μL. Ex-smokers were defined as abstaining from smoking ≥ 6 months. Neutrophil-to-lymphocyte ratio (NLR) was defined as neutrophils divided by lymphocytes in the blood.

2.5. Data Collection. In our study, demographic data, underlying diseases, comorbid conditions, symptoms, and LHS were recorded and collected. Blood samples for laboratory tests and lung function tests were all collected and performed within 24 h after admission. However, for safety reasons and cooperation concerns, the spirometer test was not performed in patients with respiratory failure. All patients underwent high-resolution computed tomography (HRCT) scans within
48 h of hospitalization, and the results were reviewed by one independent radiologist and one pulmonologist in each hospital. Additionally, the participating centers shared the same methodologies and normal values in the laboratory measurements.

2.6. Statistical Analysis. Data were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation (SD), and categorical data were expressed as frequencies. The data distribution was analyzed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were analyzed by one-way ANOVA with LSD and SNK’s post hoc test. Continuous variables with abnormal distribution and ordinal variables were measured using the Kruskal–Wallis H test. The chi-squared test was used to analyze categorical variables. Multiple logistic regression was performed to investigate the independent risk factors associated with blood EOS in AECOPD patients. The Spearman rank correlation coefficient was calculated to analyze correlations. A threshold of $P < 0.05$ was considered to be significant.

3. Results

3.1. Baseline Characteristics of AECOPD Patients. A total of 643 hospitalized patients with AECOPD were screened (Figure 1). Finally, 214 (47.03%) NEOS-AECOPD patients, 63 (13.85%) MEOS-AECOPD patients, and 178 (39.12%) SEOS-AECOPD patients were eligible. The ratio of eosinophilic AECOPD (MEOS-AECOPD+SEOS-AECOPD) was 52.97%. The demographic data of the patients are shown in Table 1. The rate of CTD was significantly higher in SEOS-AECOPD patients.

3.2. Clinical Features and Laboratory Data of AECOPD Patients. As shown in Table 2, the rates of fever and mechanical ventilation (MV), white blood cells (WBCs), neutrophils (NS), NS%, lymphocyte%, NLR, procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anion gap (AG), serum sodium (Na+), serum potassium (K+), serum calcium (Ca2+), serum magnesium (Mg2+), blood urea nitrogen (BUN), direct bilirubin (DBIL), and LHS were significantly different among the three groups.

3.3. Multiple Logistic Regression Analysis in AECOPD Patients. To explore independent factors associated with blood EOS in AECOPD patients, multiple logistic regression analysis was performed. In the multiple logistic regression model, the factors significantly associated with blood EOS in univariate analysis, including the rates of CTD, fever, MV, WBC, NS, NS%, lymphocyte%, NLR, procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anion gap (AG), serum sodium (Na+), serum potassium (K+), serum calcium (Ca2+), serum magnesium (Mg2+), blood urea nitrogen (BUN), direct bilirubin (DBIL), and LHS were included. As shown in Table 3, lymphocyte%, NS%, PCT, and AG were independently associated with blood EOS in AECOPD patients by multiple logistic regression.

3.4. Correlations between Blood EOS Counts/EOS% and Lymphocyte%, NS%, PCT, and AG in AECOPD Patients. Since lymphocyte%, NS%, PCT, and AG were independently associated with blood EOS in AECOPD patients, their correlations with blood EOS counts and EOS% were explored. Significant correlations were found between blood EOS counts and lymphocyte%, NS%, PCT, and AG and between blood EOS% and lymphocyte%, NS%, PCT, and AG in AECOPD patients (Table 4). Among them, lymphocyte% was positively and NS%, PCT, and AG were negatively correlated with blood EOS counts and EOS%.

Figure 1: Flow diagram of the study.
4. Discussion

In this multicenter cross-sectional study, we found that lymphocyte%, NS%, PCT, and AG were the independent factors associated with blood EOS in AECOPD patients. Our results indicate that viral-dominant infection is probably related to eosinophilic AECOPD. Noneosinophilic AECOPD is more likely to be associated with bacterial-dominant infections.

As the most common lung disorder, the prevalence of COPD is still increasing [1, 3, 5]. Globally, the prevalence of COPD was 11.7% (8.4%-15.0%), and the COPD case number was approximately 384 million in 2010 [1, 4]. Wang et al. showed that the overall prevalence of COPD in mainland China was 8.6% (95% CI 7.5-9.9) in a population aged ≥40 years or approximately 99.9 (95% CI, 76.3-135.7) million cases [3]. Simultaneously, COPD is a chronic disease with high mortality and disability. It was reported that approximately 3 million people die from COPD every year [1, 31]. Patel et al. showed that COPD caused an average of 5 more days of work absence and short-term disability-associated extra costs of $641 each year in the USA [32]. It was estimated that the number of years living with disability of COPD was about 29.4 million in 2010 [33].

Nevertheless, COPD is a highly heterogeneous disease with significant differences in treatment response and outcomes in patients. Mounting evidence suggests that individual therapy and target therapy are the major trends of COPD in the future. Therefore, exploration and differentiation of the phenotypes of COPD are valuable in clinical practice. Recently, a number of studies have shown that blood EOS (EOS counts and EOS%) are an effective, stable, and available biomarkers in COPD and can be used to define the phenotypes of COPD [17, 22, 34, 35]. However, the cutoff value of blood EOS is still debated, ranging from 150 to 400 cells/μL and/or 2% to 4% in different studies [17, 18, 22, 23, 25, 34–36]. Therefore, in this study, both 200 cells/μL and 300 cells/μL and 2% and 3% were considered the cutoff values of blood EOS counts and EOS% in AECOPD patients (Figure 1).

| NEOS-AECOPD (n = 214) | MEOS-AECOPD (n = 63) | SEOS-AECOPD (n = 178) | Statistical values | P |
|-----------------------|---------------------|----------------------|--------------------|---|
| Sex (male, n)         | 159                 | 51                   | 138                | 1.375 | 0.503 |
| Age (years)           | 71.2056 ± 9.31175   | 73.1429 ± 9.89437    | 70.2528 ± 9.06961  | 2.272 | 0.104 |
| BMI                   | 21.908271 ± 3.6468114 | 22.739524 ± 3.3535515 | 22.285506 ± 4.0060567 | 1.329 | 0.266 |
| Smoking               |                      |                      |                    | 0.366 | 0.833 |
| Nonsmoking            | 74                   | 24                   | 71                 | 5.875 | 0.053 |
| Ex-smoking            | 56                   | 11                   | 36                 |      |      |
| Current smoking       | 84                   | 28                   | 71                 |      |      |
| GOLD stages           |                      |                      |                    |      |      |
| Stage I: mild (≥80%)  | 25                   | 10                   | 21                 |      |      |
| Stage II: moderate (50-79%) | 62                 | 24                   | 59                 |      |      |
| Stage III: severe (30-49%) | 54                 | 17                   | 52                 |      |      |
| Stage IV: very severe (<30%) without respiratory failure | 17 | 4 | 13 |      |      |
| Respiratory failure   | 56                   | 8                    | 33                 |      |      |
| Underlying diseases/comorbidities |       |                      |                    |      |      |
| Pneumothorax          | 2                    | 0                    | 3                  | 1.317 | 0.518 |
| Pleural effusion (PE) | 11                   | 0                    | 6                  | 3.684 | 0.158 |
| Community-acquired pneumonia (CAP) | 96 | 26 | 74 | 0.525 | 0.769 |
| Cor pulmonale         | 43                   | 6                    | 26                 | 4.698 | 0.095 |
| Coronary artery disease (CAD) | 46 | 12 | 27 | 2.567 | 0.277 |
| Hypertension          | 80                   | 21                   | 73                 | 1.288 | 0.525 |
| T2DM                  | 39                   | 14                   | 20                 | 5.595 | 0.061 |
| Atrial fibrillation (Af) | 11               | 3                    | 5                  | 1.383 | 0.501 |
| Connective tissue disease (CTD) | 0 | 0 | 4 | 6.280 | 0.043 |
| Metabolic acidosis    | 35                   | 12                   | 20                 | 3.116 | 0.211 |
| Abbreviation | Definition |
|--------------|------------|
| Fever | 29 0 7 18.622 0.000 |
| WBCs (×10^9/L) | 9.127710 × 4.033688 |
| NS (×10^9/L) | 7.495327 × 6.445053 |
| Lymphocytes (×10^9/L) | 1.365327 × 0.9015292 |
| EOS (×10^9/L) | 0.053933 × 0.0508252 |
| NS% | 78.291729 × 37.4499608 |
| Lymphocyte% | 16.887710 × 9.9761204 |
| EOS% | 0.747570 × 0.6408311 |
| NLR | 7.945654 × 9.5498819 |
| RBCs (×10^12/L) | 4.416748 × 0.7819829 |
| Hb (g/L) | 132.35514 × 17.8379520 |
| Hct (%) | 40.175467 × 5.3567446 |
| PLTs (×10^9/L) | 203.242991 × 7.3462106 |
| PCT (ng/mL) | 0.218766 × 0.7493592 |
| CRP (mg/mL) | 27.364953 × 40.8671745 |
| ESR (mm/first hour) | 24.635514 × 20.9070973 |
| ABG | pH 7.412682 × 0.2818535 |
| PaCO₂ (mmHg) | 43.564486 × 13.6961751 |
| PaO₂ (mmHg) | 82.598131 × 28.5118738 |
| Oxygen index (OI) | 343.990654 × 97.8380856 |
| AB (mmol/L) | 28.489252 × 6.1881931 |
| SB (mmol/L) | 27.662150 × 3.4513572 |
| AG | 12.104299 × 4.3290494 |
| Serum Na⁺ (mmol/L) | 137.636916 × 0.056556153 |
| Serum K⁺ (mmol/L) | 3.896262 × 0.4741605 |
| Serum Ca²⁺ (mmol/L) | 2.223738 × 0.1488486 |
| Serum Mg²⁺ (mmol/L) | 0.839720 × 0.0951594 |
| ALB (g/L) | 37.813551 × 4.3179452 |
| BUN (mmol/L) | 6.562897 × 2.5492516 |
| Cr (μmol/L) | 72.299533 × 27.8074237 |
| ALT (U/L) | 24.677570 × 38.0325258 |
| AST (U/L) | 27.925234 × 43.1549672 |
| IBIL (μmol/L) | 6.397243 × 3.3865077 |
| DBIL (μmol/L) | 5.060234 × 3.6063036 |
| RBG (mmol/L) | 6.878692 × 2.8710151 |
| LHS (days) | 9.9112 × 4.90727 |
blood eosinophils was considered to be a good predictor of EOS in airways in COPD patients [23, 37, 38]. Eltboli et al. identified a strong correlation between blood EOS% and the submucosal EOS count \((r = 0.57)\) and reticular basement membrane thickness \((r = 0.59)\) in COPD patients [37]. Kolsum et al. reported that compared with COPD with blood EOS < 150 cells/μL, EOS% in induced sputum, BALF, and submucosa were all higher in COPD with blood EOS > 300 cells/μL [38]. Nevertheless, several studies found that the correlation between lung EOS and blood EOS was not very well [36, 39]. Turato et al. explored the correlations between blood EOS and EOS in central airways, peripheral airways, and lung parenchyma, using samples of COPD patients who underwent lung resection for solitary pulmonary nodules without additional complications [36]. Initially, no differences in EOS densities among central airways, peripheral airways, and lung parenchyma were observed in COPD, and pulmonary EOS counts were not associated with COPD severity. Subsequently, they revealed that the correlations between blood EOS and EOS in any of the three lung compartments were not significant. Additionally, in a randomized, double-blind, placebo-controlled trial, EOS counts and EOS% in induced sputum were markedly reduced after 16 weeks of roflumilast (a PDE4 inhibitor) treatment in COPD [39]. However, blood EOS counts were not changed by roflumilast. Meanwhile, a significant difference was confirmed between eosinophilic and noneosinophilic AECOPD [17, 20, 22, 24, 25, 30, 35, 40]. Mounting evidence has shown that increased blood EOS was associated with higher risk of readmission, severe lung function impairment, longer LHS and survival time, and better ICS response in COPD patients [22, 24, 25]. Nevertheless, the clinical features, particularly laboratory parameters, of eosinophilic AECOPD are still not well studied. In this study, commonly used laboratory parameters, including blood routine, PCT, ESR, CRP, ABG, electrolytes, liver function, and renal function, were included. Our data showed that the rates of fever and MV, WBC, NS, NS%, lymphocyte%, NLR, PCT, CRP, ESR, AG, serum Na⁺, serum K⁺, serum Ca²⁺, serum Mg²⁺, BUN, DBIL, and LHS were significantly different among the three groups (Table 2). Subsequently, 19 variables with significant differences in univariate analysis were included in the multiple logistic regression analysis. We identified that lymphocyte%, NS%, PCT, and AG were independently associated with blood EOS in AECOPD patients.

Furthermore, as shown in Table 4, lymphocyte% was positively associated with blood EOS counts and EOS% in AECOPD. In this study, asthma was strictly excluded, which was considered to be the most common confounder of COPD studies [18, 24, 40]. Meanwhile, COPD patients with recent systemic steroid and immunosuppressive agent use were also excluded. These data indicate that inflammatory types are significantly different between eosinophilic and noneosinophilic AECOPD patients. EOS and lymphocytes were the major inflammatory cells in eosinophilic AECOPD, and neutrophils were the dominant inflammatory cells in noneosinophilic AECOPD. It is well known that respiratory tract infection is the leading cause of acute exacerbation in COPD [1, 35, 41–43]. Among them, bacteria and viruses are the most common pathogens. In a prospective observational study, Bafadhel et al. showed that 55% and 29% of acute exacerbations were related to bacterial and viral infections in COPD [43]. Meanwhile, Papi et al. demonstrated that bacterial and/or viral infection was found in 78.1% (29.7% bacterial, 23.4% viral, and 25% viral/bacterial coinfection) AECOPD patients [41]. Several studies have shown that airway eosinophilic inflammation is related to viral infection in AECOPD [35, 41]. Additionally, it was confirmed that blood neutrophils and PCT are biomarkers of bacterial infection in COPD [44]. In a meta-analysis, Ni et al. showed that the sensitivity and specificity of PCT in diagnosing bacterial infections were 0.60 and 0.76, respectively, and the AUC of the ROC curve was 0.77 [44]. Ergan et al. found that compared with culture-negative patients, PCT was markedly increased in culture-positive patients in AECOPD [45]. They also showed that 0.25 ng/mL was the optimal cutoff value, with 63% sensitivity, 67% specificity, and 0.73 AUC, to predict bacterial infection in AECOPD. Collectively, our results suggest that viral and virus-dominant infections are probably the major etiologies of eosinophilic acute exacerbation in COPD. Noneosinophilic acute exacerbation in COPD is more likely associated with bacterial and bacterial-dominant infection.

### Table 3: Multiple logistic regression analysis of independent factors associated with blood eosinophils in AECOPD \((n = 455)\).

|                      | Estimate | S.E  | Wals | df | Sig. | 95% CI       |
|----------------------|----------|------|------|----|------|--------------|
| Lymphocyte%          | -0.238   | 0.037| 41.127| 1  | 0.000| -0.311--1    |
| NS%                  | -0.254   | 0.041| 38.431| 1  | 0.000| -0.334--1    |
| PCT                  | -1.494   | 0.355| 17.739| 1  | 0.000| -2.189--1    |
| AG                   | -0.099   | 0.022| 19.587| 1  | 0.000| -0.142--1    |

**Estimate S.E Wals df Sig.**

Abbreviations: NS: neutrophils; PCT: procalcitonin; AG: anion gap.

### Table 4: The correlations between EOS counts/EOS% in blood and lymphocyte%, NS%, PCT, and AG in AECOPD patients \((n = 455)\).

|                      | Lymphocyte% | NS%  | PCT | AG  |
|----------------------|-------------|------|-----|-----|
| EOS counts           |             |      |     |     |
| \(R\)                | 0.221       | -0.365| -0.214| -0.184|
| \(P\)                | 0.000       | 0.000| 0.000| 0.000|
| EOS%                 |             |      |     |     |
| \(R\)                | 0.335       | -0.481| -0.262| -0.222|
| \(P\)                | 0.000       | 0.000| 0.000| 0.000|

Abbreviations: NS: neutrophils; PCT: procalcitonin; AG: anion gap.
Circulation and tissue hypoperfusion are associated with severe infection in clinical practice. Commonly, hypoperfusion-induced hyperlactacidemia is the major reason for increased AG in patients with infection without renal failure and ketoadidasis. Durmus et al. revealed that lactate clearance in hospitalized AEOPD patients (severe patients) was significantly lower than that in AECOPD patients without hospitalization (nonsevere patients) [46]. These results collectively indicate that bacterial infection and systemic inflammation in noneosinophilic AEOPD are more severe than in eosinophilic AEOPD.

Due to low positive rates of sputum cultures, specimen contamination, and airway bacterial colonization in COPD patients, the pathogen results were not included to reduce biases and confounders, which was also one of the major limitations of our current study. Therefore, direct correlations between pathogen types and blood EOS were not evaluated. The main strength of our study was that relatively comprehensive laboratory data were collected, which accurately classified the severity and complications of the underlying diseases. In particular, a chest HRCT scan was performed in each patient, which effectively promoted the diagnosis accuracy and excluded most other lung diseases. Furthermore, the different cutoff values of blood EOS were considered, making our data more convincing.

5. Conclusions
Collectively, our results revealed that lymphocyte%, NS%, PCT, and AG were independent factors associated with blood EOS in AECOPD patients. Our data indicated that viral and viral-dominant infections are probably the major etiologies of eosinophilic AECOPD. Noneosinophilic AEOPD is more likely to be associated with bacterial and bacterial-dominant infections. Systemic inflammation in noneosinophilic AEOPD is more severe than in eosinophilic AEOPD. Nevertheless, further studies with high sensitivity and specificity in pathogen tests, including bronchoscopy, should be developed to validate our results.

Data Availability
Due to the respect to and the protection of patient privacy, the data generated and/or analyzed in this study are not publicly available. However, they are available from the corresponding authors on reasonable request.

Conflicts of Interest
The authors declare no conflict of interest.

Authors’ Contributions
All authors read and approved the final manuscript. Guangming Dai, Jiajia Wang, Yajuan Ran, Xingru Chen, Junnan Peng, and Xinglong Li collected the data. Guangming Dai, Yajuan Ran, Jiajia Wang, Huoijn Deng, Min Xiao, and Tao Zhu analyzed and interpreted the data. Guangming Dai, Yajuan Ran, Jiajia Wang, Min Xiao, and Tao Zhu drafted the manuscript. All authors read and approved the final manuscript. Guangming Dai, Yajuan Ran, and Jiajia Wang contributed equally to this work.

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